Ocular manifestations of common pulmonary diseases: a narrative review

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Abstract

Several pulmonary disorders can cause ocular involvement. Understanding these manifestations is critical for early diagnosis and treatment. Hence, we set out to examine the most common ocular manifestations of asthma, chronic obstructive pulmonary disease (COPD), sarcoidosis, obstructive sleep apnea (OSA), and lung cancer. Allergic keratoconjunctivitis and dry eye are two ocular manifestations of bronchial asthma. The inhaled corticosteroids used to treat asthma can cause cataract formation. COPD is associated with ocular microvascular changes as a result of chronic hypoxia and systemic inflammation spillover into the eyes. Its clinical significance, however, is unknown. Ocular involvement is common in sarcoidosis, occurring in 20% of cases of pulmonary sarcoidosis. It can affect nearly any anatomical structure of the eye. Obstructive sleep apnea has been linked to floppy eye syndrome, glaucoma, non-arteritic anterior ischemic optic neuropathy, keratoconus, retinal vein occlusion, and central serous retinopathy, according to research. However, while an association has been established, causality is yet to be established. The effect of positive airway pressure (PAP) therapy used to treat OSA on the aforementioned ocular conditions is unknown. PAP therapy can cause eye irritation and dryness. Lung cancer can affect the eyes through direct nerve invasion, ocular metastasis, or as part of a paraneoplastic syndrome. The goal of this narrative review is to raise awareness about the link between ocular and pulmonary disorders in order to aid in the early detection and treatment of these conditions.

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Introduction

Ocular involvement in pulmonary diseases can have a myriad of presentations. A few of them can result in significant morbidity. The association of ocular diseases with lung disorders can be an extension of the primary pathology itself or a manifestation of treatment-related complications. The development of screening protocols, early diagnosis and treatment, and the avoidance of related complications largely depend on a comprehensive understanding of these manifestations. In this article, we aim to review the common ocular manifestations of asthma, chronic obstructive pulmonary disease (COPD), sarcoidosis, obstructive sleep apnea, and lung cancer. We also reviewed the ocular side effects of the medications used to treat these diseases. The pulmonologists should be familiar with the ocular associations, and a team approach between a pulmonologist and an ophthalmologist can achieve prompt referral, diagnosis, and treatment of these diseases.

Search strategy and screening

We searched PubMed from its inception until June 2022 for peer-reviewed, published articles in English. We included systematic reviews and meta-analyses, randomized controlled trials, observational studies, narrative reviews, and case series in our search. The search engine Google Scholar was also used to search for relevant articles. The references cited in the papers identified were also reviewed. Two authors were assigned a topic, and articles relevant to each topic were searched independently by them. Any conflicts

were resolved by a third author. All the authors reviewed and edited all the drafts.

Bronchial asthma

Ocular diseases in patients with bronchial asthma can be an extension of the primary pathogenesis or a secondary effect of medications being used in treatment.

Ocular allergy and asthma

Although ocular allergy is not a direct part of the spectrum of the "one airway, one disease" concept, it is a frequent association in patients with bronchial asthma and is referred to as "allergic rhino-conjunctivitis". In a questionnaire-based survey, it was found that 40% of 1242 patients with allergic conjunctivitis, asthma, rhinitis, or a combination of these conditions had allergic conjunctivitis [1]. The prevalence of allergic conjunctivitis in children with asthma ranges from 24 to 44% [2-4]. Allergic conjunctivitis can present in the form of seasonal, perennial, atopic, or vernal keratoconjunctivitis. Although systemic evaluation for allergic disorders does not have a diagnostic role in ocular allergy, any patient with allergic conjunctivitis and relevant systemic allergy disorders should be investigated and treated as per the standard recommendations. Also, considering the high prevalence of ocular allergy in patients with asthma, it would be imperative to screen all patients, especially children diagnosed with asthma, for symptoms of ocular allergy. The diagnosis of ocular allergy is primarily clinical. The classical symptoms include itching, redness, and mucoid or watery secretions from the eyes. The treatment involves the judicious use of topical corticosteroids, immunomodulators, antiallergics, and dual-acting mast cell stabilizers.

