Monaldi Archives for Chest Disease

eISSN 2532-5264 https://www.monaldi-archives.org/

Monaldi Arch Chest Dis 2024 [Online ahead of print]

To cite this Article:
Singh M, Deokar K, Sinha BP, et al. **Infective pulmonary diseases and the eye: a narrative review.** *Monaldi Arch Chest Dis* doi: 10.4081/monaldi.2024.2988

Infective pulmonary diseases and the eye: a narrative review

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Contributions: KD, MS, conceived the idea; MS, KD, BPS, JD, CDSK, performed the literature search; KD, MS, prepared the manuscript; BPS, JD, CDSK, revised the manuscript.

Conflict of interest: the authors declare no potential conflict of interest.

Ethics approval and consent to participate: not applicable.

Patient consent for publication: not applicable.

Funding: none.

Availability of data and materials: not applicable.

Abstract

Several infectious pulmonary diseases affect the eye. An understanding of the association between infectious pulmonary and ocular diseases is pivotal to their successful management. We aimed to review the infections affecting both the lungs and the eye. The electronic database PubMed and the search engine Google Scholar were searched for relevant articles. Ocular tuberculosis (TB), usually not associated with clinical evidence of pulmonary TB, can affect almost all the ocular structures. Confirmation of the diagnosis of ocular TB requires demonstration of *Mycobacterium tuberculosis* in ocular fluids/tissues. Among the drugs used to treat TB, ethambutol, isoniazid, and linezolid may cause toxic optic neuropathy. Elderly, those with renal disease, diabetes mellitus, malnourished, alcoholics, and those who will receive ethambutol at doses greater than 15 mg/kg/day and for prolonged periods are at high risk of developing toxic optic neuropathy. These individuals should be referred to an ophthalmologist before initiating ATT for a baseline ophthalmic evaluation. Linezolid may also cause toxic retinal neuropathy. Rifampicin may cause yellowish-orange discoloration of tears and contact lenses. Adenovirus, coronavirus, influenza virus, respiratory syncytial virus, and rhinovirus exhibit both pulmonary and ocular tropism. Pneumocystis jirovecii choroiditis is rare and mainly seen when aerosolized pentamidine is used for pneumocystis pneumonia prophylaxis. Further research is needed to develop non-interventional strategies to diagnose ocular TB. Biomarkers for early detection of toxic optic neuropathy are a need of the hour. Genetic factors and mechanisms behind the development of ethambutol, isoniazid, and linezolid-induced toxic optic neuropathy need further study.

Key words: eye, ocular tuberculosis, toxic optic neuropathy.

Introduction

In the category of the "big five" lung diseases responsible for a significant portion of the global burden of lung disease, infective lung pathologies such as acute lower respiratory tract infections and tuberculosis have been recognized as key contributors [1]. They continue to pose an important threat, especially in developing countries due to lack of sufficient immunity, adequate nutrition, vaccine, and sanitation [2]. Involvement of the eye in these diseases can be a primary presentation or signal a recurrence of the disease, offering a crucial indicator of the underlying status of the pulmonary condition. A vigilant clinical approach coupled with an understanding of the association between ocular diseases and infective pulmonary diseases is pivotal to successful management. This review seeks to provide a clear and informative

account of this association, facilitating pulmonologists and ophthalmologists in establishing an efficient system for timely referrals and targeted treatment interventions.

Search strategy

The electronic database PubMed and search engine Google Scholar were searched for relevant articles. Two authors independently reviewed systematic reviews, meta-analyses, narrative reviews, randomized controlled trials, observational studies, and case series in the initial search. Any discrepancies were resolved through mutual agreement and, when needed, with the assistance of a third author. The final draft was collaboratively prepared, incorporating input from all contributing authors.

Ocular tuberculosis

Ocular tuberculosis (TB), a less common presentation of systemic TB, varies in overall incidence in these patients from as low as 1.4% to as high as 18% [3,4]. It can affect any ocular structure with uveitis being the most common clinical presentation. The prevalence of ocular TB in the Indian population is variable in different zones. It contributed to 0.39% of the uveitis cases in a South Indian study and 9.86% of the cases in a North Indian study [5,6]. As nearly 60% patients of extrapulmonary TB can present without clinical evidence of pulmonary TB, a high index of suspicion is required to diagnose these cases [7]. Ocular involvement in TB can be a primary involvement, or secondary to direct extension from adjacent structures, hematogenous spread or hypersensitivity reaction.

External disease

Orbit - Orbital involvement in TB can be in the form of periostitis, soft tissue tuberculoma or cold abscess with or without bony destruction and dacryoadenitis [8]. These patients can present with proptosis, pain, restricted ocular motility and diplopia, headache, and visual field defects. Ocular imaging and biopsy showing epithelioid granuloma, with Langhans giant cells and caseation necrosis on histopathology are important tools in confirmation of diagnosis.

Lid – Lid TB can be in the form of an acute abscess ("cold abscess"), soft fluctuant mass without acute inflammation, scrofuloderma (firm, painless nodules overlying a tuberculous focus leading to suppurate ulcer with undermined edges) lupus vulgaris of lid skin, characterized by solitary, small, reddish-brown nodules. When pressure is applied to these nodules they blanch to an "apple jelly" colour [9,10].

