Review Article

Neuro-ophthalmic manifestations of cancer: a narrative review

Timothy M. Janetos, Nicholas J. Volpe, Shira S. Simon

Department of Ophthalmology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Timothy M. Janetos, MD, MBA. 645 N. Michigan Ave. Suite 440, Chicago, IL 60611, USA.

Email: timothy.janetos@northwestern.edu.

Background and Objective: Neuro-ophthalmic manifestations of cancer are vast and early recognition of a serious ocular condition due to either cancer or its therapy is important for both vision preservation as well as providing valuable treatment and prognostic information regarding the underlying malignancy. This review focuses on direct and indirect effects of cancer on the eye and its adnexa, hematologic malignancy, complications of traditional and novel oncologic therapies, and paraneoplastic syndromes as they relate to the eye as these disorders can lead to potentially devastating or irreversible vision loss.

Methods: PubMed was searched primarily for the following topics: optic nerve infiltration, primary vitreoretinal lymphoma (PVRL), ocular paraneoplastic disorders, and ophthalmic complications of cancer therapeutics. Literature was selected based on historical significance and landmark studies (e.g., Cross *et al.* series of paraneoplastic optic neuritis patients; Chan's textbook on primary intraocular lymphoma) as well as publications published after 2000. References from select studies were additionally included. Given the sparsity of literature on many subjects, most publications were included during this time frame in our review.

Key Content and Findings: There are several ophthalmic entities that the oncologist should be aware of including leukemic optic nerve infiltration, PVRL, paraneoplastic syndromes as they related to the eye, and adverse effects of therapeutics. Unfortunately, given the rarity of some of these entities [e.g., paraneoplastic optic neuropathy (PON), cancer-associated retinopathy (CAR)], diagnosis can be difficult and treatment options are often limited.

Conclusions: Oncologists can develop a set of basic ophthalmology examination skills that will help to triage and manage patient eye complaints. In certain instances, oncologists have the potential to avert devastating vision loss with early recognition of neuro-ophthalmic complications.

Keywords: Neuro-ophthalmology; ophthalmology; optic neuropathy; paraneoplastic; hematologic malignancy

Submitted Oct 03, 2021. Accepted for publication Jun 22, 2022.

doi: 10.21037/cco-21-137

View this article at: https://dx.doi.org/10.21037/cco-21-137

Introduction

With an increasing number of novel cancer therapies and the subsequent prolonged lifespan of cancer patients, ophthalmic complications due to therapy, primary or metastatic disease, and paraneoplastic syndromes are encountered by the oncologist and ophthalmologist alike. In order to avoid vision loss, early and close collaboration between the ophthalmologist and the oncologist is necessary for recognition and proper management of neuro-ophthalmic complications of cancer. Often, ocular symptoms provided by patients are nonspecific (e.g., blurry vision, redness, etc.) and could represent a range of pathology from benign to potentially vision threatening. Therefore, it is important for the oncologist to recognize situations and develop some basic ophthalmic skills and vocabulary to triage ocular complaints. For instance, leukemic infiltration of the optic nerve can present with

© Chinese Clinical Oncology. All rights reserved.

Table 1 Methods of literature search

Items	Specification
Date of search (specified to date, month and year)	5/01/2021–8/01/2021
Databases and other sources searched	PubMed
Search terms used (including MeSH and free text search terms and filters)	"neuro-ophthalmology, cancer"; "optic nerve malignancy"; "neuro-ophthalmology, lymphoma"; "primary vitreoretinal lymphoma"; "primary intraocular lymphoma"; "ophthalmic paraneoplastic syndromes"; "paraneoplastic optic neuropathy"; "cancer associated retinopathy"; "immunotherapy ocular side effects"; "ocular side effects cancer therapeutics"
Timeframe	2000–present
Inclusion and exclusion criteria (study type, language restrictions, etc.)	All study types from case reports to randomized trials were included
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	All studies were selected based on their relevance to each subsection within the review article. Studies were initially chosen by the primary author (TMJ) and were reviewed by contributing and senior authors (SS, NJV)
Any additional considerations, if applicable	N/A

N/A, not available.

blurry vision, and if not recognized promptly and treated can lead to rapid, irreversible vision loss (1). Neuro-ophthalmic signs and symptoms of malignancy are vast but can broadly be categorized into direct effects due to primary or metastatic disease, indirect paraneoplastic syndromes, and findings secondary to therapies used for malignancy control. This review aims to comprehensively describe these neuro-ophthalmic complications of oncologic disease with a special emphasis on hematologic malignancy, complications of traditional and novel oncologic therapies, and paraneoplastic syndromes as these areas represent potentially devastating or irreversible visual loss as well as have prognostic and treatment implications for the underlying disorder. We present the following article in accordance with the Narrative Review reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-21-137/rc).

Methods

A literature review was conducted using the criteria specified in *Table 1*. Pertinent articles and their reference lists were manually reviewed for relevance to the subsections within this article. Article search strategy included all articles based on the search criteria in *Table 1* filtered for publication after 2000. References were reviewed within each article and were selected for additional primary sources. Lastly, a select few landmark publications were included [e.g., Chan's textbook on primary vitreoretinal lymphoma (PVRL)].

Direct effects on the visual pathway

A recent review estimated that approximately 50% of patients with an intracranial mass from any etiology will develop a neuro-ophthalmic sign or symptom (2). Direct effects on the visual pathway from intracranial malignancy are secondary to direct compression of the ocular structures or intracranial visual pathway, or secondary mass effects causing increased intracranial pressure (ICP). Glioblastoma multiforme is the most common primary malignancy, but metastatic disease comprises the majority of intracranial lesions (3). Additionally, meningeal infiltration can cause increased ICP and papilledema, as well as lead to direct optic nerve involvement (4,5). It is important to note that any lesion involving the visual pathway, including infectious, inflammatory, ischemic, or demyelinating, can cause similar signs and symptoms and therefore understanding clinical context, obtaining imaging, and monitoring progression of symptoms become invaluable. Signs and symptoms of increased ICP include nausea, vomiting, altered mental status and papilledema on fundoscopic examination.

Involvement within the orbit, most commonly due to breast, prostate, or lung metastases, can present with

© Chinese Clinical Oncology. All rights reserved.

signs of orbital congestion, proptosis, and double vision. Vision loss can be due to a compressive optic neuropathy or corneal exposure due to proptosis. Involvement of the prechiasmatic optic nerve leads to monocular visual decline and can produce an afferent pupillary defect (APD) in the eye with the affected optic nerve. An acute optic neuropathy is more likely secondary to a demyelinating, ischemic, or inflammatory process whereas a gradual decline in vision would be more consistent with a malignant compressive lesion. At the chiasm, a malignant lesion would characteristically present with a bitemporal hemianopia and progressive bilateral vision loss; 15–20% of all cranial malignancies are located in the sellar region and may cause chiasmal compression (6). Posterior to the chiasm, compression of the optic tract, optic radiations, or the occipital cortex can demonstrate a contralateral homonymous hemianopsia. Those within the optic tract can also produce a contralateral APD. Visual hallucinations may occur in occipital lobe tumors, whereas auditory or gustatory hallucinations due to seizure can be seen with temporal lobe tumors. Other neuropsychiatric symptoms such as panic attacks, depression, anxiety, and personality changes can be present (7,8).

Lastly, involvement of the nerves that supply the extraocular muscles (e.g., cranial nerves 3, 4, and 6) can cause diplopia and an ocular misalignment that will be demonstrated with testing extraocular movements or simple observation of the position of the patient's eyes in primary gaze. Ophthalmoplegia involving multiple cranial nerves is likely to involve the cavernous sinus or orbit. Multiple cranial neuropathies is also a frequent finding in leptomeningeal metastasis (LM), also known as carcinomatous meningitis, a typically late complication of malignancy (9). The clinical presentation of LM can be nonspecific with symptoms related to increased ICP and meningeal irritation. Cranial nerves 6, 7, and 8 are the most frequently affected leading to diplopia, facial weakness, and loss of hearing. Diagnosis of LM is difficult. Magnetic resonance imaging (MRI) of the brain and spine can show nodular leptomeningeal enhancement and high-volume lumbar puncture (LP) with cytology can reveal the malignant cells, but there are frequent false negatives depending on the technique (10). LM confers a poor prognosis with an average lifespan of two to four months.

Leukemic and lymphomatous infiltration of the optic nerve

Any metastatic optic nerve lesion or primary optic nerve tumor (e.g., meningioma, glioma) can lead to a progressive optic neuropathy. However, involvement of the nerve in leukemia and lymphoma is of particular concern as it can cause rapid, irreversible vision loss if not recognized early. Hematologic malignancies can cause a variety of manifestations within the orbit and intraocularly. Briefly, leukemic retinopathy is a term applied to the vascular changes within the retina that can cause variable degrees of vision changes (e.g., blurred vision, scotomas) secondary to hematologic abnormalities such as severe anemia, thrombocytopenia or hyperviscosity (11). Direct involvement of the optic nerve due to leukemia or lymphoma, in particular, deserves special mention as it can lead to devastating vision loss and is regarded as a neuro-ophthalmic emergency. It is also unfortunately an elusive diagnosis in which a delay may lead to permanent vision loss, though treatment is also not benign.

A new optic neuropathy in the presence of a systemic leukemia or lymphoma should always raise suspicion of nerve infiltration; however, infection, compressive lesions, and inflammation due to medication side effects of therapeutic agents are also all possible in such patients. The treatment and prognosis is unique for each condition (1). Whether or not an optic neuropathy or objective findings of optic nerve damage develops in patients with systemic leukemia or lymphoma, infiltration to some degree is not uncommon; one autopsy study noted a frequency of 18% and 16% of optic nerve infiltration in acute and chronic leukemias respectively (11). Other studies have placed the number between one and 13% in some forms of leukemia (12,13). Overall, however, the prevalence of optic nerve infiltration only comprises 5% of secondary optic nerve tumors (14,15). Additionally, although not common, disease relapse in the central nervous system can present with isolated optic nerve infiltration (16) and has been reported most frequently in patients with acute lymphoblastic leukemia (ALL) (2.2% of relapse cases) (17,18). The orbit and optic nerve are potential sanctuary sites for leukemic relapse even with initial systemic central nervous system treatment.

