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Optic neuropathy in extramedullary, blast crisis of chronic myeloid leukemia

Chronic myeloid leukemia (CML) represents 10%−20% of all leukemias. Vision loss in patients with CML is usually related directly to the disease (CML) or less likely to potential side effects of the treatment of CML (e.g., radiotherapy or chemotherapy). Extramedullary CNS or meningeal blast crisis in CML is an uncommon but well-known complication of CML. Visual loss in CML typically occurs with abnormal serum white blood cell (WBC) count, peripheral blood smear, bone marrow biopsy, cerebrospinal fluid (CSF) analysis, or neuroimaging. We describe a unique case of vision loss and optic nerve atrophy as the presenting and only sign of extramedullary CNS, CML blast crisis in a patient with initial negative serum, CSF, and neuroimaging. To our knowledge this is the first such case to be described in the English-language ophthalmic literature Table 1.

A 63-year-old man presented with chronic, progressive, painless, and bilateral asymmetric (left worse than right) central vision loss. Two years before presentation he was diagnosed with Philadelphia chromosome positive and CML and treated with hydroxyurea, imatinib, inotuzumab ozogamicin, bosutinib, and blinatumomab. At initial diagnosis, intrathecal treatment with liposomal cytarabine was administered after a lumbar puncture was positive for CNS involvement. His CSF turned negative after the fifth dose of cytarabine with good response (polymerase chain reaction [PCR] of 1.75%) and he reached minimal residual disease (MRD). Serial serum and CSF PCRs confirmed that he was stable. However, the patient relapsed showing 79% blasts in the serum for which he was switched to blinatumumab plus ponatinib. Under this regimen of treatment, he achieved complete cytogenetic response (CCyR), and PCR was 0.08%. He then developed adverse effects to ponatinib, including worsening high blood pressure that prompted serial visits to the emergency department (systolic ~200 mm Hg), peripheral neuropathy, and subjective blurry vision; he self-discontinued the medication, without the previous consent or knowledge of his physicians. A complete blood count (CBC) was within normal limits with no blasts. Magnetic resonance imaging (MRI) of the head and orbit was negative, and repeat CSF analysis showed no pleocytosis or blasts. A diagnosis of possible "ponatinib-related ocular toxicity" was made, and the patient was referred to the neuro-ophthalmology service.

His visual acuity was 20/25 OD and counting fingers OS with a left relative afferent pupillary defect. Slit-lamp biomicroscopy; external, extraocular motility; and intraocular pressure examination findings were normal. Fundus examination revealed bilateral optic nerve pallor. No cotton wool patches, arteriolar narrowing, intraretinal hemorrhages, or optic disc

Table 1—Presenting ophthalmological findings in reported cases

	Ophthalmic Findings	MRI and Laboratory Findings
Jain and Gupta[1]	• Bilateral visual loss and retinal hemorrhages	• MRI: Pachymeningeal enhancement and bilateral optic nerve thickening • LP: Myeloid blast cells
Mbekeani et al.[2]	• Profound bilateral vision loss • OD: Counting fingers • OS: Light perception	• MRI: Chiasm and bilateral optic nerve enhancement • LP: Myeloid blast cells • BM: Normal
Schocket et al.[3]	• Painless, progressive left eye vision loss • OD: 20/20 • OS: No light perception • Normal fundoscopy	• MRI: No optic nerve enhancement, CN VII and VIII enhancement • LP: 16% lymphoblasts. Predominant population of TdT+, cCD79a+ B-cell lymphoblasts
Present case	• Chronic, progressive, painless, and bilateral asymmetric (left worse than right) central vision loss • OD: 20/25 • OS: Counting fingers with a left relative afferent pupillary defect • Fundus exam: Bilateral optic nerve pallor	• Initial studies negative • Brain MRI: Negative • LP: No pleocytosis or blasts Follow-up studies showed: • Brain MRI showed enhancement of the left optic nerve, and bilateral sheath enhancement was suspected • Spinal MRI: Enhancement and thickening of the nerve roots of the cauda equina • LP: Lymphocytic predominant pleocytosis with rare blasts

MRI, magnetic resonance imaging; LP, lumbar puncture; BM, bone marrow examination.