Conjunctiva, cornea, and sclera – Primary involvement of conjunctiva is usually a chronic disease presenting with redness, and mucopurulent discharge with regional lymphadenopathy often leading to scarring [11]. Hypersensitivity reaction to mycobacterial proteins leads to

phlyctenular keratoconjunctivitis and interstitial keratitis, causing symptoms like pain, redness, and defective vision. Tuberculous interstitial keratitis (Figure 1 – Healed keratouveitis) is typically unilateral. In addition to topical treatment for these pathologies, confirmed cases of TB require systemic anti-tuberculosis treatment [9]. Sclera can be involved as anterior nodular scleritis or as sclero-keratitis due to involvement of adjacent cornea [12]. In addition to topical steroids, they often require anti-tuberculous treatment (ATT) [13].

Intraocular disease

Among the intraocular presentations of TB, posterior uveitis is most common followed by anterior uveitis, panuveitis, and intermediate uveitis. TB is a leading cause of granulomatous anterior uveitis characterized by mutton-fat keratic precipitates (Figure 2), and anterior and posterior synechiae. The posterior uveitis can present in the form of choroidal tubercles (most common), choroidal tuberculoma, subretinal abscess, serpiginous-like choroiditis, and retinal vasculitis. Choroidal tubercles are usually multiple, can be associated with serous retinal detachment, greyish white to yellow with an indistinct border in the active stage. They can grow to develop a solitary mass called tuberculoma or heal with pigmentation and atrophy with ATT [10,14]. Patients with choroidal tuberculoma can present without evidence of systemic TB [15,16]. Serpiginous-like choroiditis is a relentless progressive autoimmune disease starting around the disc and spreading centrifugally. They respond to systemic corticosteroids and immunosuppressants but may require ATT for complete healing. Paradoxical worsening of ocular disease on starting ATT may require corticosteroid treatment with or without immunosuppressants [14]. Retinal vasculitis in these patients can be tuberculous vasculitis or Eales disease (Figure 3). Tuberculous vasculitis is obliterative peri phlebitis usually starts at or anterior to the equator and presents with vitritis, neuroretinitis, retinal haemorrhages and vascular proliferation which may lead to traction retinal detachment, rubeosis iridis, and neovascular glaucoma [7]. Treatment involves the use of local and systemic corticosteroids, laser photocoagulation and ATT. The detection of Mycobacterium tuberculosis in intraocular fluid by polymerase chain reaction can be taken as a guide to start ATT in these cases [14]. Eales disease is an idiopathic, occlusive vasculopathy of the mid-peripheral retina primarily affecting young male individuals and presents with vitreous haemorrhage and sequelae of neovascularization. Hypersensitivity to tuberculoprotein is one of the most widely accepted etiopathogenesis. Most of these cases have been reported from Southeast Asia, particularly from India. 70% of the epiretinal membrane samples and more than 50% of vitreous samples have been reported to have laboratory evidence of Mycobacterium tuberculosis in these patients [17,18]. The treatment modality includes intravitreal anti-

vascular endothelial growth factor injection, external or endo-laser application, systemic or local corticosteroid, and vitrectomy as and when required.

An untreated tuberculous subretinal abscess may burst to cause endophthalmitis and panophthalmitis, a vision-threatening destructive presentation of intraocular TB [14].

Involvement of optic nerve and retina can occur either due to direct spread from choroid or due to hematogenous spread. Some of the common clinical presentations include papillitis, neuroretinitis, optic nerve tubercle, and compressive optic neuropathy leading to symptoms like defective vision, pain, field defect etc. In a study of 49 patients of tuberculous optic neuropathy 16.3% patients had pulmonary tuberculosis [19]. These patients require systemic/ local corticosteroids along with ATT.

Ocular TB and HIV infection – In comparison to HIV seronegative individuals, the risk of TB is 20-fold higher in seropositive patients [20]. Majority of these patients present with posterior segment pathologies, primarily infective (tubercle/ chorioretinitis/abscess) and largely in the context of pulmonary and disseminated TB [21]. These patients require corticosteroids under ATT cover, with close monitoring of immune status.

Diagnosis –

Due to a lack of clearly defined diagnostic criteria, a combination of ocular clinical signs with systemic laboratory and radiological evidence is required to diagnose these cases. Ocular investigations like fundus fluorescein angiography, optical coherence tomography, and ultrasound B-scan can be utilized as per the patient's clinical presentation. Gupta et al have proposed diagnostic criteria for confirmed and presumed intraocular TB, based on clinical signs, corroborative evidence and direct evidence [14].

