

Sudden unilateral visual loss as an initial presentation of chronic myelogenous leukemia

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Abstract: Leukemia is a cancer of the white blood cells. Many patients with leukemia are unaware of their disease until routine blood work up for other conditions reveals incidental findings leading to a diagnosis of leukemia. Up to 50% of patients with leukemia have ocular manifestations. In fact, floaters or decreased vision may be the initial symptom of leukemia.

Case study: A 51-year-old Caucasian female patient with sudden unilateral visual loss in the left eye was found to have bilateral retinal neovascularization and Roth spot hemorrhages. Blood work up and cytological analyses confirmed the Philadelphia chromosome, which has been implicated in the development of chronic myelogenous leukemia (CML). Further testing confirmed a diagnosis of chronic phase CML. After a two-month course of imatinib and close monitoring by a hematological oncologist, her vision has improved and the retinal vascularization has significantly resolved.

Conclusions: Eye care professionals are in a unique position to identify this devastating disease early on. A delay in diagnosis of the disease may lead to conversion into the acute phase, which has a poor prognosis for survival. A prompt referral to internal medicine and oncology for co-management is crucial.

Keywords: chronic myelogenous leukemia, retinal hemorrhages, Roth spot, imatinib (Gleevec®) Philadelphia chromosome, vision loss

Background

Leukemia is a group of blood disorders defined by neoplastic production of white blood cells. It is classified into myelogenous and lymphocytic origins, which are further subdivided into four types based on acute or chronic manifestations: acute myelogenous leukemia (AML), acute lymphocytic leukemia (ALL), chronic myelogenous leukemia (CML), or chronic lymphocytic leukemia (CLL).¹ Chronic myelogenous leukemia (CML, chronic myelocytic or chronic myeloid leukemia) accounts for approximately 15% to 20% of leukemias in adults and is associated with a reciprocal chromosomal translocation t(9; 22) (q34; q11) resulting in a BCR-ABL fusion gene (Philadelphia chromosome).² This translocation results in a new hybrid protein (BCR-ABL) with overactive tyrosine kinase activity and is implicated in the development of CML.³ Approximately 95% of patients with CML have this Philadelphia chromosome, which has been the target for drug design and treatment of this disorder.¹ CML is estimated to have an annual incidence of 1 to 2 cases per 100,000, with a slight male predominance. The age at presentation is approximately 50 to 60 years, with exposure to ionizing radiation being the only known risk factor.⁴

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Ocular complications

Leukemia can cause ocular complications in three ways: direct tissue infiltration by excess white blood cells, infections by immunosuppression, and abnormal homeostasis of blood cells such as anemia, thrombocytopenia and hyperviscosity.⁵ Approximately 50% or more of all leukemias have some form of ocular manifestations.⁶ Leukemic retinopathy is a common manifestation of leukemia and is found in both the acute and chronic forms.^{6,7} The authors present a rare case of retinopathy secondary to CML in which unilateral visual symptoms were the initial presentation that led to its diagnosis and timely management.

Case report

A 51-year-old Caucasian female presented to the Pacific University Optometry Clinic in October 2009 with a chief complaint of severe blurry and cloudy vision OS for the last two months. She did not seek care because of lack of health insurance. Medical history was unremarkable, and without any ocular injury or surgery. Family medical history was negative for hypertension, glaucoma, or blindness, with the exception that her brother had diabetes with major complications. Her last eye examination was in August 2009 at a franchised optometric clinic. At that time, her examination was unremarkable, with distance visual acuity of 20/20 OD, OS and OU without correction.

At the current visit, her distance visual acuity was 20/20 OD and 20/400 OS with no improvement with pinhole. Both eyes showed smooth, accurate, full, and equal extraocular muscle movements in all fields of gaze. No apparent pupillary defect was observed. Finger counting confrontation visual fields were full OD and OS. Anterior segment findings, as observed with biomicroscopy, demonstrated no abnormalities. Her conjunctiva was pale but no jaundice was noted. Goldmann applanation tonometry was 16 mm Hg OD and 17 mm Hg OS at 2:15 p.m.

Dilated fundus examination showed multiple vascular abnormalities including retinal hemorrhages and Roth spots OU (Figures 1A, 1B). Optical coherence tomography of the macula revealed foveal vacuoles or holes and thinning, OS significantly greater than OD (Figure 2). The cup-to-disc ratios were normal 0.30V/0.30H both eyes.

