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Punctiform Keratopathy: Bilateral Uniformly Diffuse Punctate Corneal Opacities in Workers of a BCMP Manufacturing Plant

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Abstract

We present the features and management of 2 cases presenting simultaneously with a novel bilateral, uniformly diffuse punctate keratopathy. A 40-year-old woman (Patient 1) and a 56-year-old woman (Patient 2) working together in a BCMP manufacturing facility presented simultaneously to the outpatient clinic at Fudan Eye and ENT Hospital, Shanghai, China with a gradual reduction in vision. Examination revealed bilateral corneal opacities extending from the sub-epithelium, through to the anterior stroma, observed with slit-lamp biomicroscopy, *In-vivo* Corneal Confocal Microscopy (IVCCM) and Fourier-domain Optical Coherence Tomography (FD-OCT). Patient 1 underwent LASEK and PTK on her right eye for both refractive correction and removal of the corneal deposits, achieving favourable clinical and visual outcomes. Patient 2 received no surgical treatment due to more dense opacities and severe vision loss. We are unable to prove that the corneal deposits were a direct result of their occupational exposure to BCMP, and the etiology remains unclear. LASEK combined with PTK was demonstrated to be useful in improving vision via both refractive corneal surface ablation and direct removal of corneal deposits, with good improvements in both clinical signs and symptoms.

Keywords: Cornea; Punctiform opacities

Abbreviations

FD-OCT	:	Fourier-domain Ocular Coherence Tomography
NCT	:	Non-contact Tonometry
UCVA	:	Uncorrected Visual Acuity
BCVA	:	Best-corrected Visual Acuity

Background

Occupational injuries are a common cause of presentations to hospital, and many are preventable with the use of personal protective equipment, safety protocols and safe work environments. This is especially true for occupational eye injuries, where many can be prevented with simple protective eyewear. This is of particular relevance as many occupational eye injuries have the potential to cause a significant morbidity burden in the adult working population, with a risk of permanent vision loss, as well as personal and financial costs through time out of work and medical expenses.

Disorders of the cornea can range from acute emergencies to chronic disorders that may be detected incidentally. Particular features in the history of presenting complaint, as well as specific signs or investigation findings can help to direct clinicians towards an accurate diagnosis and appropriate treatment. Occupational-related eye injuries are a serious concern and may pose serious visual and practical implications for the sufferer. They occur most frequently in the construction and manufacturing industries, with the majority of presentations typically being corneal abrasions

or foreign body injuries [1]. For this reason, many presentations are acute, with a clear precipitating event, and with often very symptomatic patients.

The following cases describe a unique incident of diffuse punctiform corneal opacities in two patients who presented simultaneously following long-term exposure to BCMP (4,4'-Bis(chloromethyl)-1,1'-biphenyl) in the workshop of a BCMP manufacturing plant. BCMP belongs to a group of chemicals known as Polychlorinated Biphenyl (PCB) compounds. PCBs were once widely used in a range of products and manufacturing processes, before they were found to be the cause of a range of environmental and health problems, with previously reported cases of both systemic and ocular toxicity secondary to BCMP exposure [2-4].

The cases we present here illustrate two unusual presentations of a uniformly diffuse punctate keratopathy in an occupational setting, with their presentations, treatment and outcomes presented. In each case, both women presented after long-term visual changes and ocular symptoms, but no acute precipitating factor or trigger. Their histories of occupational exposure to BCMP correlated well with their symptoms, and their clinical signs were inconsistent with those expected in a range of known corneal disorders. As these cases do not correlate with any previously described corneal disorders, we have termed it 'Punctiform Keratopathy'. This case study aims to highlight the significance of considering occupational exposure and toxicity as a cause of corneal disorders and vision reduction, and the importance of obtaining a thorough history and examination in determining appropriate management options to achieve favourable outcomes in unknown conditions with no clearly prescribed treatment options. To the best of our knowledge, this is the first case report of symmetrical corneal opacities in an occupational setting.

Case Presentation

Patient 1: Patient 1 was a 40-year-old woman who presented to the ophthalmic outpatient clinic at the Fudan Eye and ENT Hospital in Shanghai, China with complaints of a gradual loss of vision and conjunctival congestion in both eyes over the preceding five months. She denied any significant pain or history of ocular injury. On further questioning, she recalled a long-standing history of intermittent red and watering eyes, with occasional stabbing ocular pain, which began over 12 months prior.

