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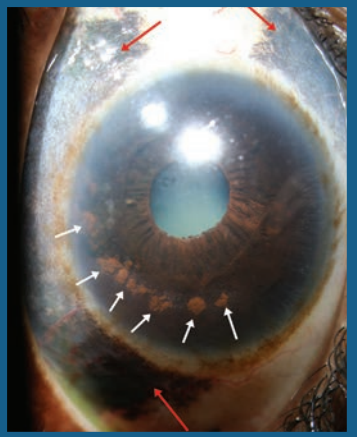

Conjunctival melanosis evident on slit-lamp examination.

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open access journal est. 1998

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Asian Journal of Ophthalmology is the peer-reviewed journal for The Asian Pacific Glaucoma Society (APGS) and The Asia Pacific Ophthalmic Trauma Society (APOTS) and all others with an interest in Ophthalmology.

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The Asian Journal of Ophthalmology is published four issues per year (quarterly) electronically. Each issue will consist of approximately 48 pages. A selection of the best papers is published in print twice a year and distributed free of charge at congresses through Kugler Publications or partners.

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The Asian Journal of Ophthalmology provides immediate open access to its content after (free) registration, on the principle that making research freely available to the public supports a greater global exchange of knowledge. There are no fees required to publish in the journal.

Focus and scope

As new technologies and therapeutic interventions are continually being developed, Ophthalmology has become a field of rapid change, particularly in the Asia-Pacific region, where disease patterns and health care delivery differ greatly from those seen in the West. Asian Journal of Ophthalmology was established in 1998 with the aim of disseminating information relevant to Ophthalmology and glaucoma throughout Asia and to interested groups worldwide.

The objectives of Asian Journal of Ophthalmology are as follows:

- To provide a platform for the publication of information with a focus on Ophthalmology in Asia.
- To disseminate information that will improve the care of patients with all types of ophthalmological disorders, with a special focus on glaucoma.
- To increase the understanding of such disorders through reporting of educational activities.
- To publish the results of research programmes to expand knowledge about the causes, prevention, and treatment of ophthalmological disorders.
- To work closely with Asian and international researchers to achieve these aims.
- To provide a forum for young and relatively inexperienced researchers to present their research results as Original Articles via an international platform.
- To maintain and promote relationships with any organization with similar goals.

Although the focus of Asian Journal of Ophthalmology mainly was on glaucoma with close ties to the South-East Asian Glaucoma Interest Group (SEAGIG) in the past, the journal now focuses on the entire spectrum of Ophthalmology.

The Asian Journal of Ophthalmology and Kugler Publications have started to collaborate since mid 2012 on the publication of the journal. A new website has been launched (www.asianjo.com), which facilitates all aspects of the peer-review and publication process, from manuscript submission to publication.

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For further information and manuscript submissions please visit our website: www.asianjo.com.

Dear Readers,

I hope everyone is keeping well. The COVID-19 pandemic has certainly caused many changes in the world. All conferences have been cancelled. Teleconferences are being organized as a substitute for international conferences to facilitate sharing of knowledge. Medical journals will now play a larger role with the cancellation of conferences. Online journals have the advantage of being more accessible, especially open-access journals such as Asian Journal of Ophthalmology (Asian JO).

Asian JO is the official journal for the Asia-Pacific Glaucoma Society (APGS). We intended to dedicate this issue of Asian JO for abstracts of Asia-Pacific Glaucoma Congress, which was to be held in Kuala Lumpur in August 2020. As this conference has been postponed to 2021, the abstracts for this conference will now be published next year. Hence, we apologize for the delay in the production of this issue.

Our aim is to publish papers that contain useful information which can help us manage patients better. New information and novel ideas or techniques are welcomed. Given the volume of submissions, papers highlighting new information are given higher priority for publication than those containing information that is already common and established knowledge. By improving the quality of research papers published, we hope that Asian JO will play a crucial role in disseminating new and useful information for our readership.

With kind regards,

Dr. Keith Ong
Chief and Managing Editor of the Asian Journal of Ophthalmology

Asian J Ophthalmol. 2020;17:248-249

Never waste a good crisis: lessons from the COVID-19 pandemic

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The year 2020 has, arguably, been an annus horribilis for many of us. It also seems to be the year we could shake the dust off many well-loved aphorisms and maxims. Everything that could go wrong did often go wrong. Those who failed to learn from history were indeed doomed to repeat it. We reap what we sow.

There is one maxim, though, that we should all take heed to, particularly as we come to the end of 2020: "Never waste a good crisis". This line is attributed to Winston Churchill, who was the great wartime Prime Minister of Great Britain and led it through that 6-year long crisis.

Adopting this mindset, we can look back at the year gone by and forward to the year ahead (for the COVID-19 crisis is by no means over), learn from it, and plan ahead for the next year.

What did we as a department learn?

People can and will rise to the occasion

Many of our doctors and nurses volunteered to serve on the front lines of the COVID-19 efforts, joining swab teams, primary care teams, running facilities for housing foreign workers, providing extra manpower for the emergency department, organizing aid for the foreign workers, and so on. In the meantime, the rest of the department pulled together to re-organize workflows, reschedule appointment and surgeries, enforce safe-distancing, team segregation, conduct webinars to replace conferences, keep teaching and research going, and more. It was a tremendous team effort and everyone had a part to play in keeping the department afloat. As we move into a next phase of the pandemic with the distribution of vaccines and things change yet again, I look forward with hope that the team will rise to meet the challenges head on again.

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A crisis is a good time to shake things up

Very early in the pandemic, we learned that the old way of running our clinic was really very manpower-dependent and we had not leveraged on new systems and technology to make our lives easier. We also had inefficiencies built into the work schedule that had gone unnoticed for a long time. The pandemic has forced us to review some of these "old ways" and initiate change. We took a data-based approach to re-doing the rosters and the appointments, re-organized the clinic staff, and reset capacity, leveraging on IT to reduce the requirement for manpower. While it has been hard to make progress on this front, I hope we will sustain the momentum as we move into 2021.

Innovate, innovate, innovate

That must surely be one of the big lessons from the COVID-19 pandemic. From masks to swab kits to vaccines, from telemedicine to Zoom webinars, it has been innovations that have kept us going through the year. We had to accelerate our plans for teleconsultations in order to reduce the crowds and maintain safe-distancing. We found ourselves testing out different barriers for slit lamps and ways to reduce aerosol generation in the operating theatre. Not all innovations need be spectacular. Many were, indeed, very simple and effective. The key, though, to all the innovations really must be the Yoda principle: "Do or do not, there is no try".

The new year brings promise with the introduction of the vaccine. But it looks certain that many of the safe-distancing measures, curtailment on travel, disruptions to business, and so on will remain for quite some time more. I hope we will all be able to take the challenges in our stride and face them with fortitude, courage to change, and openness to ideas. With all that we can learn and hopefully develop, we will then not have wasted a good crisis.

Asian J Ophthalmol. 2020;17:250-262

Policy recommendations in response to the resurgence of COVID-19 cases for institutional medical practice from an ophthalmic perspective

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Abstract

Objectives: *The COVID-19 pandemic has been declared a public health emergency of international concern. Singapore was one of the first countries to identify imported cases and also experience a second wave of outbreaks. A slew of measures enacted by the government to 'flatten the curve' has directly impacted upon the way we practice.*

Study design/Methods: *This article describes steps enacted by our department to ensure sustainability of our ophthalmic practice.*

Results: *We share considerations at various time points and policies implemented in a stepwise approach in response to the worsening community situation. We further discuss our phased approach towards reinstating our services safely and effectively for patients and staff in a markedly different practice climate.*

Conclusions: *The COVID-19 pandemic has markedly upended the way we practice medicine. Reflecting on the ideal measures required for such occurrences in the future will empower practices with the ability to respond effectively to future outbreaks.*

Keywords: *COVID-19 response, ophthalmology, public healthcare system, Singapore*

Introduction

The Singaporean experience with the COVID-19 pandemic has been unique. What was initially celebrated as a model response to the pandemic[1] evolved into an entirely different situation, as the city-state reeled in horror when a second wave of outbreaks hit.[2] This unexpected second wave of cases was driven by long-standing

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Table 1. Operational considerations of our ophthalmic practice in handing the COVID-19 pandemic

Stages	Measures enacted with early signs of an outbreak	Measures during the pandemic	Escalated measures to flatten the curve (*e.g.* Circuit Breaker)	Refinement of policies for sustainability	Easing of measures	Ideal measures to have in place before outbreak
Manpower	Team segregation plans formed and refined	Deployment of segregation plans	Further limiting manpower deployment within teams to minimize exposure	Increase manpower based on operational needs	Business as usual	Drawer plans for pandemic manpower deployment Sufficient redundancy in manpower to support ability to ramp up and down easily
	Establishing cross-institutional cover plans with other ophthalmic centers	Deployment of plans as required			Maintaining collaborative networks and ties	Drawer plans for cross-cover of patients between sites
	Institutional segregation with restrictions on cross-institution movement of medical professionals	Evaluation of essential services within department and establishing need for certain skill sets		Permitting cross-institutional movement of essential health professionals	Business as usual	Revisit remuneration and incentivization of visiting specialists; even as a pandemic-related incentive
	Identification of vulnerable staff (elderly, multiple comorbidities, pregnant)	Redeployment of staff away from patient contact duties (virtual clinics, working from home, administrative roles)		Ramping up of scope of virtual clinics	Business as usual	Maintain registry of staff meeting criteria
	Consideration of social circumstances such as: 1. Households with more than one healthcare/essential worker with care of child 2. Placement issues with vulnerable individuals at home 3. Overseas-based staff	Provision of temporary accommodation Approval of no pay leave for staff		Assistance with short-term accommodation and living arrangements in view of extended *cordon sanitaire*	Business as usual	Maintain registry of staff commuting from overseas
	Identifying of volunteers to support critical services (Emergency Departments, Intensive Care Units, Pandemic Wards)		Deployment to support critical services and community-based initiatives (*e.g.* dormitory-based swabbing and community care facilities)		Recall staff to assist with ramping up of operations	Restructuring clinics to be consultant-run

Stages	Measures enacted with early signs of an outbreak	Measures during the pandemic	Escalated measures to flatten the curve (*e.g.* Circuit Breaker)	Refinement of policies for sustainability	Easing of measures	Ideal measures to have in place before outbreak
Operations	Establish disease outbreak taskforce within the operations team	Inclusion of further key personnel within taskforce as necessary			De-escalation of taskforce	Identification of essential personnel required for the disease outbreak taskforce
	Evaluation of satellite sites vis-à-vis manpower requirements	Closing of satellite community sites and recall of staff Deployment of staff to other essential sites		Reopening of sites and decanting patients from parent hospital to satellite sites	Business as usual	Establish a self-sufficient primary eye care network Develop a distributed imaging network and central repository system between primary eye care network and tertiary ophthalmic centers
	Determine "high-risk" patients and escalation protocol	Multi-disciplinary handshake in assessment and diagnostics with care (ie. transfer of patients from Ophthalmology to A&E/ ID)				Drawer plans for safe transfer of patients with airborne transmitted communicable diseases
	Reduction of surgical load	Deferment of non-essential elective operations	Further reduction of Operating lists by 80%. Only proceed with sight-threatening complications	Gradual increase in operating load	Business as usual	Move to automate and integrate computer-based systems to reduce man-hours needed for shifting
	Reduction of clinic numbers	Reduction in clinic numbers to comply with team segregation and social distancing requirements	Deferment of non-essential clinical consultations	Gradual increase in clinic consultations in tandem with community measures Prioritization of new consultations and patients from our glaucoma and retina service as clinic numbers	Business as usual	Move to automate and integrate computer-based systems to reduce man-hours needed for shifting Decanting patients to satellite sites and enrolment in virtual clinics
	Identification of clinical conditions and pathways suitable for virtual clinic	Deployment of virtual clinic pathways		Increasing virtual clinic capacity	Further development of virtual clinic and tele-ophthalmology capabilities	Established virtual clinic and teleophthalmology capabilities and pathways

Stages	Measures enacted with early signs of an outbreak	Measures during the pandemic	Escalated measures to flatten the curve (e.g. Circuit Breaker)	Refinement of policies for sustainability	Easing of measures	Ideal measures to have in place before outbreak
Protection **Physical defense**	Ascertain mode of transmission and determine level of protection required with targeted PPE acquisition	Sourcing and stockpiling of PPE	Establishing multiple supply chains for essentials to ensure continuity of supplies	Further diversification of supply chains including establishing local manufacturing sites to mitigate risks of export embargos	Replenishment of stockpiles	Ensure adequate stockpile of PPE
	Review of clinical practices to mitigate risks (*e.g.* wiping down high-touch surfaces, cessation of use of air-puff tonometry and minimization of aerosolizing procedures)	Constant comparison of practices against institutions locally and worldwide and published evidence Evaluation of high-risk procedures in face of urgency of treatment			Easing of changes in practice according to risk profile and impact on services	Stringent cleaning of surfaces, especially high-touch areas Maintain list of aerosol-generating procedures and investigations
	Review of reported clinical features and risk factors for contracting disease (eg. travel or contact history)	Secure facility by enforcing universal mask wearing, thermal screening and visitor registration stations Establish triage process and protocols to manage high-risk and suspect cases	Tightening of accompanying visitor policies and modification of protocols based on evolving situation		Easing of visitor limitations	Adequate equipment for thermal screening and registration stations Drawer plans for triage and escalation protocol
	Mask-fitting exercises and PPE donning and doffing retraining for frontline staff	Mask-fitting exercises and PPE donning and doffing retraining for healthcare staff			Refresher training and competency assessments	Regular refresher training and competency assessments
Psychological defense	Mental health initiatives to ensure and sustain wellbeing of staff	Ongoing evaluation of staff well-being and continuation of initiatives			Identification of post-traumatic stress disorder features and establishing avenues of support	Established mental health services and resources for healthcare staff

overcrowding issues in foreign worker dormitories. The virus spread rapidly amongst individuals housed in tight living spaces[3] and the healthcare system has had to adapt to these changes vis-à-vis public health measures enacted to curtail the rate of transmission. Through this experience, our Ophthalmology department has learnt both valuable and painful lessons which have been useful during the pandemic, yet have also exposed the vulnerabilities of our 'peacetime' setup. We hope to share our experience and the effect of these interventions at various critical time points (Table 1) with the global medical community, and hope that our international colleagues will be able to draw from our insights, enacting changes to benefit their daily practice.

To understand how this situation has impacted upon our ability to function, it is necessary to understand how the Singaporean public healthcare system is organized. The National University Health System is one of three healthcare clusters within Singapore.[4] Each cluster comprises an integrated network of medical institutions (hospitals and specialist care centers) which afford tertiary level care, as well as community hospitals (providing step-down care) and polyclinics which provide primary care services. Ophthalmic services within each cluster are coordinated through a parent site, with resources disseminated downstream into satellite sites.

In response to the 2003 Severe Acute Respiratory Syndrome (SARS) pandemic, the Singaporean government designed 'Disease Outbreak Response System Condition (DORSCON)' as a color-coded framework to detail the prevailing disease situation.[5] Singapore was one of the first countries to identify imported cases of COVID-19, and the DORSCON alert was raised to 'Orange' on 7 February 2020 in response to verified community transmission of COVID-19. Despite this, further community spread necessitated implementation of 'circuit breaker' measures which were first announced on 3 April 2020, with a further slew of measures announced on 21 April 2020.[6] Singapore has since adopted a three-phased approach to resuming social, economic, and entertainment activities, which commenced from 2 June 2020.

Operations

Upon escalation to DORSCON Orange, a disease outbreak taskforce was assembled and embedded within our operations team. This comprised of the cluster head, clinical directors, chief residents, clinic managers and heads of the nursing and allied health team.

In non-pandemic times, the department's structure was geared towards free movement of personnel to cross-cover services across the cluster. This arose from the tenets of developing a lean and economically viable service, devolving care from tertiary care centers, and upskilling of primary eye care services. Many of these plans were still in their infancy when COVID-19 hit.

Withdrawing of personnel from community-based satellite sites

Governmental directives during the initial phases of DORSCON Orange limited healthcare personnel to practicing in one institution. A decision was made to shut down satellite community ophthalmic sites and withdraw manpower to our parent site, as they were not networked and equipped with sufficient ophthalmic investigation equipment to function independently. Furthermore, satellite sites were manned by both an optometrist and ophthalmologist, with both required back at the parent site. Ideally, devolved care from tertiary centers to community-based, independent primary eye care practitioners within a distributed care network mitigates risks of developing transmission clusters within a central site. Subsequent identification of positive clusters can be dealt with by closing affected nodes sequentially. These sites should function independently and remain supported by specialist input remotely using a distributed imaging network and central repository system.

Unfortunately, Singapore is yet to possess an established primary eye care network. Furthermore, with internet separation hailed as a nationwide panacea to cyber-attacks, the health-based IT network has lost its ability to seamlessly integrate with other networks.[7] The inability to devolve care to disseminate and distribute work meant that a significant onus of postponing appointments and subsequent follow-ups fell on personnel within the parent site. The process was hampered by bureaucracy and outdated computer systems that required many man-hours to generate, sort, and manage data. Automation of these processes and integrating appointment-based systems with internet and mobile-based platforms, where patients can verify and modify existing appointments, would have been valuable in this regard.

With relaxing of restrictions surrounding movement of personnel between institutions, these community sites have been reopened. Plans are underway to implement a cluster-wide electronic medical records system to provide patients with seamless care between sites, and to facilitate teleconsultations between community-based practices and our subspecialty services, which are predominantly based at our tertiary centers.

Manpower

Team segregation

At our parent site, staff were segregated into two teams with equal representation of subspecialties in each team. At any time, one team shouldered a heavier outpatient clinic load while the other handled inpatient clinical duties and a relatively smaller number of outpatients, along with administrative tasks of screening prospective patients' medical records with the intent to reschedule

non-urgent clinic appointments. Teams were rotated weekly. The clinic was further partitioned into two separate physical spaces.

The concept of team segregation was put to the test when staff on outpatient clinic duties were inadvertently exposed to a patient (who had not displayed overt symptoms of a respiratory tract infection then) who subsequently tested positive for COVID-19. Teams were immediately swapped and staff in direct contact with the patient were promptly isolated. While this demonstrates the utility of team segregation, the obvious downside to such a plan is that the department's continuity is limited to a single contact rate, where another exposure event could have shut the department down. Further driving this issue, as a problem that is almost peculiar to ophthalmology, is the perceived pressure towards subspecialization. This pressure is influenced by increasing medicolegal concerns and reliance on subspecialty input, which is further sustained by the presence of a geographically small and densely populated country, where sub-specialists are relatively easily accessed and consults easily sourced. The benefit to such an approach is that patients obtain a focused, targeted approach to their problems. Pitfalls, however, include the need for a large team of specialists to provide comprehensive ophthalmic care.

Desegregation of teams within the institution has since been initiated at the directive of the hospital's operations team. This has provided our department with the opportunity to relook, revamp, and optimize our workflow and clinic services.

Cross-cluster and international collaboration

Interconnectivity between ophthalmology departments of each cluster permitted cross-cover of patients requiring emergent review. Staff were tested positive in another ophthalmology cluster and outpatient visits to their institution were temporarily ceased as a precautionary measure. Plans were made for cases presenting to their cluster requiring acute intervention to be diverted to our hospital to assist with ongoing management of these patients.

Our department also cares for a significant proportion of international patients within the region. Border closures and entry restrictions have limited the travel of patients into Singapore for their consultations. Care of many of these patients has been provided with the expertise of local ophthalmologists, in consultation with our specialty teams. This experience reinforced the importance of the longstanding spirit of collaboration between institutions locally and globally.

Visiting consultants

Our department has visiting ophthalmologists, who took time off from their private practice to care for patients within the public sector. When cross-institutional movement was banned, many visiting ophthalmologists were barred

from running clinics at public health institutions. This has since been relaxed, with governmental bodies recognizing the protracted duration of this pandemic. Although our present setup has limited the impact of this decision, other practices with a larger proportion of visiting specialists may have been impacted more significantly. This is translatable to situations in other healthcare systems, where visiting specialists may make up a significant proportion of the workforce within the public health system. It may therefore be timely to revisit remuneration of these specialists through the public health system; for instance, as a pandemic-related incentive, which may serve as an effective strategy to make public health institutions a more attractive proposition, should there be future occurrences.

Supporting critical services

Further assistance was sought from the Ophthalmology team to support national and cluster-based efforts to ramp up support to critical care and COVID-19 isolation-related services. Junior medical staff were deployed to support critical services through secondment to the Emergency Department to assist with the influx of patients, whilst staff were earmarked to support efforts at the National Centre for Infectious Diseases. Healthcare workers were also sent upstream to establish medical outposts and swab-testing at migrant worker dormitories, to minimize movement of patients to the acute hospitals This series of events exposed our relative reliance on junior manpower, which is inevitable especially within the public health system, where multiple consultation rooms run by junior ophthalmologists are supervised by a consultant.

This has however provided the impetus to restructure clinics, such that clinics are consultant-run rather than consultant-led, with patient numbers determined by what each consultant can see. This has been possible due to the relatively healthy manpower staffing of ophthalmologists within the public health system in Singapore.

Caring for our overseas staff

Singapore has a small labor base and is dependent on a large proportion of migrant workers, with an estimated 300,000 Malaysians commuting daily to Singapore between the land border of both countries.[8] Announcement of the Malaysian Movement Control Order; a *cordon sanitaire*, on 18 March, limited cross-border movement of individuals. This predominantly affected our nursing and allied health staff, and national plans were made to match stranded workers with temporary accommodation. Staff with families in Malaysia were permitted to take voluntary no-pay leave to spend time with their family during this period.

Protection of staff

Personal protective equipment

One of the key considerations is ensuring that staff were adequately protected, particularly given that ophthalmology has been reported as a high-risk specialty for the development of COVID-19.[9] This has been attributed to the proximity with patients required as part of the examination process, along numerous high-touch surfaces involving our investigation and examination equipment.[10] SARS-CoV-2 has also been detected on the ocular surface and its secretions.[11]

Logistical aspects included ensuring that personal protective equipment (PPE) supplies were available, and adequately protecting against exposure based on our understanding of disease transmission. This has been challenging given that information is constantly evolving; predominantly surrounding the transmission route of droplets *versus* aerosolization. This has been made complicated by differing recommendations by government agencies worldwide and practices by ophthalmology colleagues globally.[12] Although discussions were had regarding the use of N95 respirators on a regular basis, use of surgical masks for all healthcare workers facing patients was decided upon given the limited duration of exposure to patients by staff, and considerations regarding rationing of PPE supplies. Given considerations regarding aerosolization, air puff tonometry was stopped and aerosol-generating procedures were kept to a minimum.[13] Learning from our Hong Kong colleagues, we fashioned larger breath shields out of X-ray films, which have been gradually replaced by purpose-made polycarbonate shields from vendors.[14]

Meticulous and diligent wiping down of surfaces and practice of hand hygiene is also crucial in decreasing the risk of transmission amongst patients and staff.[15] However, this may not always be possible. For instance, concerns were raised surrounding cleaning of the Humphrey ®Field Analyzer (Carl Zeiss Meditec AG, Jena, Germany) machine testing bowls. Upon clarification with the vendor, it was advised that wiping these surfaces down may damage equipment and void the validity of tests performed. It was further deemed that universal mask wearing would decrease risks associated with this mode of transmission.

These experiences have taught us the importance of knowledge-sharing and staying abreast with the latest advances to ensure that staff are protected in accordance with the latest recommendations.

Mitigating exposure risks

At the clinic level, prospective patient lists are thoroughly vetted and appointments rescheduled to reduce clinic numbers. Patients are contacted prior to their appointments to enquire about their travel, contact history, and the presence of any acute respiratory symptoms via a verbal screening questionnaire. Patients providing positive responses are advised to reschedule their appointments and

seek medical attention when necessary. Any concerns regarding a deterioration in their condition or new ophthalmic complaints are escalated to the responsible ophthalmologist.

Thermal screening and visitor registration stations have been set up at the entrance of our specialist outpatient center. Besides universal masking as a condition of entry, patients and their caregivers complete a health declaration form and are triaged per their responses. Those with acute respiratory symptoms, or a positive travel or contact history are tagged with a sticky label and escorted by a security officer to isolation rooms within our clinic. A member of the Ophthalmology team subsequently evaluates both the patient's ophthalmic condition and respiratory symptoms remotely via a telephone call, and either provides an initial management plan or dons full PPE to evaluate the patient. Patients are either discharged with medical advice to self-monitor and present to the emergency department in the event of any further deterioration, or the case escalated to the COVID-19 infectious diseases team onsite for further management advice.

Plans for virtual clinics were expedited for a range of conditions including glaucoma suspect screening, diabetic retinopathy, and hydroxychloroquine screening. Although our present setup necessitates patients attending for investigations, having the ophthalmologist review results remotely reduces the number of individuals the patient comes in contact with and potentially enables some ophthalmologists to work from home. Such virtual clinic pathways have been well described in the literature.[16,17] Further initiatives include integration of telehealth pathways in our daily practice, such as phone review of symptoms for patients who had undergone uncomplicated cataract surgery at the first postoperative week.[18] These initiatives have been found to be safe and effective and have been integrated into our existing suite of clinical services.