Dry eye

A recent meta-analysis involving 45,215 patients with asthma and 232,864 control subjects reported a higher risk of dry eye disease in patients with asthma [5]. The possible causes of dry eye in patients with asthma include the presence of an ocular allergy, the pro-inflammatory milieu of the ocular surface, and the effect of medication for asthma control.

Ocular effects of drugs used in the management of asthma

Inhaled corticosteroids

Cataract

The association of cataract formation with the use of inhalational steroids (ICS) is controversial. A higher and dose-dependent relationship between inhaled corticosteroids and the prevalence of nuclear and posterior subcapsular cataract was reported in the Blue Mountains eye study [6]. The increased risk for cataract development with prolonged use of ICS in older patients may also be age-related [7]. One of the largest prospective long-term studies, the Inhaled Steroid Treatment as Regular Therapy in Early Asthma study, with more than 7000 patients (aged 5 to 66 years) from 32 countries, compared the effect of budesonide or placebo on cataractogenesis. It reported no increased risk for cataract in patients after 3 years of budesonide treatment [8]. However, Weatherall *et al*., in their meta-analysis, reported that the risk of cataract increases by approximately 25% for each 1000 ug per day increase in the dose of beclomethasone dipropionate or equivalent. Hence, elderly asthmatics and COPD patients who are on ICS should be screened for the presence of cataract [9].

Glaucoma

The initially reported high risk of ocular hypertension or open-angle glaucoma [odds ratio (OR)-1.44] in current users of high doses of inhaled steroids prescribed regularly for 3 or more months raised an important concern about the use of ICS [10]. But, as per the latest literature, the use of ICS is safe in terms of glaucoma development. A recently published meta-analysis of 31,665 individuals from 18 studies did not reveal any evidence that ICS increase the risk of glaucoma or ocular hypertension [11].

Inhaled b-2 adrenoceptor agonists and muscarinic antagonists

Nebulized ipratropium alone and in combination with salbutamol can precipitate attacks of angle closure glaucoma [12,13]. Hence, caution must be exercised while administering these drugs *via* the aerosolized route to patients predisposed to narrow-angle glaucoma. The risk factors for narrow-angle glaucoma include the elderly (more than 60 years of age), those with a history of narrow-angle glaucoma, and those with hypermetropia [14]. These patients should be counseled to report any symptoms of eye pain, blurring of vision, and redness of the eyes. An immediate ophthalmologist opinion should be sought if any of these symptoms develop. Care should be taken to protect the eyes from the mist. Mouthpiece nebulization should be preferred over mask nebulization. If a nebulization mask is being used, it should be tightly fitted [12].

Dupilumab

Dupilumab is an interleukin (IL) 4 receptor-α blocking drug that targets IL-4 and 13 signaling pathways [15]. A high incidence of conjunctivitis was observed in patients in the clinical trials of moderate to severe atopic dermatitis [16,17]. However, it was not seen in severe asthma clinical trials [15,18,19]. The exact mechanism of dupilumab-induced conjunctivitis is not known. The goblet cells present in the epithelial layer of conjunctiva produce mucin which lubricates the conjunctival surface and helps in protecting the conjunctival surface. Apart from stimulating mucin production by goblet cells, IL-13 also helps in maintaining the epithelial barrier [20]. It has been postulated that IL-13 inhibition by dupilumab may result in decreased mucin production and predispose to conjunctivitis. The other mechanisms that have been proposed include increased OX40 ligand activity and IL-17-mediated inflammation due to the thriving of Demodex mites [21].

Effect of topical eye drops on the pulmonary system

Topical b -blockers

Topical intraocular pressure-lowering agents, particularly non-selective b-blockers, can lead to bronchospasm. A large case-control study showed that the use of timolol for glaucoma in patients with asthma increased the risk of bronchospasm [22]. Another randomized, double-masked, placebo-controlled cross-over trial on the possible effect of topical latanoprost, a relatively selective prostaglandin F2α receptor agonist with minimal effect on the thromboxane recep-

tor, reported that resting and provoked airway function and asthma symptoms were unaffected by topical latanoprost treatment [23].