Patient 1 had worked in a BCMP manufacturing plant for 15 months prior to her presentation to the Fudan Eye and ENT Hospital. The history of her presenting symptoms were correlated with her period of employment in the BCMP manufacturing plant, with her symptoms of painful, red and watering eyes beginning soon after starting work and resolving within 2 months of ceasing employment at the BCMP manufacturing plant.

There was no previous history of ocular disease or any spectacle or contact lens wear. Her past medical history was otherwise unremarkable, and she denied any use of regular medications. There was no family history of corneal or systemic disorders.

Patient 2: Patient 2 was a 56-year-old woman who presented to the ophthalmic outpatient clinic at the Fudan Eye and ENT Hospital in Shanghai, China at the same time as Patient 1. She presented with similar symptoms to that of Patient 1, reporting a gradual loss of vision and conjunctival congestion in both eyes over the preceding six months. She too denied any significant pain or history of ocular injury. Further questioning also revealed a long-standing history of intermittent red and watering eyes, with occasional stabbing ocular pain; which she also attributed to her working conditions.

Patient 2 had also been working in the same BCMP manufacturing plant as Patient 1 for 15 months. Like Patient 1, her symptoms of painful, red and watering eyes began soon after starting work and resolved within 2 months of ceasing employment at the BCMP manufacturing plant.

There was no previous history of ocular disease or any spectacle or contact lens wear. Her past medical history was otherwise unremarkable, and she denied any use of regular medications. There was no family history of corneal or systemic disorders.

Occupational Conditions

Both Patient 1 and Patient 2 worked at the same BCMP Manufacturing plant at the same time. They both denied using any personal protective eyewear or clothing when working at the plant. As a result, they often experienced painful, red and watering eyes; however, as their symptoms were often temporary and tolerable, they did not seek medical attention earlier. They both attributed their symptoms and signs to their exposure to BCMP, which they used and were exposed to daily.

Both Patient 1 and Patient 2 had ceased employment at the same BCMP manufacturing plant in which they worked approximately 2 months prior to their presentation to the ophthalmic outpatient clinic at the Fudan Eye and ENT Hospital. They both reported that their symptoms of painful, red and watering eyes had resolved soon after ceasing work, but continued to complain of reduced vision. They also reported that two other plant workers suffered from similar symptoms, with one receiving treatment at another hospital, the details of which were unknown.

Examination Findings

Patient 1: On examination, Patient 1 had an uncorrected visual acuity (UCVA) of 20/200 in both eyes, and her best-corrected visual acuity (BCVA) was 20/30 in the right eye and 20/40 in the left eye. She had a refractive error of Plano/-2.00x90 in the right

eye and -0.25/-1.75x90 in the left eye. Intraocular pressures were 16 mmHg and 19 mmHg in the right and left eyes respectively.

Slit-lamp examination of both eyes revealed mild bilateral conjunctival congestion and dense white, granular and hyper-reflective corneal opacities in the superficial corneal stroma with otherwise clear corneal tissue between opacities bilaterally, which were quite symmetrical and consistent between eyes (Figures 1A, B).

Figures 1(A-D): Slit-lamp biomicroscopic examination of both eyes in Patient 1 (**A** = Right eye, **B** = Left eye) pre-surgery revealed mild bilateral conjunctival hyperemia and dense white, granular and hyper-reflective corneal opacities in the superficial corneal stroma, with clear cornea between opacities bilaterally. The opacities appeared quite symmetrical and consistent between the Right eye (**A**) and the Left eye (**B**). Post-surgery, a significant decrease in the total number of opacities was observed, especially around the optic zone (**C**). Patient 2 had a similar slit-lamp biomicroscopic appearance to Patient 1; only one eye of which is shown (**D** = Right eye). Upper eyelids were everted to exclude the presence of a foreign body. The anterior chambers of both eyes were normal. The fundus examination of both eyes was normal. No abnormalities were revealed on general physical examination or routine blood tests.

Patient 2: On examination, Patient 2 had an UCVA of 20/400 in both eyes, with no obvious stable refractive error or any significant improvement in vision with a change in refraction. The refractive error of Patient 2 could not be determined due to the severity of the corneal opacities.

