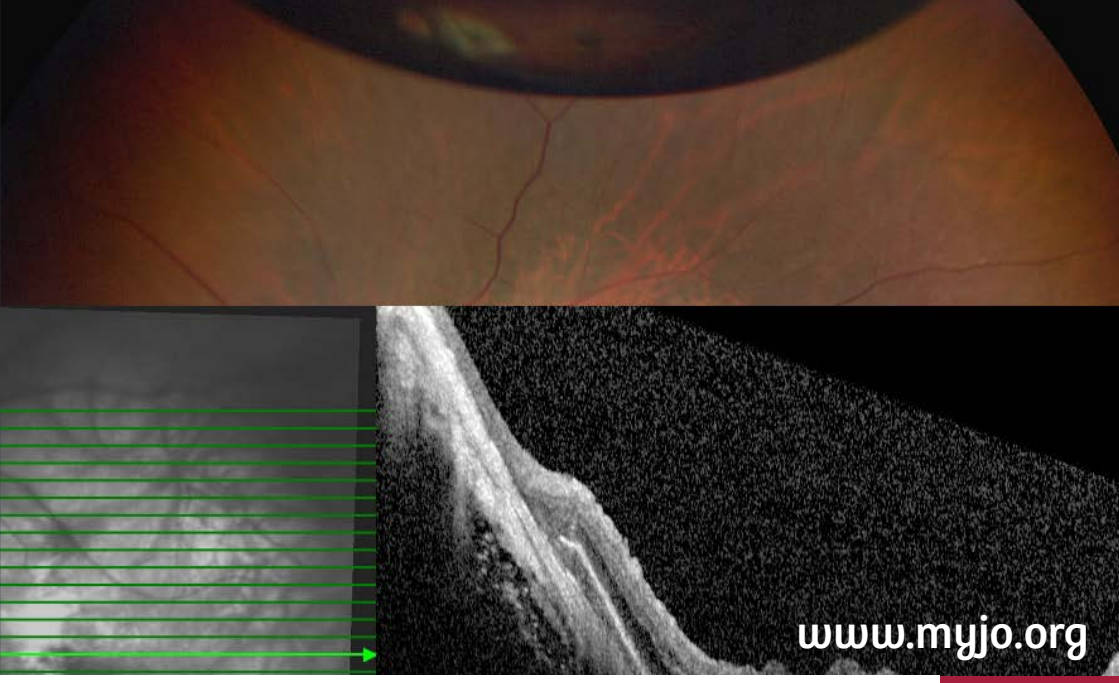

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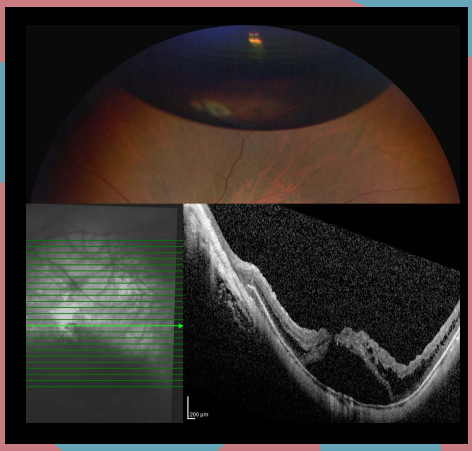

ABOUT THE COVER IMAGE

Hidden holes in high myopia from the personal collection of Professor Dr Mae-Lynn Catherine Bastion, Department of Ophthalmology, Faculty of Medicine, Universiti Kebangsaan Malaysia.

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Malaysian Journal of Ophthalmology

Editorial
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Myopia: from refractive error to a public health challenge

Norazah **Abdul Rahman**

Malaysia Advocates of Myopia Prevention (MAMP), Kuala Lumpur, Malaysia
https://www.myopiamalaysia.com/

Myopia, once considered a minor refractive issue easily corrected with glasses, is increasingly recognised as a serious public health challenge. High myopia, in particular, poses a significant risk for irreversible visual impairment and blindness. The rising prevalence of myopia locally, along with its long-term health and economic impacts, calls for a re-evaluation of how we approach this condition in this series.

Current projections indicate that by 2050, nearly half of the global population will be myopic, with about 10% experiencing high myopia.[1] While East and Southeast Asia are the most affected regions, rising rates in Europe, North America, and urbanising areas highlight myopia's global significance.[2]

This surge in myopia cannot be explained by genetics alone. Environmental and behavioural factors, such as intense educational pressures, prolonged near work, increased screen time, and reduced outdoor activities, are significant contributors.[3] These modifiable risk factors suggest that myopia is largely preventable, marking a crucial shift in perspective for healthcare providers and policymakers.

The urgency to prioritize myopia as a public health issue is underscored by its complications. High myopia elevates the risk of serious conditions such as myopic maculopathy, retinal detachment, glaucoma, and early-onset cataracts, which can lead to irreversible vision loss. As the population ages, the cumulative burden of these complications will increase, further straining healthcare systems. Additionally, myopia leads to substantial economic costs due to ongoing dependence on corrective lenses, regular monitoring, and treatment of related conditions, as highlighted by Choo *et al.*

Recent advancements have shifted myopia management from simple correction to active disease control. Increased outdoor exposure has been consistently linked to lower myopia incidence, representing a straightforward and effective public health intervention.[4] In clinical practice, methods such as optical strategies modifying peripheral defocus like myopic spectacles, multifocal contact lens, orthokeratolo-

Correspondence: Dr Norazah Abdul Rahman, Chairperson, Malaysia Advocates of Myopia Prevention (MAMP), Kuala Lumpur, Malaysia.
E-mail: azahx5@gmail.com

gy, and low-dose atropine eye drops that is thought to work on dopamine receptors, have shown promising results in slowing myopia progression and axial elongation. These interventions can significantly reduce the lifetime risk of vision impairment when implemented early.[4]

Despite the growing evidence supporting these approaches, myopia control is still under-utilised in routine practice, particularly outside specialised clinics.[5] Barriers include limited awareness among healthcare providers and parents, concerns about costs and accessibility, and the lack of universally accepted clinical guidelines.

To effectively tackle the myopia epidemic, a multifaceted strategy is essential. Responses must integrate public health initiatives, educational policies, and school-based programs that promote outdoor activities and visual hygiene. In Malaysia, the Malaysian Advocacy for Myopia Prevention (MAMP) is a national initiative established in 2019 aimed at addressing the increasing burden of myopia through awareness campaigns, early detection, and evidence-based interventions. By collaborating with clinicians, educators, researchers, and policymakers, MAMP seeks to protect the visual health of Malaysian children and future generations.

In response to the variability in myopia management and the rapid introduction of new interventions, MAMP is developing a national myopia consensus. This initiative aims to provide practical, context-specific guidance based on the best available evidence and local epidemiology.

In conclusion, myopia has transformed from a minor refractive error into a progressive, vision-threatening disease with significant public health implications. Recognising myopia as both preventable and treatable is crucial for mitigating its long-term effects. It is imperative that we take coordinated clinical and public health actions to address myopia—before blurred vision leads to blindness.

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Editorial – Position paper
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Joint position statement: Strengthening eye screening for newborns and pre-schoolers in Malaysia

The Malaysian Society of Ophthalmology, the College of Ophthalmologists, the Malaysia Advocacy for Myopia Prevention, the Association of Malaysian Optometrists, the Malaysian Association of Practising Opticians, and the Malaysian Paediatric Association firmly recommend an all-of-Malaysia effort to strengthen eye screening for all children nationwide in Malaysia, especially for newborns aged 0–30 days and for preschoolers aged 5–6. Our position is supported by colleagues from the Asia-Pacific Paediatric Retina Association (APPREA).

Normal vision is important to the development and quality of life in children as well as to their lifelong education, social skills, and contribution to the national economy. Early identification and treatment of vision impairment can identify and manage visual impairment and its related human, health, economic, educational and societal burdens. Therefore, we strongly advocate a nationwide eye screening guideline and comprehensive nationwide program to safeguard the vision and health of newborns and preschoolers, our youngest citizens.

Vision impairment is common in children

Ocular conditions such as retinopathy of prematurity (ROP), congenital cataracts, refractive errors, strabismus, and amblyopia are significant causes of childhood blindness and visual impairment. Data from 2023 from the Ministry of Health estimated the prevalence of ROP to be 12.9% among premature infants < 32 weeks in Malaysia. A 2016 study in Malaysia showed that visual impairment was present in 12.5% of children aged 5-6 years old, with 61.0% having visual impairment in both eyes. These numbers are staggering and could even be under-reported as Malaysia does not have a nationwide eye screening program.

Left untreated, these conditions can lead to irreversible vision loss and developmental delays, which in turn lead to educational gaps and a long-term reduction in national economic output, in addition to the severe human cost, suffering, and burdens of vision loss.

Current practices in Malaysia are not adequate: we must learn from international practices

Newborn eye screening is not consistently implemented in Malaysia, and preschool vision screening is often limited to urban areas. A comprehensive nationwide program is essential to address these gaps and reduce the lifelong burden of preventable blindness.

Several countries have successfully implemented newborn and preschool eye screening programs:

- **Canada, Italy, the Netherlands and the United States:** Initiated vision screening during infancy throughout the schooling period**.**
- **Canada**: Targets infants and children aged 3-5 years old, screened by nurses and trained staff.
- **The Netherlands**: Targets 1-month old infants to children aged 6 years old, screened by physicians or nurses.
- **The United Kingdom**: The UK National Screening Committee recommends vision screening for children aged 4–5 years old, under the responsibility of local authorities.
- **India**: The Rashtriya Bal Swasthya Karyakram (RBSK), launched in 2013, includes vision screening for children.

These programs underscore the feasibility and benefits of systematic screening in diverse healthcare settings, including middle-income countries, offering valuable models for Malaysia's own national program.

Implementing a nationwide eye screening program for children has three important benefits

We believe that there are three important benefits from a nationwide eye screening program for children. One, we can improve health outcomes for children. Early detection and treatment of eye disorders can prevent lifelong visual impairment, reducing the burden on individuals, families, and the healthcare system.

Two, we can help deliver educational and developmental gains for children. Good vision is crucial for learning and development during schools and during a lifelong career. Managing visual impairment early improves educational attainment and future productivity.

Three, we can achieve economic benefits. In the short-term, preventing childhood blindness and visual impairment leads to substantial cost savings. Studies from the Netherlands, England, Wales and Romania showed that screening for amblyopia in children aged 4–5 years old are cost-effective in all 4 countries. In the long-term, healthcare costs of more expensive curative interventions can be reduced, and economic gains from higher productivity can be realized.

We recommend an inter-agency task force for good vision in children

The health of children in Malaysia is multi-agency, involving the government agencies responsible for health, education, community development, rural development, and economy. Therefore, we recommend creating an inter-agency task force (IATF) dedicated to good vision in children.

This IATF can conduct relevant stakeholder engagement to co-create the roadmap for a nationwide eye screening program for children, including mobilising political and financial capital. The Health Ministry can take the lead to pilot in specific locations to assess the feasibility and plan for a nationwide scale-up. The Education Ministry can launch public awareness initiatives together with NGOs and scientific associations, on the importance of eye screening for preschoolers.

By taking these steps, Malaysia can build a robust and sustainable vision screening program that ensures every child has the opportunity to see a brighter future.

Manoharan Shunmugam, MBChB (UK), MRCS (Ed), FRCOphth (London), AM (Mal)
Founding Member, Asia-Pacific Paediatric Retina Association (APPREA)

Professor Dr Liza Sharmini Ahmad Tajudin, MBBS (Mal), MMed (Ophthal) (USM), PhD (UK), FAMM
President, Malaysian Society of Ophthalmology (MSO)

Professor Dr Shatriah Ismail, BSK, AMK, MD, MMed (Ophthal), FAMM (Mal), FAMM (Sg)
President, College of Ophthalmologists, Academy of Medicine of Malaysia

Dr Norazah Binti Abdul Rahman, MBBS (UM), MMed (Ophthal) (UM), CCFT (Mal)
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Adjunct Lecturer, UTAR School of Medicine

Dr Sunder Ramasamy, MBBS (MAHE), MSOphthal (UKM), FRCS (Glasgow), FICO, CCFT, AM (Mal)
Consultant Paediatric Ophthalmologist, OasisEye Specialists

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Review article
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Short review of myopia and its impact in the COVID-19 era

Priscilla Peixi **Choo**[1], Mae-Lynn Catherine **Bastion**[1,2], Azlindarita Aisyah **Mohd Abdullah**[3], May May **Choo**[4], Yee Fong **Choong**[5], Duratul **Ain Hussin**[6], Fazilawati A **Qamarruddin**[7], Malisa **Ami**[8], Miswan **Muiz Mahyuddin**[9], Norazah **Abdul Rahman**[10], Sunder **Ramasamy**[11,12], Shin Ying **Tang**[5], Safinaz **Mohd Khialdin**[1,2,13]

[1]Department of Ophthalmology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Cheras, Kuala Lumpur, Malaysia; [2]Department of Ophthalmology, Hospital Canselor Tuanku Muhriz, Jalan Yaacob Latif, Kuala Lumpur, Malaysia; [3]Department of Ophthalmology, Gleneagles Hospital, Kuala Lumpur, Malaysia; [4]Department of Ophthalmology, University of Malaya, Kuala Lumpur, Malaysia; [5]International Specialist Eye Center (ISEC), Kuala Lumpur, Malaysia; [6]Allied Health Sciences Division, Ministry of Health Malaysia, WP Putrajaya, Malaysia; [7]Department of Ophthalmology, Hospital Tengku Ampuan Rahimah, Klang, Selangor, Malaysia; [8]Sunway Medical Centre Damansara, Petaling Jaya, Selangor, Malaysia; [9]Optimax Eye Specialist Centre, Petaling Jaya, Selangor, Malaysia; [10]Department of Ophthalmology, Ara Damansara Medical Centre, Shah Alam, Selangor, Malaysia; [11]Department of Ophthalmology, Thomson Hospital Kota Damansara, Petaling Jaya, Selangor, Malaysia; [12]OasisEye Specialist, Bangsar South, Kuala Lumpur, Malaysia; Members of Malaysia Advocacy for Myopia Prevention (MAMP) of the Paediatric Special Interest Group, Malaysian Society of Ophthalmology; [13]Hospital Tunku Ampuan Besar Tuanku Aishah Rohani Hospital Pakar Kanak-Kanak UKM (Hospital TABTAR), Jalan Yaacob Latif, Kuala Lumpur, Malaysia

Abstract

Myopia, or near-sightedness, is a common childhood eye condition where images are focused in front of the retina, often due to excessive eye length or lens curvature. If uncorrected, myopia can lead to severe visual impairment or blindness. The global prevalence of myopia is rising, expected to affect nearly half of the world's population by 2050, with significantly higher rates in East and Southeast Asia compared to other regions. In Malaysia, studies show varying prevalence rates among different

Correspondence: Safinaz Mohd Khialdin, MD (UKM), MSurg Ophthal (UKM), Department of Ophthalmology, Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Cheras, Kuala Lumpur, Malaysia.
E-mail: safinaz@hctm.ukm.edu.my

ethnic groups, with ethnic Chinese children exhibiting the highest rates. Myopia negatively impacts quality of life, affecting children's academic performance, social interactions, and mental health. Economic burdens are substantial, with high costs for corrective measures and myopia-related complications, particularly in older adults. The COVID-19 pandemic exacerbated myopia progression due to increased screen time and reduced outdoor activities during lockdowns. Studies suggest that near work, especially using smartphones and computers, significantly contributes to myopia development, while outdoor activities have a protective effect. To mitigate myopia progression, especially during pandemics, it is crucial for parents to promote balanced eye habits, encourage outdoor activities, and monitor digital device usage. Treatments such as defocus incorporated multiple segments (DIMS) lenses, atropine eye drops, and maintaining good eye habits can slow progression. Despite limited evidence, eye exercises may also be beneficial. Proactive measures and alternative treatments are recommended when prolonged confinement is necessary.

