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Vitreous cytology as the only diagnostic evidence of central nervous system involvement in a patient with isolated leukemic infiltrative optic neuropathy

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Abstract:

A 29-year-old female with treated acute lymphoblastic leukemia in remission presented with blurred vision and pain on movement of the right eye. On examination, visual acuity was 20/25 in the right eye and 20/20 in the left eye. Direct ophthalmoscopy revealed that the optic disc was swollen with peripapillary hemorrhage in the right eye. The rest of the clinical examination was within normal limits. Magnetic resonance imaging demonstrated enhancement of her right optic nerve. Lumbar puncture and bone marrow examination revealed no malignant cells. Only vitreous fluid cytology showed blast cells. Intravitreal injection of methotrexate was given, and repeated vitreous tapping was normal. The vision of her right eye remained 20/20 until 1 year later when optic disc and retinal vascular occlusion was noted. Her vision deteriorated to no light perception within 2 weeks, and opticociliary shunt vessels occurred. Isolated disc swelling with positive vitreous cytology can be the first and only presentation of relapsed hematologic disorders. Infiltrative optic neuropathy should be considered in the differential diagnosis of optic disc edema. Vitreous tapping could be considered as the diagnostic procedure even if the results of lumbar puncture were negative.

Keywords:

Disc edema, leukemia, optic nerve infiltration, optic neuropathy, vitreous cytology

Introduction

Infiltrative optic neuropathy is a rare and severe presentation in acute lymphocytic leukemia. Disc swelling, yellowish mass infiltration, or normal appearance of the optic disc may be presented.^[1] Clinical features of infiltrative optic neuropathy can mimic optic neuritis, compressive, ischemic, toxic optic neuropathy. Making an accurate diagnosis is challenging because a number of conditions can cause optic disc edema, especially in the absence of definite systemic or central nervous system (CNS) involvement.

Magnetic resonance imaging (MRI) reveals leukemic infiltration as a ring of enhancement around the optic nerve and within the subarachnoid space and leptomeninges of the optic nerve.^[2] Lumbar puncture and cerebrospinal fluid (CSF) examination is required in such cases. Clinicians should have a high index of suspicion of this disease and prompt referral to hematologists for disease management. Herein, we report a case of isolated infiltrative optic neuropathy which is the initial sign of relapsed leukemia, and vitreous cytology is the only diagnostic laboratory evidence. This uncommon presentation posed a challenge for early diagnosis and disease management.

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Case Report

A 29-year-old woman with treated B-cell acute lymphoblastic leukemia (ALL) in remission for the past 1 year presented with acute onset of motion pain for 5 days and mild blurred vision for 1 day in the right eye. Visual acuity was 20/25 in the right eye and 20/20 in the left eye. Slit-lamp examination showed no abnormal finding in the anterior segment, and intraocular pressure was within normal limits. Positive relative afferent pupillary defect (RAPD) was detected in the right eye. She passed Ishihara test promptly in both eyes, although she reported color vision change in the right eye. She had no limitation of ocular movement but felt pain on movement of the right eye. Fundoscopy revealed prominent optic disc swelling with peripapillary hemorrhage and tortuous vessels in the right eye [Figure 1a]. Diffuse fluorescein dye leakage was shown in the optic disc of her right eye on fluorescein angiography [Figure 1b]. MRI revealed enhancement of the right optic disc and retrobulbar optic nerve [Figure 1c] without any other intracranial lesions. She denied any neurological symptoms or signs. Humphrey visual field testing showed no visual field defect in the right eye [Figure 1d]. Relapsing B-cell ALL was considered in differential diagnosis, and a hematologist was consulted. However, CSF and bone marrow aspiration cytology showed no malignant cells. Meanwhile, mild iritis and vitritis developed. Therefore,

