Chapter 35
Other Optic Nerve Maladies in Cancer Patients

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Abstract Many optic neuropathies in cancer patients are related to the direct effect of cancer on the optic nerve (e.g., orbital and parasellar skull base compressive lesions or infiltration of the optic nerve with leptomeningeal disease). However, a number of optic neuropathies occur unrelated to those mechanisms. Other mechanisms of optic neuropathy in cancer patients include those caused by raised intracranial pressure (ICP), nutritional deficiencies, drugs, and radiation injury. Optic neuropathy related to elevated ICP does not initially affect vision; therefore, early recognition of the underlying problem is important for visual preservation. In patients with nutritional or drug-related optic neuropathy, symptoms and signs usually present simultaneously and bilaterally with visual loss that is progressive and painless; color vision is affected early on, but pupil examination may remain normal. The nutritional deficiencies may present slowly and symmetrically, and potential deficiencies include vitamins B_{12}, folate, and thiamine B_1. Radiation-related optic neuropathy often manifests within about 18 months after radiotherapy and usually after cumulative radiation doses greater than 50 Gy or single doses greater than 10 Gy. Patients often do not have optic disc swelling, and they develop progressive visual loss over weeks to months, with bilateral sequential loss being more common; the end result is vision of 20/200 or worse. Rarely, paraneoplastic syndrome can result in an optic neuropathy.

35.1 Introduction

Optic neuropathy in cancer patients is often related to the anatomic site of the malignancy. Some tumors cause optic neuropathy directly, such as those in the eyeball, e.g., melanoma and retinoblastoma primary orbital lesions and metastatic orbital

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implants. Additionally, lesions of the skull base in the sella and parasellar region can cause optic neuropathy; these include primary brain tumors (e.g., pituitary adenoma, meningioma, craniopharyngioma, germinoma), tumors arising from adjacent areas (e.g., head and neck tumors such as squamous cell carcinoma, esthesioneuroblastoma), and tumors metastatic to the skull base region (breast). Optic neuropathy due to leptomeningeal disease (LMD) can occur in patients with hematogenous tumors (e.g., leukemias), solid tumors (e.g., breast, lung, melanoma), and primary brain tumors (glioma, germinoma etc.). Paraneoplastic syndromes affecting vision usually involve the retina, but may also affect the optic nerve (e.g., CRMP 5). Optic neuropathy can also result from orbital cellulitis, a serious infection in immune-suppressed patients. Optic neuropathies in cancer patients may also be the result of infectious meningeal diseases (e.g., cryptococcal meningitis). In this chapter, we will concentrate on optic neuropathies that do not have an obvious direct compressive component and in which imaging, therefore, may not be helpful. We discuss optic neuropathies related to raised intracranial pressure (ICP), nutritional deficiencies, drugs, and radiation injury.

35.2 Optic Neuropathies Related to Elevated ICP

Optic neuropathies related to elevated ICP are not rare in cancer patients. Elevated ICP leads to papilledema, and chronic papilledema can lead to vision loss.

Optic neuropathy associated with elevated ICP does not initially affect vision; therefore, early recognition of its presence is important for visual preservation. Optic neuropathy associated with long-standing papilledema initially affects the peripheral visual field (inferonasal); central vision is affected late in the process, most commonly within 6 months but as soon as 2 weeks in cases of severe and acute ICP elevation. Also, papilledema may be present for months to years without affecting visual function. Patients may not note vision impairment until central vision becomes affected; therefore, patients may have significant visual field loss before they are found to have papilledema. The optic neuropathy of papilledema may be asymmetric, i.e., one eye may have significant visual field loss while the other eye is not symptomatic.

35.2.1 Causes of Elevated ICP

Large volume brain lesions: Intracranial masses (primary brain tumors or brain metastases from a primary tumor at another site) can cause elevated ICP as a result of displacement of space in the cranium, cerebral edema, and/or obstruction of cerebrospinal fluid (CSF) flow. Supratentorial tumors may compress the falx or vein of Galen. Infratentorial tumors often obstruct the aqueduct and/or fourth ventricle and lead to hydrocephalus.