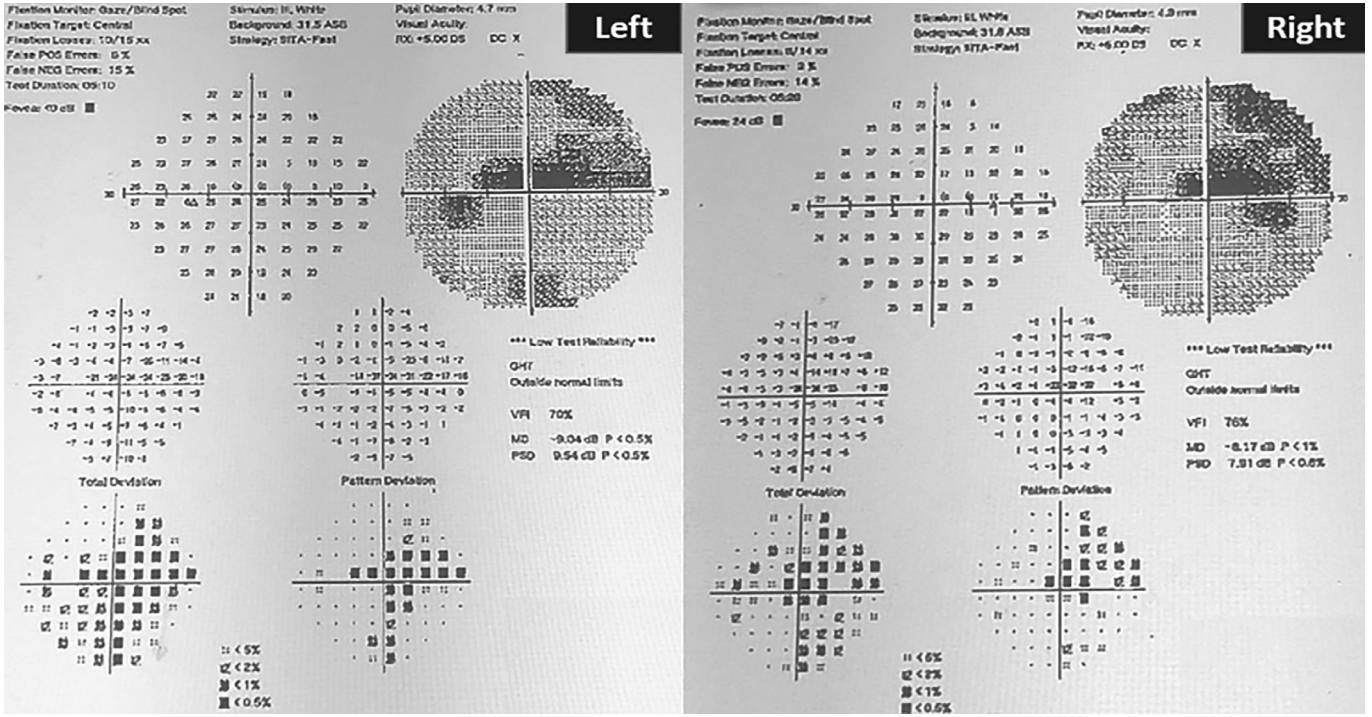

Fig. 1—30-2 Humphrey visual field showing bilateral cecocentral scotoma denser superiorly and decreased foveal threshold. Note that the test was somewhat limited by reliability indices.

