Learning objectives

MRI is the imaging modality of choice for the investigation of optic nerve disorders in the patients with hematological malignancy. Accurate interpretation of MR examinations of such cases requires an understanding of the optic nerve anatomy and histology and pathophysiology.

We propose these learning objectives:

- To review the spectrum of pathological conditions affecting the optic nerve in patients with hematologic malignancies.
- To illustrate the multi-modality imaging workup of such lesions.
- To increase awareness and recognition of various presentations.
Background

Anatomy of the optic nerve

The optic nerve is considered a special part of the central nervous system. It is formed by the non branched axons of the retinal ganglion and the glia cells. It is about 50 mm long from the back of the eye to the optic chiasm and can be divided into four segments.

- **The intra-ocular segment** (optic nerve head) is the shortest segment, about 1 to 1.5 mm long and 1.5 mm in diameter and traverses the sclera.
- **The intra-orbital segment** about 30 to 40 mm long and 3 to 4 mm in diameter, has a tortuous course that allows for considerable excursion as the globe moves. The central retinal artery penetrates and reaches the optic nerve about 8 to 15 mm behind the globe.
- **The intra-canalicular segment** is about 5 to 8 mm long, passes through the optic canal and is tightly fixed within the canal.
- **The intracranial segment** is 10 mm long and joins with the contralateral nerve to form the optic chiasm.

Histology of the optic nerve

The optic nerve head extends from the surface of the optic disc to the posterior scleral surface. It is divided into three layers, the surface fiber, the prelaminar, and lamina cribrosa regions. **The surface fiber layer** is formed by compact optic nerve fibers covered by a layer of astrocytes separating the nerve fiber layer from the vitreous. The second layer is **the prelaminar region** which is formed by nonmyelinated axons, astrocytes, capillaries, and surrounding connective tissues. **The lamina cribrosa** is a specialized, sieve-like region with many oval or round openings, through which passes the nerve fibers and the central retinal vessels. This region consists of dense, compact collagenous sheets of scleral trabeculae alternating with glial sheets.

The other 3 segments of the optic nerve (intraorbital, intracanalicular and intracranial) are composed of myelinated axon, neurological cells, and fibrovascular septa. The neurological cells including astrocytes, microglia, and oligodendrocytes. The fibrovascular septa, consists of blood vessels, fibroblasts, and pial meningotheelial cells. The axons are grouped into bundles by astrocyte columns and vascular connective tissue septa. Within a group, the axons are separated from each other by myelin sheaths, interspaced with the cytoplasmic processes of glial cells.

Anatomy of the optic nerve sheaths and their spaces
The meninges of the CNS surround the intraorbital portion of the optic nerve. **The outermost layer is the dura mater**, a dense collagenous and elastic tissue. It frays and inserts anteriorly into the sclera and rectus muscle sheaths. Posteriorly, the dura mater divides into two layers. One layer fuses with the periosteum of the bony canal and with Zinn's annulus at the apex of the orbit; the other layer is tightly adherent to the bone of the canal and the optic nerve and it then becomes the periosteum of the sphenoid bone. Thus, the nerve is at a risk of compression and damage by any canalicular lesion, even with small lesions.

**The second layer is the arachnoid**, which composed of trabeculae of collagenous and elastic fibers lined by meningothelia. The latter often proliferates in a concentric pattern and form onion-like structures, with or without calcification, known as the psammoma bodies or corpora arenacea, respectively.

**The innermost layer is the pia mater**, which lies tightly on the surface of the nerve. It consists of collagenous fibers, elastic fibers, and a fused glial layer. The pia mater invests the nerve and sends fibers into it to form the characteristic septa. It joins the sclera and choroid anteriorly and it continues through the optic foramen to form the single sheath around the intracranial portion of the optic nerve posteriorly.

The potential space between the dura mater and the arachnoid, (**subdural space**) does not communicate with the corresponding intracranial space and has little clinical significance. Whereas, **the subarachnoid space**, is continuous with the corresponding intracranial space where the cerebrospinal fluid can transmit blood, infectious agents, and tumor cells between the CNS and the eye.
Optic nerve affections in hematological malignancy

Visual problems in patients with leukaemia or lymphoma are commonly referred to the ophthalmologists. When orbital involvement is present, imaging may reveal infiltrative disease or mass-like lesions. Involvement of the optic nerve is relatively rare. Optic nerve can be involved by neoplastic infiltration, complications of therapy (radiation or chemotherapy), or by opportunistic infections.