What should a pulmonologist know?

As the prevalence of allergic conjunctivitis in children with asthma is high, a history of symptoms suggestive of ocular allergy (itchy eyes, tearing, redness of eyes) should be elicited in all children diagnosed with asthma. Ophthalmologist opinion must be sought in those with symptoms of ocular allergy. The use of inhaled corticosteroids is not associated with an increased risk of the development of glaucoma. Nebulized anticholinergics should be used with caution in patients with risk factors for narrow-angle glaucoma. Care should be taken to protect the eyes from the mist. Prompt ophthalmologist opinion must be sought if symptoms of glaucoma develop. If a nebulizer is used, a mouthpiece should be used instead of a mask. Topical b-blocker eye drops should be used with caution as they can exacerbate bronchospasm in patients with bronchial asthma. Even though the incidence of conjunctivitis was not high in asthma trials, patients receiving dupilumab should be monitored for the development of ocular symptoms, and early referral to an ophthalmologist must be sought if ocular symptoms develop.

Chronic obstructive pulmonary disease

Choroidal thinning in patients with COPD is due to decreased choroidal blood flow and decreased ocular perfusion pressure [24]. Chronic inflammation and hypoxia in subjects with COPD may lead to an increase in the diameter of the retinal veins, impaired hemodynamics, and lower retinal arterial oxygen saturation, causing thinning of the retinal nerve fiber layer, and subfoveal choroidal thickness [25,26]. In addition to smoking, how these microvascular changes can act as an independent risk factor for ocular diseases like age-related macular degeneration, cataract and glaucoma needs to be evaluated further.

Ocular effects of drugs used in the management of chronic obstructive pulmonary disease

The ocular effects of inhaled muscarinic antagonists have been described in the section on bronchial asthma.

Sarcoidosis

Although the lungs are the most commonly involved in nearly 90% of the cases, ocular involvement has been reported in 13 to 79% of cases [27,28]. Ocular sarcoidosis (OS) is the second-most frequent clinical manifestation of this disease, next to pulmonary sarcoidosis [29]. For OS, two peak ages of presentation have been reported in adults, the first between 20 and 30 years and the second between 50 and 60 years of age [30]. Uveitis is the most common presentation, but it can affect almost all the anatomical structures of the eye.

Orbit and adnexa

Within the orbit, sarcoid granulomatous involvement has been reported in the lacrimal gland, eyelids, soft tissues of the orbit, extraocular muscle, and optic nerve. The lacrimal gland is the most common site of involvement and has been reported to be involved in about 27-55% of cases [31,32]. Keratoconjunctivitis sicca, or dry eye, in patients with OS is due to infiltration/inflammation of the main lacrimal gland, leading to a deficiency of the aqueous component of the tear. The involvement of the lacrimal drainage system causing epiphora in these patients may require lacrimal bypass surgery. Long-term therapy with local and systemic corticosteroids after surgery is usually required [33]. In a case series of 26 biopsy-proven orbital and adnexal sarcoidosis, slowly progressing mass and ocular discomfort were the more common presentations, followed by proptosis, ptosis, dry eye, diplopia, and decreased vision. Most of the lesions were in the anterior orbit, especially the anteroinferior orbit [34]. Involvement of the eyelid in OS can be in the form of periorbital erythematous swelling, millet-seed nodules, or destructive lesions causing cicatricial entropion [35-57]. Unilateral permanent vision loss has been reported in a patient due to central retinal artery occlusion secondary to intraconal orbital sarcoid mass surrounding the optic nerve [38]. OS may mimic inflammatory orbitopathy, like thyroid-related ophthalmopathy. The association between OS and autoimmune thyroid disease has long been recognized and is based on an immunological and genetic basis [39].

Ocular surface

Conjunctival nodules, appearing as unilateral or bilateral, translucent, pale-yellow nodules, can be the initial clinical presentation of a patient with sarcoidosis [40]. Follicular conjunctivitis, cicatricial conjunctivitis, symblepharon, and conjunctival granuloma are other presentations [41,42]. Conjunctival biopsy has been reported to be a minimally invasive, cost-effective, and high-yield method of diagnosing ocular sarcoidosis [43].