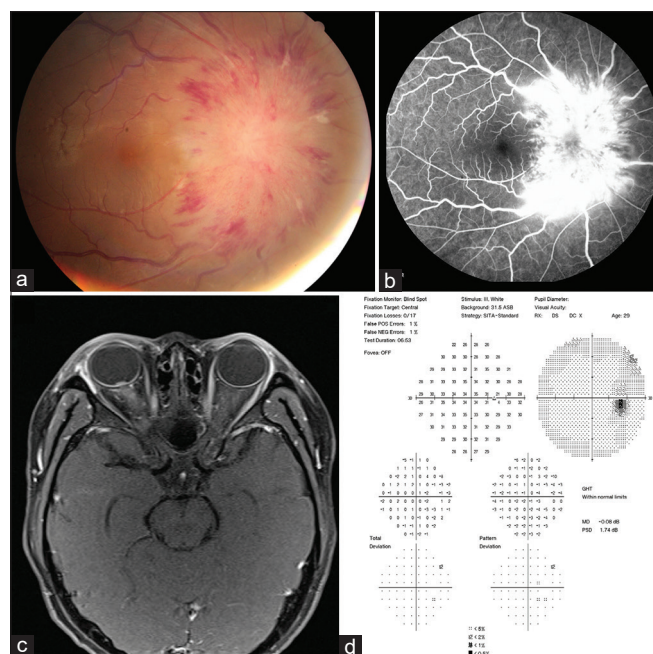


Figure 1: (a) The optic disc of the right eye was markedly swollen with diffuse peripapillary hemorrhage, and the retinal veins were tortuous. (b) Fluorescein angiography demonstrated diffuse leakage of the optic disc at the late phase. (c) Enhancement of the right optic nerve was shown on T1-weighted gadolinium contrast-enhanced fat-suppressed magnetic resonance imaging. (d) Humphrey visual field analyzer report showed no visual field loss

vitreous tapping for cytology was performed after discussion with the patient.

Cytology and flow cytometry of vitreous sample revealed scattering blasts; flow cytometry revealed expression of CD19, CD10, and CD34, compatible with B-cell precursor ALL in the vitreous fluid. The patient was diagnosed with infiltrative optic neuropathy of the right eye secondary to CNS relapse of B-cell ALL. Intravenous chemotherapy of BOMES regimen (carmustine, vincristine, methotrexate, etoposide, and methylprednisolone) and intrathecal chemotherapy of cytarabine and methotrexate were initiated. Intravitreal injection of methotrexate (0.2 mg/0.05 mL) was also administered. Iritis and vitritis then subsided.

Disc edema gradually improved and the patient remained 20/20 vision for a year [Figure 2a and b].