Confirmed IOTB – Any one or more of the clinical signs (signs of anterior, intermediate, posterior and panuveitis, retinitis and retinal vasculitis, neuroretinitis and optic neuropathy, endophthalmitis and panophthalmitis) + any of these two -

a) Ocular fluid showing acid-fast bacilli on microscopy/ culture.

b) PCR positive for IS 6110 or other conserved sequences in the M. tuberculosis genome,

Presumed ocular TB – Any one or more of the clinical signs + any of these two –

a) Any of these positive tests (Mantoux test / X-ray chest with evidence of healed or active tubercular lesion/evidence of confirmed active extrapulmonary tuberculosis (either by microscopic examination or by culture of the affected tissue for M. tuberculosis)

b) Positive therapeutic trial (A positive response to 4-drug ATT (isoniazid, rifampicin, ethambutol, and pyrazinamide) over a period of 4 to 6 weeks. + exclusion of other causes of uveitis in non-endemic areas.

Interferon gamma release assays (IGRA) (Quantiferon) measure cellular immune response to TB antigens. A positive result only indicates infection with TB bacilli and does not differentiate

between latent infection and active disease. WHO has advised against the use of IGRA,s for diagnosis of TB disease in low and middle income countries [22].

ATT and ocular TB –

The principles of treatment of extrapulmonary TB are the same as for pulmonary tuberculosis. It includes two months of intensive phase with four drugs – Isoniazid, Rifampicin, Pyrazinamide, Ethambutol, and four months of continuation phase with three drugs - Isoniazid, Rifampicin, Ethambutol. The duration of the continuation phase may be extended based on clinical and microbiological response [23]. Systemic corticosteroids under the cover of ATT reduce the inflammatory damage to the eye.

The Collaborative Ocular Tuberculosis Study – 1 is a multicentric study published from India on the response of ATT in patients of tuberculous uveitis. 89.0% of their patients treated with ATT had received corticosteroid-sparing immunosuppressive agents. This report suggests a higher treatment failure in patients treated with corticosteroids, particularly those with positive QuantiFERON-TB Gold test results. Reported treatment failure was doubled in patients who received systemic corticosteroids before initiation of ATT. This study agrees with the existing doctrine of starting systemic corticosteroids under the cover of ATT in patients with a high clinical suspicion of TB uveitis [24].

Non Tuberculous Mycobacteria can also involve the eye, however, concomitant involvement of lungs and eye is rare and can be seen in disseminated infections in immunocompromised hosts.

Ocular adverse effects of ATT

Ethambutol

Ethambutol-induced ocular toxicity has been seen in 1-18% of the patients. It is seen more commonly in adults as compared to children. It is dose and duration-dependent and is more common at doses greater than 15 mg/kg/day. It is more common with daily than intermittent therapy [25]. It usually occurs after 3-6 months of usage. Patients usually present with reduced vision, blurry vision, altered quality of vision, frequent change of glasses and difficulty in differentiating between colours. The ocular examination is suggestive of toxic optic neuropathy. The ocular examination and relevant investigation findings are summarized in Table 1. There is no definitive treatment. Early detection and discontinuation of the drug are important to prevent further damage. Recovery after stopping the drug is seen in only 50% of the patients. If the disease progresses even after 4 to 6 weeks of stopping the drug, consideration should be given to discontinuing isoniazid and linezolid as they are also known to cause toxic optic neuropathy.

Physicians treating patients with TB should be aware of the ocular side effects of ethambutol. History of any ocular symptoms should be elicited before starting ATT and if any ocular symptoms are present, baseline ophthalmic examination should be carried out. Baseline ophthalmic evaluation should be carried out in high-risk individuals (elderly, malnourished, alcoholics, those with renal disease, diabetes mellitus, those receiving ethambutol with linezolid, ethambutol dose more than 15 mg/kg, those receiving ethambutol for prolonged periods). Patients should be counselled about the ocular adverse effects of ethambutol and should be advised to report if any visual changes are noticed. In the case of children, parents should be counselled to report if they notice any change in visual tasks performed by the child. An expert panel has recommended that these patients should be encouraged to use the smartphone-based app to test for visual acuity, colour vision, and visual field [26,27].

Isoniazid

As isoniazid also causes toxic optic neuropathy, the symptoms and signs are the same as ethambutol. The mechanism of isoniazid-induced toxic optic neuropathy is unclear, the most probable being interference with pyridoxine metabolism. It has been reported within 10 days of starting the drug and even after 2 to 3 months. Discontinuation of the drug results in reversal, however, failure to do so may result in optic atrophy [28,29].

Linezolid

Linezolid can cause both toxic optic and retinal neuropathy [30-35]. Toxic optic neuropathy is usually seen when the drug is given for more than 28 days [31]. The prevalence ranges from 1.3%-13.2% [36,37]. Caution is to be exercised when prescribing linezolid for more than a month. These patients should be counselled to immediately report if they notice any ocular symptoms. It is a reversible on stopping the drug. Toxic retinal retinopathy is due to cone dysfunction [34,35]. The adverse events have been postulated due to mitochondrial dysfunction [30,38].

Rifampicin

Rifampicin is known to cause reddish-orange discoloration of body secretions and hence can cause discoloration of tears [39,40]. It will also cause reddish-orange staining of the contact lens. Patients using reusable contact lenses should be advised not to use reusable contact lenses [41].

Rifabutin

Rifabutin is rarely known to cause several adverse effects on the eyes. It can lead to corneal deposits, the anterior lens surface deposits, uveitis, and retinal dysfunction [42-47].