Keywords: COVID-19, Malaysia, myopia, quality of life

Ulasan ringkas mengenai miopia dan kesannya dalam era COVID-19

Abstrak

Miopia atau rabun jauh merupakan satu keadaan mata yang lazim di kalangan kanak-kanak, di mana imej difokuskan di hadapan retina, disebabkan oleh pemanjangan bola mata atau kelengkungan kanta yang berlebihan. Sekiranya tidak dirawat, miopia boleh menyebabkan gangguan penglihatan yang teruk atau kebutaan. Prevalens miopia di peringkat global menunjukkan peningkatan yang ketara dan dijangka menjejaskan hampir separuh populasi dunia menjelang tahun 2050, dengan kadar yang jauh lebih tinggi dilaporkan di Asia Timur dan Asia Tenggara berbanding rantau lain. Di Malaysia, kajian menunjukkan kadar prevalens yang berbeza di antara kumpulan etnik, dengan kanak-kanak berketurunan Cina mencatatkan kadar tertinggi.

Miopia memberi kesan negatif terhadap kualiti hidup kanak-kanak termasuk prestasi akademik, interaksi sosial serta kesejahteraan mental. Beban ekonomi turut meningkat disebabkan oleh kos pemulihan penglihatan dan komplikasi berkaitan miopia, terutamanya dalam kalangan warga emas. Pandemik COVID-19 telah mempercepatkan perkembangan miopia akibat peningkatan masa penggunaan skrin dan pengurangan aktiviti luar semasa tempoh sekatan perjalanan. Beberapa kajian menunjukkan bahawa kerja jarak dekat, khususnya penggunaan telefon

pintar dan komputer, merupakan faktor utama perkembangan miopia, manakala aktiviti luar memberi kesan perlindungan.
Bagi membendung kelanjutan miopia, khususnya semasa tempoh pandemik, ibu bapa disarankan untuk menggalakkan amalan penjagaan mata yang seimbang, meningkatkan masa aktiviti luar dan memantau penggunaan peranti digital di kalangan kanak-kanak. Rawatan seperti kanta Defocus Incorporated Multiple Segments (DIMS), titisan mata atropin serta amalan penjagaan mata yang baik didapati berkesan dalam memperlahankan kadar kelanjutan miopia. Walaupun bukti saintifik masih terhad, senaman mata juga berpotensi memberi manfaat tambahan. Langkah pencegahan proaktif dan penggunaan rawatan alternatif amat digalakkan sekiranya tempoh sekatan perjalanan berpanjangan diperlukan.

Kata kunci: COVID-19, Malaysia, miopia, kualiti hidup

Myopia

Myopia, also known as short-sightedness and near-sightedness, is a defect of the eye developed during childhood where the image is focused in front of the retina due to strong cornea or lens curvature, or the eye is too long. Myopia, if uncorrected or under-corrected refractive error, is considered as one of the leading causes of blindness and vision impairment in the world.[1] Myopia is defined by a spherical equivalent (SE) of ≤ -0.5 dioptres (D), whereas high myopia is defined by SE worse than -5.0 D.[2] Pathological myopia occurs with more than -8.0 D. Higher levels of myopia are also associated with the risk of adverse ocular changes and sight-threatening diseases, such as glaucoma, retinal detachment, and macular holes, leading to uncorrectable visual impairment or blindness.[3] The current global prevalence of myopia is almost 2 billion individuals (28.3% of the global population) and is estimated to increase to 4.76 billion individuals (49.8% of the global population) in 2050.[4] The prevalence of myopia in some locations in East and Southeast Asia (47.0%) is much higher than that in Central Europe (27.1%), Central Asia (17.0%) and Central Africa (7.0%),[4] with the highest prevalence of myopia and high myopia found in urbanized areas of East and Southeast Asia such as Singapore, cities in mainland China, Hong Kong, Taiwan, Japan, and South Korea.[5–13]

Zainal *et al.* noted that uncorrected refractive error was the main cause of low vision and blindness in Malaysia.[14] Since then, several studies have recorded the prevalence of myopia in parts of the country, including a study by Goh *et al.* that found the overall prevalence to be 10% in 7-year-old children, increasing to approximately 33% in 15-year-old children, with the Chinese having the highest prevalence among the various ethnicities in Malaysia.[15] Approximately 65% of Chinese school children had myopia in a rural area in Pahang, and the refractive error was significantly different between the age groups, but no significant difference was observed

between genders.[16] A smaller cross-sectional study focusing on Malay children aged 6 to 12 years in a suburban area showed a lower prevalence of myopia at 5.4% of the studied population as compared to the study in an urban area by Goh *et al.*,[15] which showed the prevalence of myopia in Malays was approximately 15.4%.[17] A recent study among the indigenous (Orang Asli) school children reported that among the 40.9% of the total subjects who have visual problems, only 5.5% of the indigenous school children had myopia.[18] Another study compared the prevalence of myopia in Malaysia and Singapore and found that Singaporeans have a higher prevalence of myopia compared to Malaysians; a higher prevalence was found in Chinese followed by Indians and Malays.[10]

Impact of myopia and quality of life

Studies have shown that myopia usually begins at the age of 7, the age which children begin their primary education in Malaysia.[15,16] Uncorrected myopia can affect children's academic performance, as shown in randomised studies from China.[19,20] Children's attention span, perseverance, and academic performance can be negatively impacted by poor vision and cause psychosocial stress, all of which can be improved by providing children with corrective spectacles.[21] However, socio-economic factors such as cost, accessibility to spectacles, and parental education, as well as psychosocial barriers such as fear of discrimination, bullying, and negative societal attitudes are proven to be barriers to spectacle wear and compliance in children.[22] Myopia impacts a person's quality of life (QOL) and the effect on QOL can be evaluated using either qualitative[23] or quantitative patient-reported outcome measures (PROMs).[24] PROMs used for myopia contain items on symptoms, activity limitation, emotional impact, social impact, and inconvenience.[25] Healthy adolescents with reduced visual acuity reported significantly lower scores for total QOL (-3.8; 95% confidence interval [CI] -7.1 to -0.5; $P = 0.03$), psychosocial functioning (-4.2 ; 95% CI -8.1 to -0.3; $P = 0.03$), and school functioning (-5.5; 95% CI -10.2 to -0.9; $P = 0.02$)[26]. On the other hand, a better vision-related QOL has been reported with contact lenses[27] and orthokeratology lenses[28] than with spectacles, as the children with myopia have increased satisfaction with correction, activities, and appearance.

A cross-sectional study from 2006 involving children aged 12 to 17 years in Singapore found a mean annual direct cost of myopia SGD$222 (USD$148) and a median cost of SGD$125 (USD$83).[29] An ancillary study from 2011 also conducted in Singapore found the annual direct cost of myopia per person aged 40 years and above was approximately SGD$900 (USD$709), which is less than 2% of the gross domestic product (GDP) per person, of which 65% (SGD$588 or USD$463) was associated with costs of spectacles, contact lenses, and optometry services.[30] The costs for older individuals as compared to costs for children were higher, as adults are more likely to undergo laser-assisted in situ keratomileusis (LASIK) surgery, wear contact lenses, or develop myopia-related ocular complications. The total cost of myopia for the whole population of Singapore was also found to be SGD$959 million

(USD$755.2 million) during 2011, and adults with 80 years' duration of myopia were estimated with a lifetime cost of SGD$21,616 (USD$17,020).[30] The global costs of myopia and direct costs (including examinations, cost of spectacles and lenses, LASIK, care for complications) were approximately USD$358.7 billion in 2019 and likely rise to USD$870 billion in 2050, while severe vision impairment led to a productivity loss of approximately USD$94.5 billion in 2019, likely to rise to USD$229.3 billion in 2050[31] due to the increase in the prevalence of myopia.

COVID-19 and myopia

In December 2019, a novel coronavirus (hereby known as coronavirus disease 2019 [COVID-19]) rapidly spread all around the world. In response to the COVID-19 outbreak, many countries closed their schools nationwide to prevent the spreading of the infection during 2020. It is estimated that approximately 1.2 billion school-aged children and adolescents[32] were affected by the COVID-19 outbreak and confined at home. In order to sustain their study progress, the duration of digital device use by children increased from 1.9 ± 1.1 ~ 2.5 ± 2.3 hours/day to 3.9 ± 1.9 ~ 6.9 ± 4.4 hours/day, depending on the location of studies.[33,34] The prevalence of myopia increased by approximately 5% after home confinement,[35,36] and the mean annualized progression of myopia was also found to increase approximately 0.1 to 0.3 D during home education;[36–38] approximately 49.5% of children showed an annual progression of ≥ 1 D during the pandemic as compared with 10.5% before the pandemic.[39] The use of different digital devices for online courses also has an impact on myopia progression, given that computer and smartphone use is shown to be associated with higher risks of myopic progression than television and projector use.[40–42] Working distance (< 30 cm) is also a factor that accounts for higher risks of myopia development and progression,[43] and myopic children tend to spend more time on activities at distances < 20 cm compared to non-myopic children.[44] During the COVID-19 pandemic, children were found to spend less time on outdoor activities, which contributed to myopia progression.[34,45,46] Indoor lighting that is either "too dim" or "too bright" was also significantly associated with myopic symptoms.[47]

Parents play an essential role in mitigating the myopigenic behaviours that emerged during the COVID-19 pandemic. To begin with, public education and forums are necessary to increase parent awareness about the effects of indoor near work and reduced outdoor time on myopia incidence and progression. It is essential to maintain good eye habits during home confinement, including taking frequent breaks from near work and limiting recreational screen time. Secondly, greater variation in home learning activities such as cooking, baking, housework, gardening, physical exercise, and other activities should be encouraged and included. Thirdly, outdoor activities with adequate social distancing should not be neglected, and children are encouraged to have 2–3 hours of outdoor time per day.[48] Last but not least, parents should ensure children have healthy digital device habits through the

use of digital applications to consciously monitor device usage and reminding users to disconnect from the digital devices, setting up daily schedules to allocate time for specific activities while building routine and discipline, supervising digital content to maximise learning experiences, and act as role models by reducing their digital device usage and engaging their children with non-digital indoor and outdoor activities. Despite its small sample, a quasi-experimental study showed that eye exercises may have an effect in reducing myopia outcomes in children.[49] However, when children are showing symptoms of myopia progression, it is advisable to bring the children for optical treatment. Optical treatment of defocus incorporated multiple segments (DIMS) lenses appeared to decrease myopia progression as compared to single vision lens (SVL) treatment during the lockdown period.[50] Low-dose 0.01% atropine was found to have decreased effectiveness for myopia control during prolonged COVID-19 lockdowns;[51] hence, it is advisable to select alternative treatments if children are required to confine at home for a longer period.

Conclusion

While myopia has been recognised as an increasing burden with rising incidence pre-COVID-19, the lockdown imposed during the COVID-19 pandemic has clearly impacted the problem. This will contribute to higher numbers of newly diagnosed myopia, leading to more adults diagnosed with high myopia and pathological myopia.

Declarations

Ethics approval and consent to participate
None to declare.

Competing interests
None to declare.

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A comparison of visual outcomes of deep anterior lamellar keratoplasty versus penetrating keratoplasty of keratoconus patients in two major corneal centres in Malaysia

Yin Peng **Lai**[1], Rohanah **Alias**[1], Shamala **Retnasabapathy**[2]

[1]*Department of Ophthalmology, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia;*
[2]*Department of Ophthalmology, Hospital Sungai Buloh, Selangor, Malaysia*

Abstract

Purpose: We conducted a retrospective study of keratoconus patients who underwent either penetrating keratoplasty (PKP) or deep anterior lamellar keratoplasty (DALK) in Malaysia from 2014 to 2018 to compare refractive and visual outcomes between PKP and DALK.
Study design: Retrospective case control study.
Methods: We studied 59 eyes of 53 keratoconus patients: 31 eyes underwent PKP and 28 underwent DALK. We obtained data that included demographic distribution, pre- and postoperative best-corrected visual acuity (BCVA in logMAR), postoperative refraction (spherical equivalent and astigmatism), postoperative topography (SimK1, SimK2, and Kcyl), type of correction (spectacles versus contact lens), incidence of rejection, and other complications.
Results: There were 22 female patients (42.0%) and 31 male patients (58.0%) with 55.0% Indians, 34.0% Malays, 7.0% Chinese, and 4.0% others. The mean age was 27.03 ± 8.68 years for the PKP group and 26.36 ± 7.26 years old for the DALK group ($p = 0.784$). There were no statistically significant differences in preoperative BCVA, postoperative refraction, and postoperative topography. However, there was a statistically significant difference in postoperative BCVA between PKP (0.16 ± 0.16)

Correspondence: Lai Yin Peng, MBSS, MMed (Ophthal), Hospital Kuala Lumpur, Jalan Pahang, 50586 Kuala Lumpur, Wilayah Persekutuan, Malaysia.
E-mail: yinpeng_lai@hotmail.com

and DALK (0.33 ± 0.17) (p = 0.001). Graft rejection was a significant complication in the PKP group, with 5 eyes (16.0%) resulting in 2 graft failures (6.0%).
Conclusions: In this study, more men than women underwent corneal transplant for keratoconus within the second to third decades of life, most of whom were of Indian origin. PKP showed better visual outcome in terms of BCVA than DALK. Regarding refractive and keratometry parameters, there were no significant differences. However, DALK had a lower rate of graft rejection and graft failure compared to PKP.

