

CASE REPORT

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Bilateral proliferative retinopathy as the initial presentation of chronic myeloid leukemia

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Abstract

The authors report a rare case of a 48-year-old male with chronic myeloid leukemia (CML) who initially presented with a bilateral proliferative retinopathy. The patient complained of recent visual loss and floaters in both eyes (BE). Ophthalmologic evaluation revealed a best corrected visual acuity (BCVA) of 20/50 in the right eye and 20/200 in the left eye (LE). Fundoscopy showed the presence of bilateral peripheral capillary dropout with multiple retinal sea fan neovascularisations, which were confirmed on fluorescein angiography. Full blood count revealed hyperleukocytosis, thrombocytosis, anemia, and hyperuricemia. Bone marrow aspiration and biopsy showed the reciprocal chromosomal translocation t(9;22), diagnostic of CML. The patient was started on hydroxyurea, allopurinol and imatinib mesylate. He received bilateral panretinal laser photocoagulation and a vitrectomy was performed in the LE. The patient has been in complete hematologic, cytogenetic, and major molecular remission while on imatinib and his BCVA is 20/25 in BE.

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Full Text

Introduction

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder of hematopoietic stem cells characterized by the reciprocal translocation t(9;22) (q34;q11), the Philadelphia chromosome (Ph). [1] The resulting breakpoint cluster region-abelson 1 BCR-ABL1 oncogene has a deregulated tyrosine kinase activity, [1] which produces a constitutive proliferative signal responsible for the transformed phenotype of CML cells. CML is estimated to account for 15-20% of adult leukemias. [2] The age-adjusted incidence rate is 1.6 cases per 100,000 individuals per year and the median age at diagnosis is 65 years, with a slight male predominance. [2] Proliferative retinopathy is a rare form of presentation of CML and few cases have been reported. [3],[4],[5],[6]

Case Report

In January 2011 a 48-year-old Caucasian male presented to the Eye Casualty Department, Hospital de Santo António-Centro Hospitalar do Porto, Porto, with a 11 day history of acute visual loss and floaters in his left eye (LE). The patient also complained of a 1 week history of blurred vision in the right eye (RE). He had been diagnosed with hypertension and dyslipidemia in 2009 and he was medicated with candesartan/hydrochlorothiazide 16mg/12.5mg once per day (qd) and simvastatin 20mg qd. His past ocular history was unremarkable. Both his parents had hypertension and dyslipidemia, without major ocular complications; besides this the remaining family history was unremarkable. In the last appointment (March 2010) his best corrected visual acuity (BCVA) was 20/20 with a myopia correction of 1D in both eyes (BE). When asked specifically about other symptoms, he stated he did note some fatigue over the last 3 months but it was not severe enough to seek medical attention as it disappeared with rest. He denied any history of radiation treatment, injury, weight loss, fever, rash, bone pain, abdominal discomfort, left upper quadrant pain or night sweats. On presentation, his BCVA was 20/50 in the RE and 20/200 in the LE with no improvement with pinhole. On slit-lamp examination, the anterior segment had no abnormalities with an intraocular pressure of 14mmHg (Goldmann Applanation Tonometry) in BE. Gonioscopy was unremarkable. No relative afferent pupillary defect was observed; ocular movements were preserved in all fields of gaze. Dilated fundus examination showed the presence of multiple vascular abnormalities in the posterior pole and in all four quadrants of the peripheral retina in BE, including, dilated and tortuous veins, widely scattered dot-blot and flame-shaped retinal hemorrhages, microaneurysms, multiple sea fan peripheral retinal neovascularisations with arteriovenous anastomosis, and vitreous hemorrhage more evident in the LE [Figure 1].1-5. Fluorescein angiography showed some degree of blockage due to the vitreous hemorrhage and the retinal hemorrhages in BE. Fluorescein angiography also showed widely scattered microaneurysms, marked areas of peripheral retinal non-perfusion due to capillary dropout, arteriovenous anastomosis, and peripheral retinal neovascularisations with a sea fan configuration but without evidence of vasculitis [Figure 2] and [Figure 3]. A diagnosis of bilateral proliferative retinopathy was made and an initial systemic evaluation was performed. The blood pressure was 124/78 mmHg. Several laboratory test results were within normal limits, including : 0 the fasting glucose and hemoglobin A1c; lipid profile; reactive protein C activity; erythrocyte sedimentation rate; homocysteine level; serum protein S, protein C, and antithrombin III. Coagulation parameters were also normal. Factor II mutation, factor V Leiden mutation, anti-cardiolipin antibodies, and lupus anticoagulant antibodies were negative. Hemoglobin electrophoresis and serum protein electrophoresis showed no abnormalities. Complete blood count and peripheral blood smear evaluation revealed hyperleukocytosis (248×10³ cells/mm³; reference value, 4.5-11.0×10³ cells/mm³), thrombocytosis (684×10³ /mm³; reference value, 150-450×10³ /mm³), normochromic normocytic anemia (10.8g/dL; reference value, 13.0-18.0g/dl), hyperuricemia and elevated serum levels of lactate dehydrogenase; the white blood cell differential count indicated an increased number of circulating mature and immature granulocytes, with the presence of blasts (1%) and a basophilia of 5%. Renal and hepatic functions were normal. {Figure 1}{Figure 2}{Figure 3}