A recent review was completed on 92 cases of optic neuropathy in the setting of leukemia and lymphoma (1). Thirty-six cases (39%) were attributed to leukemic infiltration with most cases secondary to ALL [although acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), or chronic myeloid leukemia (CML) cases were reported as well]. In these patients, malignant cells were present in 64% of cerebrospinal fluid (CSF) analysis,

© Chinese Clinical Oncology. All rights reserved.

and 43% of neuroimaging studies (either CT or MRI) were normal, with the remainder showing thickening or enhancement of the nerve. Two cases were biopsy proven. 30 cases were attributed to lymphomatous infiltration with the majority (67%) of cases due to a B-cell non-Hodgkin's lymphoma (NHL), although both T-cell NHL and Hodgkin's disease were also represented. Twelve of these cases required biopsy to confirm the diagnosis. CSF and MRI findings were similar to that of the leukemia cases. The clinical presentation was variable with optic disc edema and hemorrhage being the most frequent presentation. However, four cases had normal fundoscopic examinations likely representing more posterior involvement of the optic nerve. The remainder of the 92 cases were eventually attributed to infection or inflammation. This case series illustrates the poor sensitivity of CSF cytology. CSF cytology has a sensitivity of less than 50% due to lack of cells and even with repeated LP the false-negative rate can still be high (19-21).

Therefore, any leukemia or lymphoma patient presenting with signs and symptoms of a new optic neuropathy (decreased vision, APD in the affected eye) requires immediate ophthalmology consultation as fundoscopic examination can help to guide the differential and the order of imaging and laboratory studies to help with a timely diagnosis. If optic disc edema is present, the differential diagnosis of new optic disc edema is long, and a prompt diagnosis of optic nerve infiltration has both visual and systemic implications. Rosenthal described two distinct patterns and clinical manifestations of optic nerve infiltration (22): prelaminar (superficial) infiltration of the optic nerve head associated with a fluffy white superficial infiltrate seen on fundoscopic exam causing a variable amount of optic nerve edema and minimal changes in visual acuity, or retrolaminar (posterior to the nerve head) infiltration associated with disc edema and causing severe vision loss. If infiltration is obvious on examination, treatment can be initiated immediately. Typical treatment includes orbital radiation with a course of 2,000 cGy to the orbit over a couple of weeks, which may restore vision and resolve clinical findings (16). Treatment with intrathecal or systemic cytotoxic drugs alone are generally considered insufficient given the optic nerve is a pharmacologic sanctuary. If used in combination with irradiation, however, radiation may synergistically allow drug therapy to act on the optic nerve (23). The goal is to preserve vision.

The diagnosis ultimately involves neuroimaging, CSF analysis, and fundoscopic examination. However, even with these tools, the diagnosis is usually still unclear and radiation treatment is not benign. Optic nerve biopsy can help establish the diagnosis, but this procedure comes with risks of complete vision loss and may not be reliable in the setting of corticosteroid treatment (which patients may be placed on in the setting of disc edema and optic nerve enhancement) (1,24,25). *Figure 1* demonstrates a 16-year-old male with T-cell ALL who developed bilateral blurry vision (20/40 in the right eye and light perception in the left eye). The patient's chemotherapy regimen included cyclophosphamide, vincristine, pegaspargase, intrathecal methotrexate, and nelarabine. MRI of the brain and orbits demonstrated bilateral left worse than right enhancement and enlargement of the optic nerves and tracts. The patient was treated with intravenous (IV) corticosteroids and intravenous immune globulin (IVIG) for possible vincristine associated optic neuropathy with mild improvement in vision. Ophthalmology evaluation demonstrated moderate optic disc swelling in the right eye. The left eye demonstrated significant disc swelling with a central retinal artery occlusion. Given the fundoscopic findings, there was concern for leukemic optic nerve infiltration and the patient underwent whole brain radiation (total 1,200 cGy). Vision improved to 20/20 in the right eye and remained LP in the left eye, fundoscopic findings improved with development of optic disc pallor in the left eye, and MRI imaging showed improvement in the nerve enhancement and enlargement.

PVRL

Uveal metastases, most commonly from breast or lung primary, can present with discrete choroidal masses, and indicate a poor prognosis. Shields *et al*. reported on 2,214 uveal metastases in 1,111 patients (26). The primary tumor was known at presentation in two-thirds of cases with a 5-year survival rate of 23%. The choroidal masses can lead to exudative retinal detachments, causing central vision loss or a visual field defect.

Lymphoma can also metastasize to the uvea, retina, and vitreous, particularly from the testes, cutaneous T-cell lymphoma, or the nasopharynx, all of which have been well documented. Patients with known systemic lymphoma complaining of floaters or decreased vision should have an ophthalmologic consultation to exclude this possibility (27-29). PVRL, on the other hand, is a subset of primary central nervous system lymphoma (PCNSL) and is most often of the diffuse large B-cell lymphoma type. Rarely, T-cell lymphoma occurs. The majority of patients are over

© Chinese Clinical Oncology. All rights reserved.

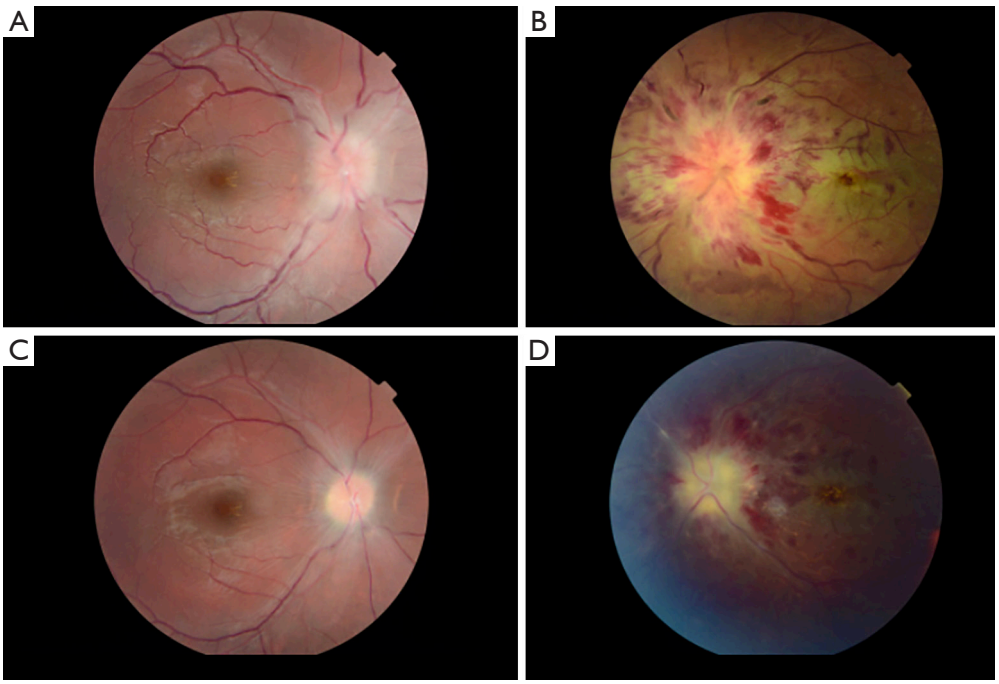

Figure 1 Bilateral ALL optic nerve infiltration in a 16-year-old male. (A) Right optic disc fundus photography demonstrating a swollen optic nerve at presentation. Vision was 20/40. (B) Left optic disc fundus photography demonstrating a swollen optic nerve with nerve hemorrhage and findings consistent with a central retinal artery occlusion at presentation. Vision was light perception. (C) Right optic disc fundus photography demonstrating interval decrease in disc swelling two weeks post whole brain radiation. Vision had improved to 20/20. (D) Left optic disc fundus photography demonstrating decreased optic disc swelling and hemorrhages. The disc developed pallor. Vision remained at light perception. ALL, acute lymphoblastic leukemia.

the age of 50 at presentation, but younger patients have been described as well—indeed, the first case described was in a 27-year-old male (30,31).

Clinical presentation most frequently involves bilateral disease with slowly progressive vision loss and floaters (32,33). The disease is often misdiagnosed as uveitis as vitreous cells may predominate the clinical findings. Additionally, the symptoms and clinical findings can respond to corticosteroid treatment, with relapse after treatment discontinuation (34-36). In this sense, PVRL is considered a masquerade syndrome and the time from clinical symptoms to a definitive diagnosis is approximately a year. The characteristic ophthalmic lesions of PVRL are sub-retinal pigment epithelium (sub-RPE) sharply defined, yellow-white, tumors. However, the disease can present with multiple manifestations. For instance, it can simulate a multifocal choroiditis, multiple evanescent white-dot syndrome, an acute retinal necrosis with retinal vasculitis and branch arterial occlusions, optic neuritis, or an isolated vitritis to name a few (31). Therefore, the diagnosis is difficult to make. MRI of the brain with gadolinium enhancement, CSF analysis with cytology, and vitrectomy are usually all necessary to establish a diagnosis but can often produce inconclusive results.

PCNSL (disease involving the brain, spinal cord, or meninges) will develop in most patients diagnosed with PVRL (estimated at 90%), and therefore MRI of the brain is mandatory in any patient with a diagnosis of PVRL. Conversely, 25% of patients with a diagnosis of PCNSL have ocular involvement at the time of diagnosis, and approximately 25% of PCNSL patients without initial ocular involvement will develop PVRL. There is usually a three-month delay between central nervous system (CNS) disease onset and diagnosis (36). Symptoms are typically related to increased ICP such as headache, nausea, as well as personality changes; similar to PVRL, PCNSL may partially respond to corticosteroid treatment, further delaying the diagnosis (37).

There is no universally accepted treatment protocol for isolated PVRL without CNS involvement (35). Local

© Chinese Clinical Oncology. All rights reserved.

treatment involves intravitreal methotrexate, rituximab, or external beam radiotherapy. CNS disease necessitates systemic chemotherapy. Currently it is debated whether isolated PVRL without CNS involvement requires systemic chemotherapy to delay CNS involvement or increase overall survival. Studies attempting to evaluate this question have shown conflicting results (38-44).

Paraneoplastic disorders of the visual pathway

Paraneoplastic syndromes can affect both the efferent and afferent visual pathway (45). Although true incidence is unknown, one estimate placed the burden at only 0.01% of oncologic patients evaluated at a tertiary care center (46). Afferent symptoms can range from painless, progressive vision loss or, in the case of retinal disease, photopsias (positive visual phenomena), scotomas and night blindness. Efferent disorders include myasthenic-like symptoms, or opsoclonus/myoclonus syndromes. Afferent involvement can lead to vision loss and will be the focus of this section. Often, there are other associated neurologic signs including encephalitis, sensory neuropathies, and cerebellar dysfunction that will prompt the consultant to consider a paraneoplastic syndrome. Pathophysiology of these disorders is likely due to immune-mediated cross-reactivity of tumor producing antigens causing collateral damage [paraneoplastic optic neuropathy (PON), cancer-associated retinopathy (CAR)] or due to production of ectopic peptides such as growth factors by the tumor causing systemic effects [bilateral diffuse uveal melanocytic proliferation (BDUMP), and polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome (POEMS)] (47).