Imaging Findings

The imaging findings of optic nerve abnormalities in a patient with hematological malignancy are categorized into three groups: Neoplastic infiltration, therapy induced changes, and opportunistic infection. The pattern of spread and enhancement may help in differential diagnosis.

1. Neoplastic infiltration

Ocular problems in patients who have hematological malignancy are increasing in incidence because of the increased survival rate associated with more effective treatment. Direct invasion of the orbit with the neoplastic cells is common, but the involvement of the optic nerve, uveal tract, and retina is relatively rare.

The optic nerve is usually involved in central nervous system leukemia. It can occur in up to 13 to 18% of leukemias. Isolated optic nerve involvement is relatively rare as an initial presentation of disease or its recurrence. The optic nerve is known to be one of the disease relapse sites in a patient with systemic or meningeal disease, as the optic nerve had been characterized to be a pharmacologic sanctuary, relatively unaffected by systemic chemotherapy.

The optic nerve may be involved by retroocular mass wrapped around the nerve, these masses are usually isointense signal on T1-weighted images and iso- hyperintense on T2-weighted images. Variable enhancement has been reported after contrast administration. It demonstrates restricted diffusion with reduced ADC value due to hypercellularity of the tumor. These criteria may be useful to differentiate the lymphoma from other orbital masses.

Direct involvement of the optic nerve and sheath by hematological malignancy may be demonstrated as optic nerve tubular enlargement with enhancement on imaging studies. We observe that the infiltration affects the dural sheath and the surrounding CSF in
the early stage, infiltration of the nerve itself is noted at the later stage. This pattern of involvement may be helpful in suggesting the source of spread of malignant cells through the CSF.

Hematological infiltration of the optic nerve represents an emergency because vision might rapidly decline. The blood-brain barrier shields the optic nerve from any systemic chemotherapy thus necessitating direct intrathecal injection for effective treatment. Emergent radiation therapy combined with intrathecal chemotherapy and continuing systemic chemotherapy is the most effective treatment strategy.

1. **Therapeutic complication**

**Radiation-induced optic neuropathy**

Radiation-induced optic neuropathy represents ischemic injury to the optic nerve, typically occurring 4-60 months after radiation therapy. The diagnosis is often difficult and usually one of clinical exclusion. The patients typically present with sudden, painless, monocular visual loss. The symptoms progress over several weeks, and may be bilateral depend on the radiation port. The injury can occur anywhere from the extraocular, intraorbital optic nerve to the optic chiasm. Visual field examination shows abnormality depend on the location of involvement. In optic nerve injury, nerve fiber bundle defects are expected. Whereas with chiasmal injury, bitemporal visual field defects are found.

The pathogenesis of radiation optic neuropathy is not fully understood. The most accepted theory is small vessel disease related to endothelial cell proliferation, thickened vessel walls, and subsequent occlusion. These regions of radiation-induced vascular injury may coalesce, resulting in a perivascular coagulative necrosis.

Most useful imaging MRI finding is pathologic segmental contrast enhancement in the optic nerve confined to the radiotherapy port. This abnormal segment usually shows isointense signal on T1WI and hyperintensity on T2WI. On the chronic stage atrophic changes of such segment are noted.

1. **Opportunistic infection**

Patient with hematological malignancy have suppressed immunity as a result of disease as well as the immunosuppressive drugs. These patients are usually victims of many opportunistic infections. Orbital involvement in such cases may be in the form of cellulitis or optic nerve involvement.
CT or MR findings of optic neuritis include enlargement and abnormal enhancement of the optic nerve and its covering meanings, with high-intensity signal abnormalities on T2-weighted images. The perineural fat planes are also affected, and may appear blurred and edematous. Optic nerve sheath dilatation may be due to inflammation of the optic nerve, with its associated swelling, interrupting the communication between the subarachnoid space of the diseased optic nerve and the chiasmal cistern.