Slit-lamp examination of both eyes revealed mild bilateral conjunctival congestion and corneal opacities, similar to those seen in Patient 1 (Figure 1D). The corneal opacities appeared densely white, granular and hyper-reflective in the superficial corneal stroma, with otherwise clear corneal tissue between them. They were quite symmetrical and consistent between eyes. The upper eyelids were everted to exclude the presence of a foreign body. The anterior chambers of both eyes were normal. The fundus examination of both eyes was normal.

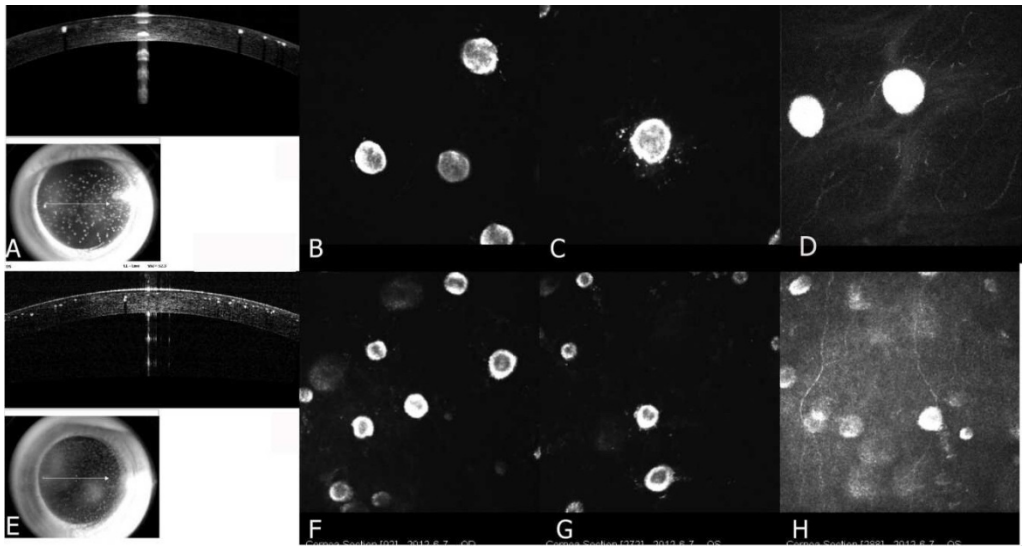
No abnormalities were revealed on general physical examination or routine blood tests.

Investigations

Both patients underwent investigation for their corneal opacities with corneal topography (Pentacam, Oculus), anterior segment Fourier-domain Ocular Coherence Tomography (FD-OCT; Optovue Inc., Fremont, California, USA) and *In-vivo* corneal confocal microscopy (IVCCM; Heidelberg Retina Tomograph III, Rostock Cornea Module, Germany).

Patient 1: Corneal topography was normal in both eyes. Both confocal microscopy (Figures 2B-D - IVCCM) and anterior segment FD-OCT (Figure 2A) demonstrated large amounts of round, hyper-reflective opacities deposited in the sub-epithelium, Bowman's layer and anterior stroma of the corneas, with the depth of depositions approximately 150 to 180μm. IVCCM also demonstrated sparse and tortuous nerve fibres in the corneal basement epithelium and sub-basal corneal nerve bundles (Figure 2D).

Histopathological examination with Haemotoxylin and Eosin staining of the biopsy specimen obtained during surgery revealed mostly normal corneal epithelium except for some eosinophilic staining of a section of the basement membrane, suggesting the presence of an abnormal basal membrane reaction.



Figures 2(A-H): Both FD-OCT (**A, E**) and confocal microscopy (**B-D**, **F-H**) demonstrated large amounts of round, hyper-reflective opacities deposited in the sub-epithelium, Bowman's layer and anterior stroma, with the depth of the depositions ranging from approximately 150 to 180 µm.

Patient 2: Corneal topography was normal in both eyes. Both confocal microscopy (Figures 2F-H) and anterior segment FD-OCT (Figure 2E) demonstrated large amounts of round, hyper-reflective opacities deposited in the sub-epithelium, Bowman's layer and anterior stroma of both corneas. Investigations demonstrated a similar appearance to that seen in Patient 1, only with a greater number of opacities. IVCCM of the cornea also demonstrated sparse and tortuous nerve fibres in the corneal basement epithelium and sub-basal corneal nerve bundles (Figure 2H), like those observed in Patient 1. No histopathological examinations were conducted as there was no corneal sample obtained for Patient 2.