Obstructive hydrocephalus: Elevated ICP can be caused by obstructive hydrocephalus, such as that occurring when a mass compresses the aqueduct of Sylvius (e.g., a pinealoma or intrinsic midbrain tumor).

Communicating hydrocephalus: Communicating hydrocephalus occurs when CSF outflow is affected beyond the fourth ventricle, as with obstruction of the foramina of Luschka and Magendie or involvement of the arachnoid granulations, often by disorders that are not detectable on imaging. Meningeal disease due to either cancer (e.g., LMD) or infection often results in infiltration of the arachnoid granulations, leading to impaired CSF resorption and communicating hydrocephalus. However, sometimes cancer cells and infectious and inflammatory products result in debris that leads to arachnoid granulation failure and poor CSF drainage without the presence of communicating hydrocephalus. The presence or absence of communicating hydrocephalus does not always predict if the ICP is elevated. Therefore, elevated ICP may not be predicted accurately based on neuroimaging clues alone.

Spinal cord tumors: Spinal cord tumors can produce high protein levels in the CSF, which in turn may result in elevated ICP due to impaired resorption of fluid from the arachnoid granulations. Also, spinal cord tumors can grow from the cervical region to compress the cerebellum and obstruct CSF egress from the foramina of Luschka and Magendie, leading to a communicating hydrocephalus.

Venous sinus thrombosis: Venous sinus thrombosis can result from compression by a dural-based tumor or other appropriately situated lesion affecting the cerebral venous outflow system. Venous sinus thrombosis can also be encountered in patients with a hypercoagulable state associated with some types of cancer or treatments for cancer. Not intuitive is that venous obstruction in areas remote from the central nervous system (CNS) may result in elevated ICP. For example, proximal thoracic lesions, such as lesions causing a superior vena cava syndrome or neck lesions affecting a jugular vein, can impair venous return and may result in elevated ICP. Iatrogenic causes of venous sinus thrombosis include ligation or occlusion of a jugular vein during surgery and thrombosis resulting from indwelling venous catheters placed for chemotherapy, which may in turn cause papilledema secondary to the elevated ICP obstructive mechanism. Similarly, catheter-induced subclavian vein thrombosis and radical neck dissection have been associated with elevated intracranial venous and CSF pressures. In these latter cases, papilledema usually gradually resolves as collateral veins form to shunt the CSF.

Drugs: Some drugs may induce a hypercoagulable state resulting in cerebral venous thrombosis, such as L-asparaginase [1] and retinoids [2]. Other drugs linked to elevated ICP resulting in secondary intracranial hypertension are corticosteroids, cyclosporine, cytarabine, doxycycline, tetracycline, and others.

35.2.2 Treatment of Elevated ICP

If vision and visual fields are not affected and there is frequent surveillance to ensure continued unaffected vision, treatment of elevated ICP is not mandatory, and

treatment is aimed to symptoms, such as headaches. However, when elevated ICP is associated with visual field loss with or without visual acuity loss, elevated ICP must be treated to avoid continued damage to the optic nerve.

The treatment modality for elevated ICP depends on the cause. The goal must be reduction of ICP and/or reduction of pressure in the perioptic nerve sheath. The severity of the visual acuity loss and visual field loss determines the rapidity with which interventions need to be implemented. Specific treatment options include the following: tumor removal (for tumor-induced elevated ICP); treatment of underlying hydrocephalus or leptomeningeal disease; discontinuation of drugs (in the case of drug-induced elevated ICP); utilization of diuretics with or without steroids; shunting by means of a lumboperitoneal or ventriculoperitoneal shunt; optic nerve sheath fenestration; and chemotherapy or radiation therapy (if elevated ICP is related to a tumor or leptomeningeal disease).

Patients with severe visual field loss and involvement or fixation before initiation of treatment usually have irreversible damage. Routinely sending patients with any of the above potential causes of elevated ICP for ophthalmic examination is a way to identify the condition early and potentially stall vision loss.

35.3 Optic Neuropathies Caused by Nutritional Deficiencies

The nutritional deficiencies that most commonly affect the optic nerve are deficiencies of vitamin B_{12} (cobalamin), folate, and thiamine (B_1).