Cornea

Corneal involvement is uncommon in OS. The presentation can be in the form of dry eye-associated keratopathy, band-shaped keratopathy due to long-standing ocular inflammation, and hypercalcemia associated with sarcoidosis. Interstitial keratitis and peripheral ulcerative keratitis are other reported associations [44,45].

Sclera

Scleritis is reported in less than 3% of cases of OS and can be in the form of anterior diffuse, anterior nodular, or posterior scleritis [28,46].

Uvea

Uveitis is the most common presentation of OS, and sarcoidosis accounts for 9.6% of all cases of uveitis [47]. Anterior uveitis is the most common form and occurs in 20-70% of patients [48]. These patients present with the typical feature of granulomatous anterior uveitis, and in chronic cases, iris nodules, posterior synechiae and other complications related to anterior uveitis can be seen. Intermediate uveitis is characterized by complaints of visual loss and floaters and clinical signs like snowballs (aggregates of inflammatory cells in the vitreous) and snowbanks (accumulation of white exudates over the pars plana and ora serrata. Posterior uveitis can present as periphlebitis (candle wax drippings), formation of choroidal granuloma, multifocal choroiditis, acute posterior multifocal placoid pigment epitheliopathy, serpiginous choroiditis, chorioretinitis, choroidal and retinal neovascularization, vitreous hemorrhage, and cystoid macular edema. Cystoid macular edema is a common cause of vision loss in patients with sarcoidosis [28]. The involvement of the posterior segment is very common in patients with sarcoidosis

[49]. The American Thoracic Society clinical practice guideline recommends ophthalmological evaluation based on the onset of new symptoms like change in vision (floaters, blurring, visual field loss), eye pain, photophobia, or redness (sustained) after a negative baseline ocular examination [50].

Glaucoma and cataract

Glaucoma and cataract in patients with uveitis can be secondary to ocular inflammation or steroid-induced. Nodular involvement of angle structure has also been reported, causing defective drainage of aqueous humor [36].

Neuro-ophthalmic manifestations

The most frequent cranial nerve to get involved is the facial nerve, followed by the optic nerve [51,52]. Optic nerve involvement in sarcoidosis can be due to ischemia, granulomatous inflammation of the optic nerve, or compression or infiltration by an orbital inflammatory mass [53]. Optic nerve involvement may present as disc pallor, disc edema, periphlebitis/sheathing, or optic disc granuloma [54]. These patients can present with profound vision loss.

The mechanism of facial nerve involvement can be compressive or inflammatory. Uveo-parotid fever, or Heerfordt's syndrome, is defined by the presence of facial palsy, parotid swelling, uveitis, and fever. Other reported neuro-ophthalmic associations are oculomotor and abducens nerve palsy, Horner's syndrome, and tonic pupil [55].

Diagnosis of ocular sarcoidosis

Considering the varied clinical presentation, the diagnosis of OS requires a combination of ocular and systemic investigative modalities. The definitive diagnosis is always on tissue biopsy. The diagnostic criteria for OS, first proposed in 2009, have been revised by the International Workshop on Ocular Sarcoidosis, in 2017. It is based on seven clinical signs, eight systemic investigation results, and three diagnostic criteria [56]. High-resolution computed tomography thorax/fluorodeoxyglucose-positron emission tomography may help in detecting involved sites in other areas that may be amenable to biopsy.