Treatment

Patient 1: Patient 1 underwent Laser-assisted Sub-epithelial Keratomileusis (LASEK)combined with phototherapeutic keratectomy (PTK) of the right eye at our hospital for both refractive error correction and removal of the corneal opacities. An 8.5mm diameter epithelial flap was excised for histopathological examination. The first 42µm of corneal stroma was ablated for a refractive correction of -2.00 Diopters Sphere (DS), followed by an ablation of 60µm in depth and then a further 40µm of the cornea, which was removed to remove the corneal opacities. The deposits were gently scraped off with a crescent blade before each laser treatment. The thickness of the corneal epithelium that was removed was 142µm in total. At the end of the procedure, 0.02% Mitomycin C was applied to the surgical site for 20 seconds, then rinsed off with normal saline. A bandage contact lens was placed on the eye for 1 week after surgery to improve patient comfort. Topical fluorometholone 0.1% and gatifloxacin eye drops were applied four times daily in the right eye for two weeks. No surgical or optical treatment was performed on the left eye.

Patient 2: Patient 2 had much more severe vision loss, with deeper and more abundant opacities in her corneas (Figure 1D, Figure 2E). Her corneal thickness (472µm in the right eye, 483µm in the left eye) was also much thinner than Patient 1, and was an inadequate thickness for the surgical removal of the foreign bodies using LASEK or PTK due to the risk of corneal biomechanical instability. Therefore, due to the dense nature of her corneal opacities and severe vision loss, it was deemed at the time that there would be no significant clinical improvement with spectacles, contact lenses or corneal surgery, and Patient 2 did not receive any treatment. Further investigations are needed to determine the most appropriate treatment for the degree of keratopathy, vision loss and corneal thickness seen in Patient 2.

Outcome and Follow-up

Patient 1: Follow-up examinations were scheduled for 1 week, 2 weeks, 2 months and 3 months after surgery. Post-operatively, BCVA in the Right eye (treated eye) was 20/60, 20/60 and 20/40 at 2 weeks, 6 weeks and 3 months respectively. The BCVA in the left eye was 20/40 at all three-month review periods. Corneal topography was performed at 1 week, and demonstrated good corneal healing with no abnormalities in the right eye. Slit-lamp biomicroscopy showed a significant decrease in the total number of granular opacities, especially around the optic zone(Figure 1C) in her Right eye that underwent surgery. The vision recovery process in the Right eye was slow, but stable (Table 1).

	1 week	2 weeks	2 months	3 months
NCT(mmHg)	7.8	8.6	8.0	10.4
UCVA	20/200	20/200	3/10	20/40
BCVA	20/200	3/10	3/10	20/40

Table 1: Intraocular pressure, UCVA and BCVA of the right eye of Patient 1 in 1 week, 2 weeks, 2 months, 3 months.

NCT, non-contact tonometer; UCVA, uncorrected visual acuity; BCVA, best spectacle-corrected visual acuity. In the left eye, which received no surgical treatment, the amount of opacities observed on slit-lamp biomicroscopic examination did not appear to change at 6 months, with no obvious increase or decrease in the extent of corneal opacities observed. We found that the left eye of Patient 1 (untreated eye) had a slight decrease in UCVA at 6 months; however, this may have been due to inaccurate testing, as she was unable to focus on the vision chart as she found the right eye was too painful to close. This pain in the Right eye resolved after a few weeks without the need for any further management and Patient 1 reported an overall improvement in her subjective vision and ocular symptoms.

Patient 2: As there were no treatment options available for Patient 2, she was discharged from the ophthalmic outpatient clinic at Fudan Eye and ENT Hospital. No further follow-up or outcome data was available.