Keywords: deep anterior lamellar keratoplasty, keratoconus, Malaysia, penetrating keratoplasty

Perbandingan hasilan penglihatan pesakit keratokonus antara keratoplasti lapisan depan mendalam dengan keratoplasti ketebalan penuh di dua pusat kornea utama di Malaysia

Abstrak

Tujuan: Kita menjalankan kajian retrospektif tentang pesakit keratokonus yang telah melalui pembedahan keratoplasti ketebalan penuh dan keratoplasti lapisan depan mendalam di Malaysia dari tahun 2014 sehingga 2018 untuk membandingkan hasil penglihatan dan refraktif antara dua pembedahan tersebut.
Kaedah kajian: Kajian pemerhatian secara retrospektif
Langkah kajian: Kajian sebanyak 59 mata dari 53 pesakit keratokonus melibatkan 31 mata yang telah menjalani keratoplasti ketebalan penuh dan 28 mata yang dijalankan keratoplasti lapisan depan mendalam. Data yang diperolehi adalah taburan demografi, ketajaman penglihatan (logMAR) sebelum dan selepas prosedur, refraksi selepas prosedur (setara sfera dan astigmatisme), topografi selepas prosedur (Simk1, SimK2 dan Kcyl), jenis pembetulan (cermin mata atau kanta sentuh), kejadian penolakan organ kornea dan komplikasi lain-lain.
Keputusan: Seramai 22 pesakit perempuan (42%) dan 31 pesakit lelaki (58%) dengan 55.0% bangsa India, 34.0% bangsa Melayu, 7.0% bangsa Cina and 4.0% lain-lain. Umur minima adalah 27.03 ± 8.68 tahun untuk kumpulan keratoplasti ketebalan penuh dan 26.36 ± 7.26 tahun untuk kumpulan keratoplasti lapisan depan mendalam (p = 0.784). Ketajaman penglihatan yang terbaik sebelum dan selepas prosedur, refraksi selepas prosedur dan topografi selepas prosedur tidak menunjukan perbezaan yang signifikan secara statistik. Tetapi, ketajaman

penglihatan yang terbaik selepas pembedahan adalah signifikan secara statistic antara keratoplastiketebalan penuh (LogMAR 0.16 ± 0.16) and keratoplasti lamellar anterior dalam (LogMAR 0.33 ± 0.17) (p = 0.001). Penolakan graf kornea adalah satu komplikasi utama di dalam kumpulan keratoplasti ketebalan penuh, iaitu sebanyak 5 mata (16.0%) dengan akibatnya 2 kegagalan graf kornea (6.0%).
Kesimpulan: Dalam kajian ini, insiden pembedahan pemindahan kornea untuk keratokonus didapati adalah lebih tinggi di kalangan lelaki berbanding perempuan, antara umur dua puluhan hingga tiga puluhan, dan majoriti dari kaum India. Hasil ketajaman penglihatan yang terbaik adalah lebih baik untuk kumpulan keratoplasti menembusi ketebalan penuh. Refraksi dan keratometri antara kedua-dua Kumpulan tidak mempunyai perbezaan yang signifikan secara statistik. Walau bagaimanapun, kumpulan keratoplasty lapisan depan mendalam mempunyai kadar yang lebih rendah untuk penolakan dan kegagalan graf kornea.

Kata kunci: keratokonus, keratoplasti lamellar anterior dalam, keratoplasti menembusi ketebalan penuh, kesihatan yang baik dan kesejahteraan

Introduction

Keratoconus is a non-infectious and non-inflammatory disease where the paracentral or central cornea experiences continuous progression of corneal thinning and ectasia causing an irregular astigmatism and often coupled with myopic shift, which may severely impair vision.[1] The reported keratoconus incidence ranges from 1.3 to 25 per 100,000 per year across different populations and has been reported to have higher prevalence with earlier onset and advanced progression in Asian descendants such as Arabs, Indians, Pakistanis, and Polynesians compared to Caucasians.[2] A study conducted in a specialised corneal centre in Malaysia reported a prevalence of 1.2%, approximately 1 per 100, with higher percentage in Malays and Indians.[3]

The nature of the disease progression is variable, and the severity can range from very mild to moderate irregular astigmatism that can be corrected with glasses, contact lenses, intracorneal ring segments, and corneal cross-linking[4] to extreme thinning, ectasia, and acute hydrops leading to scarring warranting keratoplasty.[5] Corneal transplant has been stipulated when visual rehabilitation is insufficient with spectacle correction, unsupportable contact lens wear, and very poor, unacceptable vision[6] in approximately 12% to 20% of affected keratoconus patients.[7-9]

Penetrating keratoplasty (PKP) has been the mainstream surgical treatment for advanced keratoconus for more than 7 decades[10,11] as it is well established with good reported safety profile and visual acuity outcomes, usually past 18 to 24 months.[11,12] Nevertheless, full thickness corneal transplant poses risks

of immune-mediated endothelial rejection, attrition of endothelial cells, and intraoperative complications such as expulsive haemorrhage, expulsion of eye content, and endophthalmitis.[13,14] Deep anterior lamellar keratoplasty (DALK) has gained attention in the past 2 decades for the management of keratoconus with the notion of preserving the host's own endothelial cells, reducing the risk of endothelial graft rejection.[15,16] Moreover, early tapering of steroids is feasible in DALK, with decreased risk of secondary glaucoma and cataract as well as increased wound strength.[15] However, DALK is taxing on the surgical skills, posing a steeper learning curve for surgeons. Additionally, unlike PKP, which has established a good visual acuity outcomes profile, DALK outcomes wage heavily on the regularity and clarity of host-donor interface. DALK cases have drastically increased parallel to advancement in techniques and surgical instruments, with the most pertinent techniques being reported by Melles[17] and Anwar.[18]

Methods

A retrospective case-control study was conducted whereby the clinical data of keratoconus patients having received corneal transplant in Hospital Sungai Buloh or Hospital Kuala Lumpur from June 2014 to June 2018 were traced and reviewed. Ethical approval for this study was obtained from by the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (MOH), and adhered to the tenets of Declaration of Helsinki.

The study included a total of 59 eyes (53 patients): 31 eyes underwent PKP and 28 underwent DALK. These data were retrieved from the clinical examination records including diagnosis, pre- and postoperative best-corrected visual acuity (BCVA in logMAR), postoperative refractive and keratometry parameters, and clinical events including any postoperative complications such as graft rejection, graft failure, glaucoma, and cataract. All the patients were clinically diagnosed as keratoconus from the history, slit-lamp examination, refraction, and topography. The patients included in the study had either BCVA of 0.6 logMAR or worse with contact lenses, could not tolerate contact lenses, or had corneal scarring. All patients with scarring involving Descemet's membrane underwent PKP. The severity of keratoconus was matched for both groups, with a mean pre-operative BCVA of 1.36 ± 0.53 for the PKP group and 1.41 ± 0.52 for the DALK group (p = 0.316). Patients who had previous ocular surgeries, incomplete or missing data, and defaulted follow-up were excluded. Selective suture removals were applied for all patients for visual rehabilitation.

DALK was performed according to surgeon preference with the Melles technique[17] or big bubble technique,[18] while PKP was performed using manual corneal trephine for both recipient and donor tissues. Full thickness graft tissue, preserved in Optisol (Bausch and Lomb, Rochester, NY, USA) was used for both

groups and trypan blue (Vision Blue, D.O.R.C. International, The Netherlands) was used for removal of endothelium-Descemet's membrane complex from donor tissue for DALK cases. Sixteen interrupted sutures were placed for both techniques.

Statistical analysis

Descriptive analysis was performed by calculating mean ± standard deviation for quantitative data. For qualitative data, frequencies were represented by a number and percentage. A between-group comparison was performed using Fisher's exact test for categorical variables and with rank-sum test for non-parametric continuous variables. A *P* value less than 0.05 was considered statistically significant.

Results

Patient data

A total of 53 patients (59 eyes) were studied, with bilateral eyes in 6 patients and unilateral eye in 47 patients. There were 22 female patients (42.0%) and 31 male patients (58.0%). The racial distribution was 55.0% Indians, 34.0% Malays, 7.0% Chinese, and 4.0% other (Iban) (Fig. 1). The analysis was on the total number of eyes that underwent corneal transplant rather on the total number of patients in view that patients with bilateral eyes had similar or different corneal transplant procedure performed. Thus, a total of 59 eyes were analysed: 31 eyes underwent PKP and 28 underwent DALK. Thirteen right eyes and 18 left eyes underwent PKP, while 9 right eyes and 19 left eyes underwent DALK (Fisher's exact test, $p = 0.591$). There were no significant differences in age and gender between the PKP and DALK

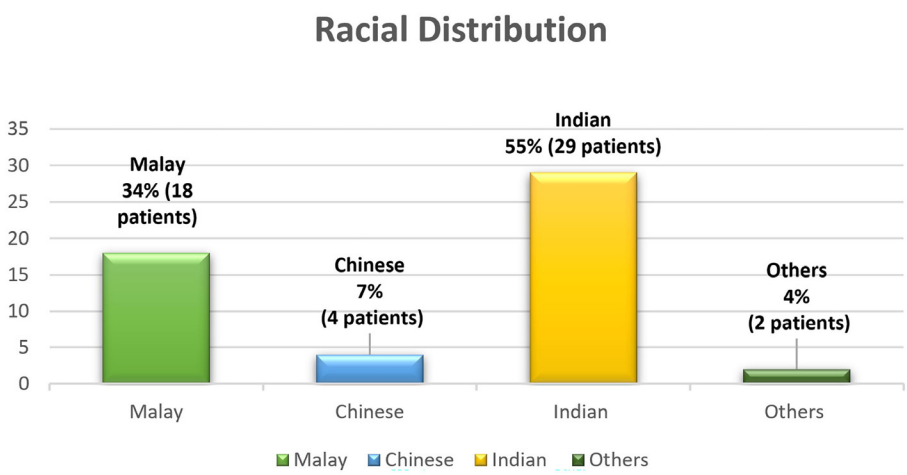

Fig. 1. Racial distribution pattern.

Table 1. Characteristics and surgical data

Variable	PKP (*n* = 31)	DALK (*n* = 28)	*P* value
Male: Female	17:14	16: 12	
Right: Left	13:18	9: 19	
Age (mean ± standard deviation) years	27.03 ± 8.68	26.36 ± 7.26	0.749

groups. The mean age was 27.03 ± 8.68 years for the PKP group and 26.36 ± 7.26 years for the DALK group (Mann-Whitney test, $p = 0.784$) (Table 1).

Visual acuity and refractive results

There were no statistically significant differences in mean preoperative BCVA, postoperative unaided visual acuity, postoperative refraction (spherical equivalent and astigmatism), and postoperative topography (SimK1, SimK2, and Kcyl) (Table 2). However, there was a statistically significant difference in mean postoperative BCVA between PKP (0.16 ± 0.16) and DALK (0.33 ± 0.17) (Fisher's exact test, $p = 0.001$).

Most of the patients were satisfied with unaided vision. Three patients from the PKP group (10.0%) and 4 patients from the DALK group (14.0%) preferred spectacles. Three patients from the PKP group (10.0%) and 5 patients from the DALK group (18.0%) required contact lenses to achieve BCVA (Table 3).

Complications

Graft rejection was a significant complication in the PKP group, with 5 eyes (16.0%) resulting in 2 graft failures (6.0%). There were no graft rejections nor graft failures reported in the DALK group. Three patients (1 in the PKP group [3.0%] and 2 in the DALK group [7.0%]) developed cataract postoperatively; 1 patient from the DALK group underwent cataract surgery. One patient from the PKP group (3.0%) and 2 from the DALK group (7.0%) developed glaucoma. Both groups had 1 patient that underwent glaucoma surgery (Table 4).

Discussion

The mean age of the patients in this study was comparable to a study[18] conducted in Singapore, which found that the onset was earlier with progression to severe keratoconus requiring corneal transplant in the second to third decades of life in the Asian community. There were more male patients (58.0%) than female patients

Table 2. Preoperative and postoperative comparison of vision and postoperative refractive parameters of eyes that underwent PKP and DALK for keratoconus (Fisher's exact test)

Parameters	**PKP Mean ± SD (Min to max)**	**DALK Mean ± SD (Min to max)**	**Sig**	***P* value**	**95% CI**
Preoperative BCVA (logMar)	1.36 ± 0.53 0.6 to 3.0	1.41 ± 0.52 0.6 to 2.0	0.316	> 0.05	1.25 to 1.52
Postoperative unaided VA (logMar)	0.51 ± 0.33 0.0 to 1.6	0.65 ± 0.32 0.2 to 1.6	0.298	> 0.05	0.49 to 0.67
Postoperative BCVA (logMar)	0.16 ± 0.16 0.0 to 0.5	0.33 ± 0.17 0.0 to 0.6	0.001	< 0.05	0.19 to 0.29
Postoperative SE (SD)	-2.33 ± 2.79 -8.50 to +4.75	-2.5 ± 3.31 -11.50 to 4.00	0.154	> 0.05	-3.20 to -1.63
Postoperative astigmatism (DC)	-4.22 ± 2.20 -0.50 to -11.00	-4.39 ± 1.83 -8.00 to -1.00	0.163	> 0.05	-4.83 to -3.77
Postoperative Sim K1 (D)	42.32 ± 5.4 25.90 to 52.70	44.60 ± 3.10 38.80 to 50.60	0.308	> 0.05	42.21 to 44.59
Postoperative Sim K2 (D)	45.17 ± 5.14 28.90 to 55.60	47.50 ± 3.9 40.40 to 55.20	0.773	> 0.05	45.05 to 47.50
Postoperative Kcyl (D)	4.99 ± 3.52 1.00 to 13.80	5.18 ± 2.42 1.40 to 13.80	0.722	> 0.05	4.29 to 5.87

VA: Visual acuity
DC: Diopter count
SE: Spherical equivalent
Kcyl: Keratometric cylinder
Sig: Statistical significance

Table 3. Preferred correction used to achieve best-corrected visual acuity

Preferred correction	**PKP (*n* = 31)**	**DALK (*n* = 28)**	**Total (*n* = 59)**
Unaided	25 (81.0%)	19 (68.0%)	44 (75.0%)
Spectacles	3 (10.0%)	4 (14.0%)	7 (12.0%)
Contact lenses	3 (10.0%)	5 (18.0%)	8 (13.0%)

Table 4. Complications of PKP and DALK

Complications	**PKP (*n* = 31)**	**DALK (*n* = 28)**	**Total (*n* = 59)**
Graft rejection	5 (16.0%)	0 (0.0%)	5 (8.0%)
Graft failure	2 (6.0%)	0 (0.0%)	2 (3.0%)
Cataract	1 (3.0%)	2 (7.0%)	3 (5.0%)
Glaucoma	1 (3.0%)	2 (7.0%)	3 (5.0%)
Faint scar at interface	-	1 (4.0%)	1 (2.0%)
Microbial keratitis	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cataract surgery	0 (0.0%)	1 (4.0%)	1 (2.0%)
Glaucoma surgery	1 (3.0%)	1 (4.0%)	2 (3.0%)

(42.0%) in this study. The racial distribution was 55.0% Indians, 34.0% Malays, 7.0% Chinese, and 4.0% others (Iban). This distribution was consistent with a study by Bariah and associates[3] that observed a higher percentage of keratoconus in Malays and Indians origin than other races.