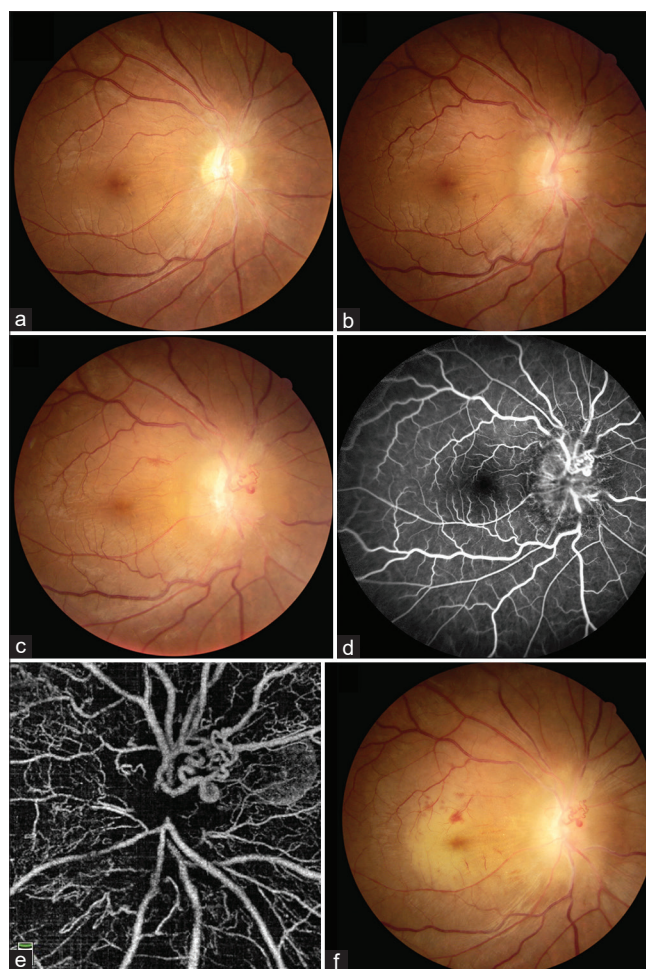


Figure 2: (a) Optic disc swelling gradually improved, and vessel sheathing in the optic disc and peripapillary area resulted in 6 months after initial presentation. (b) One year after the first visit, the optic disc was persistently swelling. (c) Optociliary shunt vessels of the right optic disc were noted. (d) Fluorescein angiography showed delayed filling of the optic disc and optociliary shunt vessels. (e) Optical coherence tomography angiography revealed vascular occlusion and tortuous collateral vessels in the optic disc. (f) Retinal artery occlusion, retinal whitening, cherry-red spot, and optic atrophy occurred

As vitreous cytology is the only positive laboratory evidence of relapsed ALL, vitreous tapping for cytology was used to evaluate the treatment response. Repeated vitreous tapping was carried out after 2 weeks, 1 month, 2 months, and 6 months of chemotherapy, and no blast cell was detected. She received intravenous and intrathecal chemotherapy regularly. Unfortunately, the patient reported a sudden onset of pain and blurred vision in the right eye 14 months after the initial presentation. Visual acuity was 20/100 in the right eye and 20/20 in the left eye. No iritis or vitritis was noted. Optociliary shunt vessels of the right optic disc developed [Figure 2c]. Fluorescein angiography showed delayed optic disc filling in the right eye [Figure 2d]. Vascular occlusion and tortuous collateral vessels in the optic disc were shown on optical coherence tomography (CT) angiography [Figure 2e]. Visual acuity progressed to no light perception in 2 weeks. Retinal artery occlusion, cherry-red spot, and optic atrophy were found [Figure 2f]. Headache and vomiting subsequently developed. MRI showed progressed swelling of the right optic nerve [Figure 3]. Cytology in CSF revealed a positive blast cell this time. Due to progressive CNS relapse of B-cell ALL, the patient was commenced on whole-brain and right optic nerve radiotherapy combined with intrathecal chemotherapy. However, the vision of her right eye did not recover.

Discussion

Infiltrative optic nerve neuropathy is a rare but severe condition in acute lymphocytic leukemia. Diagnosis can be challenging, especially in the circumstances of isolated ophthalmic presentation. The initial visual acuity varies, but the visual outcome is usually poor. Our patient presented with distinct clinical features of isolated leukemic infiltration of the optic nerve. The absence of neurological signs, negative results of CSF examination, and bone marrow cytology added to the diagnostic dilemma.^[3] Vitreous tapping for cytology is the only laboratory evidence of disease relapse and was further taken as evaluation of treatment effect. Moreover, our case remained 20/20 vision for 1 year despite prominent disc swelling.

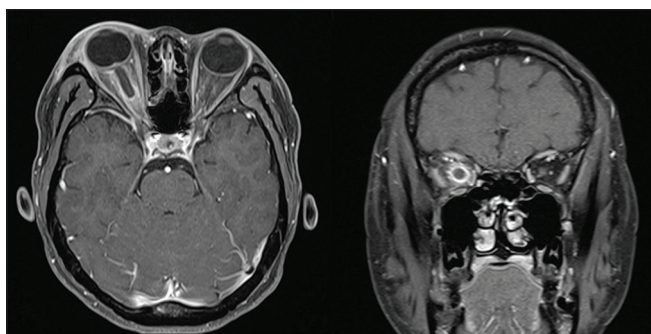


Figure 3: Axial and coronal T1-weighted gadolinium contrast-enhanced fat-suppressed magnetic resonance imaging showed severe swelling of the right optic nerve