PON

PON is rare, and the signs, symptoms, and radiographic workup is variable. Most cases are related to an underlying small-cell lung carcinoma, although many other case reports have been described in the literature associated with other malignancy including hemopoietic cancers (48-66). Visual acuity can be reduced by any degree, and there are other signs of optic nerve dysfunction such as color vision defects and visual field defects (67). Inflammation of the vitreous is often present. Optic disc edema or atrophy may be present on fundoscopic examination. In 2003, Cross *et al*. described a cohort of 16 patients with suspected PON (48). Fifteen had optic disc edema and subacute vision loss. Nine had vitreous inflammation with vitrectomy showing reactive lymphocytosis, and five had an associated retinitis. CSF analysis demonstrated lymphocytosis, elevated protein, and oligoclonal bands. Most patients had multifocal neurologic complaints, with three patients having a syndrome specifically resembling neuromyelitis optica. Eleven of these patients had confirmed small-cell lung carcinoma, with the remainder having renal or thyroid carcinoma. Cross *et al*. placed patients into two groups: those with an inflammatory optic neuropathy with multifocal manifestations of encephal omyeloradiculoneuropathy and those with optic neuropathy and a myelopathy resembling neuromyelitis optica. All were found to have an antibody directed against collapsing response-mediating protein 5 (CRMP-5). This antigen is expressed throughout the central and peripheral nervous system and is abundantly expressed in small-cell lung carcinoma; molecular mimicry is thought to play a role (64). Given its wide expressivity throughout the nervous system, other neurologic symptoms are common. Thromboembolic phenomena were also noted in 14% of patients. Indeed, isolated PON is rarely reported (64). There have been multiple other paraneoplastic antibodies identified since CRMP-5 including anti-Hu, anti-Tr, anti-Yo, anti-Ri, anti-Ma2/TA, and antiamphiphysin which have led to variable phenotypes (68-74). A more recent series of seven patients found that the majority presented with severe vision loss and optic disc edema. These patients had anti-Ma2/Ta, anti-CRMP-5, anti-Yo, and antiamphiphysin antibodies and two patients had concurrent anti-AQP4 (the antibody implicated in neuromyelitis optica) (75).

There remains no clear treatment algorithm for this rare entity. Treatment with corticosteroids has produced variable results (49,76). One case described successful treatment with mycophenolate mofetil, prednisone, and plasmapheresis in a patient with cutaneous melanoma (77). As this entity is rare, it is important to rule out other more frequent cases of optic neuropathies such as optic neuritis, compressive, toxic, nutritional, or ischemic optic neuropathies as well as leptomeningeal metastases (75).

CAR

CAR is a paraneoplastic retinopathy characterized by autoimmune loss of retinal photoreceptors. Symptoms are related to loss of cones (e.g., photosensitivity, glare, scotomas, decreased visual acuity) and rods (e.g., nyctalopia, photopsias) and specialized retinal testing is necessary to make a diagnosis. Frequently, the suspected diagnosis of

© Chinese Clinical Oncology. All rights reserved.

CAR may occur in the absence of a known malignancy, and therefore a thorough systemic workup is necessary if suspected. The pathophysiology of CAR involves molecular mimicry with antibodies directed against retinal proteins. However, the diagnostic utility of antibody testing is variable. For instance, a large series of suspected CAR patients showed only 61% positivity to antibodies targeted against retinal proteins, with only 10% having antibodies against recoverin, the most well characterized antibody in CAR (78). On the other hand, out of nearly all 3,000 retinopathy samples in a large study, only those associated with cancer were found to have anti-recoverin antibodies (79). Techniques for antibody detection include Western blot, enzyme-linked immunosorbent assay (ELISA), and immunohistochemistry which all require a donor protein scaffold. Fresh human tissue within six hours of death may be optimal, although many other techniques are described which likely influences laboratory reliability (80,81). A positive result may be more meaningful than a negative result in this disease.

Recoverin is a protein located within the retinal photoreceptor cells, and this gene has been mapped to several oncogenic loci, including the *p53* tumor suppressor gene, leading to increased expression within tumor cells (82). In several series of CAR patients with small-cell lung carcinoma, recoverin or recoverin-like peptides have been found in tumor tissue on histopathology (83-86). Other antigens found to be associated with CAR include enolase, Tubby-like protein 1, aryl hydrocarbon receptor interacting protein-like 1, interphotoreceptor retinoid binding protein, photoreceptor cell-specific nuclear receptor, glyceraldehyde 3-phosphake dehydrogenase, aldolase, transducin-a, and heat shock cognate protein 70 and 60, among others (87-91). The phenotype of CAR may be dependent on the specific autoantibody. For instance, anti-recoverin CAR presents with degeneration of both rods and cones leading to severe loss of retinal function with rapid progression to blindness whereas anti-enolase or anti-transducin-a retinopathy can have a more indolent course with preserved visual function. An underlying malignancy is only found in a minority of cases with the latter two (78,92,93). Treatment for CAR attempts to reduce tumor burden in combination with immunosuppression including the use of cyclosporine, azathioprine, rituximab, and corticosteroids (94-96). The primary tumor in CAR is most often small-cell lung carcinoma, but reports of different malignancies, including hematologic, are in the literature (97). Women may be more susceptible than men (78).

Melanoma-associated retinopathy (MAR) is a separate entity with retinal antibodies directed against retinal ON-bipolar cells, although an antibody specific to the disease is not well-defined. Melanoma tumors are known to produce visual phototransduction proteins, with presumed multiple targets in this condition. Prior reports have identified antibodies directed against transducin-a, transducin-b, arrestin, rhodopsin, and TRPM1 (98-102). TRMP1 is a protein specifically found in retinal ON-bipolar cells in the inner nuclear and outer plexiform layers of the retina. This disease causes more rod cell dysfunction and symptoms include bilateral peripheral photopsias and nyctalopia. Unlike in CAR, the diagnosis of cancer (melanoma) often precedes the diagnosis of MAR. These patients typically do not respond to corticosteroids and there is limited evidence for use of IVIG in treatment of the disease (103).

BDUMP

BDUMP is characterized by sudden bilateral vision loss due to massive proliferation of melanocytes in the uveal tract, often leading to exudative retinal detachments and cataract development. The disease is associated with reproductive tract, lung, colon, or pancreatic tumors. In contrast to the previously discussed paraneoplastic disorders, the pathophysiology of BDUMP is hypothesized to be caused by production of tumor-expressed growth factors, specifically melanocytic growth factors, leading to ectopic proliferation of melanocytes. The disease often precedes the diagnosis of cancer, and once identified prognosis is typically poor with an average expected lifespan of less than 15 months (104,105).

Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome

POEMS is thought to be due to production of proangiogenic growth factors, specifically vascular endothelial growth factor (VEGF) causing multisystem dysfunction (106-108). Patients also have higher levels of circulating inflammatory cytokines. By definition, this disorder is due to an underlying plasma cell neoplasm. The diagnostic criteria require a demyelinating polyneuropathy and a monoclonal plasma cell-proliferative disorder, in addition to one other major criterion (VEGF elevation, Castleman disease, or sclerotic bone lesions) and one minor criterion (organomegaly, extravascular volume overload, endocrinopathy, skin changes, papilledema, or

© Chinese Clinical Oncology. All rights reserved.

thrombocytosis/polycythemia). The disease is defined by a symmetric, bilateral, proximal peripheral neuropathy that typically starts as a sensory neuropathy and then leads to motor involvement. Papilledema, a minor criterion of the disease, can be asymptomatic. In a series of 33 patients diagnosed with POEMS, 17 had bilateral disc edema, with only five patients complaining of ocular symptoms (e.g., blurry vision, diplopia, pain) (109). Cystoid macular edema has also been reported in this entity which causes blurry vision (110-113). One report described bilateral serous retinal detachments associated with the condition (114). The etiology of disc edema and macular edema is unknown and there is no agreed upon treatment. Anti-VEGF treatments have not yet been evaluated (109).

Ocular manifestations secondary to therapeutic agents

New developments in immunotherapy and chemotherapy have come with a variety of new side effects, many of which involve the ocular adnexa. The initial clinical trials of these agents as well as post market studies often have inconsistent reporting of adverse events making the incidence and type of ocular side-effects difficult to determine (115,116). However, there is now an abundance of case reports and patient series identifying several trends within categories of agents, though the incidence of these side effects is often difficult to determine with newer drugs. It is also important to note that many of the reported side effects are from case reports in patients with metastatic malignancy and therefore causation of some presentations may be difficult to determine. Given the breadth of reported side effects of malignancy treatments, focus for this review has been placed on immune modulators, checkpoint inhibitors, epidermal growth factor receptor (EGFR) inhibitors, BCR-ABL inhibitors, anaplastic lymphoma kinase (ALK) inhibitors, mitogen-activated protein kinase (MEK) inhibitors, and several traditional chemotherapy agents.

Monoclonal antibodies directed against EGFR such as cetuximab and trastuzumab have reported ocular side effects. EGFR is present in corneal epithelial cells and is paramount in corneal and meibomian gland epithelial health and proliferation (117,118). EGFR is also involved in hair follicle formation and is expressed in conjunctival goblet cells which produce the mucin layer of the ocular surface (119). As such, EGFR inhibitors can lead to symptoms of severe dry eye, blepharitis, or eyelid and eyelash malposition and disorders. Eyelash abnormalities such as overgrowth (trichomegaly) and misdirected eyelashes (trichiasis) has been frequently reported (120-124). This most frequently manifests with swollen lids, tearing, irritation, and redness. Additionally, in a recent review, trastuzumab has been associated with papilledema, retinal hemorrhages, artery, and vein occlusions (125). Small molecule EGFR inhibitors (afatinib, erlotinib, gefitinib, lapatinib and vandetanib) have shown similar side effects. Uveitis has also been reported with this class of agents (125).