Discussion and Conclusions

Ocular injuries in major industrial occupations occur most commonly in the construction and manufacturing industries, and are responsible for 45% of all work-related eye injuries [1]. A lack of personal protective equipment further increases the risk, with one epidemiological report on ocular injuries by Wong et al. finding that only 25% of workers who had an ocular injury were wearing eye protection at the time of sustaining the injury [5]. The cases we have presented here illustrate two unique presentations of a uniformly diffuse punctate keratopathy in an occupational setting. In each case, both women presented simultaneously to the ophthalmic outpatient clinic at Fudan Eye and ENT Hospital after long-term visual changes and ocular symptoms, but no acute precipitating factor or trigger. Their histories of occupational exposure to BCMP, without the use of any eye protection, correlated well with their symptoms, and their clinical signs were inconsistent with those expected in a range of known corneal disorders. As these cases do not correlate with any previously described corneal disorders, we have termed it 'Punctiform Keratopathy'. To the best of our knowledge, this is the first case report of symmetrical corneal opacities resulting from long-term chemical exposure to BCMP in an occupational setting.

The first injury caused by BCMP in humans was reported in China in 1997 [4] when eight workers in a BCMP manufacturing workshop suffered systemic acute poisoning after washing plastic buckets containing BCMP particles for two hours. In addition to systemic poisoning, the patients experienced ocular toxicity, suffering from swollen eyelids, tearing and conjunctival hyperemia; which recovered after symptomatic and supportive treatment. Therefore, people working in an occupational setting where there is exposure to BCMP should be aware of the risk of toxicity (short-term or long-term), which has the potential to result in serious ocular consequences. Workers in BCMP production factories should be aware of such potential occupational injuries and should take appropriate personal protective measures to minimize the potential harms.

BCMP (or BCMBP, formulaC14H12Cl2, CAS No.1667-10-3) is one of a groups of Polychlorinated Diphenyls (PCBs). They have been used as crosslinking reagents to synthesize certain polymeric adsorbents and have been widely utilised in modern adsorption separation processes since the 1970s [3]. Their ubiquitous presence and their lipophilic nature have led to the biomagnification of PCBs in aquatic organisms, but little is still known about their physical and chemical properties, their environmental transport and fate, or the presence of PCBs in humans [2]. There are worrying initial indications that some Flame Retardants (FRs), of which BCMP is one example of, exhibit PBTL (persistence, bioaccumulation, toxicity and long-range transport) characteristics [6]. We should be concerned about PBTL when considering the effects of BCMP on humans and the environment because BCMP is an analogue of PCBs and FRs.

Occupational exposure of humans to BCMP occurs mainly via a combination of exposure to indoor dust and the inhalation of indoor air. In the two patients presented in this case study, routine blood tests and ophthalmoscopy revealed no abnormalities. The patients experienced ocular pain because of dust in the workshop getting into their eyes. It is possible that they may have also inhaled BCMP particles, however, because they had no other physical complaints, examinations of the lungs were not performed. When chemical substances accumulate in the cornea and penetrate the corneal epithelium, patients often experience intense corneal pain and scarring, which was not the case in the two patients we have presented here. The histopathological findings of the biopsy specimen of Patient 1 with Haemotoxylin and Eosin staining revealed mostly normal corneal epithelium except for some eosinophilic staining of a section of the basement membrane, suggesting the presence of an abnormal basal membrane reaction. Nevertheless, there is no definitive evidence to suggest that the deposits and corneal opacities were BCMP itself or any of its' by-products after chemical degradation following human metabolism.

These patients also exhibited sparse and tortuous nerve fibres in their corneal basal epithelium and sub-basal corneal nerve bundles (Figures 2D, H), which were observed to decrease in density over time. This might explain their tolerance of symptoms, as adequate corneal innervation plays an essential role in nociceptive symptoms and in influencing corneal epithelial metabolism, cell adhesion and wound healing. Some disease such as diabetes, dry eye, keratoconus and herpes zoster ophthalmicus also demonstrate a decreased density of sub-basal corneal nerve fibres, and are often associated with decreased corneal sensation and compromised corneal structure and function. The appearance of the sub-basal nerve fibres in Patients 1 and 2 could be due to age or the deposits, but the relationship between them in these two cases are still unknown.

Although the aetiology of the corneal opacities presented here are not entirely definitive; given their presentation, histories and the circumstances of their development, corneal injury secondary to chemical exposure to BCMP was deemed to be the most likely cause. It is unlikely that these cases are indicative of an inherited corneal dystrophy. Although corneal opacities are typical in CDs, many CDs often demonstrate recurrence after treatment [7], with neither of our patients experiencing any exacerbations or recurrences of corneal deposits during the follow-up period. The mechanism underlying many CDs remains to be solved [7], and if these opacities were not due to foreign bodies, their formation might share a similar mechanism to that of some known CDs. Both patients, however, claimed that the opacities were caused by their exposure to BCMP, which was the substance they dealt with on a daily basis, with reports of at least two other colleagues presenting with similar corneal opacities. The clinical histories of both Patients 1 and 2 were strongly correlated with their time of exposure to BCMP and support the conclusion that their signs and symptoms were caused by their exposure ocular to BCMP.