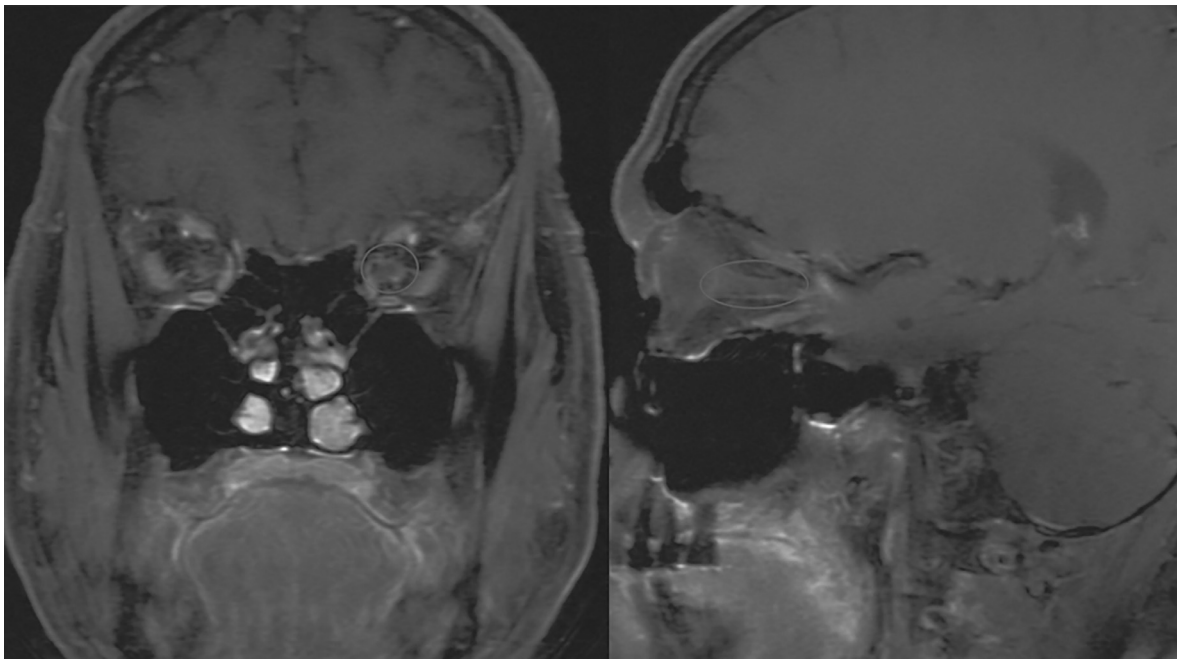

Fig. 2—MRI brain and orbital T1 postcontrast images show left optic nerve and optic nerve sheath enhancement.

edema was seen to suggest hypertensive retinopathy. Automated perimetry (Humphrey visual field 24-2) confirmed a bilateral cecocentral scotoma (Fig. 1). Optical coherence tomography (OCT) showed bilateral mild nerve fibre layer thinning at the papillomacular bundle. The macular ganglion cell was markedly diminished OU.

The lumbar puncture was repeated, and the CSF showed lymphocytic predominant pleocytosis with rare blasts. Brain MRI showed enhancement of the left optic nerve, and bilateral sheath enhancement was suspected (Fig. 2). Spinal MRI showed enhancement and thickening of the nerve roots of the cauda equina. A diagnosis of extramedullary, CNS blast crisis from CML was made. The patient proceeded with holistic medicine alone, and despite no further medical treatment, his vision improved from 20/CF to 20/60 OS. He declined any further medical management at his last visit.

CML is characterized by 3 phases: chronic, accelerated, and blast crisis. Our patient presented with the chronic phase that progressed to accelerated and blast crisis. Optic neuropathy as the presenting sign of CNS blast crisis in CML is rare. Jain and Gupta reported a case of a 35-year-old man with CML who had bilateral visual loss and retinal hemorrhages and a positive CSF for myeloid blasts. MRI showed pachymeningeal enhancement and bilateral optic nerve thickening.[1] Mbekeani et al. reported a case of a 45-year-old woman with CML who developed bilateral no-light-perception vision with optic disc edema, and the MRI confirmed optic nerve infiltration.[2] Schocket et al. described a case of 58-year-old man with CML of 5 years' duration who presented with painless, progressive left eye vision loss. A contrast MRI showed no enhancement of the optic nerves, but there was subtle enhancement of cranial nerves VII and VIII suggestive of leptomeningeal involvement.[3]

In our patient, the initial negative serum complete blood count, CSF analysis, and neuroimaging led to the presumption of ponatinib-related ischemia as the cause for the visual loss. Although ponatinib can cause arterial and venous thrombotic events, no intraocular ischemic event was ever documented in our patient. There was no evidence of hypertensive retinopathy, central retinal artery occlusion (CRAO) or central retinal vein occlusion (CRVO), nonarteritic anterior ischemic optic neuropathy (NAION); or CML retinopathy.

Our patient did experience presumed ponatinib-related elevated blood pressure. The traditional stages of hypertensive retinopathy, however, include arteriolar narrowing (stage 1), arteriovenous nicking (stage 2), retinal hemorrhages and cotton wool patches (stage 3), and optic disc edema (stage 4). In our patient, none of these retinal or optic nerve features of hypertensive retinopathy was documented. In addition, the MRI findings of optic nerve and sheath complex enhancement would not be expected in hypertensive retinopathy, CRAO, CRVO, or NAION.