Corneal deposits can be secondary to uveitis but can also occur in the absence of uveitis. When it occurs in the absence of uveitis, the corneal deposits are due to the drug itself. It is not associated with signs of ocular inflammation. The deposits are stellate, yellowish brown, and mainly involve the periphery of the cornea. It is a duration-dependent and irreversible adverse event. It does not affect vision as the deposits are peripheral, fine and transmit light [45,46]. Rifabutin is also known to result in anterior lens surface deposits [44]. Rifabutin-induced uveitis is dose-dependent and uncommon at doses of 300 mg/day [44,47].

Clofazimine

It may result in brownish-red discolouration of peripheral conjunctiva and cornea due to the deposition of multiple polychromatic crystals [48-50]. It is also reported to cause retinal dysfunction. It is usually seen at doses of 200 mg/day [51-53].

Thioacetazone

Thioacetazone is no longer used today for the treatment of tuberculosis. As a part of Stevens Johnsons syndrome due to thioacetazone, the eye can be involved resulting in conjunctivitis which can heal with scar formation affecting vision [41].

What a pulmonologist should know

Ocular TB is usually not associated with clinical evidence of pulmonary TB. It can affect almost all the ocular structures. Uveitis characterized by recurrent redness, pain and defective vision of eye is the most common presentation. In South-East Asia, Eales disease, a vasculopathy probably of tuberculous origin, commonly presents as vitreous haemmorhage leading to visual diminution in young males. Confirmation of diagnosis of ocular TB require demonstration of Mycobacterium tuberculosis in ocular fluids/tissues. Control of associated severe inflammation or paradoxical worsening of ocular disease on starting ATT requires treatment with corticosteroids. Corticosteroids should preferably be deferred until the start of ATT in patients with a high clinical suspicion of TB uveitis. Ethambutol induced ocular toxicity is rare, more common in adults than children, usually reported at higher doses (more than 25 mg/kg/day) and is preventable. Elderly, those with renal disease, diabetes mellitus, malnourished, alcoholics, those who will receive ethambutol at doses more than 15 mg/kg/day and for prolonged periods are at high risk of developing toxic optic neuropathy. These individuals should be referred to an ophthalmologist before initiating ATT for a baseline ophthalmic

evaluation. Early detection and discontinuation of the drug are important to prevent further damage. Apart from ethambutol, the first line anti-tubercular drug isoniazid and the second line anti-tubercular drug linezolid can also result in toxic optic neuropathy. Linezolid can cause both toxic optic and retinal neuropathy. Patients receiving linezolid for more than a month should be counselled to immediately report if they notice any ocular symptoms. Rifampicin can result in reddish-orange discoloration of tears and contact lenses. Rifabutin is known to cause several adverse effects in the eyes. It can lead to stellate corneal deposits, anterior lens surface deposits, and uveitis.

The ocular adverse events of antitubercular therapy are rare, however, the treating physician must be aware of the potential adverse events so that they are picked up early.

Respiratory viruses and eye

Viral diseases of the respiratory system, caused by adenovirus, coronavirus, influenza virus, respiratory syncytial virus, coronavirus, and rhinovirus have a propensity to affect the ocular tissues. The spectrum of ocular diseases caused by respiratory viruses is summarized in Table 2.

Adenovirus ocular infection

Adenovirus is a double-stranded DNA virus and is responsible for many ophthalmic and respiratory diseases [54]. It has been reported as the most common cause of tonsillitis, responsible for up to 3% of acute respiratory illnesses and as many as 20% of cases of pneumonia [55]. Adenovirus is the leading cause of conjunctivitis worldwide and is responsible for 15% to 70% of all cases of infectious conjunctivitis [56]. Adenovirus conjunctivitis has 4 recognized clinical presentations - Epidemic keratoconjunctivitis, pharyngoconjunctival fever, acute non-specific follicular conjunctivitis and chronic keratoconjunctivitis. Epidemic keratoconjunctivitis is the most severe ocular presentation, it has no systemic features. It is mainly due to serotypes 8 and 19. In contrast, patients with pharyngoconjunctival fever (PCF) complain of systemic symptoms of sore throat and fever. The serotypes of adenovirus responsible for PCF are 3, 5, 7, and 11 (species B and C) which are also the pathogens of many lung diseases [54,57]. The incubation period is 5 to 12 days. PCF is characterized by watery nonpurulent ocular discharge, conjunctival congestion, subconjunctival haemorrhages, follicular conjunctivitis, fever, pharyngitis, rhinitis, regional lymphoid enlargement and tender preauricular adenopathy. Corneal involvement is not common in PCF but if present, it follows the course of epidemic keratoconjunctivitis i.e. punctate staining, subepithelial infiltrates and opacities. The clinical symptoms last for 3-5 days.

Diagnosis – Primary diagnosis is based on clinical signs and symptoms. It can be confirmed with cell culture, polymerase chain reaction, direct immunofluorescence, and rapid antigen detection immunoassays. The rapid antigen detection immunoassay is a simple, inexpensive, office-based, highly sensitive (89%) and specific (94%) test approved by the U.S. Food and Drug Administration, for rapid detection of adenovirus infection [58].