Bevacizumab, a monoclonal antibody targeted against VEGF, has been consistently associated with a higher risk of hemorrhagic cerebral stroke (126,127). The development of posterior reversible encephalopathy syndrome leading to cortical blindness has also been implicated with this drug. Purely ocular side effects are less frequent with few reports of serous retinal detachments. One case series of six patients who were being treated with bevacizumab, radiation therapy, and temozolomide for glioblastoma developed optic neuropathy, however causation is difficult to discern in these cases (128).

Checkpoint inhibitors are novel monoclonal antibodies that target cytotoxic T lymphocyte antigen 4 (CTLA4), programmed death-1 (PD-1), or programmed death-ligand 1 (PD-L1) (129). These agents are fundamentally different from other therapeutics in that they upregulate T-cell activity by blocking tumor induced inhibitory pathways. The CTLA4 inhibitor, ipilimumab, acts at the level of the lymph nodes to block the T-cell CTLA4 interaction with antigen presenting cell (APC) receptors CD80 and CD86, which would typically downregulate T-cell activation. This inhibition allows for activation of T-cells presented with tumor antigen by allowing T-cell CD28 receptor interaction with CD80 and CD86. In contrast, PD-1 and PD-L1 inhibitors function at the level of the tumor cell. PD-L1 is expressed on tumor cells and binds with PD-1 on T-cells causing deactivation and immune evasion of the cancer. PD-1 inhibitors, nivolumab and pembrolizumab, and PD-L1 inhibitors, atezolizumab, avelumab, and durvalumab, therefore function to increase T-cell activity at the level of the tumor. The eye is considered to have immune privilege and RPE cells have been shown to express both CD86 and PD-L1, leading to downregulation of T-cell activity (130).

Upregulation of T-cell activity is often related to autoimmune related side effects. Adverse events are common with immune checkpoint inhibitors, occurring in up to 90% of patients and involving nearly every organ system (131,132). Development of autoimmune conditions such as rheumatoid arthritis, Graves thyroiditis, myasthenia

© Chinese Clinical Oncology. All rights reserved.

gravis, giant cell arteritis, multiple sclerosis, lupus, and the ocular syndrome Vogt-Koyanagi-Harada disease have all been described (133-136). Ocular specific side effects are much more infrequent with estimates of an incidence of 1% (137). They often start within weeks of commencing therapy. The most common side effects include ocular surface irritation such as dry eyes, followed by inflammatory conditions. Combination therapy results in the highest incidence of adverse events, and is typically higher with the CTLA4 inhibitor ipilimumab (138). In terms of ophthalmic complications, however, a recent systematic review identified pembrolizumab as the most common cause of a neuro-ophthalmic complication (32.1%) (139).

Nearly every inflammatory ocular toxicity has been described with the use of ipilimumab ranging from conjunctivitis, keratitis, scleritis, retinal vasculitis and uveitis to serous retinal detachments and the development of choroidal neovascularization (125,137,140-142). Many cases are related to an inflammatory process or orbital inflammation (143,144). Bilateral optic neuropathy has also been described in one case report associated with ipilimumab treatment for metastatic melanoma (145). Therefore, nearly any ocular complaint can be induced by immune checkpoint inhibitors and ophthalmology consultation is recommended to document the severity of the ocular condition and need for treatment. Additionally, in patients with newly diagnosed metastatic disease, ocular metastasis, CAR, and PON should also be on the differential and ophthalmology examination is needed to investigate these entities. Typically, local therapy with topical or periocular corticosteroids can treat many inflammatory conditions induced by immune checkpoint inhibitors while continuing the immune checkpoint therapy (146-148). Severe, vision threatening side effects may require cessation of therapy (138,149). Dry eye symptoms can be effectively managed with artificial tears and cyclosporine eye drops.

BCR-ABL inhibitors (imatinib, bosutinib, dasatinib, nilotinib, and ponatinib) have been associated with periorbital edema, conjunctival hemorrhage, epiphora, and keratitis. Up to 70% of patients on imatinib can develop periorbital edema that at least in one instance has led to a compressive optic neuropathy requiring surgical intervention (150). The mechanism behind this side-effect is unclear but may be due to inhibition of platelet-derived growth factor receptor (PDGRF) which is involved in interstitial fluid balance (151). Optic neuritis with profound vision loss was reported in one patient on imatinib; vision recovered after discontinuation of the drug as well as treatment with corticosteroids (152). Additionally, bilateral optic disc edema was reported in one patient; this also resolved after discontinuation of the medication (153). Of note, the disc edema did not recur after restarting imatinib in this case.

ALK inhibitors (brigatinib, lorlatinib, alectinib, crizotinib, and alectinib) and, in particular, crizotinib have had a high incidence of reported visual disturbances in clinical trials (41–71%) (154-156). These tyrosine kinase inhibitors are used in the treatment of non-small-cell lung carcinoma. Interestingly, a high percentage (41%) of patients assigned to a 28-day cycle of 250 mg twice daily crizotinib in clinical trials reported visual disturbances of post-flashbulb effects such as brief image persistence or trails of light following moving objects, which were particularly bothersome during transitions from dark to light. In three patients examined during the clinical trial by ophthalmology, no ocular abnormalities were noted. Other reported visual changes include photopsias, blurred vision, accommodation disorders such as presbyopia induction, and reduced visual acuity. The reported side effects waned with treatment duration. A more serious side effect of bilateral optic neuropathy on crizotinib was reported, however the ocular symptoms continued to progressed to blindness after the medication was held making causation difficult to determine (157). Several *in vivo* studies on retinal cell function in rats treated with ALK inhibitors have been inconclusive on elucidating a mechanism behind these visual disturbances (158,159). In total, the majority of side effects appear to be benign, and providers should be aware of post-flashbulb effects, photopsias, and dark to light adaptations problems in patients on ALK inhibitors.

The mitogen-activated protein kinase (MAPK) pathway involves several protein kinases that are oncologic targets and plays a fundamental role in a diverse set of cellular processes such as cell proliferation and differentiation, motility, stress response, and apoptosis (160). In broad terms, the pathway involves activation of RAS, subsequent activation of several protein kinases (BRAF, ERK, and MEK), that then leads to MAPK activation. Mutations that lead to continuous activation of this pathway have been shown to be central to oncogenesis of several tumors such as cutaneous melanoma and lung cancer (161,162). Additionally, this pathway has been implicated in the maintenance of RPE cells in the retina (163-166). MEK inhibitors are one class of therapy in which retinal toxicity has been frequently reported leading to recognition of the potential need for routine ocular examinations for

© Chinese Clinical Oncology. All rights reserved.

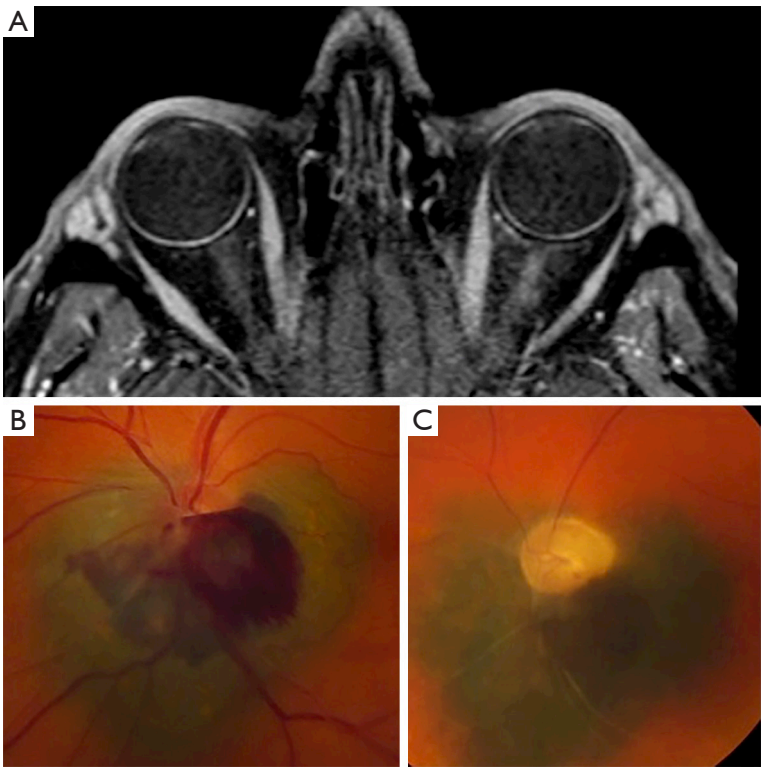

Figure 2 Radiation optic neuropathy three years post treatment in a 53-year-old male who received 50 Gy in five fractions for a choroidal melanoma. (A) T1 post-contrast fat-suppressed MRI of the orbits with gadolinium enhancement demonstrating optic nerve enhancement of the left eye. (B) Fundus photography of the left optic nerve demonstrating a choroidal melanoma surrounding the optic nerve with overlying optic disc hemorrhage prior to radiation treatment. The visible portion of the optic nerve appears pink. (C) Fundus photography of the left optic nerve three years after radiation treatment with subsequent pallor and atrophy of the optic nerve. This eye lost all vision. MRI, magnetic resonance imaging.

patients on these therapies (167). In the clinical trials for several MEK inhibitors, a wide variety of ocular toxicities and orbital inflammation was reported, including uveitis, episcleritis, scleritis, blepharitis, and conjunctivitis (168-174). The most well recognized and frequent ocular manifestation is MEK associated retinopathy. This entity presents most frequently with bilateral blurred vision, central scotomas, and photopsias due to subretinal fluid and a disease process that closely resembles central serous chorioretinopathy (175,176). Patients may also be asymptomatic. Visual acuity typically recovers after resolution of the subretinal fluid and discontinuation of the therapy.

External cranial irradiation can lead to a progressive optic neuropathy which is usually delayed until month to years after treatment typically presenting as painless, monocular (although bilateral cases have been reported), acute, irreversible visual loss. Radiation induced optic neuropathy (RON) is rare and usually occurs with cumulative dose of at least 50 Gy or a single dose of 10 Gy. Both targeted and whole brain irradiation can lead to RON. The average timeframe from treatment to development of symptoms is estimated at 18 months (177,178). The optic disc may appear normal or pale at time of diagnosis and MRI imaging is essential for the diagnosis and to rule out other causes of optic neuropathy. A recent case series of 12 patients (15 eyes) with RON identified a characteristic MRI finding of prechiasmatic optic nerve enhancement accompanied by expansion and T2 hyperintensity in the enhancing region that may preceded vision loss, and only rarely develops after symptoms. Most patients had optic disc pallor at presentation suggesting subclinical optic nerve damage and an APD was present in all patients on presentation. Though several treatments have been pursued (e.g., hyperbaric oxygen therapy, systemic bevacizumab, corticosteroids, anticoagulation, among others), there remains no definitive treatment for RON and vision loss is generally

© Chinese Clinical Oncology. All rights reserved.