Non-urgent surgery was also been postponed, resulting in a reduction of approximately 80% of cases. Only urgent ophthalmic surgeries were allowed to proceed, contingent upon approval from the department head and chairperson of the operating theatre committee. These restrictions have since been relaxed. In situations where general anesthesia is necessary, only essential staff are allowed into the operating theatre during the intubation process. We debated the use of N95 masks for ophthalmic surgery, as the practice varies internationally. Based on the current level of evidence, this was only used with aerosol-generating procedures, such as pars plana vitrectomies.[19]

Protecting vulnerable staff

Vulnerable staff, such as pregnant personnel, were reassigned to assist with administrative tasks and virtual clinics. When possible, staff were allowed to work from home to complete these tasks.

Mental health care

The impact of this pandemic upon an individual's mental health is frequently overlooked and understated. Plans to ensure that staff were adequately prepared included hospital-wide initiatives to bolster morale, including mask-fitting exercises for respirators, while refresher courses on donning and doffing of PPE were conducted. This provided staff with the confidence to utilize protective equipment and handle suspected or positive cases.

Understanding the need to ensure the wellbeing of our staff and bolster team morale, initiatives by our medical and nursing staff included planned lunch treats for the entire team and provision of 'care packs'. Many of these initiatives have been performed in collaboration with our food and beverage contacts, along with other industry networks whom have been extremely generous with their contributions.

A flat organizational structure and supportive work-place culture has further built team rapport and solidarity amongst staff. Our staff have initiated informal 'peer-support' networks to check in on each other, providing platforms to discuss challenging encounters or workplace situations.

Ramping up of services

The restriction on patient visits during this period has resulted in a marked increase in the waiting time required for ophthalmic appointments. Plans have been put in place to gradually increase clinic numbers whilst adhering to safe-distancing requirements, in line with easing of restrictions nationally. Priority has been provided to patients in our first-visit, glaucoma, and retina services, particularly those with chronic conditions requiring active therapy, or poorly-sighted patients requiring active management.

Patients are also reviewed through virtual clinic and telehealth services that have been established and refined during this period, while stable patients with conditions necessitating review are decanted into satellite sites that will be gradually reopened.

Conclusion

While the pandemic has upended the way we practice ophthalmology, every cloud has a silver lining. This crisis has provided us with the opportunity to critically analyze and optimize our daily operations, augment our services with telehealth and virtual clinic initiatives, and renew our commitment to establish our primary eye care capabilities. It has also highlighted the need to review a range of national and institutional-based policies across various fronts, to enable healthcare delivery services to take the next step forward in a technologically-enabled society.

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References

1. Teo J. Coronavirus: WHO praises Singapore's containment of Covid-19 outbreak. Straits Times. 2020.
2. Bowie N. Cracks show in Singapore's model Covid-19 response. Asia Times. 2020.
3. Han K. Covid forces Singapore to confront conditions for its migrant workers. The Interpreter. 2020.
4. Ministry of Health Singapore. Reorganisation of healthcare system into three integrated clusters to better meet future healthcare needs [Internet]. 2017. Available from: https://www.moh.gov.sg/news-highlights/details/reorganisation-of-healthcare-system-into-three-integrated-clusters-to-better-meet-future-healthcare-needs.
5. Ministry of Health Singapore. MOH Pandemic Readiness and Response Plan for Influenza and other Acute Respiratory Diseases2014. Available from: https://www.moh.gov.sg/docs/librariesprovider5/diseases-updates/interim-pandemic-plan-public-ver-_april-2014.pdf.
6. Singapore Government. Circuit Breaker extension and tighter measures: What you need to know. Available from: https://www.gov.sg/article/circuit-breaker-extension-and-tighter-measures-what-you-need-to-know.
7. Chua A. Current model of Internet separation unsustainable in longer run: MOH chief data advisor. Today. 2018.
8. Lau J. Malaysians with work permits can continue working in Singapore, says MFA. Straits Times. 2020.Available from: https://www.straitstimes.com/singapore/health/malaysians-with-work-permits-can-continue-working-in-singapore-says-mfa.
9. Breazzano MP, Shen J, Abdelhakim AH, et al. Resident physician exposure to novel coronavirus (2019-nCoV, SARS-CoV-2) within New York City during exponential phase of COVID-19 pandemic: Report of the New York City Residency Program Directors COVID-19 Research Group. medRxiv. 2020.
10. Kuo IC, O'Brien TP. COVID-19 and ophthalmology: an underappreciated occupational hazard. Infect Control Hosp Epidemiol. 2020:1-9.
11. Xia J, Tong J, Liu M, Shen Y, Guo D. Evaluation of coronavirus in tears and conjunctival secretions of patients with SARS CoV 2 infection. J Med Virol. 2020;92(6):589-594.
12. Naveed H, Scantling-Birch Y, Lee H, Nanavaty MA. Controversies regarding mask usage in ophthalmic units in the United Kingdom during the COVID-19 pandemic. Eye. 2020:1-3.
13. Britt JM, Clifton BC, Barnebey HS, Mills RP. Microaerosol formation in noncontact air-puff tonometry. Arch Ophthalmol. 1991;109(2):225-228.
14. Wong DH, Mak ST, Yip NK, Li KK. Protective shields for ophthalmic equipment to minimise droplet transmission of COVID-19. Graefes Arch Clin Exp Ophthalmol. 2020:1-3.
15. Qiao C, Zhang H, He M, et al. Symptomatic COVID-19 Infection in Eye Professionals in Wuhan China. Ophthalmology. 2020;127(9):1268–1270.

16. Zaidi FH, Rennie CA, Drinkwater AK, Sahu D, Akyol E, Lotery AJ. How to set up a Hydroxychloroquine Retinopathy Screening Service. Eye. 2019;33(11):1679-1682.
17. Kotecha A, Bonstein K, Cable R, Cammack J, Clipston J, Foster P. Qualitative investigation of patients' experience of a glaucoma virtual clinic in a specialist ophthalmic hospital in London, UK. BMJ Open. 2015;5(12):e009463.
18. Lim CH, Chai CH, Goenadi CJ, Zhao PS, Tan CW, Lin HA. Feasibility of Post-operative Cataract Surgery Telehealth Consultations in the COVID-19 Era. Unpublished Manuscript. 2020.
19. The Royal College of Ophthalmologists. PPE and staff protection requirements for ophthalmology. In: The Royal College of Ophthalmologists, editor. COVID-19: infection prevention and control (IPC): GOV.UK; 2020.

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Results of early versus standard silicone stent removal following external dacryocystorhinostomy under local anesthesia

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Abstract

Introduction: *Many patients in Nepal travel vast distances to have their surgeries in Kathmandu. They often remain close by until their follow-up visit for their silicone tube removal, which contributes to a large financial burden on them and their families. Hence, reducing the time for which silicone tubes remain in situ following external dacryocystorhinostomy (DCR) provides significant benefits to patients. Furthermore, this is the first comparative study which has successfully demonstrated the earliest timeframe for which silicone tubes can be removed following DCR in the medical literature.*

Methods: *A randomized controlled trial consisting of 144 patients was designed to compare patient outcomes after early (2 weeks postoperatively) versus standard (6 weeks postoperatively) removal of silicone stents. The success of their procedures was determined when patients were assessed both symptomatically and anatomically at their 6-month follow-up.*

Results: *The surgical success in both groups was high at 97.8% collectively in both groups and there were only a small number of patients who were lost to follow-up (5 patients) at 6 months. There was no statistical difference at removing silicone stents at 2 or 6 weeks postoperatively.*

Conclusion: *These results were consistent with our pilot study, which showed no statistical difference in long-term success following silicone tube removal at 2 and 6 weeks.*

Keywords: *dacryocystorhinostomy, nasolacrimal duct obstruction, silicone intubation*

Introduction

Nasolacrimal duct obstruction (NLDO) is a common, often idiopathic condition which causes epiphora and is treated with either an external or endonasal dacryocystorhinostomy (DCR). The use of silicone intubation is common practice in both external and endonasal DCRs; its purpose is presumed to prevent fibrous

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closure of the rhinostomy during the postoperative healing period and maintain the patency of the fistula.[1] We believe that silicone tubing prevents retrograde flow of blood into the canalicular system, which lasts up to 7 days and contributes significantly to fibrosis and subsequent poor results.[2]

The necessity of using silicone tubes following surgery is questionable and, when used, the timing for the duration of its use is controversial. Leaving silicone tubes *in situ* for an extended period of time does not necessarily confer better postoperative success and doing so can lead to complications such as obstruction from granulation tissue, stenosis and adhesions, bleeding, discomfort, punctal laceration, stent extrusion, and difficult stent removal. The current accepted length of time for silicone stent removal is between 6 weeks and 3 months. In our pilot study, we noted no statistical difference between a small randomized cohort of 50 patients who had their silicone stents removed at 2 and 6 weeks at their 3-month review both symptomatically and anatomically.[2] In this randomized controlled trial, we compared the anatomical and symptomatic improvement following removal of silicone tubing at 2 and 6 weeks, respectively, at 3 and 6 months.

In Nepal, due to the harsh mountainous terrain and poor transportation infrastructure, patients often travel with their families over vast distances to Kathmandu for their surgeries, leaving their livestock and crops often untended over the span of their surgery and their follow-up review. Not only is there significant expenditure on accommodation and food during their stay, but also a simultaneous loss of income due to not being able to work. Consequently, reducing this social impact became the primary motivation for this study.

Reducing the length of time to remove the silicone stent not only has significant clinical impacts on developing countries like Nepal, where patients travel over large distances for their surgery but also in developed countries. Removing the stent at 2 weeks would reduce complication rates and improve overall patient comfort and satisfaction.

Materials and methods

This study was a prospective, randomized, masked single-centre study designed to compare the safety and efficacy for the removal of silicone tubing following external DCR surgery for primary NLDO at 2 *versus* 6 weeks. This study adheres to the guidelines of the Declaration of Helsinki and was approved by the Institutional Review Committee of Tilganga Institute of Ophthalmology.

To determine the sample size for this study, we considered a DCR success rate following stent removal of 94.1% at 6 weeks and 83.5% at 2 weeks, a confidence interval of 1.96, and an 80% statistical power. Compensating for a 3% loss to follow-up, we estimated a minimum sample size of 144 patients. The inclusion

and exclusion criteria for this study were as follows:
Inclusion criteria:
1. age >16 years old who can tolerate surgery under local anesthesia; and
2. diagnosis of primary acquired NLDO.

Exclusion criteria:
1. post-traumatic NLDO;
2. redo external DCR surgery;
3. canalicular obstruction ≤ 5 mm; and
4. patients who refused or were unable to undergo surgery under local anesthesia (*e.g.* mental health issues)

This cohort was then classified by their age (20–39, 40–59, and 60+), gender, and diagnosis (*e.g.* epiphora, chronic dacryocystitis). Following this, patients were randomized equally into two treatment arms via a sealed envelope method by the timing of their tube removal: early (Group A at 2 weeks) *versus* standard

Table 1. Clinical features of patients prior to surgery in Groups A and B

Clinical features	Group A	Group B
Mean age	50.2 years (SD: 17.19)	49.2 years (SD: 16.2)
Sex	Male: 17 (23.6%) Female: 55 (76.4%)	Male: 13 (18%) Female: 59 (82%)
Mean duration of epiphora	39.77 months (SD: 48.2)	35.7 months (SD: 38.8)
Mean duration of discharge	20.8 months (SD: 24.6)	16.6 months (SD: 19.2)
History of acute dacryocystitis	5 (7%)	6 (8%)
Duration of mucocele	13.1 months (SD: 23.2)	11.4 months (SD: 18.08)
Dacryocutaneous fistula	1 (1%)	1 (1%)

SD: standard deviation

Table 2. Issues noted intraoperatively in Groups A and B

Clinical features	Group A	Group B
Sac fibrosis	2 (3%)	4 (6%)
Sac diverticula	1 (1%)	1 (1%)
Inadequate tissue for anterior/ posterior flap formation	3 (4%)	1 (1%)

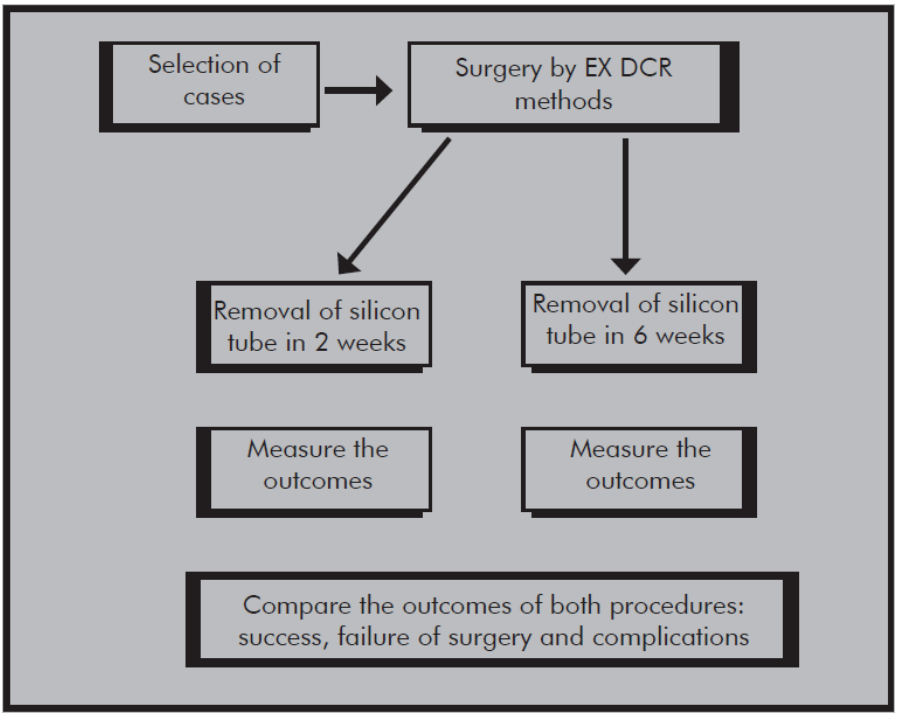

Fig. 1. Research process for the study.

(Group B at 6 weeks). There were 72 patients each in both Groups A and B. Patients with a history of acute dacryocystitis, presence of a mucocele, dacryocutaneous fistula, and sac fibrosis were included in this study and were equally and randomly distributed between the two groups (Tables 1 and 2).

Postoperatively, both groups were followed up at 1 day, 1 week, and at the time of their silicone tube removal, which was either at 2 or 6 weeks postoperatively. Following silicone tube removal, patients were assessed on their degree of symptomatic relief and anatomical patency by independent assessors who were blinded to the nature of the study to reduce observer bias at their 3- and 6-month postoperative visits (Fig. 1).

Surgery was considered successful if the patient had:

1. no watering or occasional watering plus freely patent on irrigation of nasolacrimal apparatus at six months; or
2. partial patency on syringing plus subjectively, no watering at six months.

Surgery was considered failed if the patient had:
1. complaints of persistent watering and partial patency at 6 months: or
2. complete regurgitation of fluid back to punctum at 6 months regardless of watering.

Data was analyzed using R Commander (R software, version 3.3.2). The chi-squared test was used to evaluate baseline characteristics of the two treatment arms, whilst Fisher's exact test was chosen to assess surgical outcome. A p value of < 0.05 was considered significant. We also obtained approval from the institutional review board and all patients were consented for their procedures and involvement in the study.

Surgical technique

All patients underwent a similar surgical procedure by senior oculoplastic surgeons at the Tilganga Institute of Ophthalmology. Preoperatively, intramuscular injection of diclofenac sodium 1.5 mg/kg was administered to patients. After prepping and draping the surgical area, local anesthetic (2% lidocaine with adrenaline 1:10,000 plus 0.5% bupivacaine) was injected over the medial canthal tendon area and the nasal edge of the inferior orbital rim. A nasal gauze pack soaked in oxymetazoline 0.05% plus adrenaline 1:1000 nasal drops was inserted into the ipsilateral nostril. Using a number 15 Bard Parker surgical blade, a straight incision 10 mm in length was made 10 mm medial to the medial canthal tendon. The orbicularis muscle was bluntly dissected to expose the medial canthal tendon attachment site and the overlying periosteum. A sufficient flap of periosteum was made after incision near the anterior lacrimal crest. A rectangular-shaped osteotomy of approximately 15 mm by 15 mm was made with Kerrison rongeurs. An H-shaped incision at the posterior-inferior lacrimal sac was made, with a long anterior flap and shorter posterior flap. A similar H-shaped incision was made at the nasal mucosa. The posterior flap of the lacrimal sac was trimmed without suturing. Wherever a distal canalicular block was encountered, the probe was more firmly inserted until it was seen in the nasal passage and the common canaliculus was enlarged using a number 11 surgical blade. Subsequently, anterior flap reconstruction using 6-0 vicryl was performed following placement of a silicone tube to stent. Finally, the orbicularis muscle and skin were closed with 6-0 vicryl sutures. Each patient received postoperative nasal packing with gauze soaked in oxymetazoline 0.05% plus adrenaline 1:1000. Antibiotic ointment along with a cotton gauze was applied over the external wound.

After 30 minutes of observation, patients were discharged with oral antibiotics (ampicillin/cloxacillin 250/250 mg, four times per day) and oral anti-inflammatories (serratiopeptidase, three times per day) for 1 week. Analgesics

were prescribed as needed and topical antibiotics (ciprofloxacin 0.3% eye drops, three times per day) were administered.

Results

Of the 144 patients in this cohort, 142 (98.6%) and 139 patients (96.5%) were reviewed at their 3- and 6-month follow-up appointments, respectively (Fig. 2). The mean age was 49.7 years (range: 20–89 years; SD: 16.6). The majority of our participants were female, with a male-to-female ratio of 1:4.8. The percentage of successful operations at the 6-month follow-up was 97% in Group A and 98.6% in Group B. The complication rate was 1.4% in each group at the 6-month follow-up.

This study did not show any statistical difference between silicone tube removal at 2 or 6 weeks following a final assessment at 6 months both from a symptomatic and anatomical point of view. Furthermore, the presence of a history of acute dacryocystitis, presence of a mucocele, dacryocutanenous fistula, or sac fibrosis did not alter this difference in the overall result (Table 3). Both groups studied had minimal complications, with one patient in Group A experiencing tube prolapse which was subsequently removed and one patient in Group B experiencing cheesewiring of their canalicular system (Table 4).

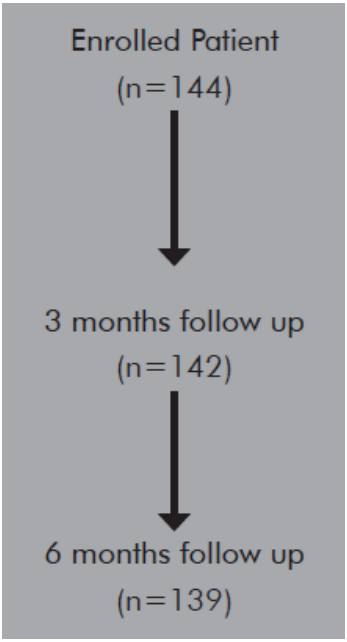

Fig. 2. Number of patients at the start and at the end of the study.

Table 3. Results of surgical outcome between Groups A and B

Surgical outcome		Group A (Tube removal at 2 weeks)	Group B (Tube removal at 6 weeks)	Total	*P*-value
3 months (*n* = 142)	Success	70 (98.6%)	70 (98.6%)	140 (98.6%)	1.00
	Failure	1 (1.4%)	1 (1.4%)	2 (1.4%)	
6 months (*n* = 139)	Success	68 (97%)	68 (98.6%)	136 (97.8%)	1.00
	Failure	2 (3%)	1 (1.4%)	3 (2.2%)	

Table 4. Complication rates between Groups A and B

Presence of complications	Group A (Tube removal at 2 weeks)	Group B (Tube removal at 6 weeks)	Total	*P*-value
3 months (*n* = 142)	1 (1.4%)	1 (1.4%)	2 (1.4%)	1.00
6 months (*n* = 139)	1 (1.4%)	1 (1.4%)	2 (1.4%)	1.00

Discussion

In Nepal, many patients travel large distances over harsh hilly terrain for their surgeries in Kathmandu, which often take many days. As a result, they often stay in Kathmandu from the time of their surgeries until their follow-up, resulting in a loss of income from cessation of work and expenditure to live in the city, which outweighs the cost of their actual surgery. This study was designed to minimize the time taken to remove their silicone tube following DCR surgery, which eventually reduces their follow-up time postoperatively.

The results of this study showed a high success rate following external DCR for all cases (136 of 139; 97.8%) at 6 months. This study concludes that early tube removal at 2 weeks showed no statistical difference in the symptomatic and anatomical success as compared to its removal at 6 weeks. The results at 6 months following surgery was consistent with the results of our initial pilot study, which examined a smaller sample size of patients.[2] The complication rate at the 6-month mark did not differ in either groups and neither did a history of acute dacryocystitis, presence of a mucocele, dacryocutaneous fistula, and sac fibrosis alter the statistical difference of success in both groups.

The necessity for silicone intubation after a DCR is not universally accepted. While some previous studies and systematic reviews have shown that there is no

difference with or without the use of silicone tubes in both external and endonasal DCRs,[1,3-5], others have suggested that its presence improved the overall outcome of the surgery.[6,7] Silicone tubes have certainly been beneficial in selected situations. Choung *et al.*[4] found that silicone tubing can be avoided in 50% of cases of external DCR, such as in cases with a large lacrimal sac and a wide nasal cavity. Kim *et al.*[8] also suggested that silicone intubation is effective when used after cases of external DCR that are anatomically patent but have functionally failed.

When inserted, the silicone tubes have traditionally been placed for 6 weeks to 3 months, with no universally agreed timing for its removal. Its purpose is to prevent fibrous closure while allowing sufficient epithelialization of the rhinostomy and canalicular system during the postoperative healing period, thus maintaining the patency of the fistula.[1,9] A retrospective study by Charalampidou and Fulcher[10] revealed that, following external DCR, there was no statistical difference in success between removing silicone tubes before 2 months as compared to between 2–4 months and after 4 months in patients with anatomically confirmed NLDO. This study is the closest comparative study to ours present in the literature to evaluate the efficacy of early stent removal following external DCR. However, it was a retrospective study that did not mention how early the tubes were removed nor did it provide anatomical confirmation of NLD patency in its long-term evaluation. This study has sought to improve on these factors and provide a more definitive evaluation on the topic.

In this prospective randomized study, a high success rate was achieved in all surgeries performed. There was also no statistical difference in the anatomical patency and symptomatic relief to patients following external DCR whether the silicone tube was removed at 2 or 6 weeks, when evaluated at 6 months postoperatively. This is consistent with other studies where early tube removal from spontaneous extrusion, tight tubes, and tube intolerance did not alter the outcome of a successful external DCR procedure.[10,11]

There are no universally agreed upon pathophysiological reasons for the placement of silicone tubes after DCR in the literature to date. From first principles, during the wound healing process, the initial inflammation occurs with clot formation and platelet aggregation, followed by the formation of granulation tissue, proliferation of connective tissue cells, and re-epithelialization of the new tract. During the second week, the leukocytic infiltrate, edema, and increased vascularity largely disappear.[12] We suggest that the pathophysiological basis for success this early following surgery is that the 2-week period the silicone stents are in place reduces retrograde blood flow into the canalicular system, provides sufficient time for the rhinostomy and canalicular system to re-epithelialize and structurally stabilize, and allows for a reduction in fibrosis and scar formation to remain patent in the long term.[2] Leaving silicone tubing *in situ* for an extended

period of time has also been known to be counterproductive, as silicone is an inorganic surgical material that can lead to numerous complications. These include peripunctal granulation, erosions of puncta and canaliculi, chronic nasal irritation, corneal erosion, canalicular laceration, interpunctal symplepharon, inflammatory mass, and pyogenic granuloma formation.[13]

Finally, the findings of this study positively impact patients who travel long distances for their surgeries — as seen in many developing countries — who experience a significant loss of income and financial burden from living away from their hometowns and villages whilst awaiting their follow-up appointments. Moreover, these results may also benefit patients in developed countries by improving patient comfort and satisfaction with early removal as well as compliance to appointments, ensuring tube removal in cases where patients fail to present for their follow-up for tube removal.

Conclusion

The findings of this study were consistent with our pilot study, which showed no statistical difference in long-term success following silicone tube removal at 2 and 6 weeks after external DCR. Removing tubes at 2 weeks would avoid a significant financial burden for patients in developing countries as well as improve overall patient satisfaction and reduced complication rates from silicone intubation.

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References

1. Kang MG, Shim WS, Shin DK, et al. A Systematic Review of Benefit of Silicone Intubation in Endoscopic Dacryocystorhinostomy. Clin Exp Otorhinolaryngol. 2018;11(2):81-88.
2. Limbu B, Lyons HS, Shrestha MK, et al. Comparison of early versus standard timing for silicone stent removal following External Dacrocystorhinostomy under local anaesthesia. Nepal J Ophthalmol. 2019;11(21):24-28.
3. Kashkouli MB, Parvaresh M, Modarreszadeh M, et al. Factors affecting the success of external dacryocystorhinostomy. Orbit. 2003;22(4):247–255.
4. Choung HK, Khwarg SI. Selective non-intubation of a silicone tube in external dacryocystorhinostomy. Acta Ophthalmol Scand. 2007;85(3):329-332.
5. Feng, YF, Cai, JQ, Zhang, JY, et al. A meta-analysis of primary dacryocystorhinostomy with and without silicone intubation. Can J Ophthalmol. 2011;46:521–527
6. Rather S, Singh T. External dacryocystorhinostomy with & without silicon tube intubation in chronic dacryocystitis with nasolacrimal duct block. JK Sci. 2013;15:24–27.
7. Xie C, Zhang L, Liu Y, et al. Comparing the Success Rate of Dacryocystorhinostomy With and Without Silicone Intubation: A Trial Sequential Analysis of Randomized Control Trials. Sci Rep. 2017;7(1):1936.