Based on the ocular findings and hematological abnormalities, the patient was referred to a hematologist for further management. The physical examination revealed a palpable splenomegaly 10cm below the left costal margin and mild signs of anemia. Bone marrow aspiration and biopsy were performed. The bone marrow was hypercellular with an elevated myeloid-to-erythroid ratio and increased number of megakaryocytes but without fibrosis; the blast percentage was 4%. The morphologic findings combined with the cytogenetic analysis showing the reciprocal chromosomal translocation t(9;22) were diagnostic of CML. The patient was started on hydroxyurea (2g twice a day), allopurinol (300mg qd) and imatinib mesylate (400mg qd) which brought about a reduction in his white cell and platelets counts over a period of 5 weeks. Subsequently, hydroxyurea and allopurinol were discontinued but imatinib 400mg qd was maintained. The patient achieved complete cytogenetic remission 6 months after initiation of therapy, and after 9 months of therapy he had undetectable levels of BCR-ABL.

Bilateral scatter panretinal photocoagulation (PRP) of the peripheral avascular retina was performed in several sessions. A vitrectomy with peripheral proliferative membrane peeling and endolaser was also performed in the LE as the persistent vitreous hemorrhage did not allow the laser photocoagulation to be performed. The vitreous hemorrhage in the RE gradually cleared over a period of 3 months. Following treatment the proliferative retinopathy completely regressed in BE. The patient has been stable for the last 10 months and his BCVA is 20/25 in BE at the most recent visit.

The patient is being monitored closely by his oncologist and by his ophthalmologist. The patient will continue imatinib treatment for the foreseeable future.

Discussion

The natural history of CML in the absence of treatment is characterized by a triphasic course comprising a chronic phase (CP-CML), followed by an accelerated phase and an invariably progression to a final fatal blastic phase in a variable period of time. [7] Our patient was in the chronic phase at the time of diagnosis. The prompt recognition of his ocular fundus findings and early referral to oncologists for adequate management may have been a major factor in determining his long-term outcome because patients with CP-CML at the time of diagnosis have the best long-term prognosis with treatment. [7]