Treatment

Adenovirus conjunctivitis is a self-limiting disease with complete resolution seen within 3 weeks. Treatment involves symptomatic relief with the use of cold compression and artificial tear substitutes. Topical antibiotics have no role in the treatment of primary pathology. It is only indicated if a bacterial coinfection is suspected or in high-risk patients such as children [55]. Use of topical anti-histamines and vasoconstrictors can provide symptom relief but has associated limitations of local toxicity. Topical steroid eye drops and non-steroidal anti-inflammatory agents, and immunomodulators like topical cyclosporine and tacrolimus can be considered for use in patients of PCF with associated keratitis and subepithelial infiltrates [59]. The role of trifluridine, vidarabine, and ganciclovir in the treatment of adenoviral conjunctivitis is still controversial [57]. In experimental studies, Cidofovir, an acyclic nucleoside phosphonate and nucleotide analogue of cytosine has shown good efficacy against adenovirus but its use in clinical practice still needs to be evaluated considering the associated ocular surface toxicity. Povidone iodine is a broad-spectrum microbicide, that has been extensively studied for its virucidal properties and it has been reported that in the concentration of 0.1% solution, it is most effective against adenovirus 3 [60].

What a pulmonologist should know

Adenovirus ocular infection can be associated with respiratory disease. As there is no specific therapy and prophylactic treatment for this disease, primary prevention in the form of avoiding close contact and sharing fomites of an infected person, disinfecting the instruments and surfaces with 70% ethyl alcohol or 1:10 diluted bleach solution should be advised and followed. A timely referral is particularly helpful in cases with corneal involvement.

COVID–19

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2(SARS–COV–2) was declared a global pandemic on March 11, 2020. It is a multi-system disorder having significant ophthalmic manifestations. Tissue manifestations of SARS–COV–2 are dependent on the binding of the viral spike protein to angiotensin-converting enzyme 2 (ACE2) cellular receptor and interaction with the transmembrane protease serine 2

(TMPRSS2), which are known to be expressed in the human cornea, retina, and conjunctival epithelium. Although SARS-CoV-2 has been detected in tears and on the conjunctival surfaces, it remains unclear whether the virus can be transmitted via ocular surface. Ocular exposure leading to systemic transmission has been proposed [61-63]. A meta-analysis involving 38 cross-sectional studies has reported a pooled prevalence of 11.3% of all ocular manifestations among COVID-19 patients [64]. The reported risk factors for ocular involvement are old age, high fever, increased neutrophil/lymphocyte ratio and high levels of acute phase reactants [65]. The published literature has documented the following ocular presentations in COVID–19 patients –

Orbital Involvement in COVID-19

Retro-orbital pain, orbital sinusitis, and orbital mucormycosis can be the presenting feature of COVID-19. The immune dysregulation associated with SARS–CoV–2 infection, uncontrolled blood sugars, widespread use of steroids, monoclonal antibodies, and broad-spectrum antibiotics, all are possible risk factors of rhino-orbital cerebral mucormycosis (ROCM) [66]. The orbital involvement is secondary to systemic immunosuppression and not directly due to the virus.

Anterior segment manifestations

Eyelid involvement in COVID–19 can be in the form of meibomian orifice abnormalities, lid margin hyperemia/telangiectasia and blepharitis [66]. Acute conjunctivitis (pink eye) presenting with redness, watering, ocular irritation, foreign body sensation, mucoid discharge, eyelid swelling, congestion and chemosis; is one of the most common presentations of SARS–COV–2 infections. Clinical examination may reveal features of follicular conjunctivitis, hemorrhagic conjunctivitis, pseudomembrane formation and keratoconjunctivitis resembling viral keratitis and episcleritis. In children, a very high incidence of Kawasaki-like illness termed multisystem inflammatory syndrome has been observed, with conjunctivitis being the most common presentation. Sporadic Case reports have been published on the association of COVID–19 and episcleritis, anterior scleritis and acute anterior uveitis [67].

Posterior segment manifestations

The median time between the onset of ocular symptoms related to posterior segment involvement and the onset of COVID-19 symptoms/diagnosis, according to Sen et al, is 12 (17.6 ± 13.1, 4–55) days. (67) Posterior segment involvement in COVID–19 is secondary to vasculopathy, neuropathy or a consequence of inflammatory cascade. These cases can present in the form of vitritis, acute retinal necrosis, serpiginous choroiditis, vascular involvement in

the form of central retinal artery and venous occlusion, acute macular neuro retinopathy and paracentral acute middle maculopathy [68-70].

Other ocular associations

Valsalva retinopathy, neuro-ophthalmic involvement - Horner's syndrome, papillophlebitis, optic neuritis, neurogenic ptosis, Miller Fisher Syndrome and cranial nerve palsy; are reported associations of COVID-19 [67,71,72].

Ocular Association of COVID–19 vaccine

COVID-19 vaccine has been associated with infective and immunogenic response in the eye, with anterior uveitis followed by panuveitis as the most common presentation. Other reported adverse events are - episcleritis, scleritis, keratouveitis and sclerokeratouveitis, paralytic strabismus following third, fourth, and sixth nerve palsies, and optic neuritis after various live attenuated and mixed vaccines [73,74].