8. Kim NJ, Kim JH, Hwang SW, et al. Lacrimal silicone intubation for anatomically successful but functionally failed external dacryocystorhinostomy. Korean J Ophthalmol. 2007;21(2):70–73.
9. Buttanri IB, Serin D, Karslioglu S, et al. The outcome of silicone intubation and tube removal in external dacryocystorhinostomy patients with distal canalicular obstruction. Eur J Ophthalmol. 2012;22(6):878-881.
10. Charalampidou S, Fulcher T. Does the timing of silicone tube removal following external dacryocystorhinostomy affect patients' symptoms? Orbit. 2009;28(2-3):115-119.
11. Vicinanzo MG, McGwin G, Boyle M, et al. The consequence of premature silicone stent loss after external dacryocystorhinostomy. Ophthalmology 2008;115(7):1241–1244
12. Kumar V, Abbas AK, Fausto N, et al. Robbins and Cotran pathologic basis of disease. Philadelphia: Elsevier Saunders; 2005.
13. Nuhoğlu F SK, Ozdemir FE. Outcome of External Dacryocystorhinostomy with Bicanalicular Silicone Tube Stenting. JAREM. 2014;4:88-92

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Original Article

Assessment of quality of life in glaucoma patients using the Glaucoma Quality of Life-15 questionnaire

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Abstract

Purpose: *The purpose of this study was to assess quality of life in glaucoma patients using the Glaucoma Quality of Life-15 (GQL-15) questionnaire. The GQL-15 questionnaire is a glaucoma-specific quality of life questionnaire used to assess the degree of functional disability caused by glaucoma.*

Design: *Cross-sectional, prospective study with comparison group at a tertiary care hospital.*

Material and methods: *The GQL-15 questionnaire was used to evaluate the quality of 80 patients in the glaucoma group and 80 normal subjects in the control group. The data were analyzed by test of proportions and Chi-square test. A p-value of < 0.05 was considered significant.*

Results: *Glaucoma patients (mean age: 60.5 ± 9.2 years; range: 43–86 years) and comparison group (mean age: 58.9 ± 4.5 years; 52–72 years) were matched with respect to age ($p = 0.18$). Glaucoma patients had significantly worse quality of life compared to the non-glaucoma group ($p < 0.001$). Significant differences ($p < 0.05$) between the scores of the mild, moderate, and severe glaucoma groups were observed, suggesting poorer quality of life as the severity of glaucoma increases.*

Conclusions: *The GQL-15 revealed that quality of life worsens with increasing severity of glaucoma increases. This fact is important when educating patients about the disease course and its therapy.*

Keywords: *Glaucoma Quality of Life-15 (GQL-15) questionnaire, primary open-angle glaucoma, quality of life*

Introduction

Glaucoma is a chronic, progressive, and irreversible disease resulting in severe visual disability, which has severe implications on the quality of life of affected

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patients. Quality of life can be defined as subjective wellbeing, which depends on a patient's values, priorities, experiences, and aspirations, and reflects the difference between the hopes and expectations of a person and their experiences. Assessment of quality of life has been used to understand the impact of various factors linked to the disease process in a patient's life and this understanding has led to better outcomes of treatment.[1] The various tools available for measuring quality of life can be generic or disease-specific. While there is no gold-standard quality of life assessment scale, glaucoma-specific and vision-specific instruments are better than generic tools to assess the impact of disease per se on the patients' overall wellbeing. There are a number of such well-documented tools, such as the Short Form-36 (SF-36) or Short Form-12 (SF-12), 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25), Visual Activities Questionnaire (VAQ), Activities of Daily Vision Scale, and Glaucoma Quality of Life-15, (GQL-15) that have been used to quantify the subjective status of glaucoma patients.[2] Our study aims to assess the quality of life in glaucoma patients by using the GQL-15 questionnaire.

Methods

The study was conducted in a tertiary care at the Kasturba Medical College Hospital (Manipal, Karnataka State, south India) from October 2012 to September 2014. The study was conducted after clearance from the Institutional Ethical Committee.

Sample size

A standard deviation of 8 and a clinically significant difference in the mean GQL-15 score of 5 among glaucoma patients and non-glaucoma comparison group was anticipated based on the pilot study. At 95% confidence level, for a power of 80%, the calculated minimum sample size was 40 subjects with glaucoma and 40 non-glaucoma subjects. The present cross-sectional, prospective study was conducted at a tertiary care hospital, enrolling 80 patients who were diagnosed as primary open-angle glaucoma (POAG) and 80 non-glaucoma subjects who were healthy participants without any ocular pathology causing poor vision or family history of glaucoma.

Patients with an established diagnosis of POAG, on minimum of one antiglaucoma medications were included in the group of cases. Healthy age- and sex-matched individuals (above 40 years of age), with no family history of glaucoma, and who were able to speak and/or read English and/or the local regional language fluently were included in the group of controls. The subjects were briefed about the study and written informed consent was obtained from those willing to participate in the study.

The exclusion criteria were: patients with other ocular diseases that could cause visual field defects or that led to poor performance on Humphrey Field Analyzer (HFA, (Carl Zeiss Meditec, Jena, Germany) test. Hence, patients with any non-glaucomatous condition or disease affecting visual function significantly, such as cataract, diabetic retinopathy, macular degeneration, retinal pathology, and non-glaucomatous optic neuropathy, were excluded. Patients suffering from any comorbidities severe enough to cause their own psychological morbidity and patients who were not fit to be subjected to clinical interview were also excluded from the study.

After enrollment, all the cases and controls were interviewed for demographic data comprising age, sex, occupation, and educational status. Patients were inquired about the number of topical antiglaucoma medications they were on, disease duration, and number of scheduled follow-up visits per year. All participants were subjected to general and systemic examination and asked for the detailed history of any systemic disease. A complete ophthalmic evaluation was done for all the participants, including visual acuity recorded using the Snellen chart, detailed anterior segment examination and IOP measurement according to standard protocol using calibrated Goldmann applanation tonometry (Haag Streit, Köniz, Switzerland). Gonioscopy was done to rule out any narrow angles. Detailed fundus examination under mydriasis was done by direct and indirect ophthalmoscopy examination and optic discs were evaluated using 90 D with the slit lamp.

A visual field examination by the Humphrey Field Analyzer (C HFA 750 or 720), program 30–2 standard SITA (as per the department protocol) was performed on all the cases to assess the latest status of visual fields.

On the basis of severity of visual field loss, patients were divided into the following three categories using the Hodapp-Parrish-Anderson (HPA) criteria:

1. Early defect
   - Mean deviation (MD) less than -6 dB
   - Less than 25% of the points (18) are depressed below the 5% level and less than 10 points are depressed below the 1% level on the pattern deviation plot
   - All points in the central 5° must have a sensitivity of at least 15 dB
2. Moderate defect
   - MD less than -12 dB
   - Less than 50% of the points (37) are depressed below the 5% level and less than 20 points are depressed below the 1% level on the pattern deviation plot
   - No points in the central 5° can have a sensitivity of 0 dB
   - Only one hemifield may have a point with sensitivity of <15 dB within 5° of fixation

3. Severe defect (any of the following results)
   - MD greater than -12 dB
   - More than 50% of the points (37) are depressed below the 5% level or more than 20 points are depressed below the 1% level on the pattern deviation plot
   - At least one point in the central 5° has a sensitivity of 0 dB
   - Points within the central 5° with sensitivity < 15 dB in both hemifields

After conducting the detailed eye evaluation, all the cases and controls were subjected to the GQL-15 questionnaire.

GLQ-15 questionnaire

The GLQ-15 is a glaucoma-specific questionnaire consisting of 15 items (Annex 1). Each question has scores ranging from 0 to 5, where 0 is difficulty to perform the task due to non-visual problems, 1 is no difficulty, and 5 is severe difficulty. These 15 items are grouped into four subscales:
1. Factor 1: central and near vision (two items);
2. Factor 2: peripheral vision (six items);
3. Factor 3: dark adaptation and glare (six items); and
4. Factor 4: outdoor mobility (one item).

The highest score is 75 and the lowest is 15. Higher scores represent more difficulty with vision-related activities and are associated with poorer quality of life.

Results

The age of the cases ranged from 43 to 86 years, with a mean age of 60.51 ± 9.18 years. The mean age among the three glaucoma severity groups was as follows: early: 57.9 years; moderate: 61.10 and severe 62.55 years. The age of the controls ranged from 42 to 72 years, with a mean age of 58.98 ± 4.5 years. The difference between the mean age of cases and controls was 1.53, which was statistically not significant ($p = 0.18$).

The difference in the number of males and females in both the cases (55%, $n = 44$ males) and controls (50%, $n = 40$ males) group was statistically not significant.

The educational level and working status of the cases and controls was noted. An educational level below Grade 10 was found in 40% ($n = 32$) of cases and 46.2% ($n = 37$) of controls. The working status was divided into two groups: working and non-working, the latter of which included all those who were housewives/retired. The subjects in the non-working category were 37 (46.2%) among the cases and 45 (56.3%) among the controls.

The duration of diagnosis in each group of glaucoma severity was compared. The mean duration of diagnosis was highest in patients with severe glaucoma (*p*

< 0.001). The details are as follows: 0–5 years: 37 patients; 6–10 years: 30 patients; 11–15 years: 10 patients; and > 15 years: 3 patients.

The number of eye drops used by the patients in the glaucoma groups is shown in Table 1. There were four patients in the severe group with four medications; two of them were not willing to undergo trabeculectomy and the other two were not fit for surgery.

The frequency of follow-up in the glaucoma groups were the following: 23 of 30 patients in the early group had a follow-up every year, 26 of 30 patients in the moderate group had a follow-up every 6 months, and 13 of 20 patients in the severe group had a follow-up every 3 months.

Table 1. Number of eye drops used by the patients in the glaucoma groups

Number of drops/ day	Early glaucoma ($n = 30$)	Moderate glaucoma ($n = 30$)	Severe glaucoma ($n = 20$)
1	16	8	4
2	14	18	2
3	0	4	10
4	0	0	4

GQL-15

The mean GQL-15 score for glaucoma patients was 33.04, while for controls it was 14.36. The difference between the mean scores for cases and controls was found to be 18.67 at a 95% confidence interval of 16.6–20.7. This was statistically significant, with a p-value < 0.001. The scores of each severity group of glaucoma patients were also compared. The mean GQL-15 score for early glaucoma patients was 23.13, for moderate glaucoma patients was 34.9, and for severe glaucoma patients was 45.1. The differences between the scores of all the glaucoma groups was statistically significant (Table 2). The difference between the GQL-15 score of controls compared to the early glaucoma group was also statistically significant ($p < 0.001$). Among glaucoma patients, duration of glaucoma diagnosis showed a strong correlation with higher GQL-15 scores, with a correlation coefficient of 0.6 (Fig. 1).

Subscale GQL-15 analysis

As detailed in the Methods section, the GQL-15 is divided into four main factors or subscales. The overall highest mean percentage score was for Factor 3: 49.7%, followed by Factor 1: 46.38%, Factor 2: 38.6%, and Factor 4: 36.25% (Table 3).

Table 2. Comparison of GQL-15 score amongst glaucoma severity groups

	Mean difference	*p*-value	Confidence interval
Early-moderate	11.76	< 0.001	10–13.5
Early-severe	21.9	< 0.001	19.9–23.9
Moderate-severe	10.2	< 0.001	8.2–12.1

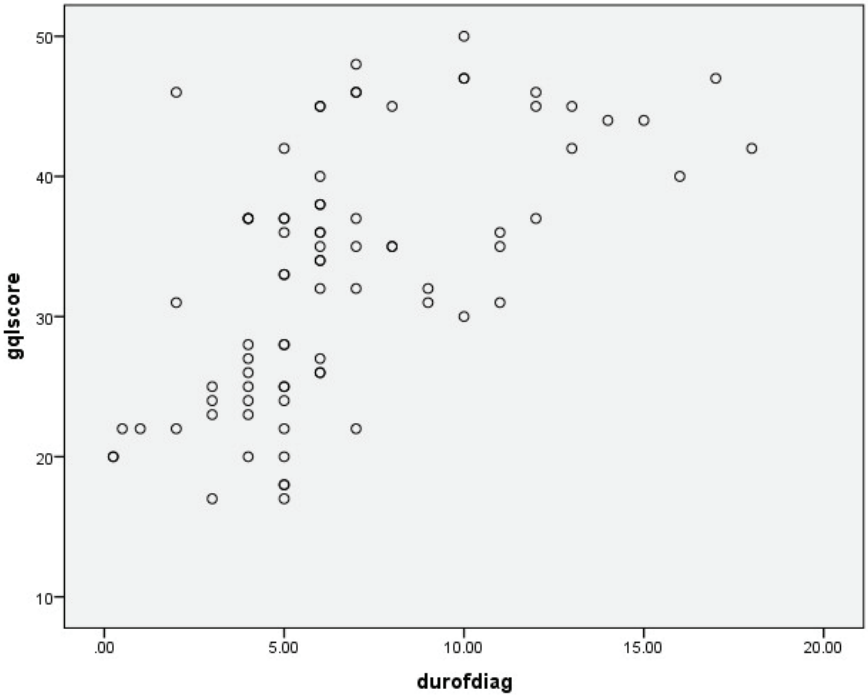

Fig. 1. Duration of diagnosis in relation to quality of life.

Correlations of the subscale analysis for each group of glaucoma severity showed that the highest score was for Factor 3 in early (37.4 ± 5.9 standard deviation) and moderate (53.6 ± 4.9) glaucoma and for Factor 2 in severe glaucoma (74.5 ± 9.4).

Effect of demographic factors on GQL-15

The effect of factors such as age, gender, educational level, and working status was analyzed to evaluate whether they had on influence on the GQL-15 scores.

Table 3. Overall GQL-15 scores of subscales in glaucoma cases

Factors	Minimum % score	Maximum % score	Mean % score (± SD)
Factor 1 Central and near vision	20%	90%	46.38 (± 21.5)
Factor 2 Peripheral vision	16%	63%	38.6 (± 10.6)
Factor 3 Glare and dark adaptation	23%	73%	**49.7 (± 11.4)***
Factor 4 Outdoor mobility	20%	100%	36.25 (± 22.1)

***This was the factor with highest mean score.**

Age

A positive correlation was seen between age and GQL-15 scores, with a correlation coefficient of 0.28. This showed increasing GQL-15 scores with increasing age.

Gender

When gender was evaluated for its effect on GQL-15 score, it was observed that there was no significant statistical difference between males and females.

Educational level and working status

The patients who were educated above Grade 10 had similar GQL-15 scores to those with educational level below Grade 10. Both groups of working and non-working patients showed similar scores ($p > 0.05$) This indicated that educational level and working status had no effect on subjects' performance (Table 4).

Discussion

In glaucoma, disease progression and efficacy of treatment are evaluated by clinical indicators such as visual acuity, IOP level, perimetric findings, and treatment side effects. These are essentially objective measures to assess the disease. However, chronic diseases such as glaucoma lead to physical, psychological, and social dysfunction that affect the individual's quality of life.

Glaucoma affects quality of life in several ways. The diagnosis itself has a psychological impact, as the knowledge of suffering from a chronic and potentially blinding disease causes anxiety and fear in patients and their families. Glaucoma also causes functional disability as well as side effects and inconvenience due to treatment and follow-up.[3,4]

Demographic factors like age, gender, educational level, and working status

Table 4. Educational level and working status in relation to GQL-15 scores

	Educational level		Working status	
	> 10th Grade	< 10th Grade	Working	Non-Working
Mean GQL-15 scores	24.13 (11.2)	23.13 (11.6)	23.4 (10.3)	23.9 (12.2)
Mean difference	1.01		0.5	
***p*-value**	0.5		0.7	
95% CI	2.5–4.6		3–4.1	

may also have an impact on quality of life. The Collaborative Initial Glaucoma Treatment Study (CIGTS) found age to be significant in determining quality of life.[5] According to this study, younger subjects reported more problems than older age groups. This is probably due to the fact that expectations of health status decrease with increasing age. This study also showed gender to be an important factor, with females reporting more problems than males. In addition to this, patients with lower income reported more problems.[6,7]

Age was reported to have a negative impact on quality of life as measured by NEI VFQ-25 and GQL-15 in a study conducted on the Nigerian population,[8] affecting all subscales of the GQL-15 and most subscales of the NEI VFQ-25. The same study also found women to have better vision-related quality of life scores ($P = 0.001$ for the NEI VFQ-25 and $P = 0.005$ for the GQL-15).

In our study age, gender, educational level, and working status were studied to assess their impact on quality of life. Age was found to have a positive correlation with GQL-15 scores; thus, age had a negative impact on quality of life. In our study, males were found to have higher scores (poorer quality of life) compared to women, but this difference was not statistically significant.

In accordance with other studies,[9-13] we also found a consistent pattern of worsening of functioning (higher GQL-15 scores) with increasing visual field loss correlating with glaucoma severity. In our study, the mean GQL-15 score for glaucoma patients was more than double compared to the age- and sex-matched controls, indicating a significant impact of disease on quality of life for glaucoma patients.

We divided glaucoma patients into three groups: early, moderate, and severe, based on the severity of visual field loss. Comparing the GQL-15 score of these groups, the scores obtained in the early glaucoma group were significantly different from the scores of moderate ($p < 0.01$) and advanced glaucoma ($p < 0.001$). A significant difference was also found between the moderate glaucoma group score and the advanced glaucoma group score ($p < 0.01$).

In a study conducted on the Australian population by Goldberg *et al.* using the GQL -15 questionnaire, scores differed significantly among patients with mild, moderate, and severe glaucoma.[9] Similar results were obtained by Iester *et al.* using Viswanathan *et al.*'s questionnaire, where they found significant differences among the three groups.[14] Vishal *et al.* used the 3-item Indian Vision Functioning Questionnaire (IND-VFQ-33) questionnaire, which revealed that newly diagnosed glaucoma patients have a significant worsening of quality of life after initiation of topical ocular hypotensive therapy.[15]

Four domains were analyzed for each glaucoma group in our study. The subscale scores afforded us the opportunity to examine loss of quality of life in the context of daily activities that may be especially troublesome for glaucoma patients. Factor 3, concerning glare and dark adaptation, was the most disabling domain for glaucoma patients in our study. This finding confirms the observations of Nelson *et al.*[2] and the CIGTS,[5] both of which also found these factors to be the most troublesome. The Nigerian study also found glaucoma patients to have greatest difficulty with the glare and dark adaptation subscale of the GQL-15.[8]

The use of questionnaires to assess quality of life has advantages and disadvantages. A study by Kumar *et al.* assessed quality of life using verbally administered quality-of-life instruments comprising two glaucoma-specific instruments (GQL-15 and Viswanathan's 10-item instrument) and one vision-specific instrument (NEI VFQ-25) and found that all three questionnaires showed statistically significant correlation with decreased quality of life in glaucoma patients when compared to controls.[19] A meta-analysis by Wang *et al.*, where quality of life was measured using the GQL-15, concluded that quality of life for patients decreased as glaucoma severity increased.[20]

Despite the above-mentioned facts, the questionnaires do have pitfalls because they are subjective and therefore affected by various factors such as age, culture, language, gender, and education, among others.[4,17,18,21] Performance-based measures, which involve testing what a person can and cannot do by actually observing the person attempting to perform specified tasks, are now gaining attention.[2,22,23]

The relatively large sample size, with the inclusion of participants with mild to severe visual field loss and their comparison with an equal number of age- and sex-matched controls, is one of the strengths of our study. Ours was a cross-sectional study carried out in tertiary healthcare center; hence, our sample may not be fully representative of the population and the results cannot be generalized to glaucoma patients in a community setting. We did not explore the potential effects of loss of color vision and other psychophysical measures. These psychophysical measures have been reported to be compromised in glaucoma.[2]

Several studies to assess quality of life in glaucoma patients were conducted on Western population. Comparatively, very few studies have been conducted on Indian populations using the GQL-15 questionnaire and ours is one of them.

Conclusion

The goal of glaucoma treatment should not be limited to controlling or reducing IOP to target level, but should also aim to provide patients with good functional vision to maintain an acceptable quality of life. Thus, with increasing awareness and rising importance to achieve a good QOL, patient-reported outcomes (subjective measures) are becoming increasingly important criteria to evaluate treatment efficacy. Proper counselling regarding the nature of the disease, its course, and a sound understanding of the problems faced by individual patients may be the key to successfully managing this chronic, debilitating, and potentially blinding disease.

The correlation observed between quality-of-life scores and objective measures of visual function suggests that inclusion of quality-of-life assessments in clinical practice could be highly informative to both patient and doctor. It would also help in providing patients with the best possible treatment, not only in terms of good vision, but also in maintaining or improving their overall quality of life.

Annex 1

GQL-15 QUESTIONNAIRE Does your vision give you any difficulty, even with glasses, with the following activities? (0 = abstinence from activity owing to non-visual reasons, 1 = no difficulty, 2 = a little bit of difficulty, 3 = some difficulty, 4 = quite a lot of difficulty, 5 = severe difficulty)
1. Reading newspapers (Factor 1: Central and near vision)
2. Walking after dark (Factor 3: Dark adaptation and glare)
3. Seeing at night (Factor 3: Dark adaptation and glare)
4. Walking on uneven ground (Factor 2: Peripheral vision)
5. Adjusting to bright lights (Factor 3: Dark adaptation and glare)
6. Adjusting to dim lights (Factor 3: Dark adaptation and glare)
7. Going from light to dark room or vice versa (Factor 3: Dark adaptation and glare)
8. Tripping over objects (Factor 2: Peripheral vision)
9. Seeing objects coming from the side (Factor 2: Peripheral vision)
10. Crossing the road (Factor 4: Outdoor mobility)
11. Walking on steps/stairs (Factor 2: Peripheral vision)
12. Bumping into objects (Factor 2: Peripheral vision)
13. Judging distance of foot to step/curb (Factor 2: Peripheral vision)
14. Finding dropped objects (Factor 3: Dark adaptation and glare)
15. Recognizing faces (Factor 1: Central and near vision)

References:

1. Glen FC, Crabb DP, Garway-Heath DF. The direction of research into visual disability and quality of life in glaucoma. BMC Ophthalmol. 2011;11(1):19.
2. Nelson P, Aspinall P, Papasouliotis O, Worton B, O'Brien C. Quality of life in glaucoma and its relationship with visual function. J Glaucoma. 2003;12:139–150.
3. Heijl A, Traverso CE, editors. European Glaucoma Society Terminology and Guidelines for Glaucoma, 3rd ed. Italy; European Glaucoma Society: 2008. p. 119-120
4. lester M, Zingirian M. Quality of life in patients with early, moderate and advanced glaucoma. Eye. 2002;16(1):44-49.
5. Mills RP, Janz NK, Wren PA, et al. Correlation of visual field with quality-of-life measures of diagnosis in the Collaborative Initial Glaucoma Treatment study (CIGTS). J Glaucoma. 2001;10(3):192-198.

6. Ramulu P. Glaucoma and disability: Which tasks are affected and at what stage of disease? Curr Opin Ophthalmol. 2009;20(2):92-98.
7. Janz NK, Wren PA, Lichter PR, Musch DC, Gillespie BW, Guire KE. Quality of life in newly diagnosed glaucoma patients: The Collaborative Initial Glaucoma Treatment Study. Ophthalmology 2001;108:887-97.
8. Onakoya AO, Mbadugha CA, Aribaba OT, Ibidapo OO. Quality of life of primary open angle glaucoma patients in Lagos, Nigeria: clinical and socio-demographic correlates. J Glaucoma. 2012;21(5):287-295.
9. Goldberg I, Clement CI, Chiang TH, John WG, Lauren JL, Suart G, Paul H. Assessing quality of life in patients with glaucoma using the Glaucoma Quality of Life-15 (GQL-15) Questionnaire. J Glaucoma. 2009;18:6–12.
10. Skalicky S, Goldberg I. Depression and quality of life in patients with glaucoma: a cross-sectional analysis using the Geriatric Depression Scale-15, assessment of function related to vision, and the Glaucoma Quality of Life-15. J Glaucoma. 2008;17:546–551.
11. Van Gestel A, Webers CA, Beckers HJ, et al. The relationship between visual field loss in glaucoma and health-related quality-of life. Eye. 2010;24:1759–1769.
12. Hirneiss C. Measurement of glaucoma-specific functionality with the GQL-15 and correlation with parameters of visual function. Ophthalmology. 2011;108(10):939-946.
13. Wang B, Aung T, Marella M, et al. Impact of bilateral open and closed-angle glaucoma on glaucoma-specific functioning in Asians. J Glaucoma. 2013;22(4):330-335.
14. Iester M, Zingirian M. Quality of life in patients with early, moderate and advanced glaucoma. Eye. 2002;16:44-49.
15. Arora V, Bali SJ, Gupta SK, Vashisht P, Agarwal T, Sreenivas V, Dada TI. Impact of initial topical medical therapy on short-term quality of life in newly diagnosed patients with primary glaucoma. Indian J Ophthalmol. 2015;63:511-515.
16. Emerick GT. Quality of life and glaucoma medications. Do our prescriptions make a difference? Glaucoma Today. 2005;5:38–39.
17. Robin AL, Covert D. Does adjunctive glaucoma therapy affect adherence to the initial primary therapy? Ophthalmology. 2005;112(5):863-868.
18. Nordmann JP, Auzanneau N, Ricard S, Berdeaux G. Vision related quality of life and topical glaucoma treatment side effects. Health and Quality of Life Outcomes. 2003;1:75.
19. Kumar S, Ichhpujani P, Singh R, Thakur S, Sharma M, Nagpal N. The impact of primary open-angle glaucoma: Quality of life in Indian patients. Indian J Ophthalmol. 2018;66(3):416-419.
20. Wang Y, Alnwisi S, Ke M. The impact of mild, moderate, and severe visual field loss in glaucoma on patients' quality of life measured via the Glaucoma Quality of Life-15 Questionnaire: A meta-analysis. Medicine (Baltimore). 2017;96(48):e8019.
21. Varma R, Richman EA, Ferris FL, Bressler NM. Use of patient reported outcomes in medical product development: a report from the 2009 NEI/FDA Clinical Trial Endpoints Symposium. Invest Ophthalmol Vis Sci. 2010;51:6095–6103.
22. Khadka J, Pesudovs K, McAlinden C, Vogel M, Kernt M, Hirneiss C. Reengineering the glaucoma quality of life-15 questionnaire with Rasch analysis. Invest Ophthalmol Vis Sci. 2011;52(9):6971-6977.
23. Nelson P, Aspinall PA, O'Brien C. Patients' perception of visual impairment in glaucoma: a pilot study. Br J Ophthalmol. 1999;83:546–552.