Although macular edema, retinal vein occlusion, and retinal hemorrhage occurred in 2% of ponatinib-treated patients,[4] we do not believe that the ponatinib was the cause of the patient's optic atrophy. Also, conjunctival irritation, corneal erosion or abrasion, dry eye, conjunctivitis, conjunctival hemorrhage, hyperemia, and edema or eye pain occurred in 14% of patients during clinical trials,[4] and our patient had no other ocular symptoms or signs to suggest ponatinib toxicity.

In summary, visual loss and optic neuropathy can occur secondary to isolated, extramedullary, CNS blast crisis in patients with CML, despite normal serum WBC and negative CSF analysis for blasts. Although ocular side effects,

including visual loss, can occur after treatment for CML, including ponatinib-related ocular ischemia, this should be considered a diagnosis of exclusion in the setting of optic atrophy. Imaging of the spine and serial CSF analysis may disclose CNS leptomeningeal disease and extramedullary CNS blast crisis despite negative brain imaging and normal peripheral blood smear and cell counts in CML.

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Amaurosis fugax as the presenting symptom of metastatic lung adenocarcinoma

An 80-year-old Caucasian female with a remote history of nonarteritic ischemic optic neuropathy of the left eye presented with transient vision loss in the right eye, occurring once or twice per week, for the month before presentation. The onset of each episode was abrupt, rather than gradual, and described as "things fading in the right eye," and "objects looking duller than usual" over the entire visual field. She had no positive visual phenomena with these episodes, which often lasted approximately 1−5 minutes. Each episode was neurologically isolated, without headache or focal neurologic symptoms. After each episode, the vision slowly returned to her previous baseline. She identified no precipitating factors related to her symptoms.

She had a negative review of systems, including fevers, chills, weight loss, fatigue, headache, jaw claudication, scalp tenderness, weakness, numbness, vertigo, diplopia, oscillopsia, slurred speech, facial droop, chest pain, palpitations, dyspnea, cough, or hemoptysis.

Examination at presentation was notable for a visual acuity of 20/40 OD and count fingers OS, as well as a left afferent pupillary defect, which was unchanged from baseline with her left ischemic optic neuropathy. Intraocular pressures were 14 mm Hg OU. Slit-lamp and fundus examination of the right eye showed no anterior segment disease, vessel occlusion, Hollenhorst plaques, or other retinal or vascular abnormalities. Her temporal artery pulses were strong bilaterally and she had no scalp tenderness. She had no other focal neurologic defects and the rest of her physical examination was unremarkable.

She was hospitalized for urgent evaluation of transient monocular vision loss. Laboratory work-up was notable for a troponin elevation, as well as mild anemia, thrombocytopenia, and hyponatremia. Erythrocyte sedimentation rate and C-reactive protein were unremarkable. Head computed tomography (CT) was negative for intracranial hemorrhage. Brain magnetic resonance imaging (MRI) was obtained and revealed multiple punctate cortical and juxtacortical areas of diffusion restriction, involving all vascular territories (Figure 1).

Carotid Dopplers showed smooth plaques in the internal carotid arteries causing less than 50% stenosis, but were otherwise unremarkable.

Given the involvement of multiple vascular distributions, a trans-thoracic echocardiogram was performed, which was negative for valvular abnormalities or right-to-left shunt. A transesophageal echocardiogram was then performed, which showed characteristic mobile echodensities on both leaflets of the mitral valves, including a 6×5 mm lesion on the posterior leaflet and 4×1 mm lesion on the anterior leaflet, without significant regurgitation or valve destruction (Figure 2). Blood cultures were obtained and negative for bacterial or fungal growth.

A CT of the chest, abdomen, and pelvis was performed that showed spiculated lesions in the lingula and right upper lobe of the lung, as well as mediastinal lymphadenopathy.

Positron emission tomography−CT showed increased uptake in the spine, pelvis, sternum, and thoracic wall, consistent with metastatic osseous disease. An ultrasound-guided biopsy of a paratracheal lymph node was performed. Pathology revealed malignant cells, strongly positive for thyroid transcription factor (TTF-1) and NapsinA, consistent with metastatic pulmonary adenocarcinoma.

Discussion

"Transient monocular vision loss" (TMVL) is a broad term used to describe sudden, nonpermanent vision loss in one eye. The etiology of TMVL comprises a wide range of ophthalmic, neurologic, and systemic disease. Commonly, "amaurosis fugax" is the term used when TMVL is