OCULAR MANIFESTATIONS OF PRIMARY MYELOFIBROSIS

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Purpose: To report ocular manifestations of idiopathic primary myelofibrosis in a patient with relapsed primary myelofibrosis.

Methods: Observational case report.

Results: A 57-year-old African American male with history of primary myelofibrosis, diagnosed by bone marrow aspirate and biopsy, believed to be in remission was referred to us for bilateral angle-closure glaucoma refractory to medical treatment and laser peripheral iridotomy. His fundus examination revealed serous retinal detachments, choroidal effusions, and Roth spots, and B-scan revealed his angle closure was due to annular anterior ciliochoroidal effusions. The patient was taken to surgery for a pars plana vitrectomy with radial sclerotomies performed to relieve the patient's eye pressure in the left eye. Cytologic analysis of the choroidal effusions revealed neutrophilic infiltrates with immature forms and erythroid precursors, suggesting a neoplastic infiltration from the patient's primary myelofibrosis. The patient's vision and ocular symptoms significantly improved after chemotherapy. Repeat bone marrow aspiration and biopsy confirmed the patient's primary myelofibrosis with no progression to acute leukemia despite his high leukocyte count.

Conclusion: Neoplastic infiltration of primary idiopathic myelofibrosis into the eye and surrounding structures, which is scantly described in the current literature, may be an early sign of new onset or relapsing primary myelofibrosis. Chemotherapy can be very effective in the ultimate treatment and remission of these ocular symptoms.

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Ocular neoplastic infiltration primary of idiopathic myelofibrosis, a myeloproliferative disorder of the bone marrow, into the eye is extremely rare. Primary myelofibrosis, formerly called chronic idiopathic myelofibrosis, is the least frequent among the chronic myeloproliferative diseases.[1] An epidemiologic study in Minnesota reported an incidence of 1.5/100,000 per year in Olmstead County, and the incidence primary occurs in middle-aged and elderly people, with a median age of 67.[2] Ophthalmic manifestations are rare as well; there are few documented cases of ocular myelofibrosis at the time of this writing. Myeloproliferative neoplasms can have ocular manifestations, usually as retinal hemorrhages in the retina, but sometimes different parts of the eye can be involved simultaneously. We present a case of relapsed idiopathic primary myelofibrosis that initially presented with refractory bilateral acute angle-closure glaucoma.

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Case Report

A 57-year-old African American male with a history of myelofibrosis, and no ocular history was referred to us for acute bilateral angle-closure glaucoma. He reported three days of increasing eye redness and pain. The patient was initially examined by a local ophthalmologist and had visual acuity of 20/40 in both eyes, an intraocular pressure (IOP) of 40 mmHg in the right, and 60 mmHg in the left, and bilaterally closed angles on gonioscopy. The patient was initially treated with maximum medical treatment to reduce his IOP along with bilateral laser peripheral iridotomies. However, his IOP in both eyes remained elevated, and the patient was then transferred to our service.

Visual acuity at arrival was 20/400 in the right eye and hand motion, worsening to light perception, in the left eye. His

examination revealed an IOP of 34 mmHg in his right eye and 52 mmHg in his left eye. On examination, the patient had prominent proptosis of the left eye and restricted extraocular movements with injected chemotic conjunctiva in both eyes. Anterior chambers were very shallow in both eyes and gonioscopy confirmed bilateral angle closure. Fundus examination of the right eye revealed multiple serous retinal detachments involving the macula, scattered choroidal and retinal infiltrates, and Roth spots. Fundus viewing in the left eye was poor but showed similar findings as the right eye, but worse. B-scan ultrasonography revealed bilateral choroidal and annular anterior ciliochoroidal effusions with anterior rotation of the ciliary body and confirmed serous retinal detachments with thickened sclera and the presence of a "T" sign. Initial laboratory work at presentation revealed leukocytosis (83,000 per cubic millimeter) with thrombocytopenia (43,000 per cubic millimeter). After evaluation by the glaucoma and vitreoretinal services, the patient was taken to surgery for a vitrectomy with radial sclerotomies to decompress the patient's left eye (Figure 1).