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Using tropicamide and phenylephrine without cyclopentolate for pupil dilation in cataract surgery reduces postoperative intraocular pressure rise

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Abstract
The aim of this retrospective study was to evaluate whether intraocular (IOP) elevation post-cataract surgery can be reduced by using tropicamide and phenylephrine only, without cyclopentolate. Medical records across two surgical facilities were analyzed. One surgical facility (Cohort A) used a combination of tropicamide, cyclopentolate, and phenylephrine preoperatively, while the other (Cohort B) used tropicamide and phenylephrine only. Of patients in Cohort A, 63.6% (n = 7) had a higher IOP in the operated eye, while it was only 27.3% (n = 3) in Cohort B. Therefore, it is preferable to exclude the use of cyclopentolate in the preoperative dilation regimen of patients undergoing cataract surgery. However, a study with a larger sample population is required to further evaluate the significance of these results.

Keywords: *cataract, cyclopentolate, intraocular pressure, pupil dilatation*

Introduction

A combination of tropicamide, cyclopentolate and phenylephrine is commonly used for preoperative pupil dilation in cataract surgery. In addition, ketorolac can be included in the preoperative eye drop regimen or be given 24 hours prior to surgery to help maintain pupil dilation by blocking prostaglandin-induced pupil constriction.[1]

In a day surgery operating facility, it is unlikely to experience delays in planned operating schedules. Hence, it may be appropriate to omit the longer acting cyclopentolate, using only tropicamide and phenylephrine preoperatively. The author (KO) has been using tropicamide, phenylephrine, and Acular (Allergan,

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Australia) as part of the preoperative regimen in a private day surgery facility. However, in a general public hospital, cyclopentolate is included in the preoperative eye drop regimen as eye surgery can occasionally be delayed due to priority being given to more urgent, life-threatening surgery.

It has been noted that at Day 1 postoperative, the pupils were functioning normally and there was less intraocular pressure (IOP) elevation when cyclopentolate was excluded in the preoperative eye drop regimen. Hence, a retrospective audit of cases was conducted with and without the use of cyclopentolate in preoperative pupil dilation for cataract surgery.

Materials and methods

This study was a consecutive, retrospective audit of preoperative and postoperative IOP of patients in two surgical facilities. Cohort A consisted of 11 cataract surgery cases performed at Royal North Shore Hospital (RNSH), Sydney, Australia from March to September 2020. Cohort B consisted of 11 cataract surgery cases done at Chatswood Private Hospital (CPH), Sydney, Australia in August 2020. Patients with glaucoma were excluded in this study.

Centurion® Vision System (Alcon, Fort Worth, Texas, USA) was used at RNSH and Constellation® Vision System (Alcon, Fort Worth, Texas, USA) was used at CPH. All cases were routine cataract phacoemulsification with insertion of SN60WF (Alcon, Fort Worth, Texas, USA) posterior chamber intraocular lens (PCIOL). DuoVisc (Viscoat and ProVisc, Alcon, Fort Worth, Texas, USA) was used in all cases; Viscoat being employed during nucleus phacoemulsification and ProVisc employed for PCIOL insertion. All patients had removal of viscoelastic after PCIOL insertion with Simcoe Irrigation-Aspiration. Two drops of pilocarpine 2% were instilled after subconjunctival injection of cephazolin and dexamethasone. The principal operating surgeon was the same for all cases.

The preoperative and Day 1 postoperative IOP of the operated and non-operated eyes were obtained retrospectively. Patients had their operation between 8 am and 5 pm and were examined between 8 am and 10 am the days after. IOP was measured with Goldmann applanation tonometry (Haag-Streit, Bern, Switzerland).

Results

Patients routinely have the IOP of both eyes recorded preoperatively and postoperatively on Day 1; this information was obtained from the medical records. Postoperative IOP rise was defined as higher IOP in the operated eye compared to the non-operated eye, which served as a control.

Cohort A consisted of seven males and four females, while Cohort B consisted of three males and eight females. The range in age of patients in Cohort A was

62–88 years (average 67.9 years), while in Cohort B it was 58–85 years (average 68.8 years).

In Cohort A, the percentage of patients with a higher IOP in the operated eye on Day 1 postoperative was 63.6% ($n = 7$). In Cohort B, the percentage of patients with higher IOP in the operated eye was 37.3% ($n = 3$) (Fig. 1). There were three patients in Cohort A and two patients in Cohort B who had a higher IOP in the operated eye of 20 mmHg or higher, which is an IOP elevation that is clinically significant.

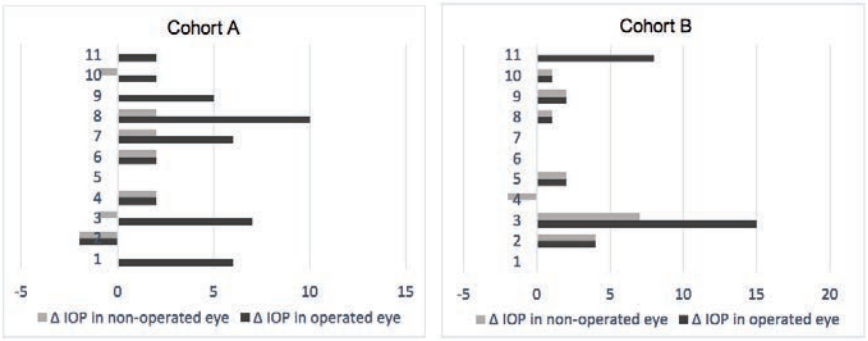

Fig. 1. IOP difference between operated and control eye in Cohorts A and B.

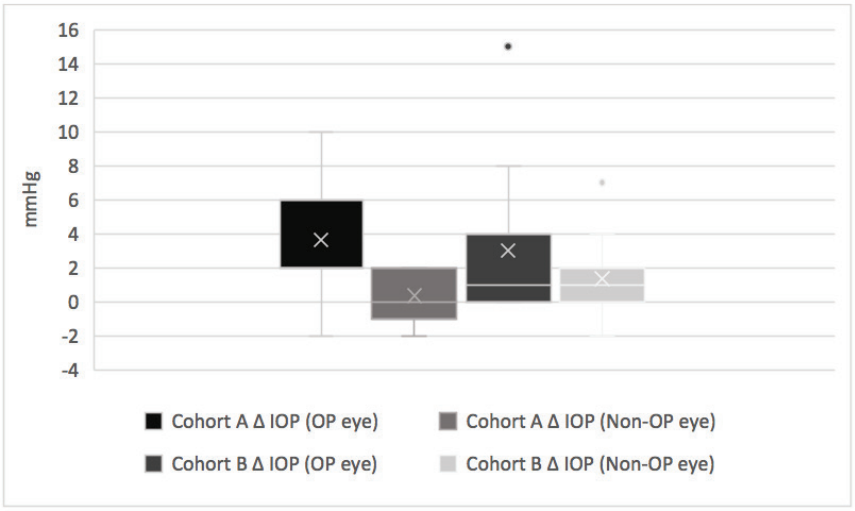

Fig. 2. Mean and range in IOP difference between operated vs control eye in Cohorts A and B, including outliers.

Table 1. Comparison of clinical characteristics and mean IOP rise in Cohorts A and B

	Cohort A		Cohort B	
Population	11		11	
Mean age (years)	67.9		68.8	
	Operated eye	Non-operated eye	Operated eye	Non operated eye
Mean IOP rise (95% CI) mmHg	3.64 ± 1.18	0.36 ± 0.37	3.00 ± 1.07	1.36 ± 0.72
***p*-value**	0.003		0.06	

IOP: intraocular pressure

A higher rise was detected in the operated eye of patients who received cyclopentolate in their preoperative pupil dilation regimen: we found an average IOP rise of 3.64 ± 1.18 (95% CI; *p*-value = 0.003) in Group A compared to 3.0 ± 1.07 (95% CI; *p*-value = 0.06) in Group B (Table 1). The difference in mean IOP rise was not statistically significant. We observed a significantly higher mean IOP rise in Cohort A (3.27 ± 0.81) compared to Cohort B (1.64 ± 0.35) (Fig. 2).

Discussion

This study showed that the incidence of postoperative IOP rise following cataract surgery was reduced when cyclopentolate was excluded in the preoperative eye drop regimen to dilate the pupil. In patients with increased IOP, there was no correlation identified for age or gender.

Anticholinergics such as tropicamide and cyclopentolate block the function of the sphincter pupillae and ciliary muscle. When the ciliary muscle contracts, it pulls on the trabecular meshwork and opens its filtration channels, which can help drain aqueous and any viscoelastic that remains in the anterior chamber after cataract surgery.[1] This helps explain the findings of our study, in which normal ciliary muscle function helps prevent IOP rise. The instillation of pilocarpine postoperatively further helps increase outflow through the trabecular meshwork, as pilocarpine stimulates contraction of the ciliary muscle, which then opens up the spaces in the trabecular meshwork.[2]

Tropicamide has a half-life of 30 minutes and its effect on the pupil and ciliary muscle wears off after 4 hours, while cyclopentolate has a half-life of 111 minutes and usually lasts for up to 24 hours.[1–4] This explains the mid-dilated

pupil in patients who had cyclopentolate on Day 1 postoperative, and the normal functioning pupil in patients who were not given cyclopentolate.

Conclusion

This small retrospective audit study demonstrates that using tropicamide and phenylephrine only, without xyclopentolate, reduces the incidence of postoperative IOP rise following cataract surgery. However, a larger study would be useful to ascertain the significance of these results.

It would be preferable to avoid or minimize the use of cyclopentolate for preoperative pupil dilation in cataract surgery, especially in patients with glaucoma. If there is a delay in surgery schedule and the pupil becomes less dilated, extra drops of tropicamide can be used to re-dilate the pupil without compromising surgical safety.

References

1. Zanetti F, Fulco EA, Chaves FR, da Costa Pinto A, Arieta CE, Lira RP. Effect of preoperative use of topical prednisolone acetate, ketorolac tromethamine, nepafenac and placebo, on the maintenance of intraoperative mydriasis during cataract surgery: A randomized trial. Indian J Ophthalmol. 2012;60(4):277-281.
2. Hancox J, Murdoch I, Parmar D. Changes in intraocular pressure following diagnostic mydriasis with cyclopentolate 1%. Eye (London, England). 2002;16(5):562-566.
3. Li G, Farsiu S, Chiu SJ, et al. Pilocarpine-induced dilation of Schlemm's canal and prevention of lumen collapse at elevated intraocular pressures in living mice visualized by OCT. Invest Ophthalmol Vis Sci. 2014;55(6):3737-3746.
4. Lahdes K, Huupponen R, Kaila T, Monti D, Saettone MF, Salminen L. Plasma concentrations and ocular effects of cyclopentolate after ocular application of three formulations. Br J Clin Pharmacol. 1993;35(5):479-483.
5. Sani RY, Hassan S, Habib SG, Ifeanyichukwu EP. Cycloplegic effect of atropine compared with cyclopentolate-tropicamide combination in children with hypermetropia. Niger Med J. 2016;57(3):173-177.
6. Stanley RG. Ocular clinical pharmacology. In: Maddison JE, Page SW, Church DB, editors. Small Animal Clinical Pharmacology (2nd Edition). Edinburgh: WB Saunders; 2008. p. 557-573.
7. Kilic O, Ozturk M, Ata Gozcelioglu E. Tropicamide ophthalmic solution reduces clozapine-induced sialorrhea: a case report. Psychiat Clin Psych. 2017;27(4):431-434.

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Multiple phakomatoses and primary open-angle glaucoma in one individual

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Abstract
A 50-year-old woman presented with conjunctival melanosis, scleral pigmentation, and Lisch nodules in her left eye. Intraocular pressure was 24 mmHg in the right eye and 14 mmHg in the left eye. She had open angles on gonioscopy. Fundus examination showed a cup-to-disc ratio of 0.7 in the right eye, with an inferior notch and a splinter hemorrhage, and 0.6 in the left eye, with a deep cup with sloping rims. Humphrey visual fields showed an evolving superior arcuate scotoma in her right eye; the left eye was normal. Systemic examination showed axillary freckling. The patient had a family history of neurofibromatosis type 1 (NF-1), her father having been diagnosed with the condition. She had hyperpigmentation of the skin over the forehead and periocular skin on the left side. These unique ocular and systemic features were suggestive of two phakomatoses, NF-1 and nevus of Ota, in one eye, and primary open-angle glaucoma (POAG) in the other eye. that is, three pathologies present together in the same individual, which is an extremely rare occurrence.

Keywords: *conjunctival melanosis, Lisch nodules, nevus of Ota, neurofibromatosis 1, phakomatosis, primary open-angle glaucoma*

Introduction

The presence of primary open-angle glaucoma (POAG) in one eye along with two phakomatoses in the other eye, amounting to three pathologies in the same patient, is an extremely rare phenomenon. In this report, we present a patient with neurofibromatosis type 1 (NF-1) and nevus of Ota in one eye and POAG in the fellow eye.

Case report

A 50-year-old woman presented to us with the complaint of dimness of vision in her left eye. On examination, her best-corrected visual acuity (BCVA) was 20/20 in the right eye and 20/80 in the left eye. Slit-lamp examination showed conjunctival melanosis and scleral pigmentation in her left eye. She had clear corneas in

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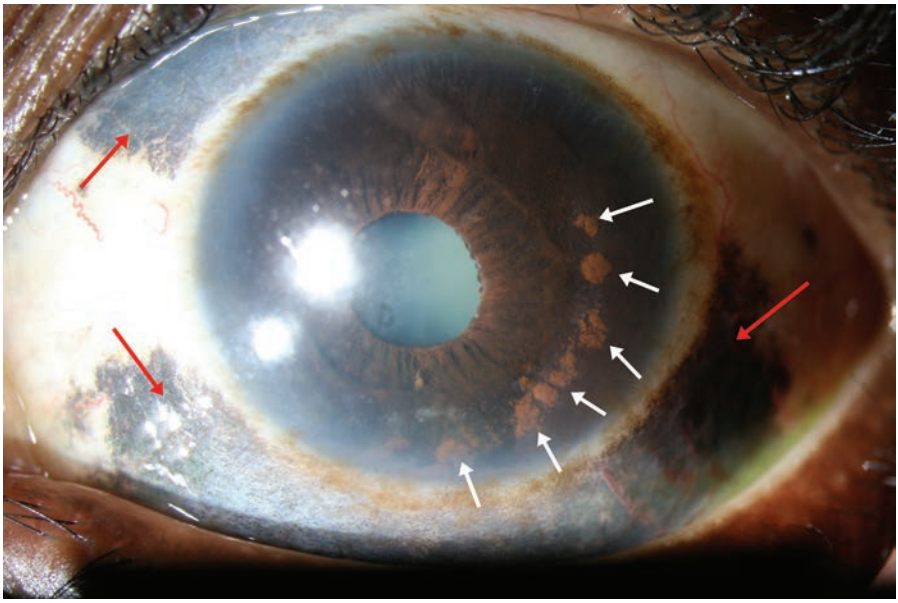

Fig.1. Conjunctival melanosis evident on slit-lamp examination in the left eye of the patient (red arrows). The image also shows iris hyperpigmentation with multiple small, oval or irregular, yellowish-brown, fleshy papules randomly spaced on the inferior and temporal surface of the left iris consistent with Lisch nodules (white arrows).

both eyes. There was normal iris pigmentation in the right eye, but the left eye had hyperpigmented iris with multiple small, oval or irregular, yellowish-brown, fleshy papules randomly spaced on the inferior and temporal surface of the iris consistent with Lisch nodules (Fig. 1).

She had undergone a cataract surgery in her right eye a few years ago a at local institute and there was a posterior chamber intraocular lens (PCIOL) in situ; she had cortical cataract along with posterior subcapsular cataract in her left eye (Fig. 2). Facial examination showed an asymptomatic, hyperpigmented, macular, bluish-black lesion on the skin over her forehead and periocular skin on the left side of her face (Fig. 2e).

Intraocular pressure (IOP) was 24 mmHg in the right eye and 14 mmHg in the left eye; central corneal thickness was 545 µ n the right eye and 546 µ n the left eye. She was noted to have Shaffer's grade 4 open angles in both eyes and Scheie's grade I pigmentation of the trabecular meshwork in the right eye. The left eye had diffuse hyperpigmentation of the trabecular meshwork (grade III) and a pigmented Schwalbe's line with patchy pigment deposition in the inferior quadrant. Fundus examination showed a cup-to-disc ratio of 0.7 in the right eye

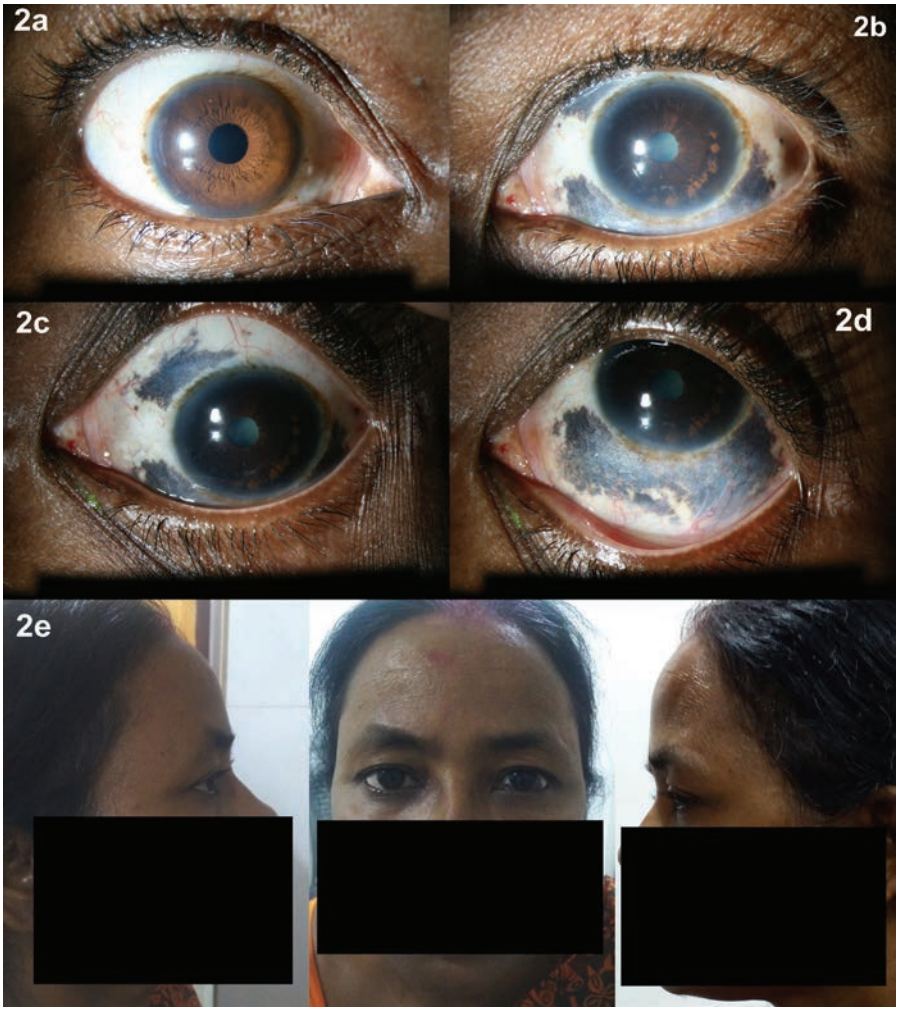

Fig. 2. Anterior segment features of both eyes. (a) The right eye, which had undergone phacoemulsification previously, had a posterior chamber intraocular lens in situ. (b) The left eye in straight gaze clearly shows the Lisch nodules and the pigmentary nevi. The left eye in the downgaze (c) and upgaze (d). (e) Face image of the patient showing evidence of pigmentary nevi in the conjunctiva of the left eye as well as hyperpigmentation of the skin over the forehead and periocular skin on the left side of the face.

with an inferior notch and a splinter hemorrhage in the inferior aspect of the disc suggestive of glaucomatous damage. The left eye had a cup-to-disc ratio of 0.6 with a deep cup with a sloping, apparently healthy, neuroretinal rim (Fig. 3a). The glaucomatous damage noted in the right eye was recorded to be present before the cataract surgery at another institute where the patient had been under treatment previously. She had been started on a single antiglaucoma medication, travoprost (0.004%) once daily, and subsequently underwent cataract surgery in that eye. However, the patient discontinued the antiglaucoma medication herself and was not using any medication for the past 6 months before she presented to us. Ultra-widefield (UWF) imaging was done using using the Optos® (Optos, Dunfermline, UK). Optomap showed normal peripheries in both eyes (Fig. 3b).

Anterior segment optical coherence tomography (AS-OCT) was done using the RTVue (Optovue, Inc., Fremont, CA) and the scans of both eyes were normal. Visual fields done using the Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, CA, USA) showed an evolving superior arcuate scotoma with a nasal step in her right eye while the left eye was normal (Fig. 3c). OCT (RNFL) using the RTVue showed retinal nerve fiber layer (RNFL) thinning in the inferotemporal and inferonasal quadrants in the right eye, while the left eye had normal RNFL thickness in all quadrants. Magnetic resonance imaging scans of the brain and orbits were normal (Fig. 4).

On physical examination, the patient had axillary freckling but did not have any skin growth, scoliosis, or other skeletal abnormalities. There were no neurofibromas or café-au-lait macules. Her head circumference was within normal range for an adult female (58 cm), and neither hypertelorism nor ear abnormalities were present. She gave no history of learning disabilities, seizures, or growth and developmental delays. There was a family history of neurofibromatosis type 1 (NF-1), with her father having been diagnosed with the condition. There was no family history of pigmentary abnormalities, or other genetic diseases. Based on the presence of the three features, Lisch nodules, axillary freckling and one parent being a diagnosed case of NF-1, she was diagnosed as a case of NF-1. Since she had the typical features of ocular melanosis in her left eye and dermal melanosis on the left side of her face, she was also diagnosed as a case of Nevus of Ota. The patient's IOP was raised in the right eye and there were glaucomatous changes in that eye on fundus examination confirmed by visual field reports, so she was diagnosed as a case of primary open-angle glaucoma (POAG). Thus, her final diagnosis was NF-1 and nevus of Ota in the left eye and POAG in the right eye; that is, the presence of three coexisting pathologies in the same individual. To the best of our knowledge this is the first case report presenting these three pathologies in one individual.

A prostaglandin analogue (travoprost 0.004%) once daily was started in her

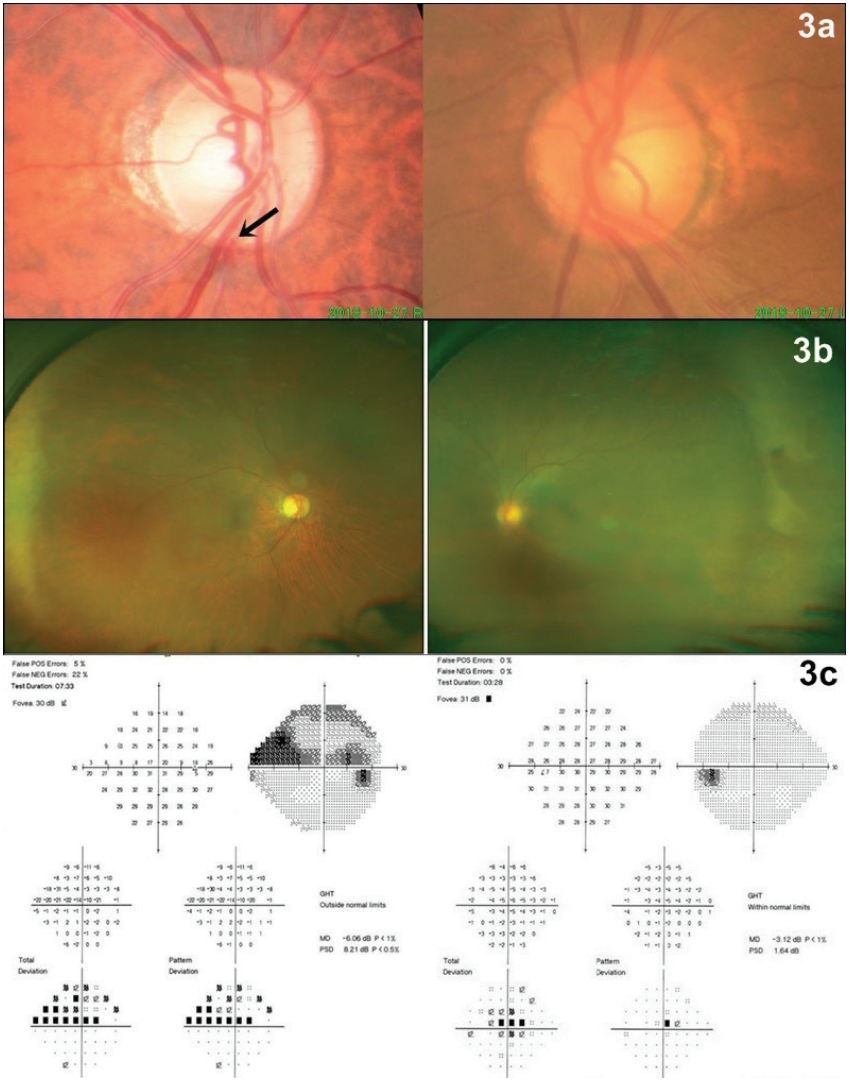

Fig. 3. (a) Disc images. The right eye had a cup-to-disc ratio of 0.7 with an inferior notch and a faint splinter hemorrhage in the inferior aspect of the disc (black arrow). The left eye had a cup-to-disc ratio of 0.6.(b) Wide field fundus image of the patient. The periphery was normal in both eyes. (c) Humphrey visual fields of both the eyes. It reveals an evolving superior arcuate scotoma in the right eye with depressed points in the superior hemifield while the left eye shows a normal field. (d) Optical coherence tomography. The report showed retinal nerve fiber layer (RNFL) thinning in the inferotemporal and inferonasal quadrants in the right eye while the left eye had normal RNFL thickness in all quadrants.