Table 2 Neuro-ophthalmic complications of cancer and therapies organized by patient complaint, clinical context, and nonspecialized physical examination

Diagnosis	Ocular complaint	Clinical context	Physical examination
Optic nerve infiltration	Painless, blurred or lost vision (unilateral or bilateral)	Patient with known metastatic disease or hematologic malignancy	Decrease visual acuity, afferent pupillary defect, decreased color vision, abnormal optic nerve appearance
Primary vitreoretinal lymphoma	Bilateral floaters, blurred vision	Patient with known primary CNS lymphoma	Abnormal opacities in vitreous or retinal infiltrate, intraocular inflammation, decreased vision
Paraneoplastic optic neuropathy	Painless, progressive vision loss	Most patients have an underlying small-cell lung carcinoma. Most frequently associated with other neurologic symptoms	Decreased visual acuity, afferent pupillary defect, decreased color vision, sometimes mild disc swelling
Cancer-associated retinopathy; melanoma-associated retinopathy	Photosensitivity, photopsias, blurred vision, scotomas, nyctalopia	History of small-cell lung carcinoma (most frequent) or melanoma	Can have normal examination, decreased visual acuity, scotomas, abnormalities detected only on specialized retinal testing
Bilateral diffuse uveal melanocytic proliferation	Bilateral sudden vision loss	History of reproductive tract, lung, colon or pancreatic tumors	Decreased visual acuity, exudative retinal detachments, cataracts
Side effect/toxicity EGFR inhibitors	Irritation, redness, dry eye, blurry vision	EGFR inhibitor use	Conjunctival injection, discharge, tearing
Side effect/toxicity Checkpoint inhibitors	Nearly any ocular complaint is possible due to ocular inflammation in any structure of the eye. May be asymptomatic	Checkpoint inhibitor use	Dependent on structure which is inflamed. Nearly any ocular structure can be involved
Side effect/toxicity BCR-ABL inhibitors	Swelling, tearing, red eye, eye pain	BCR-ABL inhibitor use	Periorbital edema, conjunctival hemorrhage
Side effect/toxicity MEK inhibitors	Blurry vision	MEK inhibitor use	Decreased visual acuity, associated retinopathy with serous retinal detachments
Side effect/toxicity ALK inhibitors	Blurry vision, photopsias, flashbulb effects, difficulty reading	ALK inhibitor use	Can have normal examination, decreased visual acuity, inability to accommodate

CNS, central nervous system; EGFR, epidermal growth factor receptor; MEK, mitogen-activated protein kinase; ALK, anaplastic lymphoma kinase.

irreversible (179). *Figure 2* demonstrates a 53-year-old with a choroidal melanoma treated with proton beam irradiation (50 Gy in five fractions) and subsequent development of RON three years later.

Lastly, traditional chemotherapy such as alkylating agents, antimetabolites, and mitotic inhibitors have been associated with non-infectious bulbar conjunctivitis. This is presumed secondary to exposure of the conjunctival mucosal tissue to a toxic concentration of the drug within the tear film; this subsides with discontinuation of the drug (180). The lacrimal drainage system can be susceptible to these agents leading to inflammation and subsequent stenosis. Taxanes, such as docetaxel, in particular, can lead to irreversible canicular stenosis and epiphora. Cessation should be considered in cases in which patients complain of epiphora.

Discussion

Ocular complaints can often be nonspecific; for instance, the symptoms of anterior uveitis induced by immune checkpoint inhibitors—pain and redness—may be remarkably similar to those of ocular surface disease or dry eyes. The major entities described in this review are summarized in *Table 2*

© Chinese Clinical Oncology. All rights reserved.

to provide a framework for the oncologist to triage ocular complaints. Additionally, there are several tools that oncologists can utilize to characterize and triage ocular complaints in a cancer patient to specifically determine whether they need an urgent ophthalmology consultation. First, characterization of the visual complaint in detail can be vital. For instance, a patient complaint of blurred vision could be used to describe a visual field defect, a scotoma, floaters, or other visual phenomena, and discerning this information is helpful in determining an etiology. Another example is double vision. Binocular diplopia (diplopia that resolves with covering either eye) generally indicates an ocular misalignment; monocular diplopia (diplopia that does not resolve with covering either eye) is often related to dry eyes or refractive error and is rarely a concerning symptom. Observing extraocular movements and ocular alignment can reveal cranial nerve palsies. Second, testing pupillary reactions can immediately reveal a more sinister cause of visual complaints; optic nerve infiltration, neuropathy, or neuritis will generally present with an APD. Third, visual examination of the patient's orbits can also provide valuable information. A change or asymmetry such as proptosis or orbital pressure can indicated a mass lesion. Finally, evaluating temporal associations between initiation of new therapies and vision changes may be helpful.

In general, new visual field defects, motility problems with binocular diplopia, an APD, and/or new complaints in relation to starting a therapeutic agent should warrant an urgent ophthalmologic evaluation. Oncologists should maintain a low threshold to pursue ophthalmic consultation if there is any concern. An MRI of the brain and orbits with gadolinium enhancement can also help to identify many vision threatening conditions as well as provide important contextual information to the ophthalmologist. The ophthalmologist should continue to work closely with the oncologist to monitor and treat ophthalmic manifestations of systemic disease as well as to monitor response to therapy. If recognized early as a potential serious ocular complication of cancer (e.g., optic nerve infiltration), early treatment and proper management can save vision. Together, the oncologist and ophthalmologist can best optimize the patient's visual potential as well as mitigate the systemic burden of disease.

Acknowledgments

The authors would like to acknowledge Dr. Jennifer Rossen for providing the case for Figure 1.

Funding: This work was supported in part by an unrestricted departmental grant from the Research to Prevent Blindness, Inc. (RPB).

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://cco.amegroups.com/article/view/10.21037/cco-21-137/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cco.amegroups.com/article/view/10.21037/cco-21-137/coif). The authors report receiving unrestricted grant to support their research activities from Research to Prevent Blindness Inc. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

References

1. Myers KA, Nikolic A, Romanchuk K, et al. Optic neuropathy in the context of leukemia or lymphoma: diagnostic approach to a neuro-oncologic emergency. Neurooncol Pract 2017;4:60-6.
2. Dermarkarian CR, Kini AT, Al Othman BA, et al. Neuro-Ophthalmic Manifestations of Intracranial Malignancies. J Neuroophthalmol 2020;40:e31-48.
3. Nolan C, Deangelis LM. Overview of metastatic disease of the central nervous system. Handb Clin Neurol 2018;149:3-23.
4. Corbin ZA, Nagpal S. Leptomeningeal Metastases. JAMA Oncol 2016;2:839.
5. DeAngelis LM, Boutros D. Leptomeningeal metastasis. Cancer Invest 2005;23:145-54.

© Chinese Clinical Oncology. All rights reserved.

6. Menjot de Champfleur N, Menjot de Champfleur S, Galanaud D, et al. Imaging of the optic chiasm and retrochiasmal visual pathways. Diagn Interv Imaging 2013;94:957-71.
7. Noll KR, Sullaway C, Ziu M, et al. Relationships between tumor grade and neurocognitive functioning in patients with glioma of the left temporal lobe prior to surgical resection. Neuro Oncol 2015;17:580-7.
8. Malamud N. Psychiatric disorder with intracranial tumors of limbic system. Arch Neurol 1967;17:113-23.
9. Wang N, Bertalan MS, Brastianos PK. Leptomeningeal metastasis from systemic cancer: Review and update on management. Cancer 2018;124:21-35.
10. Waki F, Ando M, Takashima A, et al. Prognostic factors and clinical outcomes in patients with leptomeningeal metastasis from solid tumors. J Neurooncol 2009;93:205-12.
11. Kincaid MC, Green WR. Ocular and orbital involvement in leukemia. Surv Ophthalmol 1983;27:211-32.
12. ALLEN RA, STRAATSMA BR. Ocular involvement in leukemia and allied disorders. Arch Ophthalmol 1961;66:490-508.
13. Camera A, Piccirillo G, Cennamo G, et al. Optic nerve involvement in acute lymphoblastic leukemia. Leuk Lymphoma 1993;11:153-5.
14. Killer HE, Jaggi GP, Flammer J, et al. Cerebrospinal fluid dynamics between the intracranial and the subarachnoid space of the optic nerve. Is it always bidirectional? Brain 2007;130:514-20.
15. Ridgway EW, Jaffe N, Walton DS. Leukemic ophthalmopathy in children. Cancer 1976;38:1744-9.
16. Nagpal MP, Mehrotra NS, Mehta RC, et al. leukemic optic nerve infiltration in a patient with acute lymphoblastic leukemia. Retin Cases Brief Rep 2016;10:127-30.
17. Azad SV, Banerjee M, Parmanand K, et al. Isolated optic nerve involvement in acute lymphoblastic leukaemia: a red flag for early relapse. BMJ Case Rep 2021;14:243689.
18. Monsereenusorn C, Rujkijyanont P, Srimanan W, et al. Isolated Ocular Relapse in Childhood Acute Lymphoblastic Leukemia during Second Interim Maintenance Phase of Chemotherapy: Case Report. J Med Assoc Thai 2015;98:1150-3.
19. Del Principe MI, Maurillo L, Buccisano F, et al. Central nervous system involvement in adult acute lymphoblastic leukemia: diagnostic tools, prophylaxis, and therapy. Mediterr J Hematol Infect Dis 2014;6:e2014075.
20. Glantz MJ, Cole BF, Glantz LK, et al. Cerebrospinal fluid cytology in patients with cancer: minimizing false-negative results. Cancer 1998;82:733-9.
21. Jaime-Pérez JC, Borrego-López MF, Jiménez-Castillo RA, et al. Comparison of conventional cytomorphology, flow cytometry immunophenotyping, and automated cell counting of CSF for detection of CNS involvement in acute lymphoblastic leukemia. Int J Lab Hematol 2018;40:169-74.
22. Rosenthal AR. Ocular Manifestations of Leukemia. Ophthalmology 1983;90:899-905.
23. Nikaido H, Mishima H, Ono H, et al. Leukemic involvement of the optic nerve. Am J Ophthalmol 1988;105:294-8.
24. Khan K, Malik AI, Almarzouqi SJ, et al. Optic Neuropathy Due to Chronic Lymphocytic Leukemia Proven With Optic Nerve Sheath Biopsy. J Neuroophthalmol 2016;36:61-6.
25. Shenoy SB, Karam T, Udupa K, et al. Leukaemic infiltration of the optic nerve head: a rare site of initial relapse. BMJ Case Rep 2016;2016:bcr2016217239.
26. Shields CL, Welch RJ, Malik K, et al. Uveal Metastasis: Clinical Features and Survival Outcome of 2214 Tumors in 1111 Patients Based on Primary Tumor Origin. Middle East Afr J Ophthalmol 2018;25:81-90.
27. Sobolewska B, Chee SP, Zaguia F, et al. Vitreoretinal Lymphoma. Cancers (Basel) 2021;13:3921.
28. Coupland SE, Anastassiou G, Bornfeld N, et al. Primary intraocular lymphoma of T-cell type: report of a case and review of the literature. Graefes Arch Clin Exp Ophthalmol 2005;243:189-97.
29. Cimino L, Chan CC, Shen D, et al. Ocular involvement in nasal natural killer T-cell lymphoma. Int Ophthalmol 2009;29:275-9.
30. COOPER EL, RIKER JL. Malignant lymphoma of the uveal tract. Am J Ophthalmol 1951;34:1153-8.
31. Chan CC, Gonzalez JA. Primary Intraocular Lymphoma; World Scientific Publishing Co. Pte Ltd., Hackensack, NJ, USA; 2007.
32. Freeman LN, Schachat AP, Knox DL, et al. Clinical features, laboratory investigations, and survival in ocular reticulum cell sarcoma. Ophthalmology 1987;94:1631-9.
33. Kimura K, Usui Y, Goto H, et al. Clinical features and diagnostic significance of the intraocular fluid of 217 patients with intraocular lymphoma. Jpn J Ophthalmol 2012;56:383-9.
34. Chan CC, Sen HN. Current concepts in diagnosing and managing primary vitreoretinal (intraocular) lymphoma. Discov Med 2013;15:93-100.
35. Chan CC, Rubenstein JL, Coupland SE, et al.