A diagnosis of bilateral retinopathy with potential hematologic abnormalities was made. The patient was educated about the seriousness of the retinal findings, with the potential for a similar effect to the fellow eye. She was referred to a retinal specialist for consultation regarding the possible etiology. In the interim, she went to a local health clinic

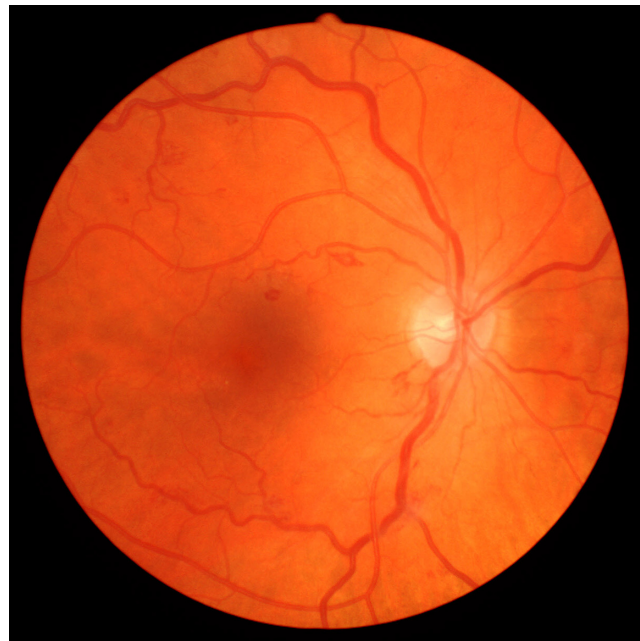


Figure 1a Fundus photography of the right eye shows multiple areas of vascular neovascularizations and engorged, tortuous veins at initial examination.

where her blood pressure and blood sugar were determined to be normal. A week later, she was examined by a retinal specialist, who confirmed the possibility of hematologic abnormalities, and was referred to internal medicine for blood work up the next day.

Laboratory data showed that she had a critical high white blood cell (WBC) count of 150,000/ μ L [normal reference



Figure 1b Fundus photography of the left eye shows clusters of Roth's spots including one at the fovea, and engorged, tortuous veins at initial examination.