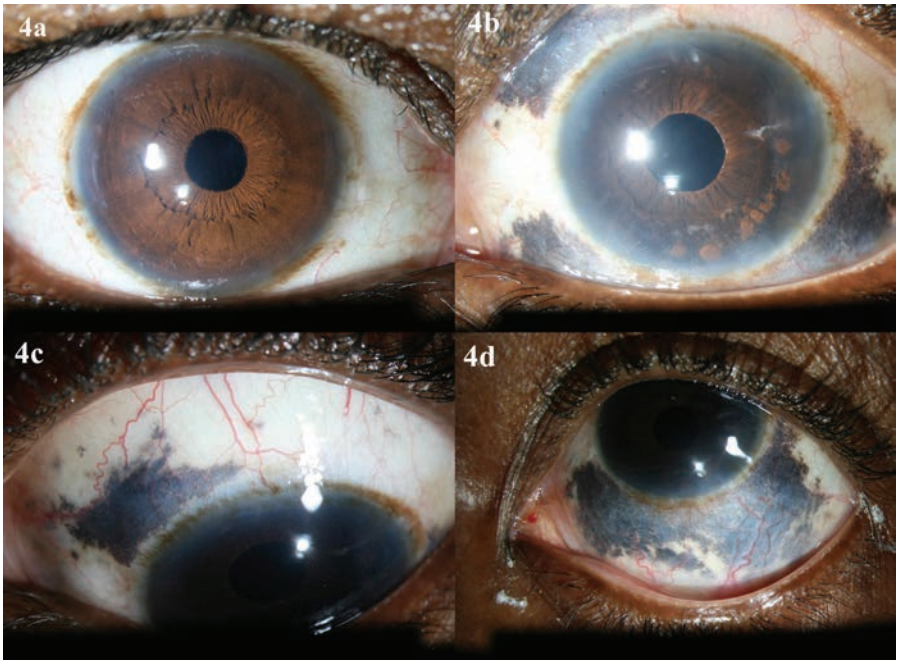

Fig. 5. Anterior segment photographs of the patient at follow-up after cataract extraction in the left eye. Both eyes had intraocular lenses in situ. (a) Right eye. (b, c, d) Left eye in straight, downgaze, and upgaze, respectively.

right eye only. She underwent an uneventful cataract extraction in her left eye, and a multipiece intraocular lens (IOL) was implanted (Fig. 5). During follow-up, IOP was 17 mmHg in the right eye and 15 mmHg in the left eye. Fundus examination revealed the resolution of the splinter hemorrhage in the right eye. She was advised continuation of travoprost in the right eye and regular follow-ups with periodical visual field examinations.

This patient is unique since she had ocular, facial, and dermatological findings suggestive of two phakomatoses in the same individual: nevus of Ota and NF-1, along with the presence of POAG in the other eye. Our literature search showed no published case reports showing the presence of these three pathologies together.

Discussion

Nevus of Ota or nevus fuscoceruleus ophthalmomaxillaris was first described by Hulke in 1869 before Ota's definitive description in 1939.[1] It is a dermal melanocytic hamartoma that presents as bluish-grey or blackish-brown hyperpigmentation

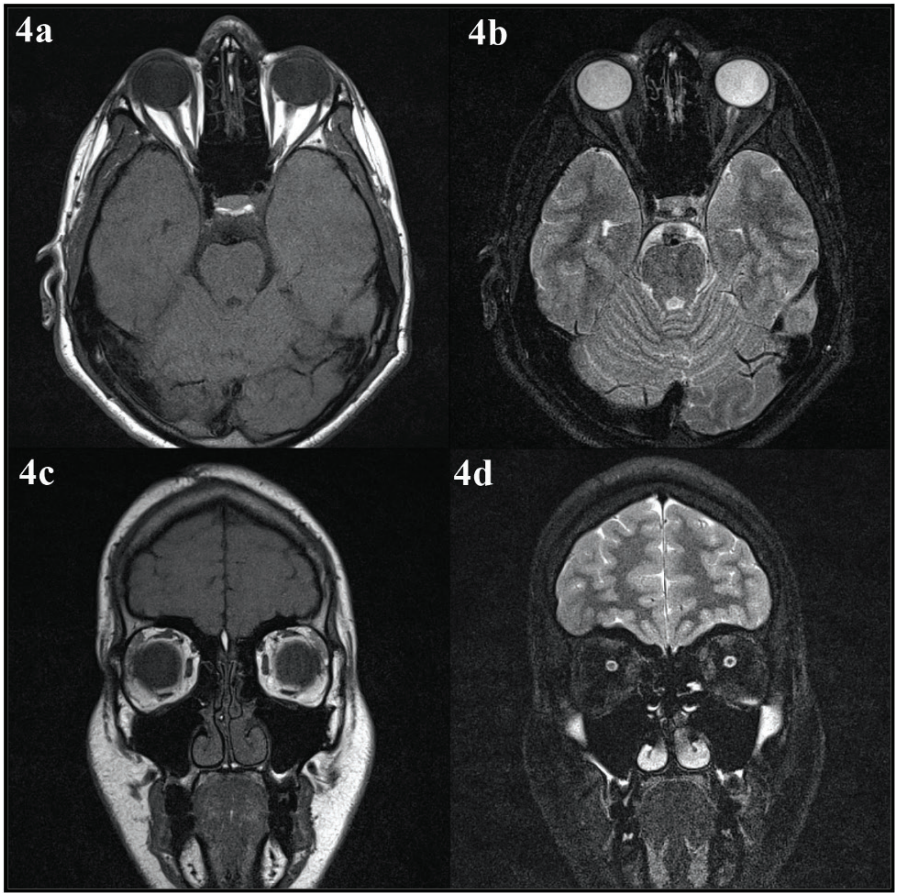

Fig. 4. Magnetic resonance scans of the patient. (a) Axial T1 and (b) axial T2 fat saturation scans showing normal optic nerves, no abnormalities of the bony orbit, and normal brain tissue. (c) Coronal T 1 scan showing normal contour of the bony orbit and normal extraocular muscles. (d) Coronal T2 fat saturation scans which shows normal optic nerves and brain tissue.

on the facial skin limited to the area innervated by the first and second divisions of the trigeminal nerve. An increased number of dermal melanocytes located in the distribution of the ophthalmic and maxillary divisions of the trigeminal nerve has been reported. Most patients have concomitant hyperpigmentation of the globe that may involve the conjunctiva, sclera, cornea, iris, and fundus. In our patient, the involvement of the conjunctiva and sclera were evident. Extracutaneous involvement, especially ocular involvement, is frequent and has been widely reported.[2-4]

In nevus of Ota, the melanosis may also affect the oral and nasal mucosa, external auditory canal, tympanic membrane, orbital tissues and brain. In our patient, however, these features were not present. Nevus of Ota affects between 0.014% and 0.034% of the Asian population.[2] The reported prevalence of ocular hyperpigmentation in patients with dermal involvement has ranged from 22% to 61.3%.[3,4] In patients with extensive dermal lesions, ocular involvement is as high as 76.6%.[3,4]

The pathogenesis of this condition is unknown, but some of the theories which have been put forward include:

1. dropping-off of epidermal melanocytes;
2. migration of hair bulb melanocytes to the dermis; and
3. reactivation of pre-existing latent dermal melanocytes, which are triggered by dermal inflammation, UV radiation, or hormonal changes during pregnancy.[3,4]

Histopathologically, in nevus of Ota, pigment-bearing cells are numerous and distributed diffusely throughout the upper and lower dermis. These are elongated, slender pigment-bearing cells dispersed in between the collagen fibers of the dermis and the long axis of pigment-bearing cells, that is, melanocytes are found along the collagen fibers.[3,4]

Even though the iridocorneal angle may be extremely hyperpigmented, there may not be any rise of IOP. This has been reported in a few studies and was seen also in our patient.[4,5] Elevated IOP with or without glaucomatous damage has been reported in 10% of patients of nevus of Ota with ocular involvement.[5] The affected eye typically has very heavy pigmentation of the trabecular meshwork and histopathological studies have shown melanocytes in the meshwork.[6]

Lisch nodules are the most common ophthalmologic manifestation of NF-1.[7,8] On histological examination, they are found to be melanocytic hamartomas, composed of melanocytes, elongated fibroblasts, and mast cells, presumably of neural crest origin, similar to other cutaneous characteristics of NF-1.[9] Lisch nodules do not represent a cause of morbidity or disability, but they are diagnostically significant, being one of the hallmark manifestations of NF-1. Examination of a Lisch nodule with the help of a slit lamp reveals characteristic nodules with dimensions of approximately 2 mm, absence of vasculature, and a certain chromatic variability ranging from white to yellow or brown.[9] The differential diagnosis of Lisch nodules includes iris mammillations, iridocornealendothelial syndrome, granulomatous iritis, iris cysts, multiple iris nevi, iris melanoma, and other malformations.[10,11]

Unilateral Lisch nodules are rare but they have been reported in cases of segmental neurofibromatosis, found associated with other pigmentary changes or neurofibromas.[12] The presence of Lisch nodules without other clinical

evidence of NF-1 has been reported, although this is also extremely rare.[8,12,13] There are only two reported cases of numerous unilateral Lisch nodules in the absence of any additional features of NF-1.[13,14] In our case, the Lisch nodules were also unilateral, but our patient had axillary freckling and a positive family history of NF-1.

Iris mammillations are a very commonly noted abnormality of the iris. They are characterized by deep brown, regularly spaced, smooth, conical iris elevations.[10] These can be differentiated from Lisch nodules by slit-lamp examination as Lisch nodules are yellowish-brown, dome-shaped, well-defined elevations rising from the surface of the iris.[9] Amelanotic iris nevi present as flat, or minimally elevated, lightly pigmented lesions with blurred margins which are visibly different from the elevated dome-shaped Lisch nodules. The amelanotic naevi are much lighter in color compared to the yellow or yellowish-brown Lisch nodules.[9]

In NF-1, the various clinical features affecting the nervous, dermatologic, ocular, and skeletal systems are usually absent at birth. Approximately 95% of NF-1 patients meet the diagnostic criteria by the age of 8 years, and almost all do so by the age of 20 years. The diagnostic criteria currently used for diagnosis were presented by the National Institutes of Health statement in 1987.[15] A clinical diagnosis is the most common way doctors diagnose NF1. A diagnosis of NF-1 is confirmed if the patient has two or more of the following:

1. six or more café-au-lait spots, at least 0.5 cm in children or 1.5 cm in adults;
2. two or more neurofibromas on or under the skin, or one plexiform (deep tissue) neurofibroma;
3. axillary (armpit) or inguinal (groin) freckling;
4. optic pathway glioma, also called a visual pathway tumor;
5. two or more Lisch nodules;
6. bone changes such as bowing of the long bones; and
7. a close relative (parent, child or sibling) with a confirmed diagnosis of NF-1.[15]

Our patient had axillary freckling, Lisch nodules, and one parent having been diagnosed as a case of NF-1 and was thus confirmed as a case of NF-1.

The axillary and/or inguinal freckling are commonly seen in patients of NF-1. They usually start as small freckles less than 5 mm in size and are localized usually in the axillary or inguinal area (Crowes sign). Freckling is found in approximately 90% of adults over the age of 30 years,[15] as was seen in our case.

Raised IOP and/or disc changes suggestive of glaucoma may be present at birth in a case of NF-1 and usually suggest congenital abnormality of the angle, while onset at a later date suggests involvement of the anterior chamber angle secondary to NF-1.[16-18] This may be due to angle infiltration by neurofibroma or

the ciliary body may show thickening leading to secondary angle closure.[16-18] Glaucoma has been reported in 1/300 NF-1 patients.[19] In our patient, there were no signs of glaucoma in the eye affected by the phakomatoses.

The presence of nevus of Ota and NF-1 in one individual is an extremely rare presentation. Our literature search showed that there are only three published case reports of the association of nevus of Ota with NF-1.[20-22] However there are no published reports of the presence of three pathologies in one individual as was seen in our case.

Medical management is the initial mode of treatment in glaucoma associated with these phakomatoses, as is the case in other forms of open-angle glaucoma.[16,17] Laser trabeculoplasty may also be attempted in some of these cases. If medical management and laser treatment fail, then trabeculectomy may be tried as a surgical option.[17,18]

POAG is usually bilateral disease but there are a number of published reports of cases of POAG where only one eye has shown glaucomatous damage.[23-25] Some authors use the term unilateral POAG for these patients.[23-25] In most of these cases, the other eye will not be affected at all and there are no disc or field changes suggestive of glaucoma in the unaffected eye over long-term follow-up. [3-25] Our case appears to be a case of unilateral POAG with evident glaucomatous changes in the right eye, with the left eye having phakomatoses. The management of these unilateral POAG patients follows the same management guidelines of POAG cases; the only difference is that the treatment is given to the affected eye only.

This case is different from published reports in two aspects. Firstly, it shows the coexistence of two phakomatoses in one individual, which is an extremely rare finding. However, even though the patient's left eye had the clinical features of two phakomatoses and a hyperpigmented trabecular meshwork, IOP was normal and there were no disc or field changes suggestive of glaucoma. Secondly, this patient had raised IOP and glaucomatous damage in the right eye suggestive of POAG, even though the left eye had the clinical features of two phakomatoses. There are no published reports of the coexistence of these three pathologies in one individual and hence, it is an extremely rare presentation.

Conclusion

Coexistence of multiple phakomatoses in an individual is rare. There are no specific treatment options for these patients. There may be underlying systemic and/or local anomalies and complications associated with these disorders or other non-associated ocular or systemic diseases which must be diagnosed, which will dictate the management of these patients. Further advancements and research into the molecular biology of neural crest development and

abnormal migration of melanocytes are warranted to determine the etiology of these coexisting neuro-cutaneous disorders. There may be additional pathologies, such as POAG, along with the existence of phakomatoses in the same individual; thus, thorough examination of these patients and proper management and follow-up are required.

Acknowledgements

The authors have written consent from the patient to publish the images in this case report.

References

1. Ota M. Naevus Fusco-caerunleus ophthalmomaxillaries. Tokyo Med J. 1939;63:1243–1245.
2. Stanford DG, Georgouras KE. Dermal melanocytosis: a clinical spectrum. Aust J Dermatol. 1996;37:19–25.
3. Ito M. Studies on melanin. XXII: Naevus Fusco-caeruleus acromiodeltoideus. Tohoku J Exp Med.1954;60:10-18.
4. Hidano A, Kajima H, Ikeda S, Mizutani, Miyasato H, Niimura M. Natural history of Naevus of Ota. Arch Dermatol.1967;95:187-195.
5. Teekhasaenee C, Ritch R, Rutnin U. Leelawongs N. Ocular findings in oculodermal melanocytosis. Arch Ophthalmol. 1990;108:1114-1120.
6. Sugar HS. Glaucoma with trabecular melanocytosis. Ann Ophthalmol.1982;14:374-375.
7. Kinori M, Hodgson N, Zeid JL. Ophthalmic manifestations in neurofibromatosis type 1. Surv Ophthalmol. 2018;63(4):518-533.
8. Huson S, Jones D, Beck L. Ophthalmic manifestations of neurofibromatosis. Br J Ophthalmol.1987;71:235–238.
9. Nichols JC, Amato JE, Chung SM. Characteristics of Lisch nodules in patients with neurofibromatosis type1. J Pediatr Ophthalmol Strabismus. 2003;40:293-296
10. Kharrat W, Dureau P, Edelson C, Caputo G. Iris mammillations: three case reports. J. Fr. Ophtalmol. 2006;29:413–417.
11. Ragge NK, Falk RE, Cohen WE, Murphree AL. Images of Lisch nodules across the spectrum. Eye (Lond). 1993;7:95–101.
12. Ceuterick SD, Van Den Ende JJ, Smets RM. Clinical and genetic significance of unilateral Lisch nodules. Bull. Soc. Belge Ophtalmol. 2005;295:49–53.
13. Lal G, Leavitt JA, Lindor NM, Mahr MA. Unilateral Lisch nodules in the absence of other features of neurofibromatosis 1. Am J Ophthalmol. 2003;135:567-568.
14. Adams EG, Stewart KMA, Borges OA, Darling T. Multiple, Unilateral Lisch Nodules in the Absence of Other Manifestations of Neurofibromatosis Type 1. Case Rep Ophthalmol Med. 2011;2011:854784. doi: 10.1155/2011/854784.
15. Neurofibromatosis. Conference statement. National Institutes of Health Consensus Development Conference. Arch Neurol. 1988;45:575-578.
16. Abdolrahimzadeh S, Plateroti AM, Recupero SM, Lambiase A. An Update on the Ophthalmologic Features in the Phakomatoses. J Ophthalmol. 2016:3043026. Epub: 2016 Jul 17.
17. Jain G, Jain VK, Sharma IK, Sharma R, Saraswat N. Neurofibromatosis Type 1 Presenting with Ophthalmic Features: A Case Series. J Clin Diagn Res. 2016;10(11):SR01-SR03. Epub: 2016 Nov 1.
18. Grant WM, Walton DS. Distinctive gonioscopic findings in glaucoma due to neurofibromatosis. Arch Ophthalmol. 1968;79:127–134.

19. Morales J, Imtiaz AC, Bosley TM. Glaucoma and globe enlargement associated with neurofibromatosis type1. Ophthalmology. 2009;116:1725–1730.
20. Croxatto JO, Charles DE, Malbran ES. Neurofibromatosis associated with nevus of Ota and choroidal melanoma. Am J Ophthalmol. 1981;92:578-80.
21. Gupta A, Ram J, Jain IS. Nevus of Ota associated with neurofibromatosis. Ann Ophthalmol. 1986;18:154-155.
22. Madke B, Kar S, Gangane N, Singh N. Phacomatosis Cesioflammea in Association With von Recklinghausen Disease (Neurofibromatosis Type I). Cutis. 2017;99(2):E35-E37.
23. Sangawe JL. Unilateral glaucoma. Trop Geogr Med. 1986;38(1):70-72.
24. Yoo YJ, Lee EJ, Kim T-W. Intereye difference in the microstructure of parapapillary atrophy in unilateral primary open-angle glaucoma. Invest Ophthalmol Vis Sci. 2016;57:4187–4193.
25. Zangalli CS, Ahmed OM, Waisbourd M, et al. Segmental Analysis of Macular Layers in Patients with Unilateral Primary Open-Angle Glaucoma. J Glaucoma. 2016;25:401-407.

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Bilateral orbital metastasis as an initial presentation of hepatocellular carcinoma

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Abstract

Purpose: *To describe a case of biopsy-confirmed bilateral orbital metastasis of previously undiagnosed hepatocellular carcinoma, presenting with bilateral proptosis.*

Case description: *A 57-year-old man presented with painless bilateral proptosis over 2 months. At presentation, the best-corrected visual acuity was 20/60 in the right eye and 20/20 in the left eye. Ocular examination revealed bilateral asymmetrical non-axial proptosis with Hertel exophthalmometer reading of 24 mm in the right eye and 22 mm in the left eye. There was mild inferior displacement in both eyes. Apart from mild exposure keratopathy in the right eye, both anterior and posterior segment examinations were not remarkable. Orbital computerized tomography (CT) scan showed soft tissue masses in the superotemporal quadrants of both orbits associated with lytic bone lesions. An orbital biopsy confirmed that it was metastatic hepatocellular carcinoma (HCC). Ultrasound abdomen revealed multifocal HCC with underlying cirrhosis. We planned for further investigations such as hepatitis serology, alfa-fetoprotein, and CT abdomen, but he refused to proceed with investigations and treatment.*

Conclusion: *Orbital metastasis, more so as a bilateral involvement, is a rare phenomenon. It may present as an initial manifestation of undiagnosed systemic cancer. Orbital metastasis should be considered when diagnosing patients with bilateral proptosis, and orbital biopsy is crucial for histopathological diagnosis.*

Keywords*: bilateral proptosis, hepatocellular carcinoma, orbital metastasis, ocular oncology, ocular pathology*

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Introduction

The orbit is an unusual site for cancer metastasis. Metastatic orbital tumors are rare conditions that account for 3–7% of all orbital neoplasms. It occurs in 2–3% of patients with systemic cancers.[1] It is more commonly associated with carcinomas of breast, lung, and prostate, and less commonly with kidney, skin, and gastrointestinal tract. Most cases present with unilateral involvement.

Hepatocellular carcinoma (HCC) is a primary malignant tumor derived from hepatocytes. It accounts for 80% of all liver cancers. It is one of the cancers with the highest mortality rates globally and the third most common cause of cancer-related deaths in the Asia-Pacific region.[2] In East and Southeast Asia, it is associated with the highest incidence and mortality among both sexes.[3] Men have a higher incidence, and it is more common in those aged 65 years and above.[2] The most common and well-known risk factor is chronic infection with hepatitis B and C viruses. Other risk factors include obesity, diabetes mellitus, cirrhosis related to heavy alcohol intake, non-alcoholic fatty liver disease, smoking, and ingestion of aflatoxin.[2,3]

Metastasis of HCC occurs in approximately 30–50% of patients. It primarily metastasizes to lung, bones, and lymph nodes. HCC metastasis to the orbit is a rare phenomenon, more so as a bilateral involvement and first presenting feature. There have been only a few reports of histopathologically proven orbital metastasis from HCC in the past. Almost all cases reported for orbital metastasis secondary to HCC were unilateral cases (Table 1). Herein, we report a case of biopsy-confirmed orbital metastasis of HCC in a 57-year-old man, who first presented with painless bilateral proptosis.

Case report

A 57-year-old man presented with blurred vision in the right eye for 15 days and bilateral, asymmetrical, painless, progressive proptosis of 2 months duration (Fig. 1). It involved the right eye first and then eventually the left eye, but was more severe on the right. He had no known chronic illnesses apart from a history of completed treatment for pulmonary tuberculosis 3 years prior. He denied any alarming social habits, such as smoking and excessive alcohol consumption. The best-corrected visual acuity was 20/60 in the right eye (RE) and 20/20 in the left eye (LE). Examination revealed superior sulcus fullness and bilateral proptosis with Hertel exophthalmometer readings of 24 mm RE and 22 mm LE. There was a mild inferior displacement of the globes. A solid, non-tender, immobile mass was palpable in the right superior sulcus. Ocular motility in both eyes (BE) showed limitations in upgaze. Anterior segment examination revealed conjunctival congestion and chemosis in the RE. There was mild haziness over the right inferior cornea due to exposure keratopathy. LE showed mild congestion

Table 1. Case reports of biopsy-proven orbital metastasis from HCC in the literature to date

	Authors	Age (years)	Sex	Presenting features	Laterality	Remark
1	Lubin (1980)[9]	69	M	Proptosis, pain	R	
2	Zubler (1981)[10]	64	M	Mass at temporal fossa, proptosis, diminished vision, ophthalmoplegia	L	
3	Wakisaka (1990)[11]	58	M	Proptosis, diplopia, ptosis	L	
4	Loo (1994)[12]	71	F	Pain, diminished vision	R	
5	Schwab (1994)[13]	19	M	Proptosis	L	
6	Tranfa (1994)[14]	85	M	Proptosis, pain, diminished vision	R	
7	Kami (1994)[15]	60	M	Proptosis, headache	L	
8	Font (1998)[16]	79	F	Proptosis, pain, diminished vision	R	
9	Scolyer (1999)[17]	77	M	Periorbital mass	R	FNAC
10	Kim (2000)[18]	56	F	Displaced eyeball (orbital mass near lower eyelid)	L	
11	Chen (2003)[19]	69	M	Proptosis, diplopia	R	
12	Gupta (2005)[5]	45	M	Proptosis	L	
13	Oida (2006)[20]	72	M	Diplopia	L	
14	Machado-Netto (2006)[21]	57	M	Proptosis	R	
15	Hirunwiwatkul (2008)[22]	74	F	Proptosis with orbital apex syndrome	R	
16	Pitts (2008)[23] (2 cases)	61	F	Painful proptosis	L	Necropsy
17		47	M	Proptosis, temporal swelling	L	Necropsy
18	Fonseca (2008)[24]	57	M	Painful proptosis	R	
19	Kolarević (2011)[25]	70	M	Painful proptosis	R	

	Authors	Age (years)	Sex	Presenting features	Laterality	Remark
20	Mustapha (2011)[26]	25	M	Painful proptosis	R	FNAC
21	Guerriero (2011)[27]	45	M	Proptosis	L	
22	Jiang (2012)[27]	44	M	Proptosis, diplopia	Both	
23	Piccirillo (2013)[29]	66	M	Mass at medial canthus	L	
24	Eldesouky (2013)[6] (6 cases)	62	M	Painful proptosis	L	
25		70	M	Painful proptosis	L	
26		55	M	Proptosis	R	
27		65	M	Painful proptosis, redness, lacrimation	L	
27		47	M	Painful proptosis	L	
29		62	M	ptosis	R	
30	Chen (2014)[30]	56	M	Epiphora with pulsatile mass in right lacrimal gland	R	
31	Chen (2015)[31]	43	M	Proptosis, headache	L	
32	Kader (2018)[32]	60	M	Swelling at lateral aspect of the eye, blurred vision, pain, watery discharge	L	
33	Present case	57	M	Bilateral proptosis , soft tissue mass	Both	

F: female; FNAC: fine needle aspiration cytology; L: left; M: male; R: right

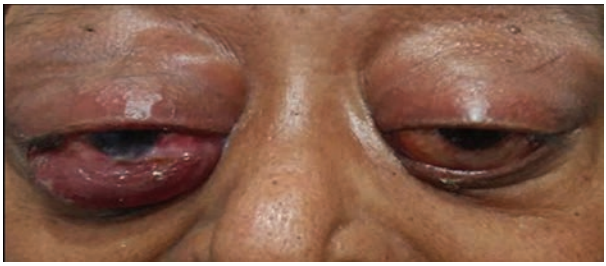

Fig. 1. Bilateral proptosis with exposure keratopathy in RE.

without exposure keratopathy. Pupils were reactive. The intraocular pressure was 18 mmHg in BE. Other anterior and posterior segment examinations were unremarkable in BE.