We were able to successfully treat one eye of Patient 1 and achieve good visual and ocular outcomes. A combination of LASEK and PTK procedures were performed on the eye with better visual acuity (right eye) in Patient 1. This procedure was chosen to improve vision via both refractive corneal ablation and the removal of corneal deposits. We had considered other treatment alternatives such as using solvents to dissolve the foreign substances, however, due to a lack of studies on the nature, toxicity and concentration of solvents, and their potential to cause serious ocular complications, this treatment option was not pursued. Corneal transplantation was another possible treatment approach that was considered; however, this would require a much longer recovery time and carries the possibility of graft rejection and induced astigmatism after transplantation, which are significant complications that should be considered. Therefore, we considered this treatment regime of LASEK and PTK to be the best treatment option for Patient 1, which was undertaken after discussion of the risks and benefits with her.

Phototherapeutic Keratectomy (PTK) is the procedure of choice for the treatment of shallow corneal deposits. For patients with CD, it is also used for improving vision and delaying the need for penetrating keratoplasty (PKP) or deep anterior lamellar keratoplasty (DALK) in the future, which is often required in the event of further deposition of corneal opacities. Refractive corneal surface ablation is one of the most commonly used procedures for the correction of refractive errors in many countries, which was an additional benefit in the visual correction of Patient 1. Although cost should not be a factor in the decision making process of a patient's management, in Fudan Eye and ENT Hospital, where patients are required to pay for their treatment, the choice of LASEK happened to also be an economically viable option for Patient 1.

The vision loss of Patient 2, however, was much more severe, with deeper and more abundant opacities in her cornea (Figure 1D, Figure 2E). Her corneal thickness was also much thinner than Patient 1, and was an inadequate thickness for the surgical removal of the foreign bodies using LASEK or PTK due to the risk of corneal biomechanical instability. Because of the lack of viable treatment options, Patient 2 was discharged from the ophthalmic outpatient clinic at Fudan Eye and ENT Hospital with no improvement in her clinical signs or symptoms. Further investigation is needed to determine the most appropriate treatment for the degree of keratopathy observed in Patient 2.

Although the aetiology and mechanism of the corneal opacities observed in Patients 1 and 2 remain unclear, their histories and presentations are highly suggestive of an occupational eye injury secondary to chronic exposure to BCMP. Further investigations will be needed to determine the precise aetiology and the most appropriate and effective treatment options for this particular punctiform keratopathy. Further investigations are also required to determine the concentrations of BCMP in indoor dust and air that is significant enough to cause complications for humans exposed to BCMP. These two cases suggest that exposure to BCMP was the primary environmental factor contributing to the corneal opacities observed, which may share a similar mechanism with the development of corneal opacities seen in a range of CDs, and therefore, may have prognostic significance and contribute to our understanding of the mechanisms underlying some CDs. Comprehensive long-term monitoring programs are urgently needed, in close collaboration with the manufacturing and production industries, to mitigate the risks of PCBs on ecosystems and human health.

As these cases do not correspond with any previously described corneal disorders, we have termed it 'Punctiform Keratopathy', which best describes its clinical features. Although the aetiology was unclear, the history and examination findings strongly suggest that the opacities were related to the working

conditions of the two patients and their exposure to BCMP. LASEK and PTK were demonstrated to be useful in improving vision by refractive corneal surface ablation and removing corneal deposits for an improvement in clinical signs and symptoms. Due to the severity of disease observed in Patient 2, however, no viable treatment options were available, and further investigation is required to determine suitable treatments for this degree of disease. This case study highlights the significance of occupational exposure and toxicity as a cause of corneal disorders and vision reduction, the importance of protective eyewear in an occupational setting and the utility of LASEK and PTK in treating corneal opacities causing visual and ocular symptoms in a previously unknown condition.

Declarations

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Patient Consent

The patients consented to publication of the case.

Acknowledgement and Disclosures

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We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

All authors attest that they meet the current ICMJE criteria for Authorship.

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