The symptoms and signs of an optic neuropathy related to nutritional deficiency are progressive symmetric painless visual loss affecting the central and the color vision early on with initially normal findings on pupil examination and central or cecocentral scotomas on visual field testing and late development of temporal disc pallor.

35.3.1 Vitamin B_{12} Deficiency Optic Neuropathy

Vitamin B_{12} deficiency optic neuropathy can occur in seemingly healthy individuals and is more common in males (80% of affected patients) than in females [3]. The risk of vitamin B_{12} deficiency and associated optic neuropathy is seen with partial or complete removal of the stomach, as in patients needing gastrectomy to remove malignant tumors, and patients who have undergone bariatric surgery, up to 40% of whom suffer from B_{12} deficiencies [4]. Vitamin B_{12} deficiency is also present in patients with pernicious anemia, an autoimmune condition that impairs the absorption of vitamin B_{12} in the ileum due to lack of intrinsic factor. Sometimes optic neuropathy is the first sign of pernicious anemia. The neurologic manifestations of this deficiency can be the earliest manifestations and include myelopathy affecting the posterior columns and cortical spinal tract, referred to as subacute combined degeneration, involving the cervical and upper thoracic posterior columns [4].

These patients can present with paresthesias and weakness [5]; rarely, sensory and autonomic disturbances [6] and neuropsychiatric manifestations such as memory problems, personality changes, and psychosis [4] can be seen as well as a megaloblastic anemia that develops slowly and can be severe.

Adenosine triphosphate (ATP) is thought to play a key role in optic neuropathy related to vitamin B_{12} deficiency [3]. The postulated mechanism is as follows: vitamin B_{12} deficiency increases the level of methyltetrahydrofolate, which in turn causes excessive depolarization and depletion of ATP. This ATP deficiency could be the explanation for the cecocentral scotoma characteristically seen in vitamin B_{12} deficiency optic neuropathy, because the parvoretinal ganglion cells of the papillomacular bundle require more energy than the magnoganglion cells [3].

In patients in whom vitamin B_{12} deficiency optic neuropathy is suspected, serum cobalamin, serum methylmalonate, and serum homocysteine levels should be checked [3]. Methylmalonate and homocysteine are metabolites of cobalamin, and if the serum cobalamin level is at low-normal or normal levels, these other metabolites can help establish a diagnosis of cobalamin deficiency. Once vitamin B_{12} deficiency has been established, a Schilling test should be done to determine the degree of cobalamin malabsorption.

Patients with vitamin B_{12} deficiency optic neuropathy are generally treated with cyanocobalamin 100 μg intramuscularly three times weekly for the first 2 weeks and then 500–1000 μg intramuscularly monthly [3]. Most patients must continue this therapy forever. Stopping maintenance therapy can result in the return of neurological symptoms. The earlier the therapy is instituted, the higher the likelihood that symptoms and signs will resolve.

35.3.2 Folate Deficiency Optic Neuropathy

Like B_{12}, folate is involved in methionine metabolism. Folate, in the form of methyltetrahydrofolate, donates a methyl group to homocysteine to form methionine and tetrahydrofolate. Tetrahydrofolate helps metabolize formate. Folate deficiency leads to the accumulation of formate, a toxic metabolite from methanol, causing optic neuropathy [4]. Folate deficiency also causes other neurological manifestations, such as polyneuropathy and even subacute combined degeneration of the spinal cord, that are many times indistinguishable from those caused by cobalamine deficiency.

In women of childbearing age who have epilepsy and are on anticonvulsant treatment, a daily dose of folate 0.4 mg is suggested to avoid future neural tube defects when these women have children [4].

Although folate deficiency often occurs with other nutrient deficiencies, isolated folate deficiency has been shown to cause optic neuropathy [7]. In the study by Hsu et al. [8], six patients with low folate levels but normal B_{12} levels developed bilateral visual loss, color defects, and central or cecocentral scotomas with optic discs that were normal or had temporal disc pallor. Measurement of erythrocyte folate was found to be more sensitive than measurement of serum folate in the early diagnosis

of this disorder. With folate replacement therapy, patients' vision improved within 4–12 weeks of symptom onset [8].