Orbital computerized tomography (CT) scan showed soft tissue masses in the superotemporal quadrants of both orbits, measuring 3.0 x 3.7 cm in the right and 2.3 x 2.6 cm in the left. There were lytic bone lesions in both lateral walls and right frontal bone (Fig. 2).

We performed percutaneous incisional biopsy from the right orbital mass through a direct sub-brow approach. The lesion was friable and bled severely upon touch. Multiple small pieces were sent for a histopathologic examination. The section revealed fibrous tissue infiltrated by metastatic deposits composed of large polygonal-shaped epithelial cells arranged in a trabeculo-sinusoidal pattern. The cells contained eosinophilic cytoplasm and hyperchromatic nuclei (Fig. 3). The features were consistent with metastatic HCC. We did not perform immunohistochemical studies as there were limited facilities.

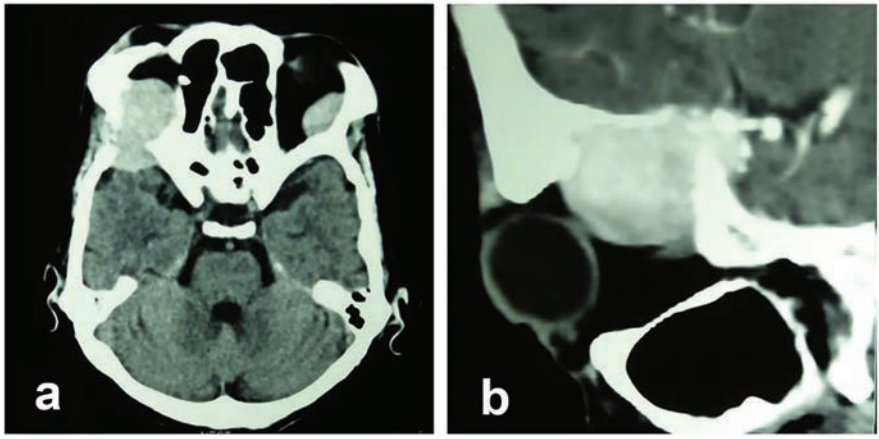

Fig. 2. CT scan. (a) Axial scan showed extraconal soft tissue masses in both orbits. (b) Right frontal bone destruction.

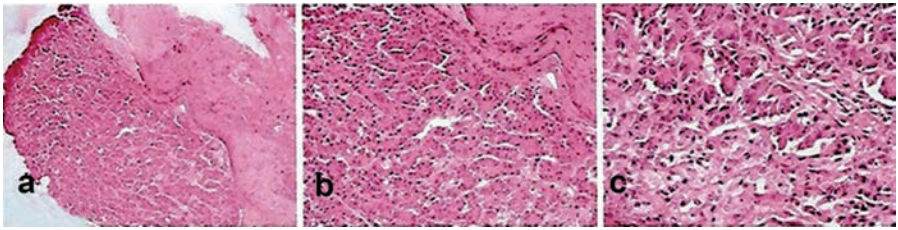

Fig. 3. Histopathological report. (a) 4x: Metastatic tumor deposit. (b) 20x: Tumor cells arranged in trabeculo-sinusoidal pattern. (c) 40x: Features of anaplasia.

We referred the patient for further assessment. Abdominal ultrasound confirmed multifocal HCC with underlying cirrhosis. We planned for further investigations such as hepatitis serology, alfa-fetoprotein, and abdomen CT, but he refused to proceed with investigations and treatment. Informed consent was taken from the patient to share and publish these findings.

Discussion

Orbital metastasis, more so as a bilateral involvement, is a rare phenomenon. When it occurs, ocular manifestations can be the primary presentations without prior history of systemic cancers in 15–19% of cases.[1,4] However, in orbital metastasis, particularly from HCC, it can be as high as 50%.[5,6] Ocular signs from orbital metastasis secondary to HCC often present earlier than that of primary cancer.[7]

Approximately 80–90% of patients with HCC have chronic liver disease and cirrhosis caused by alcoholic liver disease and chronic infection with the hepatitis B and C viruses.[2] In low- and middle-income countries, chronic hepatitis B and C infection is attributed to over 90% of HCC.[3] Our patient did not provide a history of alcohol drinking, and we could not identify the hepatitis serology status as he refused to proceed further. It is pertinent to note that exposure to aflatoxin is a significant risk factor in Southeast Asia, as the humidity in the region favors the contamination of traditional food by the fungus.[2,3]

The histopathological diagnosis of orbital metastasis from HCC is primarily confirmed by the presence of large polygonal cells, trabecular pattern, and endothelial cuffing. Renal cell carcinoma may present with a similar histological feature. The use of carcinoembryonic antigen and alfa-fetoprotein can differentiate HCC from renal cell carcinoma. Immunohistochemical (IHC) markers are useful to diagnose the primary cancers in undifferentiated types of orbital metastasis. In HCC, several markers are available; arginase-1 and hepatocyte paraffin antigen (Hep Par 1) yielded the highest sensitivity for well-differentiated type, whereas combined use of arginase-1 and glypican-3 has 100% sensitivity for poorly differentiated type.[8]

Biopsy-proven orbital metastasis from HCC was first reported in 1980 by Lubin and colleagues.[9] Since then, a few cases have been reported in the literature. We performed a literature search and identified a total of 32 biopsy-confirmed orbital metastasis from HCC to date.[5,6,9-32] It is common in males and aging adults. Most cases presented with proptosis and all cases except one were unilateral. It affects both eyes equally with no significant preference. In one series of 100 patients with orbital metastasis, only 4% had bilateral involvement, and the primary cancers were one each from breast, prostate, cutaneous melanoma, and choroidal melanoma.[1] There was one report of bilateral orbital metastasis involving multiple extraocular muscles from HCC.[28] To our best knowledge, our patient is the first

case presenting with bilateral orbital soft tissue masses from metastatic HCC. Based on imaging findings, many authors reported that HCC metastasizing to the orbits is associated with adjacent bone changes such as bone destruction, bone erosion, and notching.[5,6,22,31] Similarly, our case had lytic changes noted in both lateral walls and right frontal bones adjacent to the tumor masses.

There are multi-disciplinary treatment modalities for orbital metastasis. External beam radiation is the mainstay of treatment. Surgery, adjuvant chemotherapy, immunotherapy, or hormonal therapy can be considered in selected cases. Patients with HCC metastasizing to the orbit have a relatively poor prognosis.[5] Generally, survival is limited to 1.5 years after orbital manifestations irrespective of primary neoplasms.[4]

There are several learning points in this case report. Firstly, it was the first case of biopsy-proven bilateral orbital metastasis involving soft tissue of the orbit. Secondly, HCC may present with bilateral orbital metastasis. Thirdly, this report highlights that orbital metastatic tumors may present as an initial manifestation of undiagnosed systemic cancer and should be considered an important differential diagnosis in cases with bilateral proptosis. Furthermore, we reviewed the previously published data and presented the clinical presentations of orbital hepatocellular metastasis. However, we were unable to analyze the IHC markers for this patient nor the follow-up as the patient refused further management.

Conclusion

Orbital metastatic tumors may present as an initial manifestation of undiagnosed systemic cancer. Although bilateral orbital metastasis is extremely rare, it should be considered when diagnosing patients with bilateral proptosis, and orbital biopsy is crucial for histopathological diagnosis.

References

1. Shields JA, Shields CL, Brotman HK, Carvalho C, Perez N, Eagle RC. Cancer Metastatic to the Orbit: the 2000 Robert M. Curtis Lecture. Ophthal Plast Reconstr Surg. 2001;17:346-354.
2. Zhu RX, Seto WK, Lai CL, Yuen MF. Epidemiology of hepatocellular carcinoma in the Asia-Pacific region. Gut and Liver. 2016;1:332-339.
3. Torre LA, Siegel RL, Ward EM, Jemal A. Global cancer incidence and mortality rates and trends - an update. Cancer Epidemiol Biomarkers Prev. 2016;25:16-27.
4. Valenzuela AA, Archibald CW, Fleming B, et al. Orbital metastasis: clinical features, management and outcome. Orbit. 2009;28(2-3):153-159.
5. Gupta R, Honovar SG, Vemuganti GK. Orbital metastasis from hepatocellular carcinoma. Surv Ophthalmol. 2005;50:485-489
6. Eldesouky MA, Elbakary MA, Shalaby OE, Shareef MM. Orbital metastasis from hepatocellular carcinoma: report of 6 cases. Ophthal Plast Reconstr Surg. 2014; 30(4):e78-81.
7. Amemiya T, Hayashida H, Dake Y. Metastatic orbital tumors in Japan: a review of literature. Ophthalmic Epidemiol. 2002;9:35-47.

8. Nguyen T, Philips D, Jain D, et al. Comparison of 5 immunohistochemical markers of hepatocellular differentiation for the diagnosis of hepatocellular carcinoma. Arch Pathol Lab Med. 2015;139:1028-1034.
9. Lubin JR, Grove AS, Zarkov ZN, Albert DM. Hepatoma metastatic to the orbit. Am J Ophthalmol 1980;89:268-273.
10. Zubler MA, Rivera R, Lane M. Hepatoma presenting as a retro-orbital metastasis. Cancer. 1981;48:1883-1885.
11. Wakisaka S, Tashiro M, Nakano S, Kita T, Kisanuki H, Kinoshita K. Intracranial and orbital metastasis of hepatocellular carcinoma: report of two cases. Neurosurgery. 1990;26(5):863–866.
12. Loo KT, Tsui WMS, Chung KH, Ho LC, Tang SK, Tse CH. Hepatocellular carcinoma metastasizing to the brain and orbit: report of three cases. Pathology. 1994;26(2):119-122.
13. Schwab L, Doshi H, Shields JA, Kagame K, Chana H. Hepatocellular carcinoma metastatic to the orbit in an African patient. Ophthalmic Surg. 1994;25(2):105-106.
14. Tranfa F, Cennamoa G, Rosa N, Rosa GD, Boscaino A, Bonavolonta G. An unusual orbital lesion: hepatoma metastatic to the orbit. Ophthalmologica. 1994;208:329-332.
15. Kami H, Wada M, Matsuura J, Araya S. Case of hepatocellular carcinoma with an orbital metastasis as the initial symptom [in Japanese]. Nippon Naika Gakkai Zasshi 1994;3:622-624.
16. Font RL, Maturi RK, Small RG, Garcias-Rojas M. Hepatocellular carcinoma metastatic to orbit. Arch Ophthalmol. 1998;116:942-945.
17. Scoyler RA, Painter DM, Harper CG, Lee CS. Hepatocellular carcinoma metastasizing to the orbit diagnosed by fine needle aspiration cytology. Pathology. 1999;31:350-353.
18. Kim IT, Na SC, Jung BY. Hepatocellular carcinoma metastatic to the orbit. Korean J Ophthalmol. 2000;14:97-102.
19. Chen PH, Po HL, Lin YJ, Hseuh IH, Huang JK. Painful ophthalmoplegia as the initial manifestation of hepatocellular carcinoma: A case report and literature review. Acta Neurol Taiwan. 2003;12:93-96.
20. Oida Y, Ohtani Y, Dowaki S, et al. Hepatocellular carcinoma metastatic to the orbit: a case report. Tokai J Exp Clin Med. 2006;31(1):7-10.
21. Machado-Netto MC, Lacerda EC, Heinke T,Maia DC, Lowen MS, Saad ED. Massive orbital metastasis of hepatocellular carcinoma. Clinics (Sao Paulo). 2006;61:359–362. DOI: 10.1590/S1807-59322006000400015
22. Hirunwiwatkul P, Tirakunwichcha S, Meesuaypong P, Shuangshoti S. Orbital metastasis of hepatocellular carcinoma. J Neuroophthalmol. 2008;28:47–50.
23. Pitts J, Chang CH, Mavrikakis I, Shaikh A, Rootman J. Hepatocellular carcinoma presenting as orbital bone metastasis. Ophthal Plast Reconstr Surg. 2008;24:477–479. DOI: 10.1097/IOP.0b013e31818c9558.
24. Fonseca Júnior NL, Frizon L, Paves L, Wolosker AM, Manso PG. An unusual orbital metastatic lesion: the only finding in a case of hepatocellular carcinoma: case report. Arq Bras Oftalmol. 2008;71:865–867.
25. Kolarević D, Tomasević Z, Boricić I, et al: Metastasis of hepatocellular carcinoma presented as a tumor of the maxillary sinus and retrobulbar tumor. Vojnosanit Pregl. 2011;68:359-362.
26. Mustapha SK, Madachi DA. Orbital metastasis of hepatocellular carcinoma: a case report. West Afr J Med. 2011;30:305-307.
27. Guerriero S, Infante G, Giancipoli E, et al. Hepatocellular carcinoma metastasis to the orbit in a coinfected HIV+ HBV+ patient previously treated with orthotopic liver transplantation: a case report. Case Rep Ophthalmol Med. 2011: 2011;Article ID 549270, 4 pages.
28. Jiang H, Wang Z, Xian J, Ai L. Bilateral multiple extraocular muscle metastasis from hepatocellular carcinoma. Acta Radiol Short Rep. 2012;1:1. DOI: 10.1258/arsr.2011.110002.
29. Piccirillo M, Granata V, Albino V, et al. Can hepatocellular carcinoma (HCC) produce unconventional metastasis? Four cases of extrahepatic HCC. Tumori. 2013; 99:e19-e23.

30. Chen H, Li J, Wang L, et al. Hepatocellular carcinoma metastasis to lacrimal gland: a case report. Oncology Letters. 2014;8:911-913. DOI: 10.3892/ol.2014.2191.
31. Chen CY, Zhong JH, Liu JL. Retrobulbar metastasis and intracranial invasion from postoperative hepatocellular carcinoma: a case report and review of the literature. Oncology Letters. 2015;9:721-726. DOI: 10.3892/ol.2014.2733
32. Kader NA, Abraham RM, Sathi PP. Unusual metastases of hepatocellular carcinoma: 2 cases. OGH Reports. 2018;7(2):109-110. DOI: 10.5530/ogh.2018.7.2.26

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Microsporidial stromal keratitis: an uncommon etiology of bilateral simultaneous corneal infection

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Abstract

We report three cases of bilateral microsporidial keratitis, which is an unusual presentation. All three patients presented with bilateral, simultaneous, asymmetrical, deep stromal corneal infiltrates with symptoms ranging from 5 to 12 months. Predisposing factors were noted in two of three patients. Corneal scrapings for microbiology and histopathology of corneal tissue revealed microsporidial spores from both eyes of all patients. There was no response to medical therapy and all underwent bilateral corneal transplantation. Case one additionally had recurrences in the graft and underwent repeat keratoplasties and eventually keratoprosthesis. Microsporidial stromal keratitis is a possible cause of keratitis in cases of very long-standing, indolent, culture-negative, deep stromal corneal infiltrates. So far, this infection has been reported as unilateral; however, we report these cases of bilateral infection, which is rare. Corneal transplantation is the preferred line of management due to lack of response to medical therapy.

Keywords: *bilateral corneal infection, indolent keratitis, microsporidia outcomes, microsporidial stromal keratitis, therapeutic keratoplasty*

Introduction

Microsporidia are opportunistic pathogens and can cause keratoconjunctivitis,[1] stromal keratitis,[2] and endophthalmitis.[3] Stromal keratitis is rare, has an indolent course, and often mimics herpes simplex virus (HSV) or fungal keratitis. While there are several reports on unilateral infection, bilateral simultaneous stromal involvement has not been described before and we present our experience with three such patients. The clinical and demographic details of all three cases are summarized in Table 1.

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Table 1. Age, gender distribution, and associated history of the three cases

Cases	Age (years)	Sex	Duration of symptoms	Waxing and waning of symptoms	History of trauma	Prior use of steroids	Initial working diagnosis
Case 1 (Both eyes)	52	M	8 months	Yes	No	Yes	HSV stromal keratitis
Case 2 RE	73	M	1 year	Yes	Yes	Yes	HSV stromal keratitis
LE			6 months	Yes	No	Yes	HSV stromal keratitis
Case 3 RE	49	F	3 months	Yes	No	Yes	Filamentary keratitis
LE			3 months	Yes	No	Yes	Filamentary keratitis

HSV: herpes simplex virus; LE: left eye; RE: right eye

Case reports

Case 1

A 47-year-old woman with a 15-year history of rheumatoid arthritis presented with severe dry eye. She was on systemic infliximab infusions, ocular lubricants, punctal plugs, and scleral contact lenses. Clinical examination revealed diffuse, bilateral, elevated filament-like lesions with patchy stromal (Fig. 1A and 1B) infiltration. Corneal scrapings revealed large microsporidial spores on 10% potassium hydroxide (KOH) mount + 1% Calcoflur stain (CFW). She was started on chlorhexidine eye drops (0.02%) Q2 hourly and tablet albendazole 400 mg BID. However, there was rapid worsening over the next few weeks, and she underwent bilateral, sequential therapeutic penetrating keratoplasty (PK) (Fig. 1C and 1D). Histopathology of the corneal buttons showed microsporidial infection. Postoperatively, she went on to develop graft recurrences (Fig. 1E) and had to undergo repeat surgeries bilaterally (three grafts in her right eye [RE] and two in her left eye [LE]). Each of the previous grafts showed persistence of the spores in the stroma on histopathology. Eight months after the last surgery, there was resolution of the

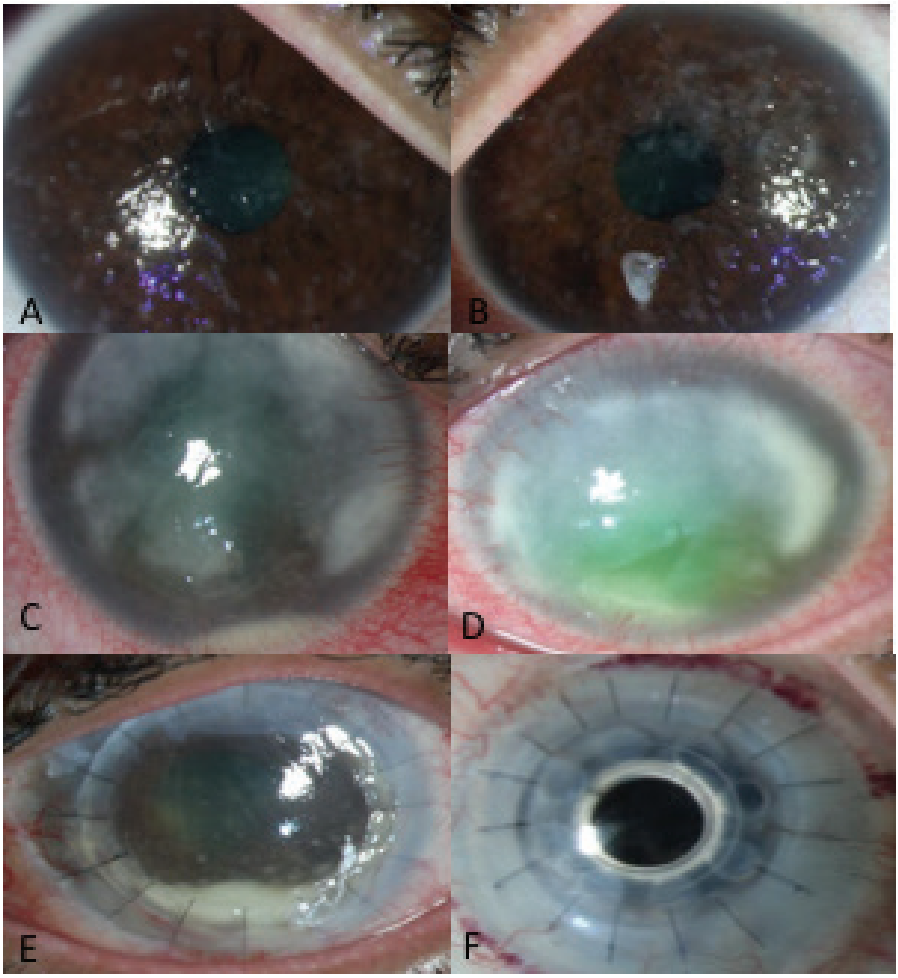

Fig. 1. (A-F) Slit lamp photography images showing the initial presentation of the first patient with diffuse anterior stromal cellularity (A, B) and subsequent worsening with corneal stromal infiltrates (C, D) and post-penetrating keratoplasty image showing recurrence in the left eye (E). (F) Boston type I Kpro in the right eye of the patient.

infection but no improvement in vision; she underwent Boston type I K-Pro bilaterally. Postoperatively, visual acuity improved to 20/30 (Fig. 1F). Subsequently she also developed secondary glaucoma for which glaucoma filtering device surgery was performed bilaterally. At the 5-year follow-up she maintained visual acuities of 20/50 and 20/80 in the right and left eye, respectively.

Case 2

A 52-year-old man presented with an 11-month history of waxing and waning symptoms. He recalled a history of foreign body in his RE 10 years prior to presentation. Examination showed bilateral anterior to mid-stromal corneal infiltrates (Fig. 2A and 2B). Corneal scrapings showed microsporidia (Fig. 2C and 2D); he was started on oral albendazole and topical polyhexamethylene biguanide (PHMB) 0.02% eye drops. Due to rapid worsening, he underwent PK in his RE. Over the next year, the LE showed gradual worsening and PK was performed. Histopathology from both eyes revealed microsporidial spores. The patient maintained clear grafts with 20/25 and 20/60 vision in his RE and LE, respectively at 28 months postoperative.

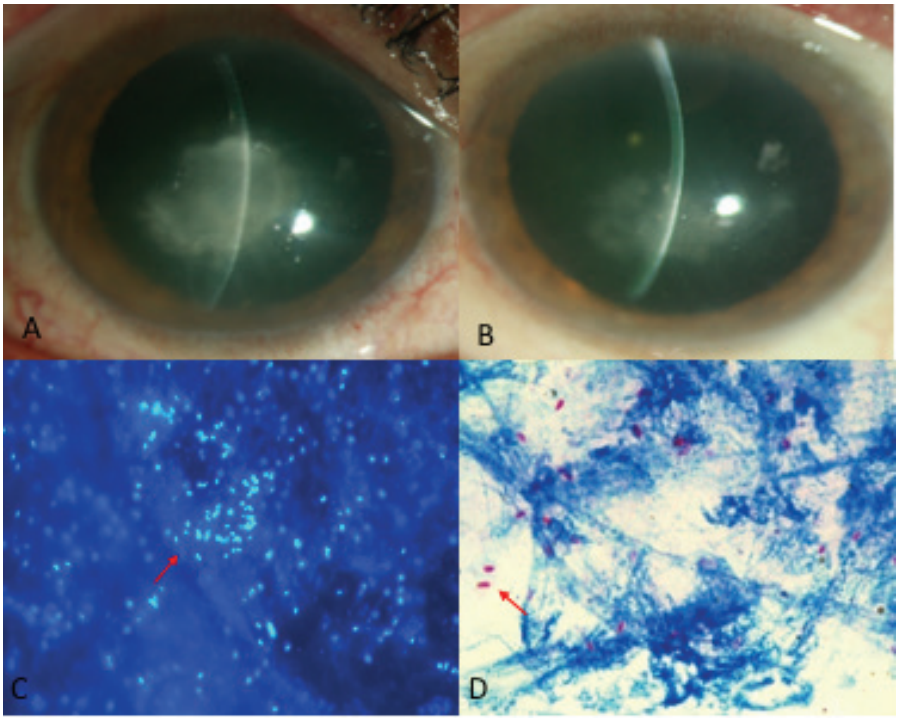

Fig. 2. (A-B) Histopathology photomicrographs of the corneal button revealing oval microsporidial spores in the intralamellar spaces on 40x (C) and 100x (D) magnification in the second patient.