The orbital infection may be in the form of cellulitis which usually results from bacterial infection. The optic nerve affection of these cases is rare. The other form of infectious optic neuritis is the viral affection. The optic nerve affection in the cases of herpetic infection is uncommon. Herpes zoster results from the reactivation of a latent varicella zoster virus. Herpes zoster ophthalmicus (HZO) usually involves the ophthalmic branch of the trigeminal nerve and may lead to severe pain. Optic neuritis following HZO appears weeks to months after the skin lesions, and usually presented by loss of visual acuity.
51 female patient presented with lymphoma, left eye proptosis and visual deficit, CT & MRI show large retro-ocular enhancing mass lesion encasing the optic nerve.

Fig. 1

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A 16-year-old female presented with proptosis, multiple subcutaneous nodules and weight loss.

CECT shows diffuse enlargement and enhancement of the right optic nerve as well as the extra ocular muscles bilaterally,

Pathologically proven AML
55 years old female patient with **AML** presented with progressive visual loss. CT&MRI show thickening and enhancing optic nerve sheath, greater on the left.

**Fig. 3**

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43 years old female with history whole-brain radiation therapy for treatment of **Hodgkin lymphoma** metastatic to the dura and leptomeninges presented with blurry vision in the left eye. MRI shows segmental enhancement of the left aspect of the optic chiasm. This segment appears iso-intense signal on T1WI & T2WI.
19-year-old male with lymphoblastic lymphoma relapsing in central nervous system. Presented bilateral visual defect, greater on the right. First MRI (a, b, c) shows blurring of the anatomic structures involving the right-sided optic nerve at its insertion into the eyeball with subtle enhancement within the nerve itself. Follow up MRI (d,e,f) show marked enhancement and enlargement of the optic nerve and the sheath.

Fig. 5

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A 70-year-old patient with **CLL** presented with severe eye pain and progressive visual loss due to **herpes zoster reactivation**. MRI shows abnormal enhancement around the left optic nerve sheath complex with blurred perineural fat and abnormal enhancement along the supratrochlear nerve. Intracranially there is abnormal enhancement of cranial nerves III. Patient symptoms improved on antiviral therapy.

**Fig. 9**

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46 years old female with history whole-brain radiation therapy for treatment of lymphoma, presented with one week history of severe visual loss, more on the RT side. MRI shows focal enhancement of the prechiasmatic segments of both nerves (a & b). 14 months later, atrophic changes of both nerves are noted (c & d).

Fig. 8

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25 years old male with lymphoma after chemotherapy presented with proptosis and visual deficit. CT & MRI show prominent retro-ocular fat with stretched optic nerves without masses or abnormal enhancement. Findings impressive of retro-ocular lipomatosis.

Fig. 7

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40-year-old patient with **leukemia** presented with vision loss. MRI shows diffuse optic nerve and optic nerve sheath enhancement involving the prechiasmatic optic nerves and intraorbital optic nerves. CSF analysis shows no malignant cells and with rare mature lymphocytes and monocytes present. **HERPES SIMPLEX VIRUS TYPE 2 DNA DETECTED.**

**Fig. 10**

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61 male patient with history of nasal lymphoma treated by radiotherapy, presented after 4 years with right visual deficit. MRI revealed marked enhancement of the intracranial segment of the right optic nerve (arrow) radiotherapy induced optic neuropathy. The patient pursued hyperbaric oxygen with the vision in his right eye improved slightly.

Fig. 6

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Conclusion

The optic nerve involvement in a patient with hematological neoplasm has many differential diagnoses. The imaging modalities are helpful in further narrowing the differential diagnoses in conjunction with the clinical and laboratory analyses. After reviewing MRI of about 20 cases of lymphoma and leukemia with optic nerve lesions, we have observed that the enhancement pattern may be helpful in establishing an appropriate diagnosis. We hypothesize that neoplastic infiltration tends to affect the nerve sheath early and later affects the nerve. Radiotherapy induced optic neuropathy affects the nerve in a focal manner coinciding to the radiation port. Infection affects nerve/sheath complex and the perineural fat as well. Additional further study of larger number of cases with pathological correlation is required to confirm our hypothesis.
References