Multiple radial sclerotomies were required for adequate drainage of loculated serous effusions. The fluid expressed from these sclerotomies was collected for cytologic analysis. A core vitrectomy was performed to debulk the vitreous. After surgery, the patient's IOP was then maintained between 20 and 25 mmHg in his left eye on maximum topical IOP medication. However, the patient's vision in the right eye continued to deteriorate, with IOP still elevated. A magnetic resonance imaging of the orbit revealed, in addition to the previous clinical findings described, signal abnormalities and enhancement of the optic nerves and sclera with scleral thickening, suggesting an infiltrative process in both eyes. Cytologic analysis of choroidal fluid obtained from surgery revealed neutrophilic infiltrates including immature forms and erythroid precursors, suggesting a myeloproliferative neoplasm.

Given the results from imaging and pathology, the patient's diagnosis was likely a paraneoplastic infiltration of the uveal tract from the patient's primary myelofibrosis. He was diagnosed with primary myelofibrosis by an outside physician in 2012 and was started on ruxolitinib. A bone marrow biopsy performed in October 2012 demonstrated myelofibrosis with secondary osteosclerosis, but not diagnostic of high-grade myelodysplasia, lymphoma, or leukemia. The core biopsy showed a hypercellular marrow for age (>90%) because of increased stromal elements with marked reticulin fibrosis, and a decreased number of trilineage hematopoietic elements with complete maturation Fluorescence in situ hybridization testing did not show any evidence of BCL-ABL1 rearrangement, and was negative for chronic myelogenous leukemia, with no evidence of deletion of 5q or monosomy 5, monosomy 7 or deletion of 7q, trisomy 8 (+8), and deletion of 20q12. However, cytogenetics revealed an abnormal male karyotype, positive for 3n deletion, 46,X,Y,del(3)[q21q26.2]{17}. No increase in blasts was shown by CD34 immunostain. Flow cytometry showed no evidence of a lymphoproliferative disorder either, but it did show CD56 aberrantly coexpressed in a subset of maturing myeloid population, consistent with a primary myeloid disorder. A left lymph node biopsy in November 2012 showed a presence of a marked extramedullary hematopoiesis, secondary to chronic myeloproliferative neoplasm. No evidence of a Hodgkin's or Non-Hodgkin's lymphoma or metastatic carcinoma was seen on the biopsy. A peripheral blood smear on that same day also confirmed a JAK2 V617F mutation, along with a neutrophilic leukocytosis with left shift, likely representing displacement of the myeloid cavity by fibrotic elements. A bone marrow biopsy was performed a year later because of concerns of progression to acute leukemia due to a rising leukocytes up to 78,000 per cubic millimeter. However, his biopsy demonstrated a markedly 4+ fibrotic marrow with marked hypercellularity and few blasts (approximately 5%), consistent with primary myelofibrosis with no transformation into acute leukemia. CD34 immunostains were negative in the biopsy.

After the second bone marrow biopsy, he presented a month later to us in November 2013 with his ocular signs and symptoms. A repeat bone marrow biopsy performed two days after his vitrectomy showed the same findings as his biopsy a month previously. A lumbar puncture performed shortly afterward did not identify any blasts but found few immature neutrophilic precursors along with few eosinophils, suspicious of central nervous system involvement of the patient's primary myeloproliferaive neoplasm. The patient was admitted to the hematology/oncology service and was given daily corticosteroids and intrathecal methotrexate. The neurosurgery service placed an Ommaya reservoir for the patient to receive intrathecal methotrexate, and the patient was discharged home afterward with scheduled follow-up in clinic once he received the maximum benefit of his hospital stay.

His clinic presentation two months later showed a drastically different picture. His vision in his right eye was 20/20 with normal IOP without any IOP medications. His fundus examination seemed normal, in stark contrast with his original presentation. His left eye was at light perception, but IOP was normal. No view of the fundus was possible because of a transpupillary membrane and dense cataract. His vision subsequently improved after removal of this transpupillary membrane and removal of his cataract (Figure 2).