Case 3

A 73-year-old man presented with bilateral, central, deep, stromal corneal infiltrates (Fig. 3A and 3B). He had undergone cataract surgery in both eyes 3 years prior to presentation. He was on antifungals, topical and oral antivirals, and topical steroids in both eyes. The RE also showed presence of vitreous echoes on B-mode ultrasound scan (Fig. 3C). He was started on topical PHMB 0.02% and chlorhexidine 0.02% Q1 hourly. In view of vitreous involvement in his RE, he underwent PK with pars plana vitrectomy (PPV). His LE also showed a similar course and he underwent sequential PK followed by PPV and vitreous biopsy. All ocular specimens showed large microsporidial spores. He did well and had no recurrence at the 1-year postoperative follow-up. Figure 3D shows the RE with a clear and compact graft.

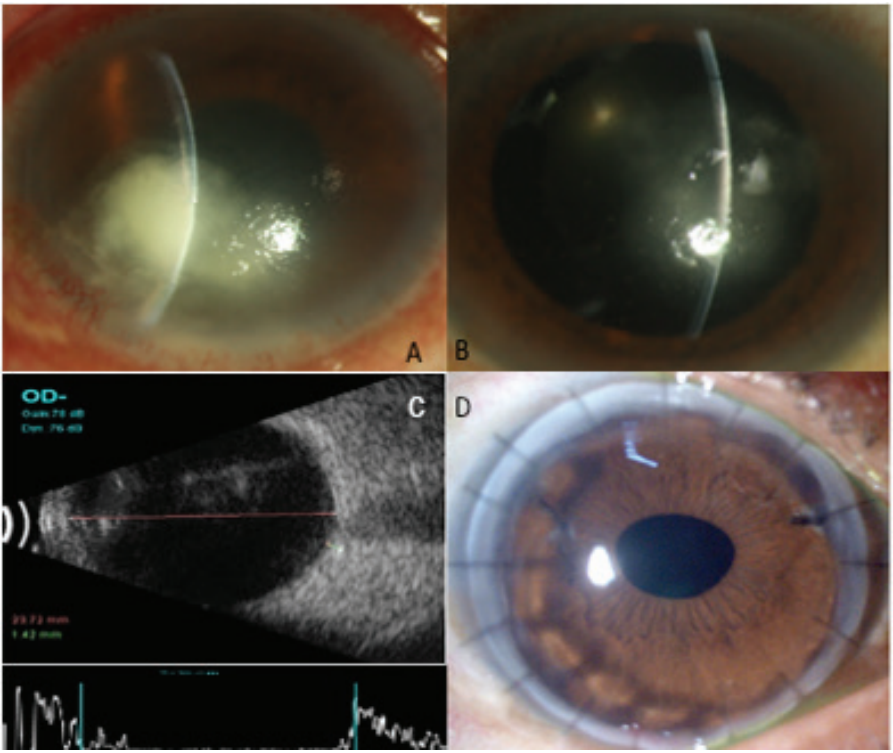

Fig. 3. (A-D) Slit-lamp photography images (A, B) show deep stromal infiltrates in the right and left eye, respectively, of the third patient. Note the echoes in the vitreous cavity on B mode ultrasound in image (C). (D) Post-keratoplasty photograph of the right eye.

Discussion

Bilateral simultaneous microbial keratitis is rare, either bacterial if acute or due to contact lenses,[4] or following bilateral surgery such as refractive surgery or collagen cross-linking.[5] The commonest causes of indolent bilateral keratitis include HSV stromal keratitis and immune-mediated peripheral ulcerative keratitis. Microsporidia is well recognized as an emerging cause of microbial keratitis,[6] with a protracted progressive course associated with waxing and waning of symptoms. However, bilateral simultaneous keratitis in the stromal form is rare. It is now established that the disease has a chronic history, with a duration from 8 months to 2 years.[3] The diagnosis is established by demonstration of spores using gram and KOH + CFW stains as well as histopathological specimens.[9]

In our cases we noted simultaneous bilateral presentations. Each case was different, with the first case developing rapid progression and multiple recurrences despite keratoplasty. which could be attributed first to the patient's immunosuppressed status and second to the peripheral corneal involvement. The second case, in contrast, mimicked HSV keratitis, maintained good vision and showed very slow progression, with excellent outcome following keratoplasty. This could be due to better host-immune response. The third case, which was pseudophakic in both eyes, developed endophthalmitis along with keratitis. Stromal keratitis along with endophthalmitis has been reported before but as a unilateral presentation.[8]

The mode of infection is presumed to be feco-oral, following trauma or from animal exposure.[9] In two of our cases, the mechanism of bilateral infection is intriguing and the mechanism of inoculation is not clear; one case had history of trauma. None had systemic infections, such as respiratory or gastrointestinal infections, which commonly occur due to microsporidia. The first case underwent a comprehensive evaluation by an infectious disease specialist in order to localize the focus of the primary infection and was also on prolonged oral treatment; this was the only patient who had multiple recurrences.

Although there are reports of successful management of microsporidial stromal keratitis with medical therapy,[10] based on our experience with these bilateral and other unilateral cases of microsporidia presenting to us, we believe it is important to consider surgical management even in bilateral cases, as medical management does not seem to work. Hence, bilateral microsporidial stromal keratitis is a rare entity but should be suspected in cases with prolonged duration and waxing and waning of symptoms. Altered and recalcitrant clinical course can be expected in immunocompromised patients.

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References

1. Metcalfe TW, Doran RM, Rowlands PL, Currey A, Lacey CJ. Microsporidial keratoconjunctivitis in a patient with AIDS. Br J Ophthalmol. 1992; 76:177–178.
2. Sabhapandit S, Murthy SI, Garg P, Korwar V, Vemuganti GK, Sharma S. Microsporidial Stromal Keratitis: Clinical Features, Unique Diagnostic Criteria, and Treatment Outcomes in a Large Case Series. Cornea. 2016;35(12):1569-1574
3. Yoken J, Forbes B, Maguire AM, Prenner JL, Carpentieri D. Microsporidial endophthalmitis in a patient with acute myelogenous leukemia. Retina. 2002;22(1):123-125.
4. On Annie LH, Ray M. Bilateral simultaneous infective keratitis. Cont Lens Anterior Eye. 2017; 40(4):224-227.
5. Tzamalis A, Romano V, Cheeseman R, Vinciguerra R, Batterbury M, Willoughby C. Bandage contact lens and topical steroids are risk factors for the development of microbial keratitis after epithelium-off CXL. BMJ Open Ophthalmol. 2019;16;4(1)
6. Vemuganti GK, Garg P, Sharma S, Joseph J, Gopinathan U, Singh S. Is microsporidial keratitis an emerging cause of stromal keratitis? A case series study. BMC Ophthalmol. 2005;5:19
7. Joseph J, Sridhar MS, Murthy S, Sharma S. Clinical and microbiological profile of microsporidial keratoconjunctivitis in southern India. Ophthalmology. 2006;113:531–537.
8. Sood AB, Debiec MR, Yeh S, Grossniklaus HE, Randleman JB. Microsporidial stromal keratitis and endophthalmitis in an immunocompetent patient. J Ophthalmic Inflamm Infect. 2016;6(1):30
9. Mathis A, Weber R, Deplazes P. Zoonotic potential of the microsporidia. Clin Microbiol Rev. 2005;18(3):423-45
10. Coca M, Kim J, Shenoy S, Chévez-Barrios P, Kapur M. Microsporidial Stromal Keratitis: Successful Treatment with Topical Voriconazole and Oral Itraconazole. Cureus. 2016 20;8(12):934.

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Pythium keratitis: clinical course of an emerging scourge

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Abstract
We hereby report two cases of the emerging and devastating Pythium keratitis for their different presentations, prolonged clinical course, and suspicion of recurrence after therapeutic penetrating keratoplasty (TPK). The history, clinical presentation, investigations including smears, cultures, polymerase chain reaction (PCR) and confocal microscopy, the tumultuous course of the infection, and outcome of TPK have been discussed for two cases having this unusual and severe emerging infection. These two cases demonstrate that Pythium keratitis can present as a central reticular or peripheral guttering corneal ulcer with dense infiltration. PCR is a valuable tool for diagnosis. Pythium keratitis has a severe and prolonged clinical course. Response to antibiotics is modest and needs to be closely monitored. It can present with inflammation after TPK that mimics the dreaded recurrence of the infection. Pythium keratitis presents variably and can be suspected from typical clinical and microbiological findings. It needs protracted treatment with close follow-up. Although the infection is known to recur in the therapeutic graft, not all recurrences are what they seem.

Keywords: pythium keratitis, recurrent infection, therapeutic keratoplasty

Introduction

Pythium keratitis is an emerging dreaded infection of the cornea due to its poor response to traditional antifungal medication, protracted course, and ocular morbidity.[1] Originally mistaken for a fungus, *Pythium insidiosum* is an oomycete of the Pythiaciae family.[2] Because its cell wall is composed of cellulose, it remains unharmed by antifungals, which target the ergosterol in the fungal cell walls.[3] Therapeutic keratoplasty (TPK) may be the only recourse in recalcitrant infections and, even then, recurrence is quite common.[4] However, it is important to distinguish recurrent infection from other causes of postoperative inflammation, as the treatments are different. We hereby report two cases of *Pythium*

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keratitis for their different presentations, prolonged clinical course, and suspicion of recurrence after TPK.

Case reports

Case 1

A 45-year-old male patient presented with redness, pain, and photophobia of the left eye for 2 weeks. There was an 8 mm corneal stromal infiltrate with reticular edges, reaching the temporal limbus (Fig. 1A). The rest of the ocular examination was normal. Corneal scraping revealed sparsely septate fungus-like filaments with ribbon-like folding. The culture grew *Pythium insidiosum*, which was confirmed by a polymerase chain reaction (PCR) test.

The patient was started on 0.2% fortified linezolid and 1% azithromycin eye drops hourly. The size of the infiltrate increased, and he developed a hypopyon in the second week of medical treatment. The patient then underwent an 11 mm TPK, during which cryotherapy of the host margins and absolute alcohol swabbing of the edges were done to reduce the chances of recurrence. The patient was then continued on topical azithromycin and linezolid hourly reduced

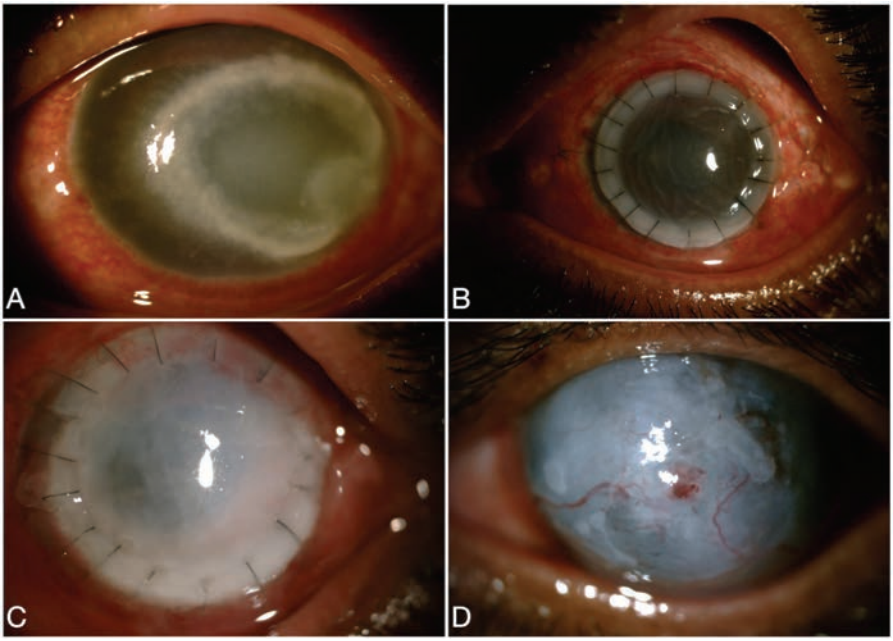

Fig. 1. (A) Pythium keratitis presenting as central corneal infiltrate in the first case. (B) Large therapeutic graft. (C) Steamy graft with cellularity at 3 weeks. (D) Resolved graft inflammation.

to eight times a day after 2 weeks along with azithromycin 500 mg once daily for 10 days. The graft remained clear with epithelial healing in the immediate postoperative period (Fig. 1B).

Three weeks later, he presented with a large epithelial defect, 20% stromal thinning, cloudy cornea, and an exudate behind the graft (Fig. 1C). Suspecting a recurrence, the corneal graft was again scraped for smears, cultures, and PCR, all of which proved negative. In vivo confocal microscopy was performed, which showed only inflammatory cells but no fungus-like filaments, indicating it was not a recurrence. An anterior chamber tap from the exudate was kept as a standby investigation should the condition worsen.

There were no keratic precipitates or other features of graft rejection. With confocal images and PCR proving negative, this was treated as an inflammatory episode with close observation. The antibiotics were reduced and copious lubricants started. After conservative treatment, tissue adhesive and bandage lens were used to heal the epithelial defect with thinning and a small temporary lateral tarsorrhaphy was also done. Topical steroids were given in a tapering dose after epithelial healing. The eye quietened down (Fig. 1D) and the patient subsequently underwent a successful optical keratoplasty 10 months later.

Case 2

A 62-year-old man presented with diminished vision of the right eye for 10 days. He was suspected to have *Pythium* keratitis and was already using 0.2% linezolid and 1% azithromycin eye drops hourly and oral azithromycin 500 mg once a day. The patient owned an aquarium business and dealt with Thai fish.[5] Vision in the right eye was counting fingers close to face. The cornea had a peripheral guttering ulcer 2–3mm wide with concentric spread (5 to 11 o'clock hours). The central edge was sloping and the peripheral edges were steep. There was a dense infiltrate at the base with 60–70% stromal thinning and the central cornea was steamy (Fig. 2A). There was no scleral involvement and no sparing of corneal tissue between the ulcer and the limbus, unlike immune disease. Ocular examination was otherwise normal. Corneal scraping was performed and the smear showed sparsely septate filaments suspicious of *Pythium*. This was confirmed on culture and by a PCR test.

Cyanoacrylate glue was applied over the thinned-out area with a bandage contact lens. The medications were continued. Confocal microscopy showed multiple, linear, hyper-reflective, lattice-like structures in the area of infiltrate, extending up to the posterior stroma suggestive of *Pythium*, which reduced with ongoing treatment. The disease followed a prolonged waxing and waning course. Later, as the symptoms and signs showed healing, topical therapy was reduced to eight times a day and stopped after 2 months.

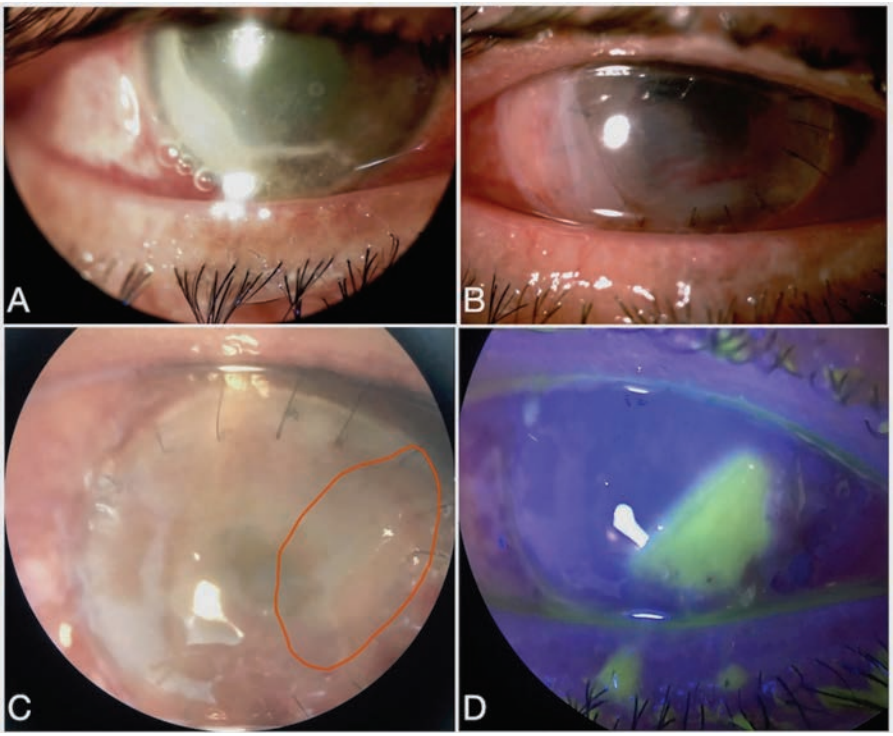

Fig. 2. (A) Pythium keratitis presenting as a peripheral gutter with infiltrate in the second case. (B) Slightly eccentric therapeutic graft. (C) Granular inflammation in the outlined area with early suture loosening. (D) Associated epithelial defect.

The patient presented after 2 weeks of stopping the topical eye drops with increased pain and discomfort. There was a corneal perforation under the glue with mild fibrinous exudate. TPK was performed along with absolute alcohol application and cryotherapy to the host edges to reduce the chance of recurrence (Fig. 2B). The corneal button showed and grew *Pythium insidiosum*. Postoperatively, the medications were continued.

This patient also presented with a 4 mm epithelial defect and aggressive granular inflammation of the graft in the third postoperative week (Fig. 2C and 2D) which, upon investigation, was neither rejection nor recurrence of infection. Topical antibiotics were reduced and loose sutures removed. After epithelial healing, loteprednol 0.5% eye drops and carboxymethylcellulose eye drops helped quieten the eye over the three subsequent months, like the previous case.

Discussion

Pythium keratitis, caused by the oomycete *Pythium insidiosum*, is an aggressive infection, non-responsive to conventional antifungal medication due to the lack of ergosterol in its cell wall.[3] It is diagnosed by its clinical features and laboratory confirmation. The clinical manifestations include reticulated edges of the infiltrate with linear tentacle-like extensions, dot infiltrates, peripheral guttering, and sometimes presence of a hypopyon.[4]

On smear in wet-field microscopy, the organism appears as a T-shaped filament with typical 90° angle, thick cell wall, sparsely septate, and a mass of vehicles inside, showing ribbon-like folding.[1] *Pythium* grows readily on potato dextrose agar and blood agar as flat, feathery-edged, partially submerged, pale colonies with filiform margins.[4] However, it has been suggested that initial scraping samples might not show the organism on smear or culture.[4] Formation of zoospores in aquatic medium is indicative but not pathognomonic of the organism.[3,6] Polymerase chain reaction-based DNA sequencing targeting the internal transcribed spacer region is used to confirm the diagnosis of *Pythium insidiosum*.[1,4] On confocal microscopy, *Pythium* filaments appear as multiple linear, hyper-reflective, well-delineated structures with a width of approximately 4 µm and length of approximately 350 µm. The filaments are X- and Y-shaped, with branching at right angles.[1,2]

Topical linezolid and oral and topical azithromycin have shown modest efficacy in the treatment of *Pythium* keratitis.[7] If the condition worsens on medical management, TPK should be performed. Adjunctive absolute alcohol and cryotherapy to the host margin may help reduce chances of infection recurrence.[3] Although recurrence after TPK is quite common,[3] this should be confirmed with laboratory investigations and the clinical course monitored closely. A sample from the anterior chamber can also be collected for microbiological confirmation when there are postoperative exudates.[1] In our case, which had a small exudate, considering the negative results on scraping and confocal microscopy, TPK was considered should the clinical condition worsen. If the condition worsens after maximum medical management, a repeat TPK should be considered.

The common site for recurrence of *Pythium* keratitis after TPK is in the graft or in the anterior chamber.[3] Since confocal microscopy and microbiology proved there was no re-infection, our patients were treated for the aggressive inflammation of the grafts with epithelial breakdown, mimicking re-infection. These could be attributed to the severe infection, toxic topical medication, and large therapeutic graft surgery with adjuvant treatments.

Conclusion

These two cases demonstrate that *Pythium* keratitis can present as a central reticular or peripheral guttering corneal ulcer with dense infiltration. It has a severe and prolonged clinical course. Response to antibiotics requires close monitoring. Although the infection is known to recur in the therapeutic graft, not all recurrences are what they seem.

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References

1. He H, Liu H, Chen X, Wu J, He M, Zhong X. Diagnosis and Treatment of Pythium Insidiosum Corneal Ulcer in a Chinese Child: A Case Report and Literature Review. Am J Case Rep. 2016;17:982–988.
2. Agarwal S, Iyer G, Srinivasan B, et al. Clinical profile of pythium keratitis: perioperative measures to reduce risk of recurrence. Br J Ophthalmol. 2018;102(2):153–157.
3. Agarwal S, Iyer G, Srinivasan B, et al. Clinical profile, risk factors and outcome of medical, surgical and adjunct interventions in patients with Pythium insidiosum keratitis. Br J Ophthalmol. 2019;103(3):296–300.
4. Hasika R, Lalitha P, Radhakrishnan N, et al. Pythium keratitis in South India: Incidence, clinical profile, management, and treatment recommendation. Indian J Ophthalmol 2019;67(1):42-47.
5. Krajaejun T, Sathapatayavongs B, Pracharktam R, et al. Clinical and epidemiological analyses of human pythiosis in Thailand. Clin Infect Dis. 2006;43(5):569–576.
6. Sharma S, Balne PK, Motukupally SR, et al. Pythium insidiosum keratitis: clinical profile and role of DNA sequencing and zoospore formation in diagnosis. Cornea. 2015;34(4):438–442.
7. Bagga B, Sharma S, Madhuri Guda SJ, et al. Leap forward in the treatment of Pythium insidiosum keratitis. Br J Ophthalmol. 2018;102(12):1629–1633.

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Successful surgical management of large conjunctival nevus in a 10-year-old child with resection and amniotic membrane transplantation

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Abstract
The purpose of this paper is to illustrate a case of large conjunctival nevus in a 10-year-old boy which was successfully treated with surgical excision and amniotic membrane transplant (AMT) reconstruction. The conjunctival nevus was initially noticed by the parents 1 year prior to presentation; they reported it had increased in size over the past 3 months. Slit-lamp examination revealed a pigmented conjunctival nevus measuring 5.5 mm vertically and 6.5 mm horizontally, with well-demarcated margins and presence of an intralesional cyst at the temporal bulbar conjunctiva, involving the limbus and encroaching onto the cornea. Complete resection of the conjunctival lesion and bulbar conjunctival reconstruction were performed. The histopathological examination showed conjunctival nevus. The wound healed well with vision of 6/6 and no recurrence. Surgical resection combined with AMT is a successful and an effective way to treat conjunctival nevus.

Keywords: *amniotic membrane transplantation, conjunctival nevus, ocular surface reconstruction, surgical resection*

Introduction

Conjunctival nevus is the commonest benign lesion of the ocular surface. It is usually found in the bulbar conjunctiva, caruncle, and plica semilunaris. Rarely, it is seen in the fornix, tarsus, or cornea.[1] Amniotic membrane transplantation (AMT) was first performed in humans as a skin substitute to treat an open wound in 1910.[2] AMT promotes epithelial wound healing, shows antibacterial, anti-inflammatory, antiscarring, and antiangiogenic properties.

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To date, there are fewer than 20 publications of conjunctival nevus with AMT worldwide. We report a case of large conjunctival nevus in a child which required AMT following nevus resection.

Case report

A 10-year-old boy was referred to our department due to a pigmented conjunctival lesion in the left eye. The lesion was noticed by the parents 1 year prior to presentation; they reported it had increased in size over the past 3 months. There was no eye pain, redness, blurring of vision, change of color or shape of the conjunctival lesion. Examination revealed vision of 6/9 in the left eye, with an interpalpebral conjunctival mass at the temporal region from 2 to 4 o'clock involving the limbus and encroaching onto the cornea (Fig. 1). It was a lightly pigmented mass, with well-demarcated margins measuring 5.5 mm vertically and 6.5 mm horizontally. There was presence of an intralesional cyst. The anterior chamber, ocular media, and fundus in the left eye were normal. Examination of the right eye was unremarkable.

Due to the recent increase in lesion size as well as cosmetic concerns, the patient and his parents requested surgery; hence, written informed consent for surgical excision and AMT was obtained. Complete surgical resection of the lesion with a tumor safety margin of 3.0 mm was performed using no-touch technique. The large conjunctival defect was reconstructed with single-layer amniotic membrane using the inlay technique, as shown in Fig 2. The amniotic membrane was secured

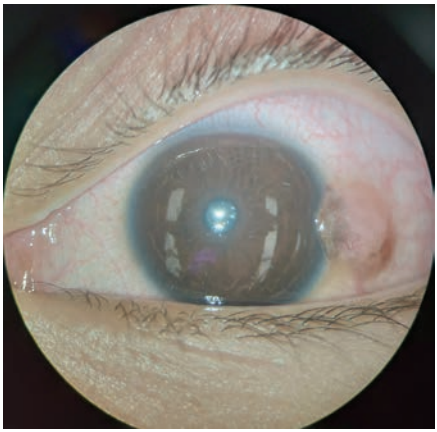

Fig. 1. Conjunctival nevus in the left eye measuring 5.5 mm vertically and 6.5 mm horizontally in the temporal region, involving the limbus and encroaching onto the cornea.