Management of ocular sarcoidosis

The principles of management for ocular sarcoidosis are the same as for pulmonary sarcoidosis. Corticosteroids are the mainstay of treatment and can be used in the form of regional or systemic medication. The regional application can be in the form of topical drops, periocular, subconjunctival, sub-tenon, or intravitreal injections, and ocular implants. A biodegradable intraocular implant containing 700 mg of dexamethasone has been approved for the treatment of uveitis involving the posterior segment of the eye. A sustained-release fluocinolone acetonide implant has been approved in the US for chronic non-infectious posterior uveitis. Systemic immunosuppressive agents are used as steroid-sparing agents in cases requiring a long duration of steroid treatment or in cases intolerant to steroids. Biologic agents are reserved for cases of refractory uveitis. Among the tumor necrosis factor (TNF)-α inhibitors, Adalimumab, a humanized monoclonal antibody directed against TNF, has been approved by the US Food and Drug Administration for the treatment of non-infectious uveitis [57]. Cases of OS that are not amenable to medical treatment may require surgery. Mass lesions giving rise to a compression effect on surrounding structures require surgical debulking. Media opacity due to cataract or hazy vitreous may require surgical treatment in the form of cataract extraction with intraocular lens implantation or vitrectomy. Non-resolving cystoid macular edema can be treated with an intravitreal injection of anti-VEGF agents like ranibizumab, aflibercept, and bevacizumab.

What should a pulmonologist know?

Ocular involvement is common in pulmonary sarcoidosis, seen in 20% of cases. The ATS guidelines recommend ocular screening by an ophthalmologist in all diagnosed cases of pulmonary sarcoidosis. An ophthalmological opinion must be sought if symptoms like change in vision, floaters, blurring of vision, visual field loss, eye pain, photophobia, or redness of the eyes develop. All cases of ocular sarcoidosis require treatment, irrespective of the requirement for treatment for pulmonary sarcoidosis.

Obstructive sleep apnea

Floppy eyelid syndrome

Floppy eyelid syndrome (FES) is characterized by hyperlaxity of the eyelids due to maladaptive remodeling of the connective tissue [58]. Gonnering and Sonneland first mentioned the association between obstructive sleep apnea (OSA) and FES in a 41-year-old obese male patient [59]. The prevalence of FES in patients with OSA is around 4.5-18%, while OSA is seen in 100% of patients with FES. FES is more common in those with severe OSA [60]. Mechanical insult to ocular tissue, lid laxity causing poor tear film distribution over the ocular surface and associated complications, local pressure-induced lid ischemia, and systemic hypoventilation followed by reperfusion oxidation injury during sleep are some of the widely accepted proposed pathogenesis behind ocular involvement in FES [60].

Important clinical features of FES are related to floppy, redundant eyelids and ocular surface inflammation. Easy eversion of the upper eyelid and/or abnormal distraction of the lower eyelid and supple tarsal plates are important features of FES. Lid eversion and clinical symptoms of exposure are seen mostly in the eye on their preferred sleeping side, secondary to the traction of a pillow against the eyelid. The presenting symptoms include redness, watering, foreign body sensation, dryness of the eye, and blurred vision, more pronounced in the morning. In long-standing cases, mechanical trauma to the eyelid can lead to dermatochalasis, blepharitis, meibomitis, lash ptosis, ectropion, and trichiasis [61]. Conjunctival irritation leads to chronic papillary conjunctivitis. Corneal signs of FES include dry eye, exposure keratopathy, punctate epithelial erosions, corneal ulcer, neovascularization, corneal scar formation, and keratoconus [62]. All patients with FES should be evaluated for the presence of OSA [58].

The first step in the management of these cases involves the protection of the ocular surface from mechanical damage. Maintaining a proper posture during sleep, night-time patching of the eye, application of an eye shield, and artificial lubrication, all help in managing these cases. The patient should be advised not to sleep in the prone position or on the affected side. Patients not responding to medical treatment need surgical treatment to correct the lid deformity and allow better apposition of the eyelid and globe.

There is conflicting evidence on the response of ocular symptoms to continuous positive airway pressure (CPAP). While no effect of CPAP on FES was observed in a study with 89 patients with OSA, one-third of whom had FES [63], another study showed that 1 year

of positive airway pressure (PAP) therapy can improve the clinical symptoms of FES in patients with OSA [64]. More studies are required to elucidate the role of PAP therapy on FES in patients with OSA-FES.