DALK has gained popularity considering the advantages over PKP over the years. The advantages of DALK encompass less postoperative immune reaction, conserving the patient's own endothelium, thus minimising the risk of graft rejection, shorter duration of steroid usage, and elimination of complications entailing open-sky system such as expulsive haemorrhage, anterior synechiae, angle narrowing and cataract. The visual acuity outcomes were reported to be inconsistent in many studies comparing DALK and PKP,[20-22] as the inclusion criteria, follow-up criteria, and outcome measurements varied. However, in our study, PKP yielded a better postoperative visual outcome compared to DALK, which is similar to many reported studies.[23-31]

Watson *et al.*[23] and Han *et al*[19] reported no significant difference in spherical equivalent and astigmatism between the 2 groups, which is consistent with our study. We found that the keratometry parameters outcomes of Sim K1, Sim K2, and K cylinder were equivalent in both groups. Similar to a previous study by Watson and colleagues, our study included several techniques under DALK; thus, DALK subgroups could not be compared to the PKP group.

Overall, most of our patients were satisfied with unaided vision, with 25% of patients requiring spectacles (3 patients in the PKP group, 4 in the DALK group) and contact lenses (3 patients in the PKP group, 5 in the DALK group) for vision optimisation.

The incidence of graft rejection and graft failure was higher in the PKP group compared to the DALK group, consistent with many reported studies. However, other complications, such as cataract and glaucoma, were not significantly different between the 2 groups. No microbial keratitis cases were reported in our study. While DALK has lower immunological response and risk of graft rejection, PKP generally yields better visual acuity and refraction as the surgical interface of DALK contributes to higher-order aberrations and astigmatism.

To the best of our knowledge, this is the first comparative corneal transplantation study for keratoconus patients in Malaysia. However, our study has some limitations. A large, randomised series of patients with detailed surgical techniques, assessment of visual function using contrast and glare sensitivity, quality of life post-keratoplasty, and longer follow-up are required.

Conclusion

Both PKP and DALK are effective treatment options for keratoconus patients. The PKP group had better postoperative BCVA outcomes. Even though PKP showed a better postoperative visual outcome compared to DALK, its disadvantages of higher graft rejection and graft failure cannot be overlooked, consistent with several reported studies. Despite DALK having a steeper learning curve for beginners and being technically more challenging, it has a distinct and higher safety profile.

Declarations

Ethics approval and consent to participate
Ethical approval for this study was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (MOH).

Competing interests
None to declare.

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Local experience of concurrent three-weekly high-dose pulsed intravenous methylprednisolone and orbital radiotherapy in thyroid eye disease

Ru Jian Jonathan **Teoh**[1], Rathinamsvannie **Selvam**[1], Kala **Sumugam**[1], Sharifah Intan Hosnaliza **Syed Osman**[1], Ros Suzanna **Bustamam**[2]

[1]*Department of Ophthalmology, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia;* [2]*Department of Radiotherapy and Oncology, Hospital Kuala Lumpur, Malaysia*

Abstract

Purpose: To analyse the outcomes of concurrent high-dose pulsed intravenous methylprednisolone (IVMP) administered every 3 weeks for 4 cycles along with orbital radiotherapy (OR) in thyroid eye disease (TED).
Study design: Retrospective case series.
Methods: The medical records of 5 patients with moderate-to-severe active TED who underwent concurrent IVMP and OR in 2022 and 2023 were reviewed. All patients received concurrent pulsed IVMP (1 g per day for 3 consecutive days, administered three-weekly for four cycles) and OR (20 Gy in 10 fractions). Improvement was assessed using the Clinical Activity Score (CAS) and International Thyroid Eye Disease (ITEDS) – Vision/Inflammation/Strabismus/Appearance (VISA) scoring system.
Results: The mean age of the 5 patients was 50.2 ± 5.2 years. The mean duration of ophthalmopathy and thyroid disease were 6.2 ± 4.2 months and 9.60 ± 9.29 months, respectively. Following treatment, there was a significant reduction in the mean CAS by 2.8 ± 1.3 ($p = 0.009$) and ITEDS-VISA scores by 5.8 ± 2.5 ($p = 0.006$). Improvement in proptosis measured by exophthalmometer was 2.3 ± 1.5 mm ($p = 0.028$). The mean follow-up duration was 6.0 ± 5.9 months.

Correspondence: Kala Sumugam, Department of Ophthalmology, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia.
E-mail: drkala77@gmail.com

Conclusion: Concurrent high-dose three-weekly pulsed IVMP with OR is a safe and effective treatment modality in the management of active TED.

Keywords: corticosteroids, Graves' ophthalmopathy, orbital radiotherapy, thyroid eye disease

Pengalaman tempatan pemberian intravena methylprednisolone yang berdos tinggi setiap tiga minggu bersama radioterapi orbital secara serentak dalam penyakit mata tiroid

Abstrak

Tujuan: Untuk menganalisis hasil daripada dos tinggi Intravena Methylprednisolone (IVMP) yang diberikan secara serentak pada setiap 3 minggu selama 4 kitaran bersama radioterapi orbital (OR) dalam penyakit mata tiroid.
Reka bentuk kajian: Siri kes retrospektif.
Kaedah: Rekod perubatan 5 pesakit dengan TED aktif tahap sederhana hingga teruk yang menjalani rawatan IVMP dan OR serentak pada tahun 2022 dan 2023 telah dikaji. Semua pesakit menerima denyutan IVMP (1 g sehari selama 3 hari berturut-turut, diberikan setiap tiga minggu selama empat kitaran) dan OR (20 Gy dalam 10 pecahan) secara serentak. Penambahbaikan dinilai menggunakan Skor Aktiviti Klinikal (CAS) dan system skor Penyakit Mata Tiroid Antarabangsa (ITEDS) – Penglihatan/Radang/Strabismus/Penampilan (VISA).
Keputusan: Purata usia 5 pesakit ialah 50.2 ± 5.2 tahun. Purata tempoh oftalmopati dan penyakit tiroid adalah 6.2 ± 4.2 bulan dan 9.60 ± 9.29 bulan, masing-masing. Selepas rawatan, terdapat pengurangan yang signifikan dalam purata CAS sebanyak 2.8 ± 1.3 (p=0.009) dan skor ITEDS-VISA sebanyak 5.8 ± 2.5 (p = 0.006). Penambahbaikan dalam proptosis yang diukur menggunakan exophthalmometer ialah 2.3 ± 1.5 mm (p = 0.028). Purata tempoh susulan ialah 6.0 ± 5.9 bulan.
Kesimpulan: Gabungan pemberian dos tinggi intravena methylprednisolone dengan radioterapi orbital adalah kaedah rawatan yang selamat dan berkesan dalam pengurusan penyakit mata tiroid aktif.

Kata kunci: kortikosteroid, oftalmopati Graves, penyakit mata tiroid, radioterapi orbital

Introduction

Thyroid eye disease (TED), also known as Graves' orbitopathy or thyroid associated ophthalmopathy, is an autoimmune condition characterised by inflammation and fibrosis of the orbital tissues.[1] It can manifest in patients who are hyperthyroid, hypothyroid, or euthyroid.[2] Euthyroidism is defined as normal serum thyroid-stimulating hormone, free thyroxine, and free triiodothyronine levels within the reference ranges. TED imposes significant morbidity primarily due to its impact on visual function and cosmetic appearance.[1] The prevalence of TED varies geographically, with rates of 0.25% observed in Western populations,[3] while a Malaysian study reported a prevalence of 34.7% in patients with Graves' disease.[4]

Despite advances in understanding its pathophysiology, managing severe TED remains challenging. Traditional therapeutic modalities for severe TED include corticosteroids, orbital radiotherapy (OR), and surgical decompression.[2] However, the optimal management of severe TED continues to evolve. An emerging approach involves the concurrent administration of high-dose, pulsed intravenous methylprednisolone (IVMP) alongside OR.[5] Corticosteroids like IVMP mitigate orbital inflammation and reduce oedema, whereas OR suppresses lymphocyte infiltration into the orbital tissues.[6] Research indicates that concurrent IVMP (administered at 15 mg/kg for 4 cycles followed by 7.5 mg/kg for 4 cycles) and OR resulted in a greater reduction in Clinical Activity Score (CAS) compared to oral prednisone combined with OR.[7]

At our centre, we have adopted a regimen involving high-dose pulsed IVMP, administered at 1 g IVMP per day for 3 days, every 3 weeks, for 4 to 6 cycles depending on the clinical response. Since 2022, we have introduced a combination therapy involving high-dose pulsed IVMP with OR, anticipating synergistic therapeutic effects. The aim of this study was to conduct a retrospective evaluation of our experience with this therapeutic regimen, elucidating its effectiveness and safety profile in managing active TED.

Methods

This was a retrospective case series analysis conducted in a tertiary hospital in Kuala Lumpur, Malaysia. Patients older than 18 years old with moderate to severe active TED who underwent concurrent pulsed IVMP and OR in 2022 and 2023 were included in this study. Patients with active infection, uncontrolled hypertension and/or diabetes mellitus, liver dysfunction, a history of previous treatment for TED, or a follow-up period of less than 3 months were excluded from this study. The baseline characteristics and clinical parameters were retrospectively collected from the medical records.

The CAS[8] and International Thyroid Eye Disease-Vision/Inflammation/Strabismus/Appearance (ITEDS-VISA) scoring system[9] was used to assess the disease activity in all patients who attended the oculoplastic clinic in the eye centre. The disease activity and severity were graded at the end of each visit. An active disease was defined by a CAS score ≥ 3, and the decision to initiate treatment was made by an oculoplastic surgeon. The pulsed IVMP protocol was 1 g IVMP per day for 3 days, every 3 weeks, for 4 cycles. Pre-steroid work-up included a full blood count, renal profile, liver function test, infective screening for hepatitis and syphilis, tuberculin skin test (Mantoux), urinalysis, electrocardiogram, and chest X-ray. IVMP was contraindicated in the presence of active hepatitis, hepatic dysfunction, severe hypertension, uncontrolled diabetes mellitus, cardiovascular morbidity, or active infections.[7] If there was no contraindication, IVMP was administered under close monitoring by trained nurses with a trained medical doctor on standby for medical alerts. Prior to the initiation of each cycle, clinical (CAS and ITEDS-VISA) and laboratory (full blood count, renal profile, liver function test, and urinalysis) reviews were performed. All patients underwent computerised tomography (CT) or magnetic resonance imaging (MRI) imaging during the treatment period before initiation of OR. The patients were co-managed with the radiation oncology team in the hospital for OR. A total dose of 20 Gy in 10 fractions over 2 weeks was administered to all patients after the first cycle of IVMP. The patients were followed up for at least 3 months after the intervention. The clinical response was retrospectively evaluated from the medical records at the latest follow-up visit to the eye clinic.

Our primary outcomes were changes in CAS and ITEDS-VISA index. Secondary outcomes included changes in the degree of proptosis, best-corrected visual acuity (BCVA), the status of diplopia, and any adverse event.

Continuous variables were expressed as means and standard deviations and compared using Student t-tests. A *p*-value of less than 0.05 was considered as statistically significant. All statistical analyses were performed using the Statistical Package for Social Science (SPSS) version 29.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 5 patients were included in this study. A summary of the patients' characteristics is shown in Table 1. The mean age of the patients was 50.2 ± 5.2 years, with 3 male patients and 2 smokers. All our patients were hyperthyroid, and 2 of them achieved euthyroid status at intervention. The mean duration of ophthalmopathy was 6.2 ± 4.2 months and the mean duration of thyroid disease was 9.60 ± 9.29 months. Two of the patients (Patients 3 and 4) were diagnosed with dysthyroid optic neuropathy on presentation. All 5 patients received 4 cycles of systemic corticosteroids (1 g IVMP per day for 3 days, every 3 weeks) and orbital irradiation (20 Gy in 10 fractions over 2 weeks).

Table 1. Clinical characteristics of patients

Case	Age	Sex	Ethnicity	Smoker	Thyroid status at intervention	Treatment for thyroid condition	Duration of TD (months)	Duration of OP (months)	Presence of optic neuropathy
1	52	Male	Chinese	Yes	Euthyroid	Carbimazole	24	2	No
2	44	Male	Malay	No	Euthyroid	Nil	1	5	No
3	57	Female	Malay	No	Hyperthyroid	Carbimazole	2	3	Yes
4	46	Female	Chinese	No	Hyperthyroid	Carbimazole	9	9	Yes
5	52	Male	Chinese	Yes	Hyperthyroid	Methimazole	12	12	No

TD: thyroid disease; OP: ophthalmopathy

Table 2. Clinical response after concurrent high-dose pulsed IVMP and OR

Case	Proptosis (Pre) (mm)	Proptosis (Post) (mm)	logMAR BCVA (Pre)	logMAR BCVA (Post)	Diplopia (Pre)	Diplopia (Post)	CAS (Pre)	CAS (Post)	VISA (Pre)	VISA (Post)
1	19	17.5	0.2	0.2	IT	IT	4	0	10	2
2	21.5	18.5	0.2	0.2	Constant	With gaze	5	1	12	3
3	18	16	0.6	0.3	Constant	Constant	4	2	10	6
4	22	21.5	0.7	0.5	None	None	4	3	8	4
5	20.5	16	0.2	0.2	With gaze	IT	4	1	10	6

Pre: pre-intervention; Post: post-intervention IT: intermittent; BCVA; best-corrected visual acuity; CAS: Clinical Activity Score; VISA: Vision/Inflammation/Strabismus/Appearance

Table 3. Comparison of clinical parameters after treatment

Clinical parameter (mean, SD)	Before treatment	After treatment	*P*-values
Proptosis (mm)	20.2 ± 1.7	17.9 ± 2.3	0.028
logMAR BCVA	0.4 ± 0.2	0.3 ± 0.1	0.189
CAS	4.2 ± 0.4	1.4 ± 1.1	0.009
VISA	10.0 ± 1.4	4.2 ± 1.8	0.006

BCVA; best-corrected visual acuity; CAS: Clinical Activity Score; VISA: Vision/Inflammation/Strabismus/Appearance

The clinical outcomes of concurrent IVMP and OR are described in Table 2. Following treatment, there was a significant reduction in the mean CAS by 2.8 ± 1.3 (p = 0.009) and ITEDS-VISA scores by 5.8 ± 2.5 (p = 0.006) (Table 3). Improvement in proptosis measured by an exophthalmometer was noted, with a mean of 2.3 ± 1.5 mm (p = 0.028) (Table 3). Patient 3 exhibited an inadequate clinical response after OR and the second cycle of IVMP (similar visual acuity and optic nerve function test), necessitating endoscopic left orbital wall decompression surgery. After the fourth cycle of IVMP, the dysthyroid optic neuropathy resolved and remained quiescent throughout subsequent follow-up examinations. For Patient 4's condition improved after high-dose pulsed IVMP and OR and remained quiescent after the third cycle of IVMP. There was no need for an additional cycle after completing the course of treatment. The mean follow-up duration was 6.6 ± 5.4 months, during which no significant complications were noted.