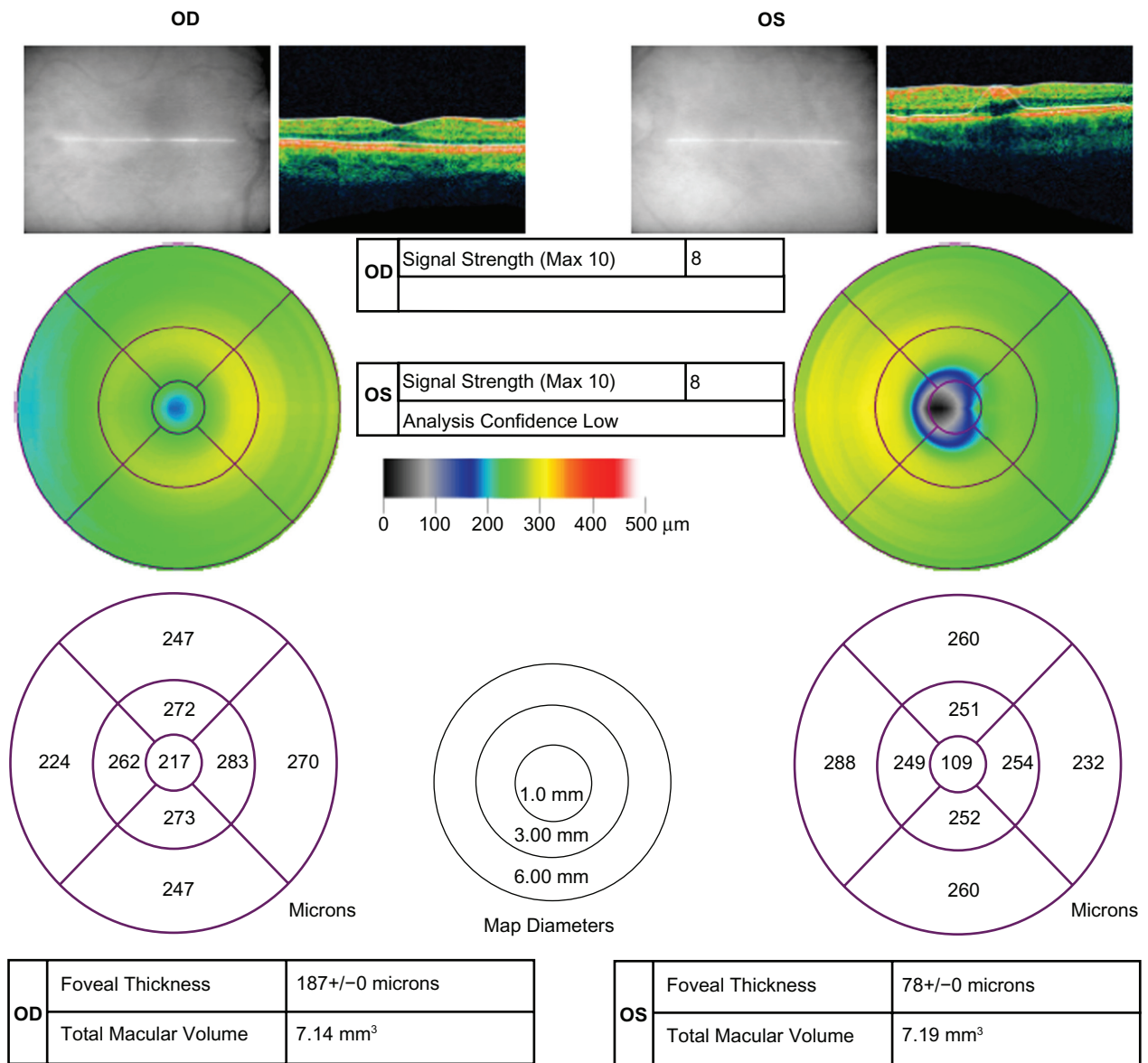


Figure 2 Optical computed topography (OCT) scans of both eyes indicate slight macular thinning OD and significant macular thinning (hole) OS at initial examination.

(ref): 3,900–10,600/ μ L], high platelet count of 448,000/ μ L [ref: 140,000–440,000/ μ L], low red blood cell count of 3,240,000/ μ L [ref: 3,800,000–5,200,000/ μ L] and low hemoglobin 9.0 g/dL [ref: 12.0–16.0 g/dL]. Manual blood cell differential indicated a remarkable high metamyelocyte of 8% [ref: <1%].

A bone marrow aspiration and biopsy were performed. Fluorescence in situ hybridization (FISH) was done on the peripheral blood cells and a t(9; 22) translocation was found. The t(9; 22) translocation results in the juxtaposition of the BCR (breakpoint cluster region) gene on chromosome 22 and the ABL (Abelson) oncogene on chromosome 9. At diagnosis, this so-called Philadelphia chromosome is

observed by routine cytogenetic karyotyping in greater than 95% of patients with CML. Her FISH result of t(9; 22) translocation combined with morphologic findings were diagnostic of CML. The patient needed treatment with imatinib (Gleevec) daily, but she did not have medical insurance. Fortunately, the local cancer center provided her with immediate treatment of hydroxyurea (50 mg/kg/day) and allopurinol (300 mg/day) while she awaited approval by a drug assistance program for imatinib. During this time, the patient’s white blood cell count decreased further. The patient was ultimately granted approval by an assistance program for a one-month supply of imatinib. She was started on imatinib 800 mg per oral (PO) daily, and discontinued

hydroxyurea and allopurinol. She was then monitored weekly at the cancer center.

Two months after her initial diagnosis, her visual acuity in the left eye had improved from 20/400 to 20/40 without correction. She had been taking a lower dose of imatinib (400 mg/d) for the past two months, because she could not tolerate the higher dose of 800 mg/d after two weeks. Fundus photography revealed significant resolution of retinal hemorrhages in both eyes (Figures 3A, 3B). Optical coherence tomography (OCT) macular analyses also indicated normalization of the macular thickness in both eyes (Figure 4). Frequency doubling technology (FDT) visual field testing revealed no defects OD and few area of loss OS (Figure 5). The patient still complained of halos and distortions in her left eye and some tolerable side effects, such as nausea and musculoskeletal pain, from the medication. She is being monitored closely by her oncologist.

Discussion

The differential diagnosis for common bilateral retinal hemorrhages includes diabetic retinopathy, central or branch retinal vein occlusion, hypertensive retinopathy, sickle cell retinopathy, and leukemic retinopathy. The patient was first suspected to have diabetic retinopathy because her brother has a medical history of severe diabetic complications. A complete blood count with differentials and cytological analyses confirmed CML and leukemic retinopathy.

CML is a relatively asymptomatic disease in up to 50% of patients. Many patients are diagnosed as a result of symptoms from splenomegaly, anemia or routine blood testing incidental to their disease.⁸ Among symptomatic patients, systemic symptoms of fatigue, weight loss, excessive sweating, easy bleeding and abdominal fullness are common.⁹ The patient in this case later recalled that she had lost some weight and constantly felt fatigued, but the symptoms were not severe enough to seek medical attention until she experienced decreased vision in her left eye that did not get better after two months. Fortunately, she presented for an eye examination and was subsequently diagnosed and treated. Most patients with untreated CML progress to acute leukemia within 3 years. Once a patient reaches the acute state, additional chemotherapy has little efficacy.⁸