Cases with optic disc infiltration usually present with disc edema, peripapillary hemorrhage, and positive RAPD sign. Visual acuity is usually poor and systemic outcome is guarded. Optic nerve infiltration may be caused by leukemic or lymphomatous origin.^[4,5] According to one review study, the majority of the leukemic origin was secondary to ALL (53%), and B-cell non-Hodgkin's lymphoma constitutes the majority (67%) of the lymphomatous origin.^[6]

An analysis of autopsied eyes showed 18% and 16% of eyes with optic nerve infiltration in acute and chronic leukemias.^[7] However, isolated infiltrative optic neuropathy is rarely reported in the literature.^[4,8] Visual acuity can range from counting finger to 20/20.^[4] Unilateral or bilateral involvement has been reported.^[8,9] Nikaido *et al.* reported 5 cases of leukemic optic nerve infiltration, and optic nerve atrophy ensued in all cases although initial improvement was noted.^[8] Our case had maintained 20/20 vision for 1 year until vessel occlusion and optic atrophy occurred which led to no light perception.

A high myriad of suspicion should be kept for infiltrative optic neuropathy clinically because CNS involvement carries a high risk of morbidity and mortality and mandates timely systemic chemotherapy.^[1] One case report has presented a patient who was initially diagnosed with primary optic neuritis, and symptoms improved temporarily with corticosteroids. Leukemic optic neuropathy was diagnosed, and treatment was given after 2 months, but visual loss was permanent.^[10] As in our case, only enhancement of the optic nerve was demonstrated on MRI and pain on ocular movement which may lead to a misdiagnosis as optic neuritis.

Diagnostic confirmation is as important as a high index of suspicion. Malignant cells were identified in the CSF in 64% of cases with leukemic optic infiltration, and neuroimaging (CT or MRI) was normal in 43% of cases.^[6] Diagnostic vitreous tapping can be taken in the absence of laboratory evidence.^[11] In addition, intravitreal methotrexate injections have been reported to improve ocular inflammation and malignant cell infiltration in a series of ocular leukemia cases.^[12] Nevertheless, vitreous tapping bares the risk of retinal break, retinal detachment, and endophthalmitis; an adequate sample may be hardly acquired, especially in nonvitrectomized eyes. We discussed with our patient, and a shared decision-making was reached before the procedure.

Retinal and disc vessel occlusion is relatively rare in infiltrative optic neuropathy. Our case subsequently developed retinal artery occlusion, retinal whitening, cherry-red spot, and optic atrophy despite aggressive

chemotherapy. We had found sparse literature describing this unusual disease feature. A case with lymphoma developed bilateral infiltrative optic neuropathy with sequential, bilateral central retinal artery occlusion.^[13] Visual acuity turned into no light perception in both eyes. Another case of a 6-year-old child with ALL manifested with sequential, bilateral retinal artery occlusion with disc edema in a few hours. The visual acuity was also no light perception.^[14] The disease course in our case was different from previous reports, and retinal artery occlusion occurred 1 year after initial optic disc infiltration. As our patient had developed retinal artery occlusion, the visual prognosis became guarded. This devastating event was likely caused by the huge disease burden of her leukemia.

Conclusion

Isolated infiltrative optic neuropathy as the first manifestation of CNS leukemic involvement and vitreous cytology as the only diagnostic evidence is a rare occurrence. Visual acuity may be maintained temporarily with aggressive treatment, but optic atrophy may ensue eventually. Vessel occlusion could be an important factor that led to visual loss. Clinical awareness, timely referral, and appropriate treatment are essential to improve visual outcome and survival in patients with leukemic CNS involvement.

Informed consent

Informed consent was obtained from the patient. The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient had given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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