35.3.3 Vitamin B_1 (Thiamine) Deficiency Optic Neuropathy

Thiamine acts as a coenzyme in the metabolism of carbohydrates, lipids, and some amino acids. Thiamine deficiency results in reduced synthesis of certain high-energy phosphates and the accumulation of lactate. Because of a short half-life, a thiamine-deficient diet may result in symptoms in a few days. Patients who are undergoing nasogastric feeding, total parenteral nutrition, bariatric surgery, and the so-called refeeding syndrome as well as those with recurrent vomiting, hyperthyroidism, gastric surgery, alcoholism, or extreme dieting are at risk of this deficiency [4].

Isolated vitamin B_1 deficiency can cause optic neuropathy as well as ataxia and polyneuropathy [4, 9].

The syndrome of Wernicke can develop in patients with a marginal thiamine diet and consists of a triad of (1) ocular abnormalities (diplopia and nystagmus due to brain stem manifestations), (2) gait ataxia, and (3) mental status changes [10].

About 80% of patients who survive Wernicke develop Korsakoff syndrome, which is an amnestic confabulatory syndrome [4].

Brain MRI findings in thiamine deficiency include increased T2 or proton density or FLAIR signal in the mamillary bodies, which is characteristic of Wernicke's. The signal abnormalities can partially resolve with treatment with resultant partially atrophic mamillary bodies. Also, this partial atrophy can affect the thalamus, hypothalamus, midbrain, pons, medulla, and cerebellum [4].

Low levels of serum transketolase (an indication of B_1 deficiency) and reduced serum and urinary thiamine levels as well as levels of RBC thiamine diphosphate can help in early diagnosis of deficiency [4].

Intravenous glucose infusion in patients with thiamine deficiency can precipitate acute Wernicke's and should be avoided by giving thiamine replacement first when needed. Suggested dose is 100 mg IV every 8 h for a few days followed by long-term oral maintenance of 50–100 mg of thiamine daily. The ocular signs improve quickly in hours, but the mental changes can take many days [4].

Other deficiencies that are less clinically significant in causing optic neuropathies are vitamin E and zinc. Copper deficiency is not linked to optic neuropathy but to myelopathy and is being recognized as a common problem in patients who have had bariatric surgery [4].

35.3.4 Vitamin E Deficiency Optic Neuropathy

Vitamin E deficiency can produce spinocerebellar syndrome with peripheral neuropathy, progressive ataxia, areflexia, ophthalmoplegia, and pigmentary retinopathy, with optic neuropathy being quite rare [4].

35.3.5 Zinc Deficiency Optic Neuropathy

Zinc is required for the metabolism of vitamin A in the eye. Zinc plays an important role in stabilizing microtubules for axonal transport. Zinc deficiency causes defective rapid axonal transport in vitro and therefore may contribute to the development of optic neuropathy but is quite rare [4].

35.4 Optic Neuropathies Caused by Drugs

A number of different drugs have been associated with optic neuropathy in cancer patients. Like the symptoms and signs of nutritional optic neuropathy, the symptoms and signs of drug-related ("toxic") optic neuropathy usually present simultaneously and bilaterally with visual loss that is progressive and painless; there is loss of high spatial frequency contrast sensitivity and color vision is affected early on (hence red Amsler grid testing is quite sensitive early on) with pupil examination being initially normal. Central visual field testing such as with the Amsler grid (preferably red color as well as white) and Humphrey VF-10-2 test is most helpful at the earliest stage.

As toxicity effect progresses, there is loss of axons, which can be documented using optical coherence tomography technology. Later optic disc pallor is seen mostly in the temporal aspect of the disc.

The mitochondria provide most of the ATP that the cells require for their metabolism. Defective mitochondrial function can affect the axonal transport and affect ATP production with predilection toward the retinal ganglion cell axons of the papillomacular bundle—this is a possible mechanism to explain toxic optic neuropathy [11].

Because cancer patients are often treated with combinations of chemotherapeutic agents, it is very often difficult to attribute optic neuropathy in a patient treated with chemotherapy to any one particular agent in isolation. In addition, in cancer patients treated with both chemotherapy and radiation therapy with the optic nerves included in the field, it can be difficult to distinguish between drug-related optic neuropathy and radiation-related optic neuropathy. Information about cancer drugs that can cause optic neuropathy mainly comes from retrospective case series and reports from Med Watch, the United States Food and Drug Administration, the World Health Organization, and the National Registry of Drug-Induced Ocular Side Effects databases [12].