Discussion

We report the first case of neoplastic infiltration by primary myelofibrosis into the eye presenting as bilateral acute angle-closure glaucoma, choroidal

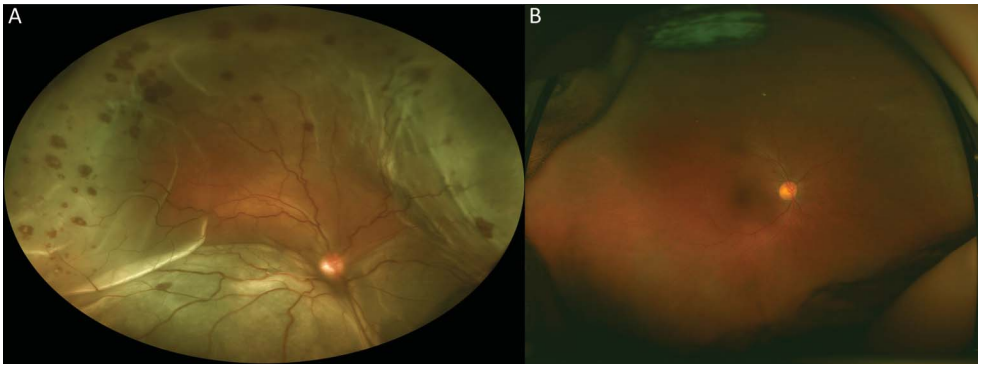

Fig. 1. A. Optos ultra-widefield photograph of the right eye. **B.** Optos ultra-widefield photograph of the right eye.

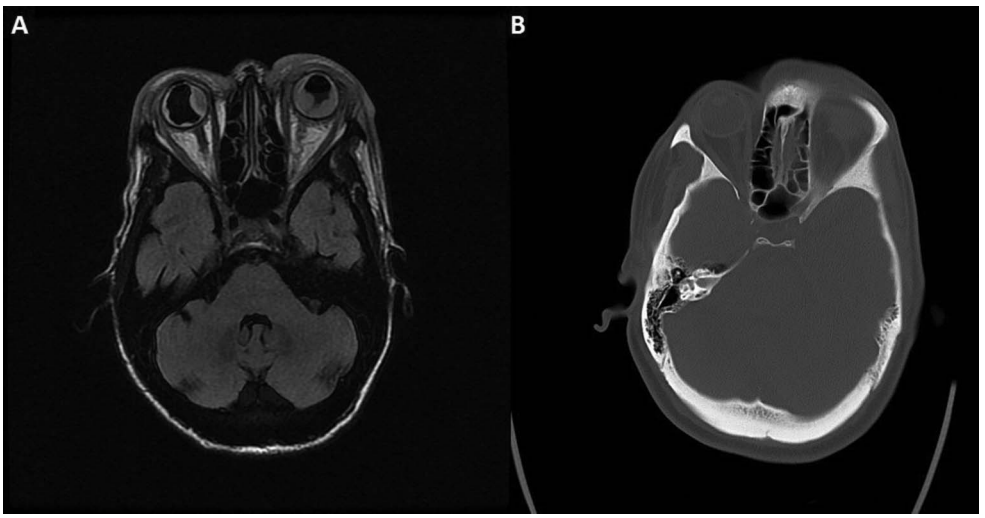

Fig. 2. A. Axial T1 magnetic resonance imaging of patient, with choroidal effusions and infiltrative processes in orbit. **B.** Axial computed tomography of same plane, showing resolution of infiltrate processes and less distension of optic nerve after administration of corticosteroids and chemotherapy.

effusions, serous retinal detachments, and scleritis. Ocular involvement of myelofibrosis is extremely rare, with few published cases.[3–5] Kim and Yu[3] describe a patient with chronic idiopathic myelofibrosis with bilateral retinal neovascularization and vitreous hemorrhages. Retinal hemorrhages in a patient with ocular myelofibrosis were reported by Haskes and Gagnon.[4] Documented extraocular manifestations of myelofibrosis include ptosis secondary to tarsitis and eyelid thickening.[5] There have also been documented cases of metastatic leukemia and lymphoma presenting as narrow angle-closure glaucoma.[6–10] In these cases, presentations of bilateral, simultaneous angle-closure suggested a systemic disease, which was the case in our patient. Although the exact diagnoses in these cases differ from our patient, these diagnoses were myeloproliferative disorders of some sort. The anterior segment and retinal findings in our patient were highly likely due to neoplastic infiltration of the uveal tract in the patient, which is similar to the findings reported by Baillif et al.[8] However, our patient differed from their findings, in that, our patient's systemic diagnosis was already established before his ocular signs and symptoms, and infiltration of the actual neoplasm may have been responsible for this patient's signs and symptoms. Cytologic analysis of his choroidal infiltrates, cerebrospinal fluid, and bone marrow biopsy did not show any conversion to leukemia, despite an unusually high leukocytes.