Discussion

This was the first study in Malaysia demonstrating the outcome of concurrent high-dose pulsed IVMP and OR in the management of moderate-to-severe active TED. All patients were followed for at least 3 months after the intervention, which was the suggested optimal time to assess response to treatment.[10] All patients in the study achieved a reduction in CAS and ITEDS-VISA. Four out of 5 patients also achieved a reduction of ≥ 2 mm proptosis. The above improvement demonstrated a positive response to treatment, which corresponded with a recently revised composite index.[10] The composite index is composed of:

1. ≥ 2 mm reduction of lid aperture
2. ≥ 1 point reduction in 5-item CAS (no spontaneous or gaze-evoked pain)
3. ≥ 2 mm reduction in proptosis
4. ≥ 8° increase of eye motility.

An improvement in ≥ 2 features in 1 eye without deterioration in the fellow eye was considered a positive response to treatment.[10]

The 2021 European Group on Graves' Orbitopathy (EUGOGO) has recommended IVMP with a cumulative dose of 7.5 g per cycle as the first-line therapy and combination therapy of systemic corticosteroids and OR as the second-line treatment for active moderate-to-severe TED.[11] A previous review showed that the combination therapy of systemic corticosteroid and OR (70.2% of 392 patients) demonstrated a better response than patients who received only systemic corticosteroid (64.0% of 442 patients).[12] This was also proven by randomised controlled trials, which showed that OR synergistically potentiated the effects of systemic glucocorticoids.[13,14]

In our study cohort, we utilised a regimen involving high-dose pulsed IVMP every 3 weeks that deviates from the usual EUGOGO recommendations, which suggested a maximum cumulative dose of 8 g per course.[11] This approach was justified by

emerging evidence suggesting that such higher-dose pulsed schedules can improve outcomes. He *et al.* randomised patients to a monthly high-dose protocol (1.5 g IVMP per month for 3 months) versus a weekly protocol (0.5 g weekly for 6 weeks followed by 0.25 g weekly for 6 weeks) and found that, although overall response rates were similar, the monthly IVMP group achieved greater symptom improvement and lower recurrence rates than the weekly group.[15] Similarly, Young *et al.* evaluated early active TED patients treated either with pulses of 1 g IVMP for 3 days (18 g cumulative), every month, for 6 months or with the standard EUGOGO protocol, and found that the high-dose monthly regimen yielded excellent results and required fewer additional therapies.[16] Only 33% of pulsed IVMP patients needed adjunctive treatment versus 58% in the weekly dose arm, and no severe adverse effects were observed in the high-dose group.[16] In Japan, Tsujino *et al.* also employed a high-dose pulsed IVMP regimen of 1 g IVMP daily for 3 days, weekly for up to 3 weeks, and did not report any severe side effects including hepatotoxicity and cardiovascular events.[17] The concept of "cumulative toxicity" in IVMP was highlighted by Young *et al.* as something that should be reconsidered, as the mean residence time and systemic clearance of IVMP were 3.50 ± 1.01 h and 0.45 ± 0.12 1 h^{-1} kg^{-1}, respectively.[16,18] IVMP has a serum half-life of 1.93 ± 0.35 h, and is widely distributed to the tissues.[18] Taken together, these findings indicated that regimens with larger, spaced pulses provided more rapid and sustained relief of ophthalmic inflammation than conventional weekly IVMP, while also demonstrating a good safety profile.

Treatment with pulsed intravenous corticosteroids was more effective and better tolerated than with oral corticosteroids.[12] Regardless of the use of concurrent OR, the use of intravenous corticosteroids showed a greater improvement in diplopia, ocular motility, and proptosis compared to its oral counterpart.[12] The rate of side effects was lower with intravenous corticosteroids (56.1% vs 85%).[5] A few of the documented side effects of intravenous corticosteroids included urinary tract infections, glucose intolerance, and an increase in serum aminotransferase levels, which recovered spontaneously.[5] Patients in our study did not show any side effects from the use of IVMP.

On the other hand, OR was generally well tolerated, with minor side effects such as transient hair loss, lethargy, myalgia, headaches, insomnia, and nausea.[12] Our patients did not report any short-term side effects from OR, in agreement with previous studies.[19,20] However, the short follow-up period represented a limitation of our study, as it precluded detection of late complications, especially in the younger population. A retrospective study from Stanford investigated the long-term side effects of OR and found 5% of patients receiving OR had malignancies and 12% developed cataracts at a median time of 11 years.[21] Due to the concern of remote carcinogenesis, OR should be avoided in patients younger than 35 years.[11] While such long-term complications were not observed in our study cohort, further investigation with longer follow-up periods is warranted to assess the long-term safety of combination therapy in TED management.

In terms of long-term effectiveness, OR was effective in managing active TED, particularly ocular motility.[6] A review by Dolman and Rath recommended that concurrent OR and glucocorticoids should only be offered in the early active phase.[22] The initiation of OR within 6 months of proptosis resulted in a better reduction of proptosis, as the retro-orbital tissues are still in the acute or subacute inflammatory stage.[23] Patients who received OR with corticosteroids were also reported to have a lower risk of compressive optic neuropathy after an average follow-up of 3.2 years.[24]

Although thyroid dysfunction has been considered as a risk factor of TED,[1] recent evidence indicates that the development and progression of TED are independent of the thyroid dysfunction, and there is currently no evidence that managing hyperthyroidism with antithyroid drugs alters the natural course of TED.[25] In our cohort, patients who presented with hyperthyroidism were managed with antithyroid drugs under endocrinology supervision. Treatment for sight-threatening TED was prioritized in accordance with international consensus recommendations, with hyperthyroidism managed concurrently.[11,25]

The main limitation of this study was the small number of cases inherent to a case series design. Within this cohort, 2 patients had dysthyroid optic neuropathy, including 1 who underwent surgical orbital decompression. As dysthyroid optic neuropathy is the most severe form of TED with distinct management and prognosis, their inclusion may have influenced the overall outcomes. Given the limited sample size, separate subgroup analysis was not feasible; nonetheless, their clinical courses were reported descriptively.

In conclusion, our study provided evidence supporting the efficacy and safety of concurrent high-dose pulsed IVMP and OR in the management of moderate-to-severe active TED, especially in the degree of proptosis and inflammation. This combination therapy proved to be effective in the local population. However, this was a small case series analysis; hence further larger-scale research is warranted to validate these findings and optimise treatment protocols for managing TED.

Declarations

Ethics approval and consent to participate:
This study was conducted in accordance with the Declaration of Helsinki and, consent and prior ethical approval was obtained from the Medical Research and Ethics Committee of the Malaysian Ministry of Health (NMRR ID NMRR-24-01311-LMX).

Competing interests
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Case report
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Posterior placoid chorioretinitis: a disguise of ocular syphilis

Low Chien Xue[1], Mimiwati binti **Zahari**[1], Roslin Azni binti **Abd Aziz**[2]

[1]UM Eye Research Centre (UMERC), Department of Ophthalmology, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia; [2]Department of Ophthalmology, Hospital Shah Alam, Shah Alam, Malaysia

Abstract

Background: To report a case of ocular syphilis presenting as acute syphilitic posterior placoid chorioretinitis.
Case presentation: A 38-year-old male presented with reduced vision in the left eye for 2 weeks. Best-corrected Snellen visual acuity was 6/60 in the affected eye and 6/9 contralaterally. Fundoscopy revealed mild vitritis, hyperaemic optic disc, a yellowish placoid lesion at the macula, and choroiditis. Optical coherence tomography of the macula showed disruption at the outer retinal layers and hyperreflective lesions in the choriocapillaris. Fundus fluorescein angiography showed a “hot” disc and patches of vasculitis. The diagnosis was delayed by spontaneous clinical resolution and false negative non-treponemal test due to the prozone phenomenon. Due to high clinical suspicion, the test was repeated with a diluted serum sample that turned out to be positive and was treated with intravenous benzylpenicillin.
Conclusion: A placoid lesion at the macula should raise high suspicion of ocular syphilis.

Keywords: chorioretinitis, education, placoid lesion, syphilis

Correspondence: Low Chien Xue, MBBS, UM Eye Research Centre (UMERC), Department of Ophthalmology, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia).
E-mail: chienxue@gmail.com

Korioretinitis plakoid posterior: penyamaran penyakit sifilis okular

Abstrak

Latar belakang: Untuk melaporkan satu kes sifilis okular yang dikenali sebagai korioretinitis plakoid posterior sifilis akut.
Pembentangan kes: Seorang lelaki berusia 38 tahun hadir dengan penglihatan yang berkurangan pada mata kiri selama dua minggu. Ketajaman penglihatan Snellen yang paling baik diperbetulkan ialah 6/60 pada mata yang terjejas dan 6/9 secara kontralateral. Fundoskopi mendedahkan vitritis ringan, cakera optic yang hiperemik, luka plakoid kuning pada makula dan koroiditis. Tomografi koheren optik pada makula menunjukkan gangguan pada lapisan luar retina dan luka hiper-reflektif dalam koriokapilaris. Fundus fluorescein angiography menunjukkan cakera 'panas' dan tompok vaskulitis. Diagnosis telah tertangguh disebabkan oleh resolusi klinikal spontan dan ujian bukan-treponemal yang negatif palsu kerana 'fenomena prozon'. Disebabkan syak wasangka klinikal yang tinggi, ujian diulangi dengan sampel serum yang dicairkan dan keputusan ternyata positif dan kes dirawat dengan benzylpenicillin intravena.
Kesimpulan: Luka plakoid di makula sepatutnya menimbulkan syak wasangka yang tinggi terhadap sifilis ocular.

Kata kekunci: korioretinitis, pendidikan, luka plakoid, sifilis

Introduction

Syphilis is a sexually-transmitted disease caused by the spirochete *Treponema pallidum*.[1,2] It is re-emerging in Malaysia with a reported incidence rate per 100,000 population of 10.63 in 2020, doubling from 5.7 in 2012.[3] Ocular involvement is reported to range from 1% to 8% and usually occurs during the secondary stage.[1,2] It is known as the "great mimicker" owing to its ability to manifest in a wide variety of clinical presentations. Posterior segment involvement is more common, of which chorioretinitis is the commonest.[4] Here, we present a specific pattern of ocular syphilis known as acute syphilitic posterior placoid chorioretinitis (ASPPC) and discuss the possible explanations for its pathophysiology.

Case presentation

A 38-year-old Malay male presented with painless central blurring of vision in the left eye associated with floaters for 2 weeks. Upon systemic review, he developed a scrotal ulcer that preceded the current presentation. He stated having unprotected sexual intercourse with multiple partners in the past. There was no skin rash and his past ocular and medical history was unremarkable.

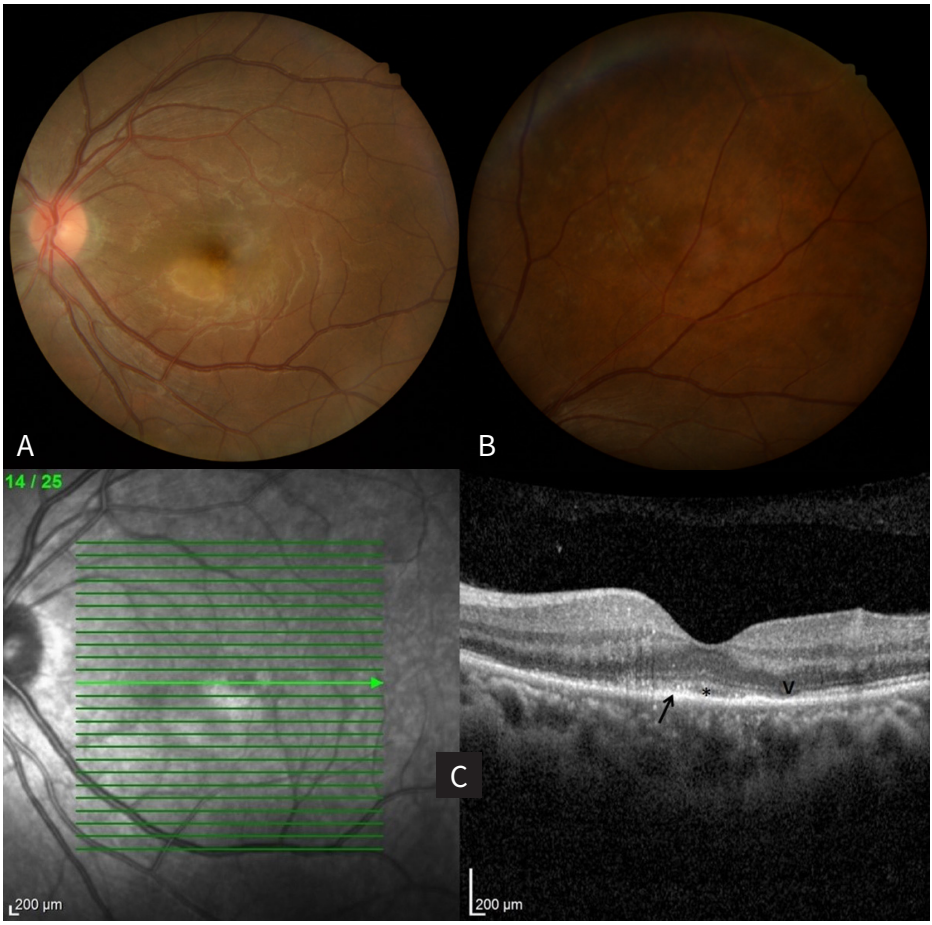

Fig. 1. (a) Fundus of the left eye showing a hyperaemic disc with a placoid lesion at the macula. *(b)* Multiple choroiditis lesions seen in the superior retina. *(c)* OCT of the left macula showing nodular thickening and hyperreflectivity of the RPE layer *(arrow)*, disruption of the photoreceptor inner segment-outer segment junction *(arrowhead)*, minimal subretinal fluid *(asterisk)*, and hyperreflective dots at the choriocapillaris-RPE-photoreceptor complex *(orange arrow)*.