Glaucoma

A case series found a higher prevalence of OSA in patients with primary open-angle glaucoma [65]. A meta-analysis showed that patients with OSA have significantly higher odds of developing glaucoma (OR=1.242; p<0.00) and *vice versa* (OR=1.746, p=0.002) [66]. Hypoxia leads to increased intraocular pressure (IOP) and predisposes to glaucoma in OSA. The intermittent hypoxemia in OSA directly damages the optic nerve, retinal ganglion cells, and its axons. An increased level of hypoxia-induced endothelin-1 causes vascular dysregulation and affects the blood flow of the optic nerve head and retina. Oxidative stress leads to mitochondrial dysfunction of retinal ganglion cells and glaucoma [67,68]. There is conflicting evidence on the relationship between AHI and intraocular pressure, corneal thickness, and retinal nerve fiber layer [69-72].

Management of glaucoma in OSA should be based on the standard guidelines for glaucoma management, using antiglaucoma medication and surgical treatment of glaucoma.

Conflicting evidence is available regarding the effect of CPAP on these patients. While Ulsoy *et al.* [73] and Pepin *et al*. [74] showed a beneficial effect of CPAP on glaucoma, Kiekens *et al*. [75] found that IOP increased with CPAP therapy, and Cohen *et al*. [76] could not find any effect of CPAP on glaucoma in OSA. However, the above studies were observational and had a short follow-up period.

Keratoconus

It is a bilateral, non-inflammatory ectatic condition of the cornea characterized by corneal thinning. A meta-analysis has reported a significant association between OSA and keratoconus, with a pooled OR of 1.841 [77].

Dry eye

A study involving 50 patients with OSA (who did not have FES and were not on CPAP) and 50 controls found that the mean ocular surface disease index scores were significantly higher, tear break up time and Schirmer test values were significantly lower in the OSA group [78]. OSA patients have been reported to have increased levels of pro-inflammatory cytokines. The ducts of the meibomian glands are thin, dilated, and distorted. These changes are responsible for the dry eye syndrome in these patients. The presence of FES and air leaks associated with PAP therapy further increases the risk of dry eye.

Nonarteritic anterior ischemic optic neuropathy

Nonarteritic anterior ischemic optic neuropathy (NAION) is due to infarction of the anterior portion of the optic nerve head supplied by the short posterior ciliary arteries. The odds of developing NAION in OSA are 6.18 (95% confidence interval, 2.00-19.11) [79]. A retrospective, longitudinal cohort study found the prevalence of NAION to be 0.36% and 0.2% in the OSA and control groups, signifying a strong association between NAION and OSA [80]. The proposed pathogenesis behind the development of NAION in OSA patients is the vascular compromise of the optic nerve. The vascular compromise is due to intermittent nocturnal hypoxemia, oxidative stress resulting in endothelial dysfunction, and altered autoregulation of posterior ciliary arteries. Raised intracranial pressure due to apneic episodes may also compromise circulation or directly damage the optic nerve [67]. It usually presents with a sudden, painless, monocular loss of vision, usually noted on awakening. It is usually associated with color vision impairment. The diagnosis of acute NAION is primarily clinical, based on defective vision with a relative afferent pupillary defect and edema of the optic nerve head.

The role of CPAP has been recommended on the basis that minimizing the metabolic, inflammatory, and ischemic consequences of OSA may normalize the altered visual-evoked potential responses in patients with OSA by restoring and preserving optic nerve function [81]. Polysomnography may be considered in patients with newly diagnosed NAION with no other identifiable risk factors [67].

Retinal vascular manifestations of obstructive sleep apnea

Retina, being a tissue with very high metabolic activity, needs a higher oxygen concentration and gets affected by hypoxia induced by OSA.

Diabetic retinopathy

OSA is associated with increased odds of developing diabetic retinopathy (DR) (OR=2.01) [82]. Apnea-hypopnea index during rapid eye movement sleep is independently associated with DR. The oxygen desaturation index has been found to be significantly lower in patients with proliferative diabetic retinopathy as compared to those with non-proliferative diabetic retinopathy [83,84]. Diabetic macular edema has an independent association with an apnea-hypopnea index (AHI) >30 and a duration of oxygen saturation below 90% [85,86].