© Chinese Clinical Oncology. All rights reserved.

Primary vitreoretinal lymphoma: a report from an International Primary Central Nervous System Lymphoma Collaborative Group symposium. Oncologist 2011;16:1589-99.
36. Grimm SA, McCannel CA, Omuro AM, et al. Primary CNS lymphoma with intraocular involvement: International PCNSL Collaborative Group Report. Neurology 2008;71:1355-60.
37. Citterio G, Calimeri T, Ferreri AJM. Challenges and prospects in the diagnosis and treatment of primary central nervous system lymphoma. Expert Rev Neurother 2018;18:379-93.
38. Grimm SA, Pulido JS, Jahnke K, et al. Primary intraocular lymphoma: an International Primary Central Nervous System Lymphoma Collaborative Group Report. Ann Oncol 2007;18:1851-5.
39. Riemens A, Bromberg J, Touitou V, et al. Treatment strategies in primary vitreoretinal lymphoma: a 17-center European collaborative study. JAMA Ophthalmol 2015;133:191-7.
40. Soussain C, Malaise D, Cassoux N. Primary vitreoretinal lymphoma: a diagnostic and management challenge. Blood 2021;138:1519-34.
41. Hashida N, Nakai K, Saitoh N, et al. Association between ocular findings and preventive therapy with onset of central nervous system involvement in patients with primary vitreoretinal lymphoma. Graefes Arch Clin Exp Ophthalmol 2014;252:687-93.
42. Lam M, Touitou V, Choquet S, et al. Intravenous high-dose methotrexate based systemic therapy in the treatment of isolated primary vitreoretinal lymphoma: An LOC network study. Am J Hematol 2021;96:823-33.
43. Akiyama H, Takase H, Kubo F, et al. High-dose methotrexate following intravitreal methotrexate administration in preventing central nervous system involvement of primary intraocular lymphoma. Cancer Sci 2016;107:1458-64.
44. Kaburaki T, Taoka K, Matsuda J, et al. Combined intravitreal methotrexate and immunochemotherapy followed by reduced-dose whole-brain radiotherapy for newly diagnosed B-cell primary intraocular lymphoma. Br J Haematol 2017;179:246-55.
45. Gordon LK. Paraneoplastic Syndromes in Neuro-Ophthalmology. J Neuroophthalmol 2015;35:306-14.
46. Darnell RB, Posner JB. Paraneoplastic syndromes involving the nervous system. N Engl J Med 2003;349:1543-54.
47. Prze dziecka-Dołyk J, Brzecka A, Ejma M, et al. Ocular Paraneoplastic Syndromes. Biomedicines 2020;8:490.
48. Cross SA, Salomao DR, Parisi JE, et al. Paraneoplastic autoimmune optic neuritis with retinitis defined by CRMP-5-IgG. Ann Neurol 2003;54:38-50.
49. Luiz JE, Lee AG, Keltner JL, et al. Paraneoplastic optic neuropathy and autoantibody production in small-cell carcinoma of the lung. J Neuroophthalmol 1998;18:178-81.
50. Margolin E, Flint A, Trobe JD. High-titer collapsin response-mediating protein-associated (CRMP-5) paraneoplastic optic neuropathy and Vitritis as the only clinical manifestations in a patient with small cell lung carcinoma. J Neuroophthalmol 2008;28:17-22.
51. Moss HE, Liu GT, Dalmau J. Glazed (vision) and confused. Surv Ophthalmol 2010;55:169-73.
52. Sheorajpanday R, Slabbynck H, Van De Sompel W, et al. Small cell lung carcinoma presenting as collapsin response-mediating protein (CRMP) -5 paraneoplastic optic neuropathy. J Neuroophthalmol 2006;26:168-72.
53. Thambisetty MR, Scherzer CR, Yu Z, et al. Paraneoplastic optic neuropathy and cerebellar ataxia with small cell carcinoma of the lung. J Neuroophthalmol 2001;21:164-7.
54. Nakayama-Ichiyama S, Yokote T, Hiraoka N, et al. A paraneoplastic neuromyelitis optica spectrum disorder associated with a mature B-cell neoplasm. Leuk Res 2011;35:e111-3.
55. Lambrecht ER, van der Loos TL, van der Eerden AH. Retrobulbar neuritis as the first sign of the glucagonoma syndrome. Int Ophthalmol 1987;11:13-5.
56. Kennedy MJ, Eustace P, O'Briain DS, et al. Paraneoplastic papilloedema in neuroblastoma. Postgrad Med J 1987;63:873-6.
57. Scott JX, Moses PD, Somashekar HR, et al. Paraneoplastic papilloedema in a child with neuroblastoma. Indian J Cancer 2005;42:102-3.
58. Antoine JC, Honnorat J, Vocanson C, et al. Posterior uveitis, paraneoplastic encephalomyelitis and auto-antibodies reacting with developmental protein of brain and retina. J Neurol Sci 1993;117:215-23.
59. Pulido J, Cross SA, Lennon VA, et al. Bilateral autoimmune optic neuritis and vitreitis related to CRMP-5-IgG: intravitreal triamcinolone acetonide therapy of four eyes. Eye (Lond) 2008;22:1191-3.
60. Carboni G, Forma G, Bond AD, et al. Bilateral paraneoplastic optic neuropathy and unilateral retinal compromise in association with prostate cancer: a differential diagnostic challenge in a patient with unexplained visual loss. Doc Ophthalmol 2012;125:63-70.
61. Hoh ST, Teh M, Chew SJ. Paraneoplastic optic

© Chinese Clinical Oncology. All rights reserved.