What a pulmonologist should know

Ophthalmic complications are present in approximately 1 in every 10 patients of COVID-19, with a considerable risk to both vision and life. Patients admitted in intensive care units, particularly on mechanical ventilation, often develop ocular surface pathology including exposure keratitis. It is imperative to safeguard the ocular surface through protective measures and ensure regular ophthalmic assessments in such cases.

Influenza virus

Ocular tropism is shown most commonly by the H7 subtype of influenza virus due to its ability to acquire specific genetic compatibility with host tissue [75]. Like the respiratory tract, the ocular surface epithelium contains the influenza virus cellular receptor [76]. H7 subtype virus infections in humans have been linked to ocular complications in about 80% of cases (frequently with concurrent mild respiratory symptoms) [77]. Conjunctivitis is the primary ocular presentation, with rare occurrences of subconjunctival haemorrhage, uveitis, retinitis, angiitis, uveal effusion syndrome, acute multifocal placoid pigmented epitheliopathy (AMPPE), serous macular detachment, and optic neuritis. [77-79]. They are treated as per their standard protocol of treatment. Ocular complications due to influenza virus are relatively rare and if present are usually mild.

Respiratory syncytial virus -

Respiratory syncytial virus (RSV) is an RNA virus belonging to the Pneumovirus group, responsible for flu-like symptoms (croup) in children. According to Bitko et al., a common pathogenic step between the human corneal epithelium and the respiratory tract is the activation of the proinflammatory cytokine NF-B [80]. RSV infection has been associated with cases of acute and allergic conjunctivitis in children [81,82].

Rhinovirus

It belongs to the family Picornaviridae and conjunctivitis is one of its rare presentations [83].

Ebola virus

The reported ocular presentations of Ebola virus disease are – conjunctivitis, subconjunctival haemorrhages, and vision loss of unknown origin. Ocular manifestations are seen in 60% of cases of post-Ebola virus disease (EVD) syndrome. Uveitis is the most common presentation, responsible for severe impairment of vision and blindness in 40% of these patients. Optic neuropathy and ocular motility disorders, episcleritis, interstitial keratitis and cataracts are other reported ocular associations [84,85].

What a pulmonologist should know

Emerging viral diseases have become an important threat to public health. An awareness towards the ocular manifestations of these viral infections will help in reporting and developing future management strategies.

Hydatid cyst and eye

Hydatid cyst or hydatidosis is primarily a disease of the lung and liver caused by tapeworm Echinococcus granulosus. Hydatid cyst of eye can manifest as orbital or intraocular hydatid cyst. Orbital cysts constitute 1% of all hydatid cysts, typically unilateral, tend to involve retrobulbar tissue and can present as proptosis, decreased vision, and restricted ocular movement [86,87].

Intraocular hydatidosis is quite rare and can present as subretinal echinococcosis, choroidal mass, or vitreous cyst. They can present with visual loss, retinal detachment, glaucoma, and other secondary effects [88-93]. In most reported cases, orbital involvement was in isolation. Betharia et al reported a case of disseminated hydatid cyst, where simultaneous involvement of orbit and lung was seen along with liver and spleen. This case was managed with surgical extirpation [94].

Serological tests for hydatid cysts are usually negative in orbital cysts and diagnosis is mainly radiological. A computed tomography scan shows a unilocular, non-enhancing homogeneous cyst. Magnetic resonance imaging shows a low-intensity signal on T1-weighted images and a high-intensity signal on T2-weighted images. Mild peripheral rim enhancement may be seen after gadolinium injection [95].

Treatment of these cases requires surgical excision with systemic albendazole as an adjunct. The approach can be orbital for orbital hydatid cysts and through pars plana for ocular cysts.

Pneumocystis jiroveci and eye

Pneumocystis jirovecii or Pneumocystis carinii is a yeast-like fungus, an opportunistic pathogen primarily responsible for pneumocystis jiroveci pneumonia (PJP) in immunocompromised individuals. One of the most common ocular presentations of this pathogen is choroiditis, mostly seen in patients with a history of PJP [96-98]. It was mainly seen in patients with AIDS who were on aerosolized pentamidine as a prophylaxis against PJP [96]. A case of Pneumocystis choroiditis while on cotrimoxazole prophylaxis for PJP has also been reported by Gupta et al [99]. These lesions are pale yellow to yellow in colour, involving the posterior pole, usually bilateral and asymptomatic [98,100]. These cases are treated with cotrimoxazole for 21 days followed by prophylaxis to prevent recurrence [101]. Another treatment option is intravenous pentamidine, at a daily dose of 4 mg/kg for 21 days [98].

Ruggli et al. have described a rare case of pneumocystic involvement of the conjunctiva in an AIDS patient that manifested as a white, placoid lesion of the tarsal conjunctiva [102].

What a pulmonologist should know

Pneumocystis jirovecii choroiditis is rare and was mainly seen in cases where aerosolized pentamidine was used for PCP prophylaxis.