A longitudinal study on OSA and DR in type 2 diabetes mellitus patients concluded that OSA is an independent predictor of progression to pre-proliferative/proliferative DR (OR=5.2) and patients receiving CPAP treatment were significantly less likely to develop pre-proliferative/proliferative DR [87]. CPAP treatment has been reported to improve visual sensitivity and macular layer thickness. Improvement of macular layer thickness in the superior-inner sector positively correlated with the AHI (r=0.405, p=0.022) and desaturation index (r=0.473, p=0.006) on pre-treatment polysomnography [88].

Retinal vein occlusion

A retrospective study from Taiwan on the association between retinal vein occlusion (RVO) and OSA revealed that of the 5965 patients with OSA, 52 patients (0.15%) experienced RVO during a 3.72-year follow-up [89]. A recently published study has reported a higher association of central RVO with OSA than branch RVO [90]. It has been recommended that screening at-risk RVO patients for OSA is pertinent to preventing associated medical morbidity in these individuals [91]. The role of OSA treatment, including CPAP therapy, in the improvement of vision in RVO cases has not been established in studies.

Central serous chorioretinopathy

Central serous chorioretinopathy (CSCR) is characterized by neurosensory detachment of the retina in the central macula. These patients present with unilateral central scotoma and image distortion. In comparison to non-OSA subjects, OSA subjects

have increased odds of CSCR (pooled OR=-2.019) [67]. CSCR is often self-limiting, showing spontaneous resorption. In non-resolving cases, laser, photodynamic therapy, subthreshold micropulse laser therapy, and anti-VEGF therapy can be tried. Patients with OSA on CPAP therapy have been found to have a lesser incidence of CSCR [92].

Effect of positive airway pressure therapy on eyes

The air leak from the upper part of the oro nasal or nasal mask and retrograde nasolacrimal air escape can cause irritation of the eyes. This may result in or exacerbate dry eye disease [93]. Matossian *et al*., in a retrospective study using IBM MarketScan Commercial and Medicare Supplemental claim databases with 350,420 patients, showed that the incidence and prevalence of dry eye were higher in patients with OSA treated with CPAP than in the general population. Also, the prevalence of dry eye increased with the cumulative duration of CPAP use [94]. Preventing air leaks by using a tightly fitting mask, using an individually molded mask rather than a standard mask, and using artificial tears can help prevent dry eye disease [93].

What a pulmonologist should know?

OSA patients with glaucoma who have been initiated on PAP therapy must be kept under the close follow-up of an ophthalmologist to note changes in visual fields, IOP, and optic disc. Patients with OSA are at increased risk of developing dry eye. Also, PAP therapy may result in or exacerbate dry eye in these patients. Preventing air leaks is crucial to preventing dry eye in these patients. Young patients with new-onset NAION and no other risk factors should be screened for OSA.

Lung cancer

Lung cancer may affect the eye by infiltration or compression of nerves, paraneoplastic effects, or distant metastases [95].

Ocular metastasis of lung cancer

The most common intraocular malignant neoplasm is metastatic carcinoma of the eye. The choroid is the most common site for ocular metastasis (88% of eye metastases), 21% of which originate from lung cancer [96]. Other sites of metastasis include the iris, ciliary body, retina, optic disc, and vitreous. The left eye is more commonly affected than the right eye as the left common carotid artery branches directly from the aortic arch. Adenocarcinoma and small-cell lung cancer can cause ocular metastases. These patients present with non-specific symptoms of proptosis, mass in the orbit, blurring or loss of vision, double vision, floaters, pain, visual field defects, red eyes, and flashing sensations [97]. Diagnosis involves the use of total body positron emission tomography-computed tomography imaging, orbital computed tomography and/or magnetic resonance imaging, and fundus photography with angiography for multifocal tumors.

Direct ocular involvement

The eyes are involved in Pancoast tumors due to the invasion of the paravertebral sympathetic chain and the inferior cervical (stellate) ganglion by the tumor. More than 95% of Pancoast tumors are non-small cell lung cancer (NSCLC), and among NSCLC, squamous cell carcinoma is the most common histological type [98]. Ocular involvement is seen in the form of Horner's syndrome or oculosympathetic paresis (ipsilateral ptosis, miosis, anhidrosis).