The World Health Organization classification helps clinicians determine the likelihood that a particular drug is the culprit in vision loss and when to stop treatment with a given drug. The most important steps are rapid identification of the toxic agent and prompt withdrawal of the same [12].

Optic neuropathies caused by drugs can be classified according to whether they are associated with disc edema due to elevated ICP or disc edema due to direct toxic effect. Drugs can cause optic disc edema by raising the ICP ("intracranial hypertension"); less commonly, drugs can induce cerebral venous thrombosis resulting in

elevated ICP with or without other focal findings. In addition, drugs can cause direct toxic optic neuropathy with associated optic disc edema, in which the disc edema is a prominent posterior pole finding and there is no significant visual dysfunction unless the condition is long-standing. In this type of direct toxic optic neuropathy, cessation of the suspected agent usually results in total or partial visual recovery. Finally, drugs can cause direct toxic neuropathy without associated optic disc edema, which is generally associated with significant visual loss, usually bilateral and progressive and early dyschromatopsia, which may or may not recover after the agent is stopped.

35.4.1 Optic Disc Edema Secondary to Drug-Induced Elevated ICP

A number of drugs have been associated with optic disc edema secondary to elevated ICP with an unknown underlying mechanism and are on the list of causes of idiopathic intracranial hypertension also known as pseudotumor cerebri. Oral, intravenous, or intrathecal administration of drugs may result in elevated ICP, depending on the particular drug.

35.4.1.1 Retinoids

Retinoids are used to arrest or reverse carcinogenesis. Retinoids and their synthetic and naturally occurring analogs, including all-*trans*-retinoic acid and isotretinoin (used in the treatment of recurrent glioblastoma multiforme), have been reported to cause increased ICP by causing elevation of the vitamin A levels in both adults and children after oral administration [2, 12, 13].

The problem resolves with discontinuation of the drug and normalization of the levels of vitamin A in the blood.

35.4.1.2 Imatinib Mesylate

Imatinib mesylate (Gleevec) is a tyrosine kinase inhibitor that has been reported to cause periorbital edema, optic disc edema, and retinal edema and elevated ICP with bilateral papilledema. Other less common side effects are headaches, confusion, and CNS hemorrhage [12].

35.4.1.3 Cyclosporine A

Cyclosporine A is used to prevent graft-versus-host disease in bone marrow transplant recipients, liver transplant recipients, recipients of other organ transplants, and patients with rheumatoid arthritis, autoimmune disorders, psoriasis, and atopic dermatitis.

Cyclosporine A is used in both intravenous and oral forms. Bilateral disc edema without elevated ICP was attributed to cyclosporine A in a patient who received

prophylactic oral treatment with this drug for 6 months after bone marrow transplantation [14]. Following cessation of cyclosporine A, vision improved in 2 months and disc edema resolved over 6 months. The mechanism by which cyclosporine A causes optic neuropathy has been variously attributed to microangiopathy, direct toxic effects on optic nerve axons, and elevated ICP. Pseudotumor cerebri-type picture has been associated with the use of cyclosporine [15].

35.4.1.4 Cytarabine

Liposomal cytarabine (Depocyt), the long-acting form of cytarabine, is an alkylating agent that has been reported to cause neurological complications, including intracranial hypertension secondary to arachnoiditis (more common with intrathecal therapy), encephalopathy, seizures, cerebellar dysfunction, and cauda equina syndrome. Some of the reported ocular changes include macular edema, cotton wool spots, optic neuropathy, and retinal neovascularization [12].

35.4.2 Elevated ICP Secondary to Cerebral Venous Thrombosis

Both cisplatin and L-asparaginase with or without methotrexate can cause elevated ICP secondary to cerebral venous thrombosis [16].

35.4.2.1 Cisplatin

Cisplatin is a heavy metal compound used in the treatment of many pediatric and adult malignancies, such as germ cell tumors and brain tumors. Nephrotoxicity due to cisplatin administration is well documented, and impaired renal function can lead to significant increase in CNS levels of cisplatin. Not only can this lead to nerve demyelination and optic neuropathy, but also intravenous cisplatin has been reported to lead to dural sinus thrombosis because of its propensity to cause coagulation disorders and thrombosis [12, 17].