Our patient was managed with maximum medical and surgical treatment. Typical measures to relieve angle-closure glaucoma did not work in this patient because the mechanism of this patient's acute angle closure was due to anterior rotation of his ciliary body from his ciliochoroidal effusions. Our decision for surgical intervention was based on rapidly declining vision to light perception from intractable glaucoma. Surgically obtained choroidal fluid analysis was essential for the diagnosis. Our decision to take the patient to surgery was twofold: to relieve the patient's IOP from causing permanent vision loss, and even if intrathecal methotrexate were initiated, it may have not reduced the infiltrative load and thus reduce IOP enough to prevent further vision loss. Definitive treatment, however, was achieved with aggressive immunomodulation and should be considered as primary treatment if possible.

This case provides further insight into this complex systemic disease that can present with devastating ocular manifestations. As in our patient, the first sign of systemic exacerbation of primary myelofibrosis may present in the eye and surrounding ocular structures, and timely recognition of the underlying etiology can result in proper treatment of both the systemic and ophthalmic manifestations of primary myelofibrosis.

Key words: angle-closure glaucoma, ocular myelofibrosis, primary myelofibrosis, scleritis, serous retinal detachment.

References

1. Mesa RA, Verstovsek S, Cervantes F, et al. Primary myelofibrosis (PMF), post polycythemia vera myelofibrosis (post-PV MF), post essential thrombocythemia myelofibrosis (post-ET MF), blast phase PMF (PMF-BP): consensus on terminology by the international working group for myelofibrosis research and treatment (IWG-MRT). Leuk Res 2007;31:737–740.
2. Mesa RA, Silverstein MN, Jacobsen SJ, et al. Population-based incidence and survival figures in essential thrombocythemia and agnogenic myeloid metaplasia: an Olmsted County Study, 1976–1995. Am J Hematol 1999;61:10–15.

3. Kim MJ, Yu HG. Case of bilateral retinal neovascularization associated with chronic idiopathic myelofibrosis. Korean J Ophthalmol 2010;24:131–133.
4. Haskes C, Gagnon K. Retinal manisfestations of idiopathic myelofibrosis, a hemotalogic disorder. J Am Optom Assoc 1998;69:319–328.
5. Neufeld KR, Price K, Woodward JA. Massive eyelid thickening in pachydermoperiostosis with myelofibrosis. Ophthal Plast Reconstr Surg 2009;25:316–318.
6. Tumuluri K, Woo T, Crowston J, et al. Bilateral leukemic orbital infiltration presenting as proptosis and narrow-angle glaucoma. Ophthal Plast Reconstr Surg 2004;20:248–250.
7. Shaikh A, Parulekar M, James B. Acute suprachoroidal haemorrhage with acute angle closure glaucoma as a presenting sign of chronic myelomonocytic leukemia. Eye (Lond) 2002;16:651–653.
8. Kozlowski IM, Hirose T, Jalkh AE. Massive subretinal hemorrhage with acute angle-closure glaucoma in chronic myelocytic leukemia. Am J Ophthalmol 1987;103:837–838.
9. Cristol SM, Baumblatt JG, Icasiano E, et al. Bilateral acute angle-closure associated with systemic lymphoma: a report of 2 cases. J Glaucoma 2011;20:115–117.
10. Baillif S, Cornut PL, Girard C, et al. Bilateral angle-closure glaucoma and multifocal choroiditis as a first presentation in Hodgkin lymphoma. Retin Cases Brief Rep 2011;5:201–205.