This disease was an incurable disease with conventional chemotherapy. However, the treatment strategies of this type of leukemia have undergone revolutionary developments in the last decade mainly due to a detailed knowledge of its molecular pathogenesis. The BCR-ABL1 fusion protein has been the target for drug design and treatment of this disorder, which have enabled the development of effective tyrosine kinase inhibitors (TKIs) that have the potential to eradicate the Ph chromosome-positive clone. [8] At the time of diagnosis our patient was started on imatinib mesylate at the initial recommended dose of 400mg qd, given orally, and to date, with good results as it has been capable of inducing complete hematologic, cytogenetic, and major molecular remission in a tolerable manner. Achieving these responses early during the course of therapy may have been one of the most important factors in determining his long-term prognosis. This drug, a first generation TKI approved by the United States Food and Drug Administration in 2001, has become the initial treatment of choice for most patients with CML [8] because it results in a marked increase in the long-term survival with preservation of an acceptable quality of life. [9] The patient reported here will be maintained on this therapy for the long-term, unless he develops resistance or intolerance to imatinib, or until other evidence regarding the duration of imatinib therapy for those in CP-CML is consistently available. [8]

The patient also underwent initial rapid cytoreduction with hydroxyurea. This drug has a rapid onset and short duration of action and so it permitted the control of the hyperviscosity syndrome without marked or prolonged myelosuppression. As the white cell count was dramatically increased to 248,000cells/ μ L hydroxyurea was started in a high dose. This drug was stopped once the white cell count decreased to less than 20,000cells/ μ L. The patient also had hyperuricemia prior to chemotherapy which reflected the high cell turnover rate and probably would have been exacerbated by the use of the antineoplastic agent hydroxyurea. Therefore, at the time of receiving cytotoxic therapy, the patient was started on oral allopurinol (a xanthine oxidase inhibitor, which inhibits uric acid production) as well as adequate hydration to maintain high urine output.

The ocular fundus findings observed are not pathognomonic of CML as they may be present in various local and systemic diseases involving the eye. According to Mahneke et al. [4] the stage of retinopathy at the time of diagnosis may not affect the overall prognosis of these patients, even though it may adversely compromise visual outcome if not timely managed as recently reported by Mandava et al. [5] This was one of our main concerns when the therapeutic approach of the bilateral proliferative retinopathy was planned. Vitreoretinal surgery with proliferative membrane peeling and endolaser was performed due to persistent vitreous hemorrhage in the LE along with bilateral PRP of the avascular zones. This ocular treatment was delineated according to the principles, which have proven beneficial for other proliferative retinopathies of various etiologies. The therapy has been performed by Mandava et al. [5] in a case of bilateral advanced proliferative retinopathy due to CML. Our patient is being carefully monitored for recurrent ocular disease because this may occur without any systemic evidence of relapse of CML as previously reported by Nobacht et al. [6]

It is important to try to elucidate the various physiopathological mechanisms that may be involved in the ocular manifestations of CML as they may reflect the effects of this disease throughout the body. In the present case, various mechanisms may have independently contributed to the final via of reduced blood flow, vascular stagnation, retinal capillary dropout, ischemia and neovascularisation. The exact pathophysiology remains obscure but different mechanisms have been proposed in other diseases that may, or not, play a role in CML, including : 0 anemia; leukostasis; hyperviscosity syndrome; leuкоembolization; endothelial lesion and localized thrombosis secondary to toxic products released by the leukemic cells; angiogenic factors released by the ischemic retina; increased serum levels of angiogenic growth factors, including increased levels of vascular endothelial growth factor, fibroblast growth factor 2, hepatocyte growth factor and matrix metalloproteinases. [6],[10],[11],[12] Nevertheless, several other mechanisms may be involved. In line with this notion, further studies are necessary to evaluate the possible pathogenic role of these various mechanisms as this may result in potential clinical implications, for instance in the evaluation and prognosis of these patients and in the development of new therapeutic targets. Treatment of the underlying causes of the ocular findings could actually result in their improvement or even resolution.

In summary, ophthalmologists should consider a thorough systemic evaluation for leukemia in patients with bilateral proliferative retinopathy as this may be the first sign of CML as previously reported by other authors. [3],[4],[5],[6],[10] Our case illustrates that prompt treatment can result in resolution of the ocular findings and allow for restoration of visual function. Finally a timely diagnosis, an adequate supportive care and the initiation of imatinib mesylate have been essential for securing a favorable prognosis in this patient.

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