35.4.2.2 L-Asparaginase

L-asparaginase used in the treatment of acute lymphoblastic leukemia can cause superior sagittal sinus thrombosis and cerebral venous thrombosis. These conditions may occur when L-asparaginase is given in combination with methotrexate or when L-asparaginase is given as a single agent and generally occur a few weeks after therapy is initiated [12, 17].

Dural venous thrombosis can cause elevated ICP and manifest as neurological events such as seizures and papilledema, which are evident on fundus examination [1].

35.4.3 Optic Disc Edema Usually Without Elevated ICP

Some of the drugs that can cause optic disc edema usually without elevated ICP include cisplatin, carmustine, vincristine, fluorouracil, cyclosporine A, and tacrolimus.

35.4.3.1 Cisplatin

Toxic effects of cisplatin have been outlined above. Treatment with cisplatin can cause both an optic neuropathy and maculopathy leading to pale optic discs and granular pigmentation of the retina. The electroretinogram may be flat [12, 17].

Cisplatin in combination with other drugs has also been implicated in optic neuropathy. Degeneration of the optic nerve and tract has been reported after supraophthalmic internal carotid artery infusion of cisplatin and carmustine [12, 17].

35.4.3.2 Carboplatin

A related platinum compound, carboplatin, has been reported to cause "optic neuritis" and blindness after intravenous administration as well as peripheral neuropathy [17].

35.4.3.3 Carmustine

Carmustine, an alkylating agent, can be given intra-arterially or intravenously. It can penetrate the blood–brain barrier and cause retinal ischemia, central retinal artery occlusion, optic disc edema, optic neuropathy, and encephalopathy [17].

35.4.3.4 Vincristine

Vincristine, a microtubule inhibitor, is more commonly used in pediatric malignancies and is known to cause reversible peripheral neuropathy and sometimes also autonomic neuropathy as well as ataxia and headaches. The patient may also have seizures and cranial neuropathies.

35.4.3.5 5-Fluorouracil

This is a fluorine-substituted analog of the pyrimidine uracil. It is an antimetabolite that inhibits thymidylate synthetase, blocking DNA synthesis. It is also known to inhibit the S phase of the cell cycle. It is more commonly given intravenously by bolus injection and sometimes also intra-arterially or by direct injection. This agent crosses the blood-brain barrier and can cause toxicity to the CNS with preferential site being the cerebellum causing a subacute cerebellar syndrome with a triad of ataxia, dysarthria, and nystagmus. Rarely acute recurrent toxic optic neuropathy may occur following administration of 5-fluorouracil [17].

35.4.3.6 Cyclosporine A

Cyclosporine A can cause both elevated ICP with optic disc edema and secondary optic nerve fiber loss or a presumed direct effect [18].

35.4.3.7 Tacrolimus

Tacrolimus may directly affect the optic nerve and may also cause optic disc edema without associated increased intracranial pressure.

35.4.4 Optic Neuropathy Without Disc Edema

Drugs that can cause optic neuropathy without disc edema include fludarabine, tamoxifen, tacrolimus, paclitaxel, methotrexate, and cytarabine.

35.4.4.1 Fludarabine

Fludarabine is an antimetabolite that can cause delayed but significant ocular and neuro-ophthalmic morbidity including optic disc edema, optic neuropathy, and transient cortical visual loss with variable degrees of visual loss [17].

35.4.4.2 Tacrolimus

Tacrolimus is an immunosuppressive agent that is used following transplants such as bone marrow transplants, pancreas transplants, and liver transplants. Like other calcineurin inhibitors, tacrolimus has been linked to optic neuropathy and also to cortical visual loss.

35.4.4.3 Paclitaxel

Paclitaxel (Taxol) is a neurotubule stabilizer that can cause neurotoxicity with sensory and motor peripheral neuropathy and also myalgias. Rarely it has been linked to transient scotomas and optic neuropathy [17].