neuropathy in nasopharyngeal carcinoma--report of a case. Singapore Med J 1991;32:170-3.
62. Pillay N, Gilbert JJ, Ebers GC, et al. Internuclear ophthalmoplegia and "optic neuritis": paraneoplastic effects of bronchial carcinoma. Neurology 1984;34:788-91.
63. Kuroda Y, Miyahara M, Sakemi T, et al. Autopsy report of acute necrotizing opticomyelopathy associated with thyroid cancer. J Neurol Sci 1993;120:29-32.
64. Asproudis IC, Nikas AN, Psilas KG. Paraneoplastic optic neuropathy in a patient with a non-small cell lung carcinoma: a case report. Eur J Ophthalmol 2005;15:420-3.
65. Murakami Y, Yoshida S, Yoshikawa H, et al. CRMP-5-IgG in patient with paraneoplastic optic neuritis with lung adenocarcinoma. Eye (Lond) 2007;21:860-2.
66. Srikantha N, Goverdhan S, Evans A. Paraneoplastic optic neuropathy associated with papillary renal cell carcinoma. Br J Ophthalmol 2011;95:429,438.
67. Calvert PC. A CR(I)MP in the optic nerve: recognition and implications of paraneoplastic optic neuropathy. J Neuroophthalmol 2006;26:165-7.
68. Yu Z, Kryzer TJ, Griesmann GE, et al. CRMP-5 neuronal autoantibody: marker of lung cancer and thymoma-related autoimmunity. Ann Neurol 2001;49:146-54.
69. Hersh B, Dalmau J, Dangond F, et al. Paraneoplastic opsoclonus-myoclonus associated with anti-Hu antibody. Neurology 1994;44:1754-5.
70. Bernal F, Shams'ili S, Rojas I, et al. Anti-Tr antibodies as markers of paraneoplastic cerebellar degeneration and Hodgkin's disease. Neurology 2003;60:230-4.
71. Peterson K, Rosenblum MK, Kotanides H, et al. Paraneoplastic cerebellar degeneration. I. A clinical analysis of 55 anti-Yo antibody-positive patients. Neurology 1992;42:1931-7.
72. Karim AR, Jacob S. Immunological markers in neurological disorders. Ann Clin Biochem 2012;49:29-43.
73. Saiz A, Dalmau J, Butler MH, et al. Anti-amphiphysin I antibodies in patients with paraneoplastic neurological disorders associated with small cell lung carcinoma. J Neurol Neurosurg Psychiatry 1999;66:214-7.
74. Graus F, Dalmau J. Paraneoplastic neuropathies. Curr Opin Neurol 2013;26:489-95.
75. Xu Q, Du W, Zhou H, et al. Distinct clinical characteristics of paraneoplastic optic neuropathy. Br J Ophthalmol 2019;103:797-801.
76. Waterston JA, Gilligan BS. Paraneoplastic optic neuritis and external ophthalmoplegia. Aust N Z J Med 1986;16:703-4.
77. Durrani A, Shah RJ, Kim SJ. Successful long-term treatment of paraneoplastic optic neuropathy with mycophenolate mofetil, prednisone, and plasmapheresis. Am J Ophthalmol Case Rep 2017;8:31-4.
78. Adamus G. Autoantibody targets and their cancer relationship in the pathogenicity of paraneoplastic retinopathy. Autoimmun Rev 2009;8:410-4.
79. Adamus G. Antirecoverin antibodies and autoimmune retinopathy. Arch Ophthalmol 2000;118:1577-8.
80. Forooghian F, Macdonald IM, Heckenlively JR, et al. The need for standardization of antiretinal antibody detection and measurement. Am J Ophthalmol 2008;146:489-95.
81. Grewal DS, Fishman GA, Jampol LM. Autoimmune retinopathy and antiretinal antibodies: a review. Retina 2014;34:827-45.
82. McGinnis JF, Austin B, Klisak I, et al. Chromosomal assignment of the human gene for the cancer-associated retinopathy protein (recoverin) to chromosome 17p13.1. J Neurosci Res 1995;40:165-8.
83. Bazhin AV, Savchenko MS, Shifrina ON, et al. Recoverin as a paraneoplastic antigen in lung cancer: the occurrence of anti-recoverin autoantibodies in sera and recoverin in tumors. Lung Cancer 2004;44:193-8.
84. Matsubara S, Yamaji Y, Fujita T, et al. Cancer-associated retinopathy syndrome: a case of small cell lung cancer expressing recoverin immunoreactivity. Lung Cancer 1996;14:265-71.
85. Polans AS, Witkowska D, Haley TL, et al. Recoverin, a photoreceptor-specific calcium-binding protein, is expressed by the tumor of a patient with cancer-associated retinopathy. Proc Natl Acad Sci U S A 1995;92:9176-80.
86. Yamaji Y, Matsubara S, Yamadori I, et al. Characterization of a small-cell-lung-carcinoma cell line from a patient with cancer-associated retinopathy. Int J Cancer 1996;65:671-6.
87. Kordyś M, Przeździecka-Dołyk J, Turno-Kręcicka A, et al. Immunopathogenesis of ophthalmological paraneoplastic syndromes: Recent findings. Adv Clin Exp Med 2018;27:1431-9.
88. Dalin F, Adamus G, Yang S, et al. Aryl Hydrocarbon Receptor-Interacting Protein-Like 1 in Cancer-Associated Retinopathy. Ophthalmology 2016;123:1401-4.
89. Yang S, Dizhoor A, Wilson DJ, et al. GCAP1, Rab6, and HSP27: Novel Autoantibody Targets in Cancer-Associated Retinopathy and Autoimmune Retinopathy. Transl Vis Sci Technol 2016;5:1.
90. Bhavsar KV, Hedges T, Thirkill CE, et al. Paraneoplastic retinopathy associated with systemic follicular cell lymphoma. Ophthalmic Surg Lasers Imaging Retina 2015;46:373-6.

© Chinese Clinical Oncology. All rights reserved.

91. Adamus G, Bonnah R, Brown L, et al. Detection of autoantibodies against heat shock proteins and collapsin response mediator proteins in autoimmune retinopathy. BMC Ophthalmol 2013;13:48.
92. Adamus G, Brown L, Weleber RG. Molecular biomarkers for autoimmune retinopathies: significance of anti-transducin-alpha autoantibodies. Exp Mol Pathol 2009;87:195-203.
93. Weleber RG, Watzke RC, Shults WT, et al. Clinical and electrophysiologic characterization of paraneoplastic and autoimmune retinopathies associated with antienolase antibodies. Am J Ophthalmol 2005;139:780-94.
94. Ferreyra HA, Jayasundera T, Khan NW, et al. Management of autoimmune retinopathies with immunosuppression. Arch Ophthalmol 2009;127:390-7.
95. Or C, Collins DR, Merkur AB, et al. Intravenous rituximab for the treatment of cancer-associated retinopathy. Can J Ophthalmol 2013;48:e35-8.
96. Audemard A, de Raucourt S, Miocque S, et al. Melanoma-associated retinopathy treated with ipilimumab therapy. Dermatology 2013;227:146-9.
97. Chan JW. Paraneoplastic retinopathies and optic neuropathies. Surv Ophthalmol 2003;48:12-38.
98. Potter MJ, Adamus G, Szabo SM, et al. Autoantibodies to transducin in a patient with melanoma-associated retinopathy. Am J Ophthalmol 2002;134:128-30.
99. Bazhin AV, Dalke C, Willner N, et al. Cancer-retina antigens as potential paraneoplastic antigens in melanoma-associated retinopathy. Int J Cancer 2009;124:140-9.
100. Hartmann TB, Bazhin AV, Schadendorf D, et al. SEREX identification of new tumor antigens linked to melanoma-associated retinopathy. Int J Cancer 2005;114:88-93.
101. Kondo M, Sanuki R, Ueno S, et al. Identification of autoantibodies against TRPM1 in patients with paraneoplastic retinopathy associated with ON bipolar cell dysfunction. PLoS One 2011;6:e19911.
102. Dhingra A, Fina ME, Neinstein A, et al. Autoantibodies in melanoma-associated retinopathy target TRPM1 cation channels of retinal ON bipolar cells. J Neurosci 2011;31:3962-7.
103. Keltner JL, Thirkill CE, Yip PT. Clinical and immunologic characteristics of melanoma-associated retinopathy syndrome: eleven new cases and a review of 51 previously published cases. J Neuroophthalmol 2001;21:173-87.
104. O'Neal KD, Butnor KJ, Perkinson KR, et al. Bilateral diffuse uveal melanocytic proliferation associated with pancreatic carcinoma: a case report and literature review of this paraneoplastic syndrome. Surv Ophthalmol 2003;48:613-25.
105. Gass JD, Gieser RG, Wilkinson CP, et al. Bilateral diffuse uveal melanocytic proliferation in patients with occult carcinoma. Arch Ophthalmol 1990;108:527-33.
106. Dispenzieri A. POEMS Syndrome: 2019 Update on diagnosis, risk-stratification, and management. Am J Hematol 2019;94:812-27.
107. Mineta M, Hatori M, Sano H, et al. Recurrent Crow-Fukase syndrome associated with increased serum levels of vascular endothelial growth factor: a case report and review of the literature. Tohoku J Exp Med 2006;210:269-77.
108. Scarlato M, Previtali SC, Carpo M, et al. Polyneuropathy in POEMS syndrome: role of angiogenic factors in the pathogenesis. Brain 2005;128:1911-20.
109. Kaushik M, Pulido JS, Abreu R, et al. Ocular findings in patients with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome. Ophthalmology 2011;118:778-82.
110. Chong DY, Comer GM, Trobe JD. Optic disc edema, cystoid macular edema, and elevated vascular endothelial growth factor in a patient with POEMS syndrome. J Neuroophthalmol 2007;27:180-3.
111. Gutierrez-Ortiz C, Castro-Rebollo M, Pareja J, et al. Bilateral non-simultaneous optic neuropathy and unilateral macular edema in a patient with POEMS syndrome. Eur J Ophthalmol 2009;19:166-9.
112. Imai H, Kusuhara S, Nakanishi Y, et al. A case of POEMS syndrome with cystoid macular edema. Am J Ophthalmol 2005;139:563-6.
113. Wiaux C, Landau K, Borruat FX. Unusual cause of bilateral optic disc swelling: POEMS syndrome. Klin Monbl Augenheilkd 2007;224:334-6.
114. Okada K, Yamamoto S, Tsuyama Y, et al. Case of POEMS syndrome associated with bilateral macular detachment resolved by autologous peripheral blood stem cell transplantation. Jpn J Ophthalmol 2007;51:237-8.
115. Scharf O, Colevas AD. Adverse event reporting in publications compared with sponsor database for cancer clinical trials. J Clin Oncol 2006;24:3933-8.
116. Zhang S, Liang F, Tannock I. Use and misuse of common terminology criteria for adverse events in cancer clinical trials. BMC Cancer 2016;16:392.
117. Celik T, Kosker M. Ocular side effects and trichomegaly of eyelashes induced by erlotinib: a case report and review of the literature. Cont Lens Anterior Eye 2015;38:59-60.
118. Agustoni F, Platania M, Vitali M, et al. Emerging toxicities in the treatment of non-small cell lung cancer: ocular

© Chinese Clinical Oncology. All rights reserved.