Future directions

Future research is required in developing non-interventional diagnostic techniques for confirmation of ocular TB. A clear diagnostic criteria and stage-wise dedicated treatment strategy will enhance the collaborative management approach between pulmonologists and ophthalmologists. The mechanisms of ethambutol, isoniazid and linezolid-induced toxic optic neuropathy are still poorly understood. The association of genetic factors and the reason why only a subset of patients develop toxic optic neuropathy need to be studied. Early detection of toxic optic neuropathy due to anti-tubercular drugs is crucial to discontinue the drugs early and prevent permanent visual damage. Research focusing on biomarkers or modalities to detect subclinical optic nerve damage are need of the hour. Micronutrient deficiency has been

proposed to exacerbate ethambutol-induced optic nerve damage. Research is needed to confirm the veracity of these findings and whether supplementation with these micronutrients will reduce the risk of optic nerve damage needs to be studied. The role of steroids in the management of linezolid-induced optic neuropathy needs to be explored. The recent COVID-19 pandemic has stressed on a pressing need for ongoing research to deepen our understanding of the pathogenesis, epidemiology, and host-pathogen interactions of all the emerging infective diseases.

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Table 1. Clinical findings and investigations in toxic optic neuropathy.

Test	Findings
Pupillary response testing	Early stage- normal, preserved pupillary response. Advanced stage – sluggish pupils, relative afferent pupillary defect (RAPD). Preservation of near response.
Fundus examination	Early stage – normal, disc hyperemia, peripapillary haemorrhage Advanced stage – pale optic disc
Visual acuity	Reduced, initially minimal but may progress to severe (no light perception)
Visual field testing	Central vision loss (Central or centrocaecal scotoma) most common, bitemporal hemianopsia in some cases.
Colour vision testing	Red-green colour defect (common) Blue-yellow colour defect (rare)
Optical coherence tomography	Retinal Nerve Fibre layer (RNFL) – decrease in thickness Ganglion Cell complex layer - decrease in thickness
Visually Evoked Potential (VEP)	Increased latency of the p100 wave (May be useful for early detection)

Table 2. Spectrum of coexistent respiratory and ocular diseases caused by respiratory viruses.

Respiratory virus	Respiratory and Ocular disease
Adenovirus species B, C (serotypes 3, 5, 7, 11)	Pharyngoconjunctival fever
Respiratory Synctial Virus	Conjunctivitis with respiratory tract infection
Influenza virus	Conjunctivitis with respiratory tract infection
Corona virus (SARS CoV2)	Conjunctivitis, Vitritis, Choriditis, Optic neuritis, cranial nerve palsies with pneumonia/ARDS
Rhinovirus	Conjunctivitis with respiratory tract infection

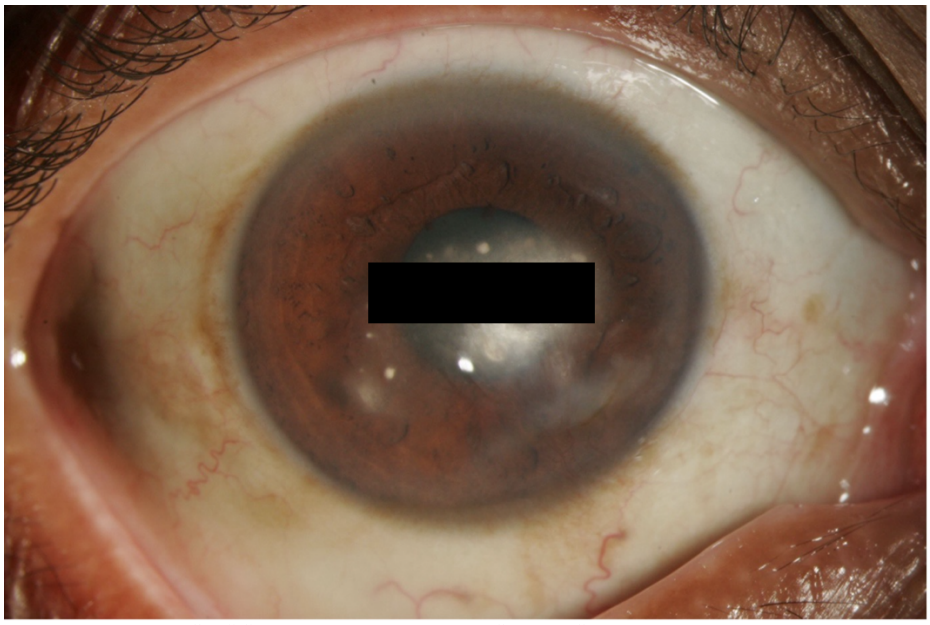

Figure 1. Healed keratouveitis in tuberculosis patient.