35.4.4.4 Methotrexate

Methotrexate is an antifolate metabolite used to decrease nucleic acid synthesis by limiting availability of reduced folate. It is given by various routes, including oral, parenteral, and intrathecal, for malignancies such as head and neck cancer, breast cancer, lymphoma, and others as well as for autoimmune diseases such as rheumatoid arthritis. High doses are linked to toxic neuro-ophthalmic problems such as optic neuropathy, optic nerve demyelination, retinal pigmentary mottling, and myelopathy as well as aseptic meningitis mostly with intrathecal administration [17].

35.4.4.5 Cytarabine

Intravenous cytarabine, an alkylating agent, is used in the treatment of leukemia and lymphoma, and intrathecal cytarabine is used for prevention or treatment of CNS lymphoma. Intrathecal cytarabine can cause neurotoxicity with arachnoiditis, cerebellar dysfunction, seizures, and encephalopathy. Optic neuropathy, macular edema, and cotton wool spots can also occur [17].

35.5 Optic Neuropathies Caused by Radiation

Optic neuropathy associated with radiation is an ischemic process presenting as a posterior ischemic optic neuropathy, on average about 18 months after radiotherapy and usually after cumulative radiation doses greater than 50 Gy or single doses greater than 10 Gy. However, the process can occur earlier or even years after radiotherapy. Optic disc swelling is usually absent. The patient experiences progressive visual loss over weeks to months, with bilateral sequential loss being more common, and the end result is vision of 20/200 or worse. The visual field may show altitudinal defect or central scotoma. The disc becomes pale in 4–6 weeks [19]. Magnetic resonance imaging is the study of choice to distinguish radiation-related optic neuropathy from recurrent tumor. In cases of radiation-related optic neuropathy, magnetic resonance imaging usually reveals the optic nerves to be slightly swollen but otherwise normal on unenhanced studies and demonstrates focal contrast enhancement of the optic nerves with TI-weighted Gd-DTPA images.

Radiation-related optic neuropathy is more often seen after radiotherapy for cancer of the paranasal sinuses and skull base, pituitary adenomas, and meningiomas [19]. Radiation dose per fraction, total dose, total duration of treatment, volume of tissue irradiated, and type of radiation (proton, electron, or neutron) can also affect the risk of developing radiation-induced optic neuropathy. Higher total dose, fraction size, and volume irradiated are associated with higher frequency of complications and shorter time to onset of complications. Preexisting medical disorders, such as diabetes and endocrinologic disturbances from Cushing syndrome or growth hormone-producing tumors, are additional risk factors. It is well known that patients who receive chemotherapy are at increased risk for radiation-induced optic neuropathies at radiation doses lower than those expected to cause optic neuropathy in patients not treated with chemotherapy.

There is no proven effective treatment for radiation-related optic neuropathy. Hyperbaric oxygen has been used with mixed results, but it has been found that early introduction of hyperbaric oxygen (e.g., within 72 h of symptoms) is more likely to be beneficial. Trental 400 mg tid and vitamin E 400 units daily are often given, although there is no definite proof of benefit. Although there are some anecdotal reports of its success in treating optic neuropathy due to radiotherapy, the role of anticoagulation in this disorder requires further investigation. Occasionally, systemic corticosteroids are successful. Their mechanism of action is not clear, but steroids may reduce overall tissue edema and retard demyelination.

Based on the experience to date with various treatments, some management strategies have evolved to help improve visual outcome. If one eye has been affected, serial eye examinations must be done over the 10- to 20-month period after treatment to monitor for any signs of recurrence in the other eye because bilateral sequential involvement is not uncommon. Serial magnetic imaging of the brain and orbits should be performed over the 20-month period after radiation therapy is completed.

The most common protocol for hyperbaric oxygen therapy: 30 sessions of therapy, with the patient breathing 100% oxygen at 2.4 atm absolute (ATA) for 90 min per session. At therapeutic pressure, ocular side effects of hyperbaric oxygen therapy include a transient myopic shift, cataract, and transient blindness (only in patients with a previous optic neuritis) and rarely seizures. Hyperbaric oxygen therapy is a safe and now proven technique used to treat various medical conditions, such as decompression sickness, anaerobic infections, postirradiation osteonecrosis, postirradiation cystitis, and complicated wounds.

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