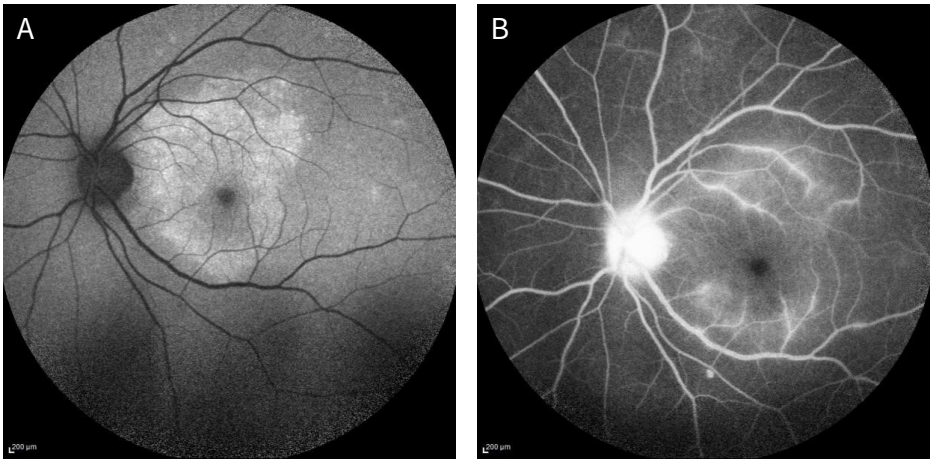

Fig. 2. (a) FA showed an area of hyperautofluorescence larger than the placoid lesion seen clinically. *(b)* FFA showed a "hot" optic disc as well as vasculitis at the perifoveal region and peripheral retina.

His best-corrected Snellen visual acuity (BCVA) was 6/60 in the left eye and 6/9 in the right eye. Relative afferent pupillary defect was negative. Anterior segment examination was unremarkable and intraocular pressure was 16 mmHg bilaterally. Fundus examination of the left eye revealed mild vitritis, hyperaemic optic disc, and a yellowish placoid lesion measuring around one disc diameter located inferonasal to the fovea (Fig. 1a). There was also a cluster of choroiditis lesions in the superior retina (Fig. 1b). Fundus examination of the right eye was unremarkable. Optical coherence tomography (OCT) of the left macula showed disruption at the ellipsoid zone (Fig. 1c), while the right eye showed no abnormalities. He was tested for syphilis and tuberculosis, and treated with topical steroid in the left eye.

Upon review 5 days later, the left eye BCVA had improved to 6/30 and the placoid lesion had mostly resolved on fundoscopy. Fundus autofluorescence (FA) showed that the placoid lesion and choroiditis lesions at the superior retina was more extensive than was clinically visible (Fig. 2a). Fundus fluorescein angiography (FFA) showed a "hot" optic disc and vasculitis at the perifoveal region and peripheral retina (Fig. 2b).

Laboratory investigations indicated normal full blood count as well as kidney and liver profile but raised erythrocyte sedimentation rate of 25 mm/hr. Chest X-ray was unremarkable and tuberculin skin test was negative (5 mm). The first serum sample for rapid plasma (RPR) test was negative, but due to high clinical suspicion, a second diluted serum sample was requested and turned out to be of high titre (1:512). This was further confirmed with a positive *Treponema pallidum* hemagglutination test. HIV testing was negative. Unfortunately, the patient

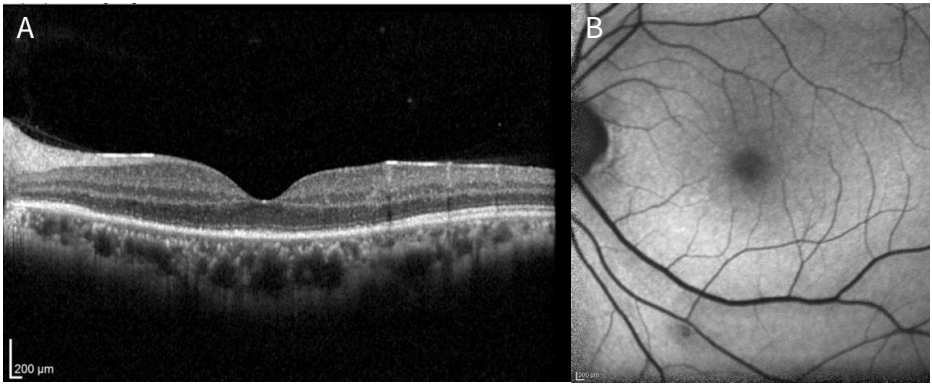

Fig. 3. (a) OCT and *(b)* FA of the macula showing resolution of previous changes.

defaulted subsequent follow-up and only returned after three weeks of initial presentation. He was then referred to the infectious disease physician and admitted for intravenous benzylpenicillin 4 MU every four hours for two weeks. By the time the antibiotic was initiated, the left BCVA had recovered to 6/6, and OCT and FA of the macula showed resolution of previous changes (Fig. 3). It is noteworthy to mention that no systemic steroid was given during the interval. The patient defaulted follow-up again after antibiotic treatment and thus a reduction in RPR titre could not be elicited.

Discussion

In 1988, de Souza and colleagues reported 3 cases of unusual central chorioretinitis in young adults with active syphilis.[1] Two years later, Gass *et al.* coined the term ASPPC to describe large, placoid, and yellowish subretinal lesions in the macula found in 6 cases of secondary syphilis.[4] As more cases had been reported the following years, it was found to involve both eyes in almost half the cases and occurred in patients regardless of their HIV status.[1,4] Presenting visual acuity varies greatly from 20/20 to no light perception.[1,2] It is usually associated with mild to moderate vitritis in up to 88% of cases and to anterior chamber inflammation to a lesser extent in nearly one-third of cases.[1,2]

The natural course and pathogenesis of ASPPC has not been well established. In most of previously reported cases, antibiotic treatment led to rapid resolution of the lesion.[4] But recently there have been reports of spontaneous resolution of ASPPC even prior to antibiotic treatment, as reflected in our case.[5,6] Noteworthy are also reports of disease progression in untreated as well as steroid-treated cases. At least 3 cases of ASPPC developing after intravitreal and systemic steroids have been reported to date.[4] Progression of untreated ASPPC has also

been reported: 1 case which progressed to panuveitis in 6 weeks and another which initially resolved but only to develop into posterior uveitis 9 months later.[7] Adding to the complexity are also reported cases of non-progression of ASPPC even under systemic steroid therapy.[8]

Various theories have been put forward to explain the pathogenesis of this disease. As initial cases showed high prevalence of HIV-coinfection, an altered immune response to syphilis by HIV was thought to be the cause.[4] However, this was later disputed as there were no consistent differences in the clinical manifestation of patients with and without HIV.[1] A more plausible explanation would be that disseminated spirochetes may enter choroidal circulation and gain access to the outer retina, causing a local immune response much similar to the mucocutaneous rash seen during secondary syphilis.[1,2] This was evidenced by multimodal imaging, where OCT showed hyperreflective dots in the choroid, nodular retinal pigment epithelium (RPE) thickening, and disruption of overlying photoreceptors in the inner segment-outer segment junction.[9] Increased autofluorescence seen within the lesions is consistent with accumulation of lipofuscin or photoreceptor outer segment remnants in the RPE.[2] Indocyanine green angiography showed persistent hypocyanescence corresponding to the areas at FA likely due to either choriocapillaris hypoperfusion or masking effect from overlying affected RPE.[2]

The spontaneous resolution of ASPPC likely points to a successful immune response in controlling the infection locally, with possible contribution from the immune-privileged status of the eye.[10] Alternatively, it can also be explained by disease latency, a pathognomonic feature of syphilis.[4] Some authors suggest that ASPPC will run its natural clinical course of onset-aggravation-resolution regardless of treatment with systemic steroids.[10] Prompt resolution with antibiotic treatment reflects early clearance of disseminated spirochetes.

Our case presents multiple diagnostic challenges that characterises syphilis. Differential diagnoses included acute posterior multifocal placoid pigment epitheliopathy and infective retinitis, which require different treatments. The diagnosis was also delayed by the prozone phenomenon seen during early infection. This, in combination with spontaneous resolution of ASPPC, may cause a missed diagnosis.

Conclusion

The presence of a placoid macular lesion should raise high suspicion of ASPPC. Although it can resolve spontaneously, timely diagnosis and antibiotic treatment is crucial in preventing the progression of neurosyphilis.

Declarations

Informed consent for publication
The patient provided informed consent for the use of the clinical images and data contained in this case report.

Competing interests
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Serum eye drops in treating recurrent corneal erosion syndrome

Nur Ain Syafira Roslee, **Muhammad Nazrin** Muhammad Nordin

Department of Ophthalmology, Hospital Enche' Besar Hajjah Khalsom, Kluang, Johor, Malaysia

Abstract

Background: Persistent recurrent corneal erosion syndrome (RCES) was successfully treated with plasma eye drops in a district hospital in Malaysia.
Case presentation: We report a case of a woman who presented with recurrent right eye pain and redness post trauma. She exhibited a chronic persistent epithelial defect despite multiple treatment modalities offered, which included medical and surgical intervention. She was initially treated with vigorous artificial tears, bandage contact lens application, and epithelial debridement; however, symptoms recurred. Significant improvement was seen 1 month after initiation of autologous serum eye drops and complete resolution was achieved following completion of this regime. No recurrence of symptoms was reported at 1 year after treatment completion.
Conclusion: The use of serum eye drops was shown to be effective in treating RCES.

Keywords: recurrent corneal erosion syndrome, serum eye drops

Correspondence: Dr Nur Ain Syafira Roslee, MBBS, Department of Ophthalmology Hospital Enche' Besar Hajjah Khalsom, KM5 Jalan Kota Tinggi, 86000 Kluang, Johor, Malaysia.
E-mail: rosainsya@gmail.com

Ubat titis mata serum dalam merawat sindrom hakisan kornea berulang

Abstrak

Latar belakang: Sindrom hakisan kornea berulang yang berterusan telah berjaya dirawat menggunakan ubat titis mata serum di sebuah hospital daerah di Malaysia.
Kes: Kami melaporkan satu kes pesakit yang mengalami gejala kesakitan mata kanan secara berulang dan kemerahan selepas trauma. Pemeriksaan menunjukkan kecacatan epitelium kronik yang berterusan walaupun pelbagai kaedah rawatan ditawarkan, termasuk rawatan perubatan dan pembedahan. Rawatan awal termasuklah penggunaan ubat titis mata buatan secara intensif, pemakaian kanta sentuh pembalut dan debridmen epitelium; namun gejala berulang. Peningkatan ketara dilihat satu bulan selepas rawatan menggunakan titisan mata serum autologous dimulakan, dan resolusi lengkap dicapai selepas selesai rejimnya. Tiada gejala berulang dilaporkan satu tahun selepas rawatan selesai.
Konklusi: Penggunaan titisan mata serum menunjukkan keberkesanan dalam merawat sindrom hakisan kornea berulang.

Kata kunci: sindrom hakisan kornea berulang, titisan mata serum

Introduction

Recurrent corneal erosion syndrome (RCES) is a common disorder worldwide first described in 1872 by Hansen as "intermittent neuralgic vesicular keratitis". It was later recognized as "recurrent erosion of the cornea" by Von Arlt in 1874 and was subsequently termed RCES in the current ophthalmic literature.[1] It is a chronic, relapsing, and debilitating condition characterised by recurrent episodes of pain, photophobia, watering, and blurred vision. It occurs due to poor adhesion of the corneal epithelium to its basement membrane.[2] Trauma is the most common factor, accounting for over half of the cases.[3] Of the cases reported, 87% involve the inferior third of the cornea.[3] RCES remains one of the most challenging conditions to manage despite advancements in corneal science. Most studies reported that recurrences occur during awakening or the rapid eye movement sleep phase.[4] The presence of superficial epithelial oedema from trauma may lead to poor epithelial adhesion. Hence, the opening of the eyelid or rapid eye movement produces a shearing force on the cornea epithelium, causing erosion.

Treatment options offered may range from simple conservative treatment to complex surgical intervention. Traditional measures include antibiotic eye drops,

vigorous preservative-free topical lubricants, cycloplegics, and oral analgesics to ease the pain. Using bandage contact lenses (BCL) may be beneficial as an adjunct to pharmacological therapies. Newer therapies include oral matrix metalloproteinase inhibitors, serum eye drops (SEDs), amniotic membrane grafts, and topical corticosteroids.[5] The reported use of SEDs for the treatment of persistent epithelial defects led us to consider its possible application in our patient, who presented with RCES despite undergoing multiple treatment modalities.

Case report

A 24-year-old woman who had multiple clinic visits presented to us with a complaint of eye pain and redness in the right eye for 3 days. She had a history of being hit by the edge of a car door on the side of her right eye before showing initial symptoms. At presentation, her best-corrected visual acuity (BCVA) was 6/12 in the right eye and 6/6 in the left eye. Slit lamp examination revealed a corneal epithelial defect with rough edges measuring 3 mm x 1.8 mm with fluorescein staining uptake in

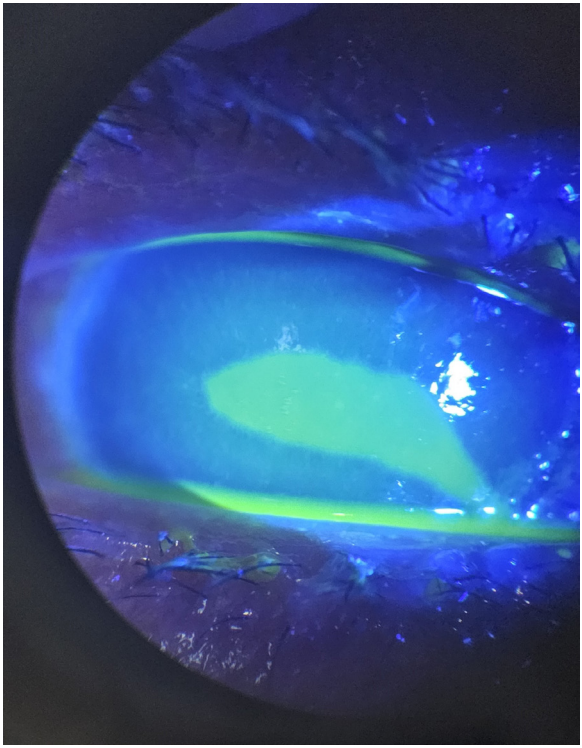

Fig. 1. Inferior epithelial defect.

the inferior region of the corneal surface, not involving the visual axis (Fig. 1). The anterior chamber was deep and quiet. Fundus was normal. Examination of the left eye revealed no significant findings. She had corneal epithelium debridement done twice; however, her condition did not improve. Therefore, the patient was treated as a case of RCES secondary to trauma.