Paraneoplastic syndromes

The paraneoplastic syndromes associated with ocular involvement include cerebellar degeneration (nystagmus and diplopia), opsoclonus (involuntary, irregular, continual and conjugated chaotic, multidirectional saccades, without intersaccadic intervals, "dancing eyes"), and myoclonus, cancer-associated retinopathy (vision loss), and Lambert-Eaton myasthenic syndrome (LEMS) [99]. In LEMS, antibodies are formed against the voltage-gated calcium channel, resulting in decreased pre-synaptic acetylcholine release. Patients present with ptosis, diplopia, and blurred vision [95]. Cancer-associated retinopathy is due to the formation of circulating antibodies against retinal proteins, such as recoverin, in patients with systemic cancer [100-102]. It is most commonly seen with small-cell carcinoma of the lung [97]. Patients present with asymmetric bilateral visual loss, photopsia, ring scotoma, and loss of rod and cone function. Treatment of paraneoplastic syndrome involves treatment of the tumor and suppression of the immune response using glucocorticoids, intravenous immunoglobulin, plasma exchange, and immunosuppressants.

The timing of ophthalmological referrals for various pulmonary diseases has been listed in Table 1. The common ophthalmological investigations performed on various pulmonary diseases are listed in Table 2.

Table 1. Timing of ophthalmological referral in various pulmonary diseases.

Disease	Timing of referral to an ophthalmologist
Bronchial asthma	1. At symptom onset (itching of eyes, redness of eyes, eye pain, change in vision, blurring of vision, photophobia) 2. Regular screening of patients over 60 years of age on ICS for cataract
COPD	1. At symptom onset (redness of eyes, eye pain, change in vision, blurring of vision, photophobia) 2. Regular screening of patients over 60 years of age on ICS for cataract
Sarcoidosis	1. At diagnosis of pulmonary sarcoidosis 2. At symptom onset (change in vision, floaters, blurring of vision, visual field loss, eye pain, photophobia or redness of eye)
OSA	1. At symptom onset (redness, watering, foreign body sensation, dryness of the eye, blurred vision, sudden painless loss of vision) 2. At initiation of PAP therapy in patients with coexistent glaucoma and regular follow-up whilst on PAP therapy
Lung cancer	1. At symptom onset (proptosis, mass in the orbit, blurring or loss of vision, double vision, floaters, pain, visual field defects, red eyes, flashing sensations, involuntary eye movements)

ICS, inhalational steroids; COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea; PAP, positive airway pressure.

Table 2. Common ophthalmological investigations performed in various pulmonary diseases.

Disease	Investigations
Bronchial asthma	Slit lamp examination, clinical tests for dry eye - Schirmer test, tear break up time, tonometry
COPD	Tonometry
Sarcoidosis	Slit lamp examination, fundoscopy, tonometry, clinical tests for dry eye - Schirmer test, tear break up time, CT/MRI of orbit, optic nerve, Fundus fluorescein angiography
OSA	Tonometry, slit lamp examination, clinical tests for dry eye - Schirmer test, tear break up time, fundoscopy
Lung cancer	Orbital CT and/or MRI, fundus photography with angiography

COPD, chronic obstructive pulmonary disease; CT, computed tomography; MRI, magnetic resonance imaging.

Future directions

Further studies are needed to elucidate the exact role of inhaled corticosteroids in cataractogenesis. If elderly patients who are on inhaled corticosteroids require screening for cataract at regular intervals, this needs to be studied. The exact mechanism of dupilumab-induced conjunctivitis is still an enigma. The fact that conjunctivitis was observed only in atopic dermatitis trials and not in severe asthma trials raises speculation about whether there is a drug-disease association. The clinical significance of ocular microvascular changes seen in COPD is an area to be explored. The effect of CPAP on FES and IOP in patients with glaucoma requires further elucidation. Studies with long follow-up periods are particularly necessary to know the exact effect of CPAP on IOP. Though many studies have found an association between OSA and glaucoma, NAION, CSR, and retinal vein occlusion, the causality is yet to be proven.

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