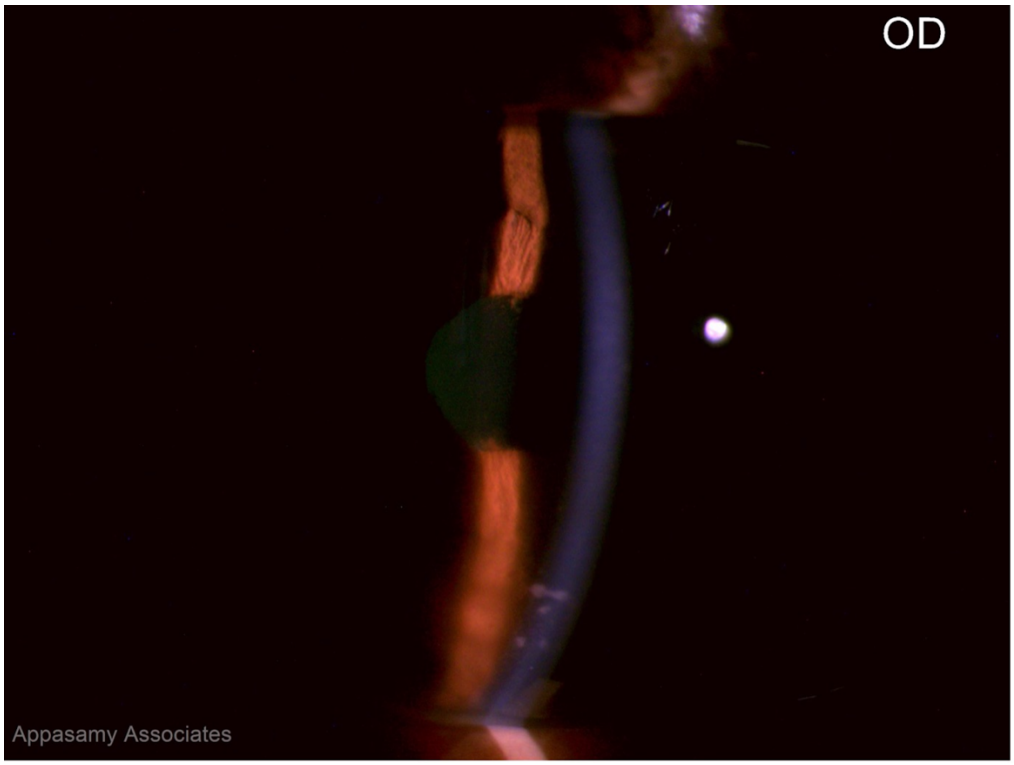

Figure 2. Mutton fat Keratic precipitate.

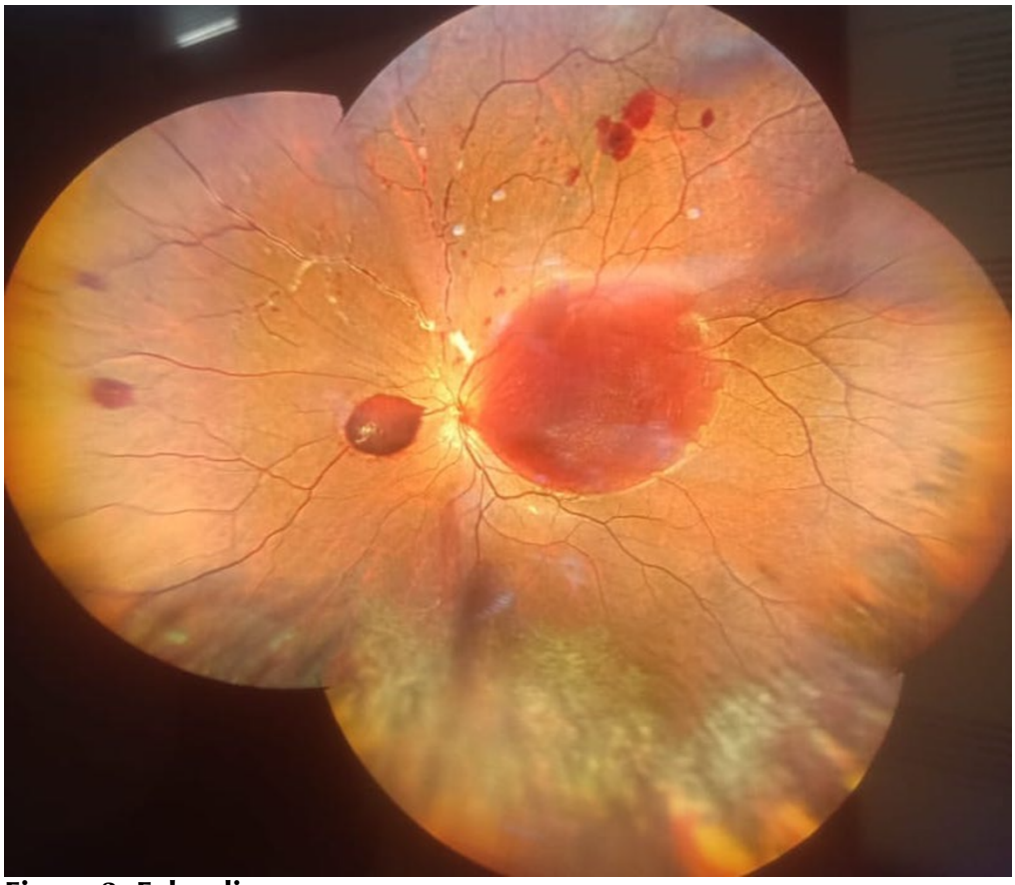

Figure 3. Eales disease.