The patient was given options for autologous SEDs treatment, and the procedures were explained. On follow-up 2 weeks after initiating of SEDs, her symptoms had improved. BCVA had improved to 6/7.5 in the right eye. Slit-lamp examination showed no epithelial defect (Fig. 2), with negative staining uptake (Fig. 3). SEDs application was continued every 2 hours for 2 months together

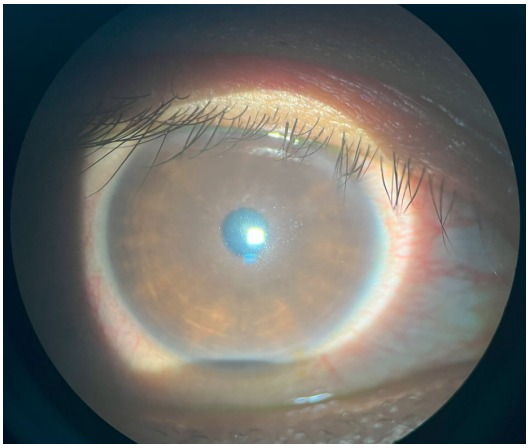

Fig. 2. Healed epithelial defect 2 weeks after treatment initiation of serum eye drops.

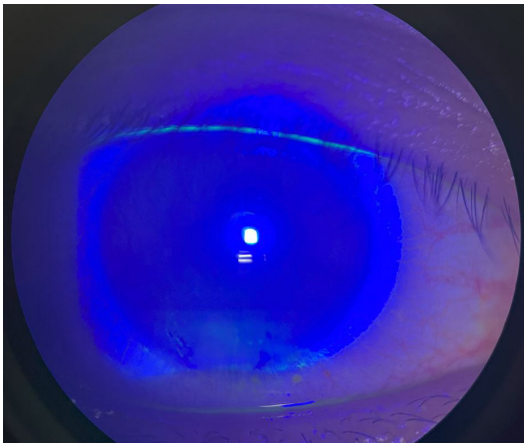

Fig. 3. Healed epithelial defect 2 weeks after treatment initiation of serum eye drops with negative fluorescent staining.

with a bandage contact lens. After 2 months, the regimen was tapered to 4 times daily for another 4 months. Upon reviewing the patient's condition 1 month after treatment initiation, her BCVA was 6/6 in the right eye, and symptoms had completely resolved. At the 1-year follow-up, she no longer had symptoms of RCES 1 year after completion of the 6-month treatment regime.

Discussion

Autologous serum was first introduced in 1975 by Ralph *et al.* to treat the ocular surface of patients with chemical burns using a mobile ocular perfusion pump.[6] Since then, it has been widely used to treat ocular surface diseases, including dry eye disease, Sjogren syndrome, persistent epithelial defects, exposure keratitis, recurrent corneal erosion, and Stevens-Johnson syndrome. Studies have documented that using blood-derived products has proven effective in treating corneal epithelial conditions. The effects of blood-derived products on the proliferation, vitality, and migration of corneal epithelial cells have been well-documented in both in-vitro and in-vivo experimental studies for the past few decades.[7]

Apart from supplementing the lack of tears, autologous SEDs also contain epitheliotropic factors that are essential for the restoration of damaged corneal epithelium, namely epidermal growth factor, transforming growth factor-beta1 (TGF-β), fibronectin, and platelet-derived growth factor-AB.[8] The presence of epitheliotropic factors, which are similar to those present in natural tears, makes it superior to lubricant eye drops.[9] The abundance of epitheliotropic growth factors aids in strengthening the epithelial adhesion complex, which is crucial to wound healing in the corneal epithelium. Based on these studies, the use of plasma eye drops was considered in our patient, who presented with a persistent epithelial defect despite being treated with both conservative and surgical methods.

SEDs are processed from whole blood through a centrifugation method. It can be obtained from the patient's blood (autologous) or donor blood (allogenic). At first, our patient used autologous SEDs. However, during the subsequent venesection, she experienced an episode of vasovagal syncope, and the procedure was abandoned. We then resorted to allogenic SEDs as an alternative. A pilot double-blind, randomised, crossover trial comparing autologous and allogeneic SEDs found no difference in efficacy.[10] Allogenic SEDs are assumed to be as effective as autologous SEDs in treating severe dry eye. We concur with this, as our patient reported improving symptoms using allogeneic SEDs. Lomas *et al.* found that treatment with both autologous and allogenic SED leads to a significant reduction in symptom severity based on the Ocular Surface Disease Index (OSDI) score. There was no statistically significant difference in OSDI score reduction between patients receiving autologous and allogenic SEDs.[11]

Tsubota *et al.* classified the efficacy of SEDs based on the time it took for epithelial defects to heal. SEDs were considered effective if the defect healed within 2 weeks, partially effective if healing was achieved in 1 month, and ineffective beyond 1 month. Based on the study, it was concluded that 43% of the total cases achieved complete resolution of the epithelial defect within 2 weeks, and 18% of cases resolved in 1 month. One-third failed to respond within the required duration.[12] Treatment with SEDs in our patient was considered effective as the epithelial defect had healed at the 2-week follow-up.

The dilution of SEDs also plays an essential role in determining its efficacy. Lekhanot *et al.* found undiluted SEDs to be more effective compared to diluted ones.[13] The rationale for diluting SEDs is to decrease the concentration of TGF-β in serum to a level equivalent to natural tears, as high TGF-β concentrations may possibly retard corneal epithelium healing, although there is no proven data. In our patient, undiluted serum eye drops were used since we believed that 100% serum eye drops would provide a higher concentration of growth factors and reduce the risk of contamination due to less serum manipulation. The major setbacks of using undiluted SEDs are the inconvenience of repeated venesection, a large volume of blood collection, and potential ocular irritation associated with the high viscosity of the eye drops. Regarding our patient, although undiluted 100% serum was used, there was no reported ocular discomfort or irritation.

We found no studies have determined SED therapy's optimal frequency and duration. The duration of treatment in studies ranges from 2 weeks to 6 months, which often coincides with the study duration.[14] No clear evidence suggests that more frequent instillation improves symptoms and clinical findings. The frequency and duration of treatment may vary depending on individual circumstances. Given its proximity to our case, we followed Lee *et al.*'s treatment regimen of 1 eye drop every 2 hours for 2 months, subsequently reduced to 4 times daily for the remaining 4 months, for a total duration of 6 months.[15] Another study by *Ziakas et al.* stated that a 6-month treatment regime was sufficient to keep patients symptom-free for at least 2.5 years.[16]

While effective in treating severe dry eye symptoms, SEDs have few limitations. Logistically, collecting blood and processing it into SEDs may result in a considerable waiting time for the patient. Additionally, patient-related factors such as poor venous access, low haemoglobin level, and fear of needles may become obstacles to collecting sufficient blood for autologous SEDs.[10] Meanwhile, allogenic SEDs might carry the risk of blood-borne disease transmission. Hence, all blood donations were tested for blood-borne diseases before processing into SEDs. Another primary safety consideration for SEDs is the risk of microbial growth during storage, as serum-based solutions are good growth media.[17] Microbial contamination remains a considerable risk in patients with compromised ocular surfaces.

Conclusion

In conclusion, blood-derived eye drops represent an exciting option for treating ocular surface disease. Our case highlights that using either autologous or allogenic SEDs proved very effective in treating RCES by resolving all symptoms in our patient at the 1-year follow-up. However, there is a clear need for a more detailed perspective involving larger studies with a more extended follow-up period to confirm our findings. Standardised treatment guidelines are needed to provide better evidence and implementation into daily clinical practice.

Declarations

Consent for publication
Informed consent was obtained from the patient to publish the data and images in this case report.

Competing interests
None to declare

Funding
None to declare.

Acknowledgments
None to declare.

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Case report
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Ocular effects of *Euphorbia trigo*na sap: a case report

Teoh Chia Yaw, Diymitra K A/P **Ganasan**

Department of Ophthalmology, Serdang Hospital, Jalan Puchong, Kajang, Selangor, Malaysia

Abstract

Background: African milk tree (*Euphorbia trigona*) sap contains toxic components, notably ingenol esters, causing cytotoxicity to corneal cells and hindering healing, thereby causing toxic keratopathy.
Case report: We present a case of ocular injury in a 45-year-old man following exposure to *Euphorbia trigona* sap during gardening. Despite immediate irrigation, the patient experienced discomfort, redness, and reduced vision in his right eye. Treatment involved aggressive topical antibiotics and subsequent corneal debridement.
Conclusion: Euphorbia trigona sap contains cytotoxic properties results in defective corneal epithelial healing. Understanding variations in latex compositions across species aid in clinical anticipation and individualised treatment.

Keywords: Euphorbia trigona, toxic keratopathy

Kesan okular Euphorbia trigona: laporan kes

Abstrak

Latar belakang: Getah African milk tree (Euphorbia trigona) mengandungi komponen toksik, terutamanya ester ingenol, yang menyebabkan sitotoksisiti terhadap sel-sel kornea dan menghalang proses penyembuhan, seterusnya mengakibatkan keratopati toksik.

Correspondence: YTeoh Chia Yaw, MBBS, Department of Ophthalmology, Serdang Hospital, Jalan Puchong, 43000 Kajang. Selangor, Malaysia.
E-mail: chowakanda@gmail.com

Laporan kes: Kami membentangkan kes kecederaan okular pada lelaki berusia 45 tahun berikutan pendedahan kepada getah Euphorbia trigona semasa berkebun. Walaupun pengairan segera dilakukan, pesakit mengalami ketidakselesaan, kemerahan, dan penglihatan berkurangan di mata kanannya. Rawatan melibatkan antibiotik topikal yang agresif dan pengelupasan kornea yang seterusnya.
Kesimpulan: Getah Euphorbia trigona mengandungi sifat sitotoksik yang mengakibatkan penyembuhan epitel kornea yang tidak sempurna. Pemahaman terhadap variasi dalam komposisi lateks antara spesies dapat membantu dalam jangkaan klinikal serta rawatan yang disesuaikan secara individu.

Kata kunci: Euphorbia trigona, keratopati toksik

Introduction

Euphorbia trigona, also referred to as the African milk tree, has garnered immense popularity due to its affordability, easy cultivation, and cultural significance. However, its latex harbours multiple toxic components that induce irritation in both skin and mucosa. Particularly, ingenol esters present in *Euphorbia trigona* exhibit potent cytotoxicity against keratocytes, hindering their proliferation and healing abilities within 24 to 48 hours of contact.[1] Furthermore, these compounds activate protein kinase C enzymes, potentially accounting for the hindered corneal epithelial healing and the likelihood of pronounced inflammation in the conjunctiva, cornea, and intraocular tissues. It's noteworthy that earlier reports have mentioned the antimicrobial properties associated with *Euphorbia* species' latex.[1-2] We present a case of rare case of alleged cactus sap chemical injury that results in defective epithelial healing.

Case presentation

A 45-year-old Malay man presented at the ophthalmology clinic experiencing discomfort, redness, and reduced vision in his right eye 1 day after exposure to *Euphorbia trigona* sap during gardening, despite immediate and thorough eye irrigation. He had no prior medical conditions, no known allergies, no pertinent systemic symptoms or family history. Examination revealed his visual acuity as OD 6/24 OS 6/9, with a bilateral intraocular pressure of 14 mmHg. Ocular pH stood at a neutral 7.4. Slit lamp examination indicated conjunctival hyperaemia and inferior corneal epithelial loss with sloughing along the superior edge, accompanied by a Descemet fold (Fig. 1). No signs of bacterial infection or foreign body presence were noted. Anterior chamber remained unremarkable, and posterior segment examination revealed no abnormalities.

Treatment commenced with aggressive topical antibiotics—ceftazidime 5% hourly and gentamicin 0.3% hourly—alongside appropriate oral analgesics. Upon review the next day, the patient exhibited improved vision at 6/18, with noticeable healing of the corneal epithelium, albeit with poor anterior stromal contact while the Descemet fold had resolved (Fig. 2). Subsequent corneal epithelial debridement was performed while maintaining the regimen of topical antibiotics and lubrication. Within 8 days from onset, the patient fully recovered with restored normal vision.

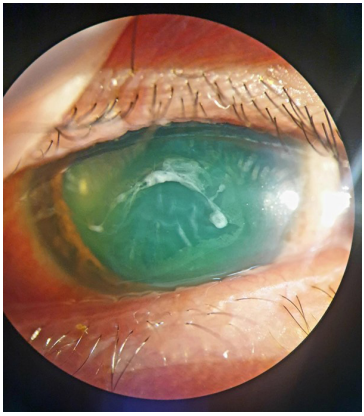

Fig. 1. Right eye, 1 day post exposure to Euphorbia trigona sap. Conjunctiva displaying hyperaemia, with a sizable area of inferior corneal epithelial loss measuring 2.6 mm x 2 mm, accompanied by epithelial sloughing along the superior border. A Descemet fold was observed over the region of epithelial loss, yet no corneal stromal oedema was present.

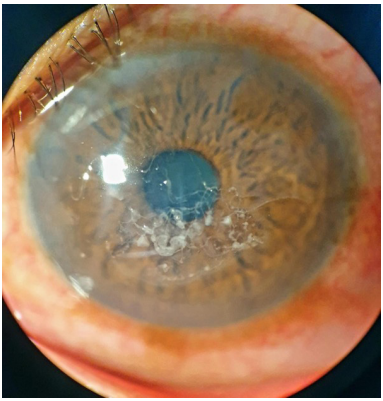

Fig. 2. Right eye, day 2 from onset. The corneal wound displayed ongoing healing, with remnants of corneal epithelial sloughing and insufficient adherence to the anterior stromal layer, making it prone to easy peeling. Both the Descemet fold and conjunctival hyperaemia had resolved.

Discussion

Comparative brief analysis with prior case reports, although involving distinct *Euphorbia* species, reveals consistent initial symptoms post-sap contact, including pain, reduced vision, lacrimation, blepharospasm, and photophobia. These symptoms often exacerbate over time. Clinically, the cornea typically exhibits a progression from a clear to minimal epithelial defect, potentially advancing to extended defects, stromal oedema, or Descemet striations by day 2. Most cases in reported series manifest conjunctival hyperaemia, with some presenting mild to moderate anterior uveitis.[3-5] Left untreated, complications may include corneal scarring, significant anterior chamber inflammation, and the development of anterior staphyloma.[3] Treatment commonly involves topical antibiotics, frequently combined with cycloplegics and steroids, resulting in satisfactory visual recovery within 1 to 2 weeks for most patients.[3-5]

In this specific case, clinical findings align closely with the chemical properties of *Euphorbia* latex. Observations revealed epithelial sloughing, partial loss, stromal oedema, and Descemet striations. Notably, poor corneal epithelial contact with the stroma on day 3 necessitated desloughing to prevent recurrent erosion. Unlike prior findings, the treatment regimen in this case included solely topical antibiotics, without the addition of cycloplegics or steroids, resulting in recovery without anterior chamber inflammation.