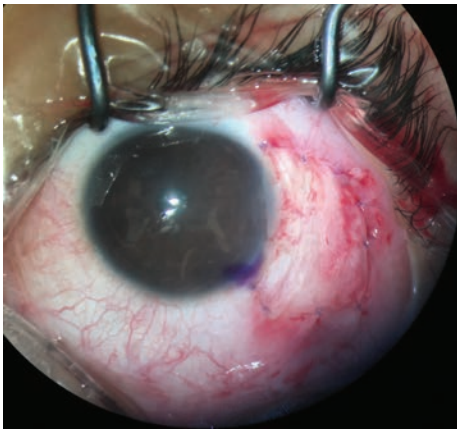

Fig. 2. AMT reconstruction was performed following excision of the conjunctival nevus. Graft was secured using interrupted 8-0 vicryl sutures.

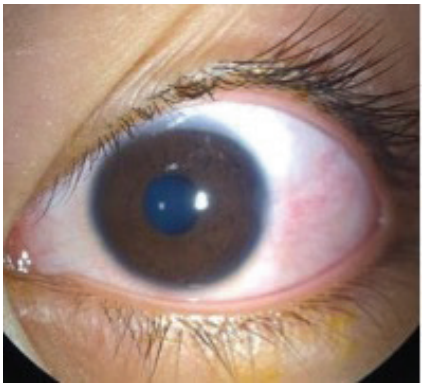

Fig. 3. Slit-lamp examination showed the surrounding host conjunctiva well integrated with graft tissue, with well-healed wound 4 months after surgery. There were no signs of recurrence or complications.

with 8-0 vicryl sutures and a bandage contact lens was applied. The histopathological examination showed conjunctival nevus. Postoperatively, the patient received topical corticosteroids (0.1% dexamethasone ophthalmic solution) and antibiotics (0.5% moxifloxacin hydrochloride ophthalmic solution) every 2 hours daily for a week, which was tapered to every 6 hours daily for the following week. Vision was recovered at 6/6 with a well-healed wound and no recurrence of the lesion was noted (Fig. 3).

Discussion

Conjunctival nevus is the most common benign conjunctival lesion of the ocular surface among pediatric patients. It is most commonly seen in young white individuals, with mean age of patients being 32 years old.[3] It is occasionally noticed at birth but more commonly it develops during childhood or adolescence, as in our patient. It displays a spectrum of variation from darkly pigmented to non-pigmented. Approximately 7% of patients may experience an increase in lesion size and approximately 5% may have a change in the nevus color.[1] Rarely, it can be a precursor of malignant melanoma among the younger age group less than 18 years old. It is of utmost importance to monitor and look for any suspicious or warning signs of malignancy. Clinical characteristics of possible malignant transformation include color variation, margin irregularity, rapid growth, and changes in size, shape, and elevation. If the lesion encroaches onto the cornea, as was the case in our patient, it may lead to amblyopia in children or progress to malignancy.[4]

Local excision of the conjunctival lesion is recommended if there are suspicions

of malignant changes, persistent ocular irritation, or cosmetic concerns; the latter was the case for our patient and his parents. The entire conjunctival lesion was removed via the no-touch technique with a tumor safety margin of 3.0 mm. Complications may develop following resection of the conjunctival lesion, especially if there is a large conjunctival defect after excision. These include scar formation, symblepharon, granuloma, and partial or complete limbal stem cell deficiency.[5] Hence, it is important to select an appropriate and reliable graft for ocular surface reconstruction in order to reduce the risk of these complications. The amniotic membrane is an excellent choice in restoring and reconstructing the ocular surface following large conjunctival lesion excision. The amniotic membrane consists of epithelium, thick basement membrane, and avascular stromal matrix. Its basement membrane exhibits many types of collagen; of these, type VII collagen is also found in conjunctival and corneal basement membranes, thus promoting cellular proliferation, migration, differentiation, and growth.[6] On the other hand, the stromal matrix of the amniotic membrane contains hyaluronic acid and cytokines, which are essential for reduction of inflammation and inhibition of fibrosis. In other words, the amniotic membrane exerts potent anti-inflammatory, antiangiogenic, antifibrotic, and antimicrobial properties on the ocular surface. Therefore, it is increasingly being used to reconstruct the ocular surface for corneal or conjunctival defects and to promote healing of persistent epithelial defects, corneal ulcers, or ocular surface inflammation. In addition, it is rich with stem cells, thus promoting conjunctival and corneal epithelialization and migration of the stem cells without requiring any limbal stem cell transplant, especially in our case, where the limbus is involved. Rarely, pyogenic granuloma originating from sutures, hematoma beneath the graft, and hypopyon secondary to an immune reaction may be observed with AMT itself.[7] However, no such complications were seen in our patient. A surgical excision combined with reconstruction via AMT is thus effective and economical for the treatment of large conjunctival lesions.[8]

In conclusion, early detection, proper diagnosis, and follow-up of conjunctival nevus are essential, especially in pediatric patients, to avoid amblyopia, persistent ocular irritation, and to detect any signs of malignant transformation. Urgent biopsy should be performed if there is any suspicion of malignancy. AMT is an excellent and reliable option for ocular surface reconstruction if there is a large conjunctival defect after excision of conjunctival lesion.

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Informed consent was taken from the patient's parents for publication of this articles and accompanying photographs.

References

1. Shields CL, Shields JA. Conjunctival Tumors in Children. Curr Opin Ophthalmol. 2007;18(5):351–360.
2. Davis JS. Skin transplantation. Johns Hopkins Hosp Rep. 1910;15:307–396.
3. Artur Zembowicz, Rajni V. Mandal, Pitipol Choopong. Melanocytic Lesions of the Conjunctiva. Arch Pathol Lab Med. 2010;134:1785-1792.
4. Khan L, Malukani M, Saxena A. Conjunctival Lesions: When Should We Perform Biopsy? Nepal J Ophthalmol. 2017;9(2):160-169.
5. Goktas SE, Katircioglu Y, Celik T, Ornek F. Surgical Amniotic Membrane Transplantation After Conjunctival and Limbal Tumor Excision. Arq Bras Oftalmol. 2017;80(4):242-246.
6. Malak TM, Bell SC. Differential expression of the integrin subunits in human fetal membranes. J Reprod Fertil. 1994;102(2):269-276.
7. Ahmad MS, Frank GS, Hink EM, Palestine AG, Gregory DG, McCourt EA. Amniotic Membrane Transplants in the Pediatric Population. J AAPOS. 2017;21(3):215-218.
8. Rock T, Bosmuller HC, Bartz-Schmidt KU, Rock D. Surgical Management of a Conjunctival Nevus with Amniotic Membrane Transplantation. Int Med Case Rep J. 2018;11:161-165.

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Isolated cortical vein thrombosis complicating orbital cellulitis

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Abstract

Background: *Orbital cellulitis is characterized by the infective inflammation of orbital structures, usually posterior to the orbital septum. Extension of infection from the paranasal sinuses is the most common etiology for orbital cellulitis. Intracranial complications of orbital cellulitis include meningitis, subdural empyema, brain abscess, and cavernous sinus thrombosis.*

Case presentation: *A 33-year-old man presented with acute onset of foul-smelling mucopurulent nasal discharge and swelling of the left eye followed by altered sensorium. On examination of the left eye, chemosis, eyelid edema, and proptosis were present. Computed tomography (CT) of the brain revealed non-axial left proptosis with inflammatory reticulation in the intra- and extraconal fat alongside sinusitis. Magnetic resonance imaging (MRI) of the brain confirmed the CT findings and additionally showed meningitis and subdural empyema along the left frontoparietal convexity with parenchymal signal changes, suggesting venous infarction in the left frontal lobe. Susceptibility weighted imaging (SWI) confirmed the thrombus in the frontal polar vein on the left side, suggesting the diagnosis of septic isolated septic cortical venous thrombosis (ICVT) as a complication of orbital cellulitis. Cerebrospinal fluid study showed polymorphonuclear cell pleocytosis with elevated protein and lowered sugar. Blood and conjunctival swab cultures were negative. He was subsequently treated with intravenous broad-spectrum antibiotics and antifungals to which he responded and was discharged in stable condition.*

Conclusions: *Our case highlights the presentation of septic ICVT complicating orbital cellulitis and paranasal sinusitis. It also underscores the higher sensitivity of SWI as a crucial tool in diagnosing ICVT. Appropriate and prompt medical treatment in orbital cellulitis can prevent further complications.*

Keywords: *cortical vein thrombosis, empyema, meningitis, orbital cellulitis*

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Introduction

Orbital cellulitis is a frequently encountered clinical condition that is potentially vision and life-threatening. The routes for the infection of orbital contents include the contiguous extension (from infected sinuses, dacryocystitis) and hematogenous spread of the systemic infections.[1] It frequently affects children and young adults. Typical clinical features include acute onset proptosis, lid edema, chemosis, and painful ophthalmoplegia. Left untreated, it can cause dreaded complications such as vision loss, meningitis, subdural empyema, brain abscess, and cavernous sinus thrombosis.[2,3] Imaging plays a crucial role in orbital cellulitis, adding not only certainty to the diagnosis but also providing information regarding the extent of spread. Being superior in its soft-tissue contrast, magnetic resonance imaging (MRI) is the preferred modality.[4] Isolated cortical vein thrombosis (ICVT) is an infrequent disease with etiologies ranging from hypercoagulable state, infections, and intracranial hypotension.[5,6] On account of its varied clinical presentation (due to differences in the afflicted anatomical region) and lack of gold-standard investigations, ICVT is an under-reported entity and often overlooked.[5,7] We herein present our observations in a case of ICVT that complicated orbital cellulitis.

Case report

A 33-year-old man presented with foul-smelling mucopurulent nasal discharge for 15 days with gradually progressive swelling of the left eyelid, painful ocular movement, excessive lacrimation and reddening of the left eye for 2 days along with altered sensorium for 1 day. He was not a known diabetic or hypertensive. Pupils were equal and reactive bilaterally. Both fundi were normal on examination. Investigations revealed severe leukocytosis (27.3 x 1000/ µL) with neutrophilia and thrombocytosis. Testing for liver function, renal function, and serum electrolytes was normal. Cerebrospinal fluid (CSF) study showed a massive cellular pleocytosis of 9,600 cells/mm^3 with 85% polymorphonuclear cells. CSF gram stain showed no evidence of bacteria. A high protein (183 mg/dl), high lactate (64.5 mg/dl), and normal glucose (70 mg/dl) were the other findings. Blood and conjunctival swab cultures were negative.

Computed tomography (CT) showed proptosis in the left eye with thickening of the preseptal soft tissue, as well as intraconal and extraconal orbital fat. Mucosal thickening with hyperattenuation of ethmoid air cells was also noted (Fig. 1a). MRI of the brain confirmed the same with a better demonstration of the inflammatory process and an evolving abscess involving the extraconal and intraconal fat as well as the extraocular muscles with ethmoid and frontal sinusitis (Fig. 1b-f). The diffusion-weighted image of the orbits showed restriction (Fig. 1c and 1d), suggesting abscess formation. The postcontrast study revealed diffuse pachymeningeal and leptomeningeal enhancement along the left frontoparietal region,

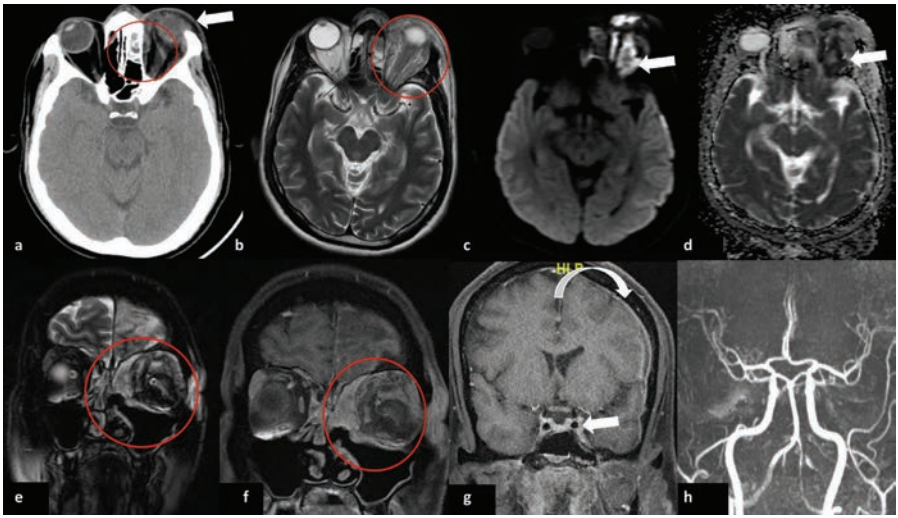

Fig. 1. (a) Axial computed tomography of the orbit showing proptosis of the left eye with thickened preseptal soft tissue (white arrow). The adjoining ethmoid air cells show hyperattenuating mucosal thickening with inflamed intraorbital fat (red circle) adjacent to the lamina papyracea. (b) Axial T2 weighted imaging (T2WI) showing inflamed intra- and extraconal fat of the left orbit with proptosis and thickened preseptal soft tissue (red circle). Note the mucosal thickening of the left ethmoid air cells with relative hypointense signal (black arrow). (c, d) Diffusion-weighted imaging and apparent diffusion coefficient (ADC) maps showing restricted diffusion (white arrows) in the infective soft tissue pointing towards abscess formation. (e, f) Coronal T2WI fat-suppressed image (e) and coronal T1WI postcontrast (T1PC) (f) showing infective soft tissue extending from the left ethmoid air cells into the left orbit (red circles). (g) T1PC at the cavernous sinus level demonstrating normal appearance of sinuses (white arrow), thereby excluding cavernous sinus thrombosis. Note the pachymeningeal enhancement (curved arrow) along the cerebral convexity. (h) Time of flight (TOF) MR angiography showing normal morphology and course of the intracranial arteries.

suggesting meningitis. The cavernous sinuses were normal (Fig. 1g). MR angiography (MRA) revealed normal course and morphology of the intracranial arteries (Fig. 1h). Cortical/juxtacortical expansile, T2/FLAIR hyperintense signal changes with foci of blooming, suggestive of hemorrhagic venous infarct involving the left anterior frontal pole, anterior cingulate gyrus, and superior frontal gyrus were seen. Subdural empyema was noted along the left frontoparietal convexity (Fig. 2a-d). Susceptibility weighted imaging (SWI) showed accentuated blooming with a serpentine morphology in the sulcal space adjoining the infarct traceable until the superior sagittal sinus, suggestive of cortical venous thrombosis (Fig. 2e and 2f). Based on the above findings, the diagnosis of left orbital cellulitis (possibly of fungal or bacterial etiology), complicated by left frontal polar cortical vein thrombosis, hemorrhagic venous infarction, and subdural empyema was made.

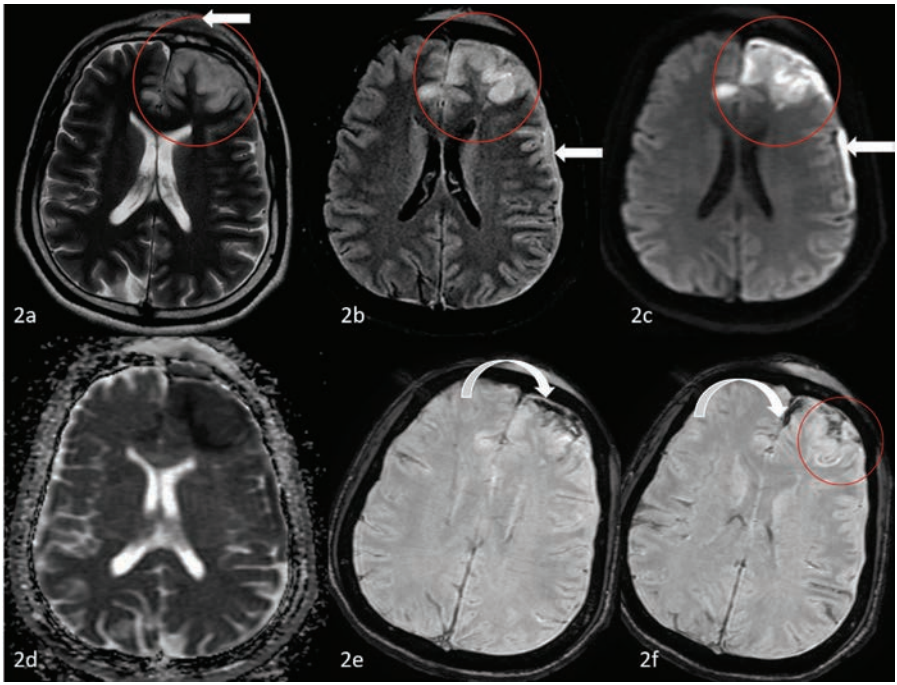

Fig. 2. (a, b) Axial T2 weighted imaging (a) and FLAIR (b) showing hyperintensity involving the left frontal lobe (red circle) with inflamed soft tissue in the subgaleal region (white arrow). Note the subdural fluid collection along the left frontoparietal region (white arrow in 2b). (c, d) Axial diffusion-weighted images and apparent diffusion coefficient images showing diffusion restriction in the involved area, suggestive of acute infarction. Diffusion restriction is also noted in the subdural fluid collection, suggestive of empyema (arrow in c). (e, f) Susceptibility weighted imaging showing serpentine hypointense (susceptibility) structure running in the sulcal space adjacent to the infarct, indicative of thrombosed vein (curved arrows). Note the multiple punctate hemorrhagic foci within the infarcted area (red circle in f).

The patient was treated with a triple injectable antibiotic regimen of ceftriaxone (4 gm/day), vancomycin (1.5 gm/day), and metronidazole (1.5 gm/day) along with injectable hydrocortisone and antifungal amphotericin B (5 mg/kg/day). He responded to treatment and was discharged in stable condition.

Discussion

Orbital cellulitis is one of the most common ophthalmological emergencies, which unless treated carries the risk of permanent vision loss and intracranial complications.[3] It commonly arises as a consequence of paranasal sinus infections. Less common etiologies include dacryocystitis, eyelid infections, and

postsurgical complications. Rarer still are hematogenous origins and penetrating ocular trauma.[1,2] It affects children and young adults predominantly. Causative agents vary with age of presentation. In children, the causative microbe is usually a single pathogen among *Staphylococcus aureus*, *Streptococci pyogenes*, and *Streptococcus pneumoniae*. In adults, orbital cellulitis is usually of polymicrobial origin.[2] Chandler *et al.* classified orbital cellulitis into five different stages in increasing order of severity and morbidity.[8] Group I is preseptal cellulitis, while Group II presents an inflammatory process extending into the orbit. Surgical management is warranted in Groups III and IV, which are characterized by abscess formation in the subperiosteal and intraorbital compartments. Group V is characterized by cavernous sinus thrombosis.[1,8]

Our index case also had a history of mucopurulent nasal discharge preceding the typical clinical features of orbital cellulitis, as has been cited earlier. Infrequently, in patients with underlying immunocompromised state such as retroviral infection and diabetes mellitus, signs of inflammation may be subtle.[1] Diagnosis is often made based on history and examination findings. Imaging of the orbits, brain, and paranasal sinuses is usually required to define anatomical extensions, and more importantly, intracranial extension. Imaging also serves as a handy tool to rule out other mimics and unsuspected foreign bodies. Sinus X-rays can show air-fluid levels within the paranasal sinuses. High-frequency probe ultrasound may help in demonstrating orbital abscess. Contrast-enhanced CT is the mainstay of imaging in orbital cellulitis. CT interpretation should be done after careful analysis of both soft tissue and bone window. On account of its superior soft-tissue resolution, MRI overscores CT in terms of demonstrating the intracranial and cavernous extensions of the disease pathology, which carries worse prognosis and warrants emergency measures.[4] Diffusion-weighted imaging (DWI), as has been demonstrated in our case, allows confident diagnosis of an abscess and may obviate the need to use intravenous gadolinium-based contrast media.[4]

Medical management with intravenous broad-spectrum antibiotic therapy is advocated.[1,2] Surgical treatment is offered to patients who fail to respond to medical therapy, those with intraorbital foreign body, and those with systemic sepsis.[1] Intracranial complications of orbital cellulitis include meningitis, subdural empyema, abscess, and cavernous sinus thrombosis.[1,2,3] In our case, blood and conjunctival swab cultures were negative. Hyperattenuation within the ethmoid air cells coupled with the T2 hypointense signal raised the possibility of a fungal etiology.[9] Our patient received intravenous broad-spectrum antibiotics as well as antifungals, to which he responded with a gradual reduction in proptosis, swelling, and redness of the eyelid. Cavernous sinus thrombosis has been reported as a complication of paranasal sinusitis as well as orbital cellulitis.[1,2,10,11] Direct as well as indirect venous drainage of orbital and facial structures into the

cavernous sinus and trabeculated nature of the sinus traps emboli and microbes, predisposing its involvement.[12] To the best of our knowledge, isolated septic ICVT with concomitant hemorrhagic venous infarction in the background of due orbital cellulitis has not been reported in the literature. In our case, a large hemorrhagic infarct was seen involving the left frontal polar region, anterior portions of the cingulate gyrus, and superior frontal gyrus; it was non-territorial in distribution (distinguishing it from arterial infarct). Additionally, the thrombosed frontal polar vein was seen on SWI as a serpentine cord-like structure running adjacent to the sulcal space, thus confirming the diagnosis. As with our case, SWI has been proven handy in diagnosing this rare phenomenon of ICVT.[5]

We wish to reflect on the origin of frontopolar vein thrombosis. Vascular complications are a relatively known phenomenon in cases of meningitis, particularly of tubercular origin, the most frequent being perforator arterial infarcts.[13] Arterial damage found in meningitis can be infiltrative, proliferative, or necrotizing. Similar changes can be seen in the cortical veins.[13] We thus postulate that the focal left frontal meningitis secondary to the osteodural breach that complicated the orbital cellulitis in our case could have caused septic thrombophlebitis of the frontal polar vein. Alternatively, the potential of subdural empyema as an inciting agent leading to ICVT also ought to be considered. Subdural empyema causing dural venous sinus thrombosis has been reported earlier as a complication in up to 10% of the cases.[14] Diploic veins serving as the route of extension of infection from the paranasal sinusitis culminating in cortical venous thrombosis is known. Such a diploic venous route of transmission of the infection cannot be ruled out in the index case.

Treatment of septic cerebral venous thrombosis (CVT) includes maintaining optimal hydration, antimicrobial therapy targeted towards the causative agent, and surgical debridement in appropriate clinical settings. Consensus about the use of anticoagulant and corticosteroids in septic CVT is lacking.[12,15]

To conclude, our case highlights the presentation of septic ICVT complicating orbital cellulitis and paranasal sinusitis. It also underscores the higher sensitivity of SWI as a crucial tool in diagnosing ICVT. Appropriate and prompt medical treatment in orbital cellulitis can prevent further complications.

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References

1. Hegde R, Sundar G. Orbital cellulitis: A review. TNOA J Ophthalmic Sci Res. 2017;55(3):211-219.
2. Chaudhry IA, Al-Rashed W, Arat YO. The hot orbit: orbital cellulitis. Middle East Afr J Ophthalmol. 2012;19(1):34–42.
3. Chaudhry IA, Shamsi FA, Elzaridi E, Al-Rashed W, Al-Amri A, Al-Anezi F, Arat YO, Holck DE. Outcome of treated orbital cellulitis in a tertiary eye care center in the middle East. Ophthalmology. 2007;114(2):345-354.
4. Sepahdari AR, Aakalu VK, Kapur R, et al. MRI of orbital cellulitis and orbital abscess: the role of diffusion-weighted imaging. Am J Roentgenol. 2009;193(3):W244-50.
5. Singh R, Cope WP, Zhou Z, De Witt ME, Boockvar JA, Tsiouris AJ. Isolated cortical vein thrombosis: case series. J Neurosurg. 2015;123(2):427-433.
6. Stam J. Thrombosis of the cerebral veins and sinuses. N Engl J Med. 2005;352(17):1791-1798.
7. Boukobza M, Crassard I, Bousser MG, Chabriat H. MR imaging features of isolated cortical vein thrombosis: diagnosis and follow-up. Am J Neuroradiol. 2009;30(2):344-348.
8. Chandler JR, Langenbrunner DJ, Stevens ER. The pathogenesis of orbital complications in acute sinusitis. The Laryngoscope. 1970;80(9):1414-1428.
9. Aribandi M, McCoy VA, Bazan III C. Imaging features of invasive and noninvasive fungal sinusitis: a review. Radiographics. 2007;27(5):1283-1296.
10. Chang YS, Chen PL, Hung JH, et al. Orbital complications of paranasal sinusitis in Taiwan, 1988 through 2015: Acute ophthalmological manifestations, diagnosis, and management. PloS One. 2017;12(10):e0184477.
11. Schupper AJ, Jiang W, Coulter MJ, Brigger M, Nation J. Intracranial complications of pediatric sinusitis: identifying risk factors associated with prolonged clinical course. Int J Pediatr Otorhinolaryngol. 2018;112:10–15.
12. Khatri IA, Wasay M. Septic cerebral venous sinus thrombosis. J Neurol Sci. 2016;362:221–227.
13. Chatterjee D, Radotra BD, Vasishta RK, Sharma K. Vascular complications of tuberculous meningitis: An autopsy study. Neurol India. 2015;63(6): 926–932.
14. Konar S, Gohil D, Shukla D, et al, Arimappamagan A, Devi BI. Predictors of outcome of subdural empyema in children. Neurosurg Focus. 2019;47(2):E17.
15. Kojan S, Al-Jumah M. Infection related cerebral venous thrombosis. J Pak Med Assoc. 2006;56(11):494–497.

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