disorders. Cancer Treat Rev 2014;40:197-203.
119. Hodges RR, Bair JA, Carozza RB, et al. Signaling pathways used by EGF to stimulate conjunctival goblet cell secretion. Exp Eye Res 2012;103:99-113.
120. Melichar B, Nemcová I. Eye complications of cetuximab therapy. Eur J Cancer Care (Engl) 2007;16:439-43.
121. Tullo AB, Esmaeli B, Murray PI, et al. Ocular findings in patients with solid tumours treated with the epidermal growth factor receptor tyrosine kinase inhibitor gefitinib ('Iressa', ZD1839) in Phase I and II clinical trials. Eye (Lond) 2005;19:729-38.
122. Foerster CG, Cursiefen C, Kruse FE. Persisting corneal erosion under cetuximab (Erbitux) treatment (epidermal growth factor receptor antibody). Cornea 2008;27:612-4.
123. Lane K, Goldstein SM. Erlotinib-associated trichomegaly. Ophthalmic Plast Reconstr Surg 2007;23:65-6.
124. Alexandrescu DT, Kauffman CL, Dasanu CA. Persistent hair growth during treatment with the EGFR inhibitor erlotinib. Dermatol Online J 2009;15:4.
125. Huillard O, Bakalian S, Levy C, et al. Ocular adverse events of molecularly targeted agents approved in solid tumours: a systematic review. Eur J Cancer 2014;50:638-48.
126. Zuo PY, Chen XL, Liu YW, et al. Increased risk of cerebrovascular events in patients with cancer treated with bevacizumab: a meta-analysis. PLoS One 2014;9:e102484.
127. Seet RC, Rabinstein AA. Clinical features and outcomes of posterior reversible encephalopathy syndrome following bevacizumab treatment. QJM 2012;105:69-75.
128. Sherman JH, Aregawi DG, Lai A, et al. Optic neuropathy in patients with glioblastoma receiving bevacizumab. Neurology 2009;73:1924-6.
129. Bhatti MT, Salama AKS. Neuro-ophthalmic side effects of molecularly targeted cancer drugs. Eye (Lond) 2018;32:287-301.
130. Dalvin LA, Shields CL, Orloff M, et al. CHECKPOINT INHIBITOR IMMUNE THERAPY: Systemic Indications and Ophthalmic Side Effects. Retina 2018;38:1063-78.
131. Michot JM, Bigenwald C, Champiat S, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. Eur J Cancer 2016;54:139-48.
132. Spain L, Diem S, Larkin J. Management of toxicities of immune checkpoint inhibitors. Cancer Treat Rev 2016;44:51-60.
133. Goldstein BL, Gedmintas L, Todd DJ. Drug-associated polymyalgia rheumatica/giant cell arteritis occurring in two patients after treatment with ipilimumab, an antagonist of ctla-4. Arthritis Rheumatol 2014;66:768-9.
134. Johnson DB, Saranga-Perry V, Lavin PJ, et al. Myasthenia Gravis Induced by Ipilimumab in Patients With Metastatic Melanoma. J Clin Oncol 2015;33:e122-4.
135. Gerdes LA, Held K, Beltrán E, et al. CTLA4 as Immunological Checkpoint in the Development of Multiple Sclerosis. Ann Neurol 2016;80:294-300.
136. Renouf DJ, Velazquez-Martin JP, Simpson R, et al. Ocular toxicity of targeted therapies. J Clin Oncol 2012;30:3277-86.
137. Antoun J, Titah C, Cochereau I. Ocular and orbital side-effects of checkpoint inhibitors: a review article. Curr Opin Oncol 2016;28:288-94.
138. Davies M, Duffield EA. Safety of checkpoint inhibitors for cancer treatment: strategies for patient monitoring and management of immune-mediated adverse events. Immunotargets Ther 2017;6:51-71.
139. Yu CW, Yau M, Mezey N, et al. Neuro-ophthalmic Complications of Immune Checkpoint Inhibitors: A Systematic Review. Eye Brain 2020;12:139-67.
140. Liu CY, Francis JH, Brodie SE, et al. Retinal toxicities of cancer therapy drugs: biologics, small molecule inhibitors, and chemotherapies. Retina 2014;34:1261-80.
141. Hager T, Seitz B. Ocular side effects of biological agents in oncology: what should the clinician be aware of? Onco Targets Ther 2013;7:69-77.
142. Mantopoulos D, Kendra KL, Letson AD, et al. Bilateral Choroidopathy and Serous Retinal Detachments During Ipilimumab Treatment for Cutaneous Melanoma. JAMA Ophthalmol 2015;133:965-7.
143. Sheldon CA, Kharlip J, Tamhankar MA. Inflammatory Orbitopathy Associated With Ipilimumab. Ophthalmic Plast Reconstr Surg 2017;33:S155-8.
144. Papavasileiou E, Prasad S, Freitag SK, et al. Ipilimumab-induced Ocular and Orbital Inflammation--A Case Series and Review of the Literature. Ocul Immunol Inflamm 2016;24:140-6.
145. Yeh OL, Francis CE. Ipilimumab-associated bilateral optic neuropathy. J Neuroophthalmol 2015;35:144-7.
146. Abdel-Rahman O, Oweira H, Petrausch U, et al. Immune-related ocular toxicities in solid tumor patients treated with immune checkpoint inhibitors: a systematic review. Expert Rev Anticancer Ther 2017;17:387-94.
147. Davis ME, Francis JH. Cancer Therapy with Checkpoint Inhibitors: Establishing a Role for Ophthalmology. Semin Oncol Nurs 2017;33:415-24.
148. Makarious D, Horwood K, Coward JIG. Myasthenia gravis: An emerging toxicity of immune checkpoint inhibitors. Eur J Cancer 2017;82:128-36.

© Chinese Clinical Oncology. All rights reserved.

149. Roberts K, Culleton V, Lwin Z, et al. Immune checkpoint inhibitors: Navigating a new paradigm of treatment toxicities. Asia Pac J Clin Oncol 2017;13:277-88.
150. McClelland CM, Harocopos GJ, Custer PL. Periorbital edema secondary to imatinib mesylate. Clin Ophthalmol 2010;4:427-31.
151. Pietras K, Ostman A, Sjöquist M, et al. Inhibition of platelet-derived growth factor receptors reduces interstitial hypertension and increases transcapillary transport in tumors. Cancer Res 2001;61:2929-34.
152. Govind Babu K, Attili VS, Bapsy PP, et al. Imatinib-induced optic neuritis in a patient of chronic myeloid leukemia. Int Ophthalmol 2007;27:43-4.
153. Kwon SI, Lee DH, Kim YJ. Optic disc edema as a possible complication of Imatinib mesylate (Gleevec). Jpn J Ophthalmol 2008;52:331-3.
154. Gadgeel SM, Gandhi L, Riely GJ, et al. Safety and activity of alectinib against systemic disease and brain metastases in patients with crizotinib-resistant ALK-rearranged non-small-cell lung cancer (AF-002JG): results from the dose-finding portion of a phase 1/2 study. Lancet Oncol 2014;15:1119-28.
155. Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med 2014;371:2167-77. Erratum in: N Engl J Med 2015;373:1582.
156. Raedler LA. Zykadia (Ceritinib) Approved for Patients with Crizotinib-Resistant ALK -Positive Non-Small-Cell Lung Cancer. Am Health Drug Benefits 2015;8:163-6.
157. Chun SG, Iyengar P, Gerber DE, et al. Optic neuropathy and blindness associated with crizotinib for non-small-cell lung cancer with EML4-ALK translocation. J Clin Oncol 2015;33:e25-6.
158. Ishii T, Iwasawa S, Kurimoto R, et al. Crizotinib-Induced Abnormal Signal Processing in the Retina. PLoS One 2015;10:e0135521.
159. Liu CN, Mathialagan N, Lappin P, et al. Crizotinib reduces the rate of dark adaptation in the rat retina independent of ALK inhibition. Toxicol Sci 2015;143:116-25.
160. Sun Y, Liu WZ, Liu T, et al. Signaling pathway of MAPK/ERK in cell proliferation, differentiation, migration, senescence and apoptosis. J Recept Signal Transduct Res 2015;35:600-4.
161. Eggermont AM, Spatz A, Robert C. Cutaneous melanoma. Lancet 2014;383:816-27.
162. Brose MS, Volpe P, Feldman M, et al. BRAF and RAS mutations in human lung cancer and melanoma. Cancer Res 2002;62:6997-7000.
163. van der Noll R, Leijen S, Neuteboom GH, et al. Effect of inhibition of the FGFR-MAPK signaling pathway on the development of ocular toxicities. Cancer Treat Rev 2013;39:664-72.
164. van Dijk EHC, Duits DEM, Versluis M, et al. Loss of MAPK Pathway Activation in Post-Mitotic Retinal Cells as Mechanism in MEK Inhibition-Related Retinopathy in Cancer Patients. Medicine (Baltimore) 2016;95:e3457.
165. Booij JC, ten Brink JB, Swagemakers SM, et al. A new strategy to identify and annotate human RPE-specific gene expression. PLoS One 2010;5:e9341.
166. Chen X, Xiao W, Wang W, et al. The complex interplay between ERK1/2, TGF /Smad, and Jagged/Notch signaling pathways in the regulation of epithelial-mesenchymal transition in retinal pigment epithelium cells. PLoS One 2014;9:e96365.
167. Méndez-Martínez S, Calvo P, Ruiz-Moreno O, et al. OCULAR ADVERSE EVENTS ASSOCIATED WITH MEK INHIBITORS. Retina 2019;39:1435-50.
168. Stjepanovic N, Velazquez-Martin JP, Bedard PL. Ocular toxicities of MEK inhibitors and other targeted therapies. Ann Oncol 2016;27:998-1005.
169. Ribas A, Gonzalez R, Pavlick A, et al. Combination of vemurafenib and cobimetinib in patients with advanced BRAF(V600)-mutated melanoma: a phase 1b study. Lancet Oncol 2014;15:954-65.
170. Planchard D, Besse B, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously treated BRAF(V600E)-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial. Lancet Oncol 2016;17:984-93.
171. Schadendorf D, Long GV, Stroiakovski D, et al. Three-year pooled analysis of factors associated with clinical outcomes across dabrafenib and trametinib combination therapy phase 3 randomised trials. Eur J Cancer 2017;82:45-55.
172. Rosen LS, LoRusso P, Ma WW, et al. A first-in-human phase I study to evaluate the MEK1/2 inhibitor, cobimetinib, administered daily in patients with advanced solid tumors. Invest New Drugs 2016;34:604-13.
173. Farley J, Brady WE, Vathipadiekal V, et al. Selumetinib in women with recurrent low-grade serous carcinoma of the ovary or peritoneum: an open-label, single-arm, phase 2 study. Lancet Oncol 2013;14:134-40.
174. Greystoke A, Steele N, Arkenau HT, et al. SELECT-3: a phase I study of selumetinib in combination with platinum-doublet chemotherapy for advanced NSCLC in the first-line setting. Br J Cancer 2017;117:938-46.

© Chinese Clinical Oncology. All rights reserved.

175. Urner-Bloch U, Urner M, Jaberg-Bentele N, et al. MEK inhibitor-associated retinopathy (MEKAR) in metastatic melanoma: Long-term ophthalmic effects. Eur J Cancer 2016;65:130-8.
176. Montana CL, Apte RS. MEKanisms of a Serous Complication. JAMA Ophthalmol 2017;135:413-4.
177. Lessell S. Friendly fire: neurogenic visual loss from radiation therapy. J Neuroophthalmol 2004;24:243-50.
178. Danesh-Meyer HV. Radiation-induced optic neuropathy. J Clin Neurosci 2008;15:95-100.
179. Indaram M, Ali FS, Levin MH. In search of a treatment for radiation-induced optic neuropathy. Curr Treat Options Neurol 2015;17:325.
180. Chiang JCB, Zahari I, Markoulli M, et al. The impact of anticancer drugs on the ocular surface. Ocul Surf 2020;18:403-17.

Cite this article as: Janetos TM, Volpe NJ, Simon SS. Neuro-ophthalmic manifestations of cancer: a narrative review. Chin Clin Oncol 2022;11(3):25. doi: 10.21037/cco-21-137

© Chinese Clinical Oncology. All rights reserved.