Conclusion

Insights gleaned from this case and previous reports emphasize the critical need for using protective gear, immediate irrigation, and early consultation, even when initial expectations are positive, to prevent severe complications. Furthermore, comprehending that diverse latex compositions across various species may contribute to varying clinical presentations and severity underscores the necessity for a broader dataset of cases to draw conclusive insights.

Declarations

Informed consent for publication
The patient provided informed consent for the publication of the clinical data and images contained in this case report.

Competing interests
None to declare.

Funding
None to declare.

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Phthisis with a threat: imaging and histopathology of a ciliary body adenocarcinoma

Sai Priyalatha Mariapan[1,2], **Gowri** Supramaniam[1], **Wan Mohd Hafidz** Wan Abdul Rahman[1], **Bastion** Mae-Lynn Catherine[2]

[1]Department of Ophthalmology, Hospital Tuanku Ja'afar Seremban, Negeri Sembilan, Malaysia; [2]Department of Ophthalmology, Pusat Perubatan Universiti Kebangsaan Malaysia, Cheras, Kuala Lumpur, Malaysia

Abstract

Background: Adenocarcinoma is a rare malignancy derived from the pigmented or non-pigmented epithelium of the ciliary body and/or iris.
Case presentation: A 35-year-old male with childhood left eye (LE) blindness developed throbbing pain and redness of LE for a few months. On examination, the LE showed conjunctival injection, chemosis, opaque cornea, and raised intraocular pressure. Computed tomography (CT) revealed LE phthisis bulbi and orbital cellulitis. Histopathology indicated a malignant epithelial tumour, likely adenocarcinoma of the ciliary body, with positive pancytokeratin immunohistochemistry. Contrast-enhanced CT showed an ocular mass without distant metastasis. Four months later, magnetic resonance imaging revealed residual tumour with local infiltration. The patient underwent exenteration and recovered well with a prosthesis.
Conclusion: A high index of suspicion for malignancy, along with appropriate laboratory tests, histopathological evaluation, imaging, and surgical intervention are essential to alleviate symptoms and preserve life.

Keywords: adenocarcinoma, ciliary body, exenteration, ocular malignancy, phthisical eye

Correspondence: Dr Sai Priyalatha Mariapan, Medical Officer, Pusat Perubatan Universiti Kebangsaan Malaysia, Jalan Yaacob Latif Kuala Lumpur, Bandar Tun Razak, 56000 Cheras, Wilayah Persekutuan Kuala Lumpur, Malaysia.

Tajuk: Pthisis dengan ancaman: pengimejan dan histopatologi adenokarsinoma badan siliari

Abstrak

Latar belakang: Adenokarsinoma adalah malignansi jarang berlaku yang berasal daripada epitel pigmen atau tidak pigmen pada badan siliari dan/atau iris.
Pembentangan kes: Seorang lelaki berusia 35 tahun dengan kebutaan mata kiri (LE) sejak kecil mengalami kesakitan berdenyut dan kemerahan pada mata kiri selama beberapa bulan. Pada pemeriksaan, mata kiri menunjukkan jangkitan konjuntiva, kemosis, kornea legap, dan tekanan intraokular yang tinggi. Tomografi berkomputer (CT) menunjukkan phthisis bulbi dan selulitis orbital. Histopatologi menunjukkan tumor epithelia yang malignan, kemungkinan adenokarsinoma badan siliari, dengan imunohistokimia positif. CT yang dipertingkatkan kontras menunjukkan jisim okular tanpa metastasis jauh. Empat bulan kemudian, pengimejan resonans magnetik mendedahkan tumor sisa dengan infiltrasi tempatan. Pesakit menjalani eksenterasi dan sedang pulih dengan prostesis.
Kesimpulan: Indeks kecurigaan yang tinggi terhadap malignansi, bersama ujian makmal yang sesuai, penilaian histopatologi, pengimejan, dan intervensi pembedahan adalah penting untuk mengurangkan gejala dan menyelamatkan nyawa.

Kata kunci: adenokarsinoma, badan siliari, eksenterasi, malignansi okular, mata phthisical

Introduction

Ciliary body tumours are rare, making up approximately 6% of all intraocular tumours.[1] Ciliary body adenocarcinoma (adenoCA) that arises from the uvea has an incidence rate of less than 3% of all ciliary body tumours, making it extremely rare.[2] They can either be melanotic or amelanotic, without sex predilection, and are often associated with a phthisical eye or underlying chronic inflammation.[3] In this case report, we describe the clinical presentation and histopathological features of a case of ciliary body adenoCA.

Case presentation

A 35-year-old man with childhood left eye (LE) blindness presented to the eye clinic with increasing LE throbbing pain and redness for a few months. He was otherwise healthy. There was no family history of malignancy and the cause of blindness of the LE was unknown. He denied recent trauma to the eye. LE examination revealed periorbital swelling, injected conjunctiva with chemosis, an opaque bulging cornea, and raised intraocular pressure (IOP) of 60 mmHg. Vision was confirmed to be no light perception by 2 specialists. There was no view of the anterior chamber, pupil, iris, or fundus. B-scan ultrasonography of the LE showed a clear vitreous, flat retina, and no T-sign or loculations. Right eye (RE) and systemic review were normal. There was Grade 2 reverse relative afferent pupillary defect elicited in his RE. Extraocular muscle movement was limited in the LE by 10% in all the gazes.

The patient was admitted for urgent imaging. Computed tomography (CT) of the orbits showed the left globe wall was thickened with calcification, suggesting underlying phthisis bulbi. Additionally, the CT showed a posterolateral collection, suggestive of globe rupture. The patient was also started on pain relief and IOP-lowering medications. Despite the medications, pain control was poor, indicating that the pain could be due to an ongoing inflammation. Topical and oral antibiotics were administered to prevent or treat possible infection.

We then proceeded with LE evisceration as the definitive management for diagnosis and symptom relief for this patient. The eviscerated tissue was sent for histopathological examination (HPE). The HPE findings of the eviscerated tissue sample revealed malignant epithelial tumour with features suggestive of ciliary body adenoCA. Immunohistochemical study showed tumour cells diffusely positive for pancytokeratin and focal positive for cytokeratin. Contrast-enhanced axial CT (CECT) (Fig. 1, left) of the orbits showed a lobulated mass at the left orbital region. CECT of the thorax, abdomen, and pelvis showed no evidence of distant metastasis. Tumour markers carbohydrate antigen 19.9, carcinoembryogenic antigen, alpha fetoprotein, and prostate-specific antigen all came back normal.

This patient subsequently developed left eyelid swelling 4 months after evisceration. Magnetic resonance imaging of the orbits revealed a residual tumour with local infiltration and a bulky left lacrimal gland (Fig. 1, right). He was then referred to the oculoplastic team and underwent exenteration. He recovered well and had a prosthesis inserted 6 months after exenteration.

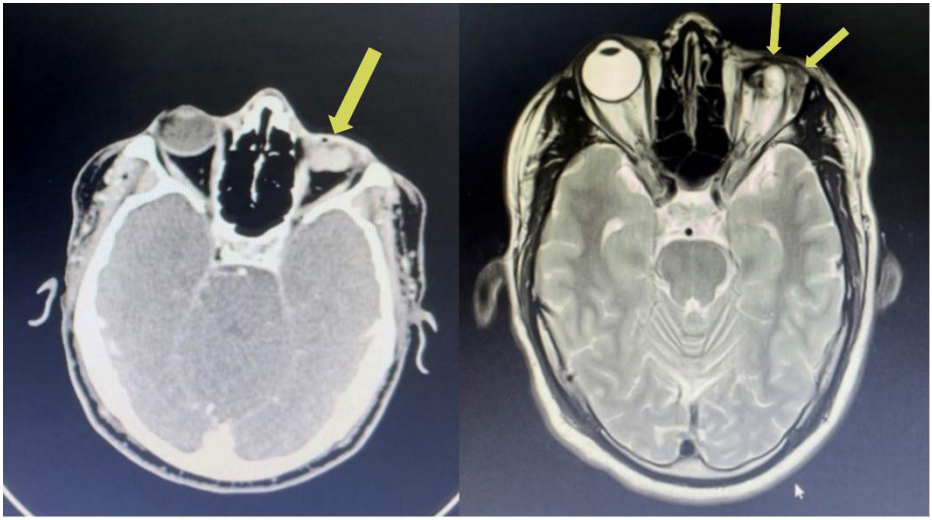

Fig. 1. (Left) CECT axial view of the orbits showing a lobulated heterogeneously enhanced mass (yellow arrow) at the left orbital region and thickening of overlying skin. *(Right)* T2W MRI axial view of the orbits showing loss of normal left globe configuration and lobulated mass measuring 1.5 x 1.1 x 1.0 cm, and a bulky left lacrimal gland (yellow arrows).

Discussion

Adenocarcinoma is a rare malignancy derived from the pigmented or non-pigmented epithelium of the ciliary body and/or iris, associated with local invasion and cellular differentiation, which may result in distant metastasis.[2] Poorly differentiated tumours such as this are commonly found in phthisical eyes with or without a history of trauma or ocular inflammation.[4]

According to the largest series on ciliary body adenoCAs to date, involving a total of 12 eyes, 9 out of 12 (75%) tumours were noted to have occurred in phthisical eyes in adults.[3] Even patients with longstanding phthisis bulbi, such as our patient, may present with new onset of proptosis, intractable pain, inflammation and swelling. Floaters, decreased vision, or increased IOP may also be one of the symptoms.[5] Some of the ocular signs that may be seen in these type of cases are as intraocular calcification, haemorrhage, secondary cataract formation, and/or subluxation of the lens. Nevertheless, when a patient presents in such fashion as our case, the first step in the presence of new symptoms of acute onset is to consider whether infection is involved; in this case, orbital infection due to the presence of chemosis. When the history is uncertain, it is appropriate to institute antibiotic prophylaxis with broad-spectrum systemic antibiotics upon admission, as even scleral buckles have been missed previously in patients with unknown history.[6] A thorough

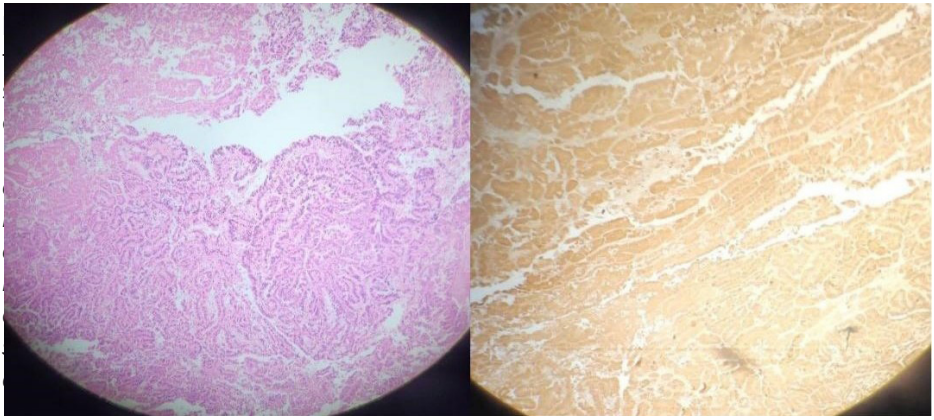

Fig. 2. (Left) Tumour cells arranged in a complex glandular pattern with prominent basement membrane. *(Right)* Tumour cells with diffuse pancytokeratin.

Indeed, renal cell carcinoma can also present for the first time with metastasis to the choroid, as has described by Feendi et al. in the absence of a primary.[9] Another type of cancer that can involve the eye and present with ocular signs and symptoms first includes leukaemia or lymphoma.[10] Hence the importance of performing systemic examination and screening for this patient to exclude a primary tumour elsewhere.

Histopathologically, primary ciliary body epithelial or retinal pigment epithelial adenocarcinomas are characterised by a prominent basement membrane, a feature also observed in the HPE of the eviscerated tissue from our patient (Fig. 2, left). This explains the inclusion of HPE findings in our report. The presence of prominent basement membrane is never a feature of metastatic carcinomas to the globe.[3] Studies have also shown that tumour cells near the iris are arranged in papillary and tubular fashion. The singular cells are round to oval in shape with hyperchromatic nuclei, high nuclear cytoplasmic ratio, and scanty cytoplasm.[5] Ciliary body adenoCAs have been described to have either one of 4 basic patterns: glandular or papillary; pleomorphic of low grade; pleomorphic with hyaline stroma; or anaplastic.[4] In our patient, the tumour cells were arranged in a complex glandular pattern (Fig. 2, left), with pleomorphic cells displaying vesicular nuclei. Microscopic examination of the eviscerated tissue from our patient revealed extensive necrosis.

Immunohistochemically, the tumour cells typically express pancytokeratins (Fig. 2, right) and cytokeratins specific to ciliary body adenoCA; these were positive in our patient as well.

Evisceration is an established treatment for the management of a painful blind eye,[3] which was the immediate management for our patient. Enucleation is typically considered when an intraocular tumour is suspected to be confined to the globe. However, our patient presented with symptoms following the initial evisceration. Fortunately, there was no evidence of tumour spread beyond the globe, aside from

extension into the adjacent orbit. The defect in the eyewall seen on the preoperative CECT scan provided an important clue, suggesting that the tumour had already extended into the orbit prior to surgery. In retrospect, exenteration would have been more prudent from this perspective. In contrast to evisceration and enucleation, exenteration is a more invasive procedure with a higher risk of disfigurement, particularly for a young man in his productive working years. If the less invasive option is pursued, then close monitoring, such as in our case, with patient education is mandatory to reduce recurrence and distant spread. Surveillance for this condition is lifelong. Our patient was also referred to the oncology team for surveillance, and an MRI 1 year after the exenteration showed no evidence of recurrence or tumour metastasis. Oncologists recommend considering systemic therapy with palliative chemotherapy to slow the progression of the disease and improve symptom control in metastatic cases. The choice between initial systemic chemotherapy and local radiotherapy depends on factors such as the patient's overall fitness, the extent of symptoms, previous treatments, and the patient's preferences.[3] Prosthesis implantation helps restore some degree of cosmesis for the patient, which goes a long way towards his self-esteem. It also has the advantage of retaining the socket shape and size, thus ensuring the eye socket and the remaining eye anatomy to function properly.

Conclusion

Ciliary body adenoCA should be suspected in patients with new symptoms and signs in their phthisical eye. Good health and well-being can be achieved through early detection and management of ocular malignancies, including the role of imaging and histopathology in diagnosis and treatment.

Declarations

Informed consent
This case report was written using the clinical data of the patient in 2021. Verbal consent was obtained in which the patient agrees with the research use of images of the eye, clinical records, and data with anonymization.

Competing interests
The authors declare that there is no conflict of interest with respect to the publication of this article.

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