Our patient presented with some of the features of leukemic retinopathy which include retinal neovascularization, white-centered hemorrhages (Roth spots), and retinal venous tortuosity. Roth spot hemorrhages refer to retinal hemorrhages with leukemic infiltration or platelet fibrin deposits



Figure 3a Fundus photography of the right eye shows resolutions of multiple areas of neovascularizations two months after beginning treatment.

that are often seen in patients with bacterial endocarditis, pernicious anaemia, and leukemia. Neovascularizations may arise secondary to retinal nonperfusion and ischemia from the hyperviscosity.¹⁰ As seen in the fundus photography of the left eye (Figure 1B), a cluster of hemes with white precipitates (Roth spots) was located in the fovea causing visual symptoms of floaters and decreased vision. OCT finding



Figure 3b Fundus photography of the left eye shows resolutions of Roth spots including one at the fovea two months after beginning treatment.

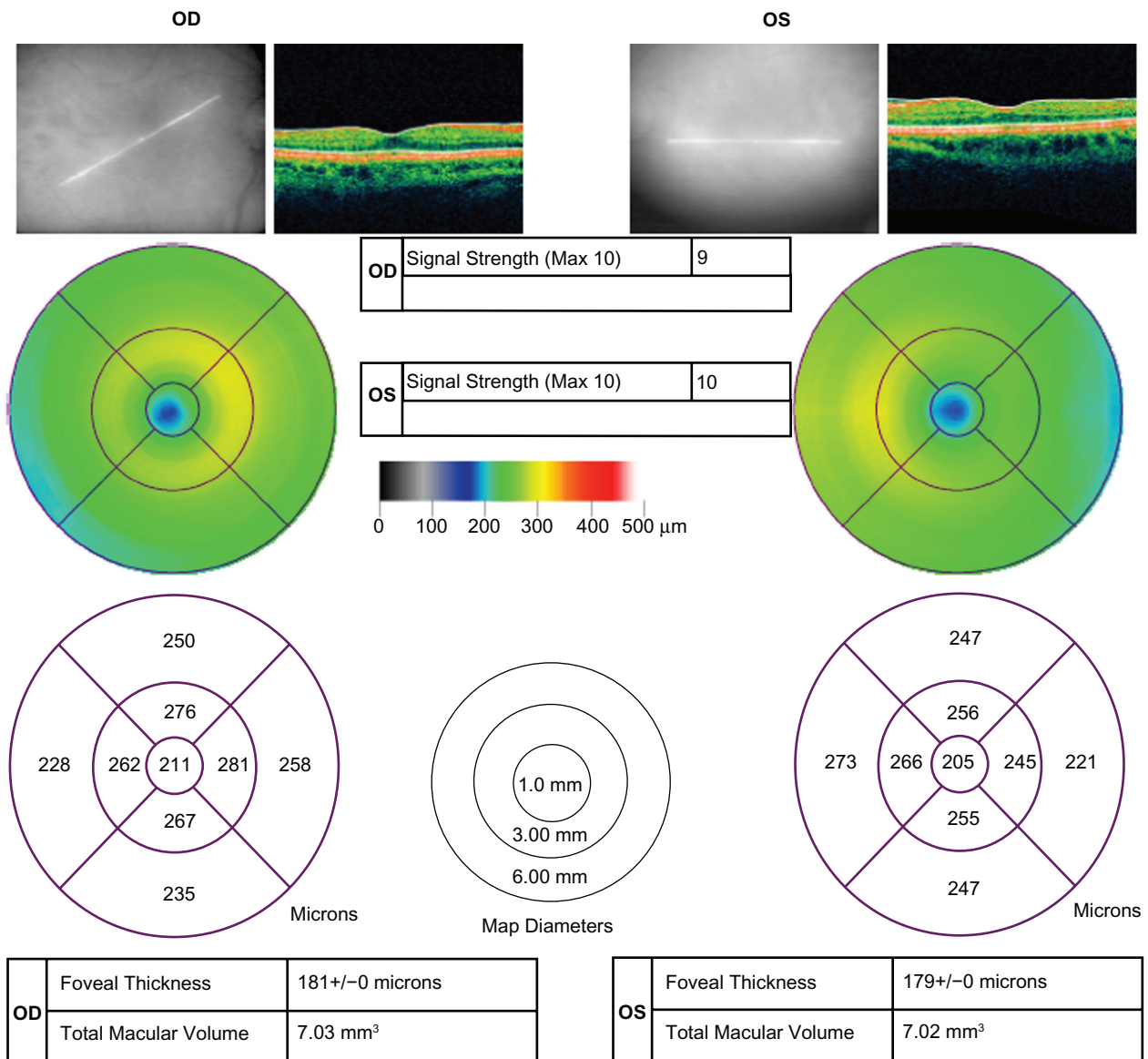


Figure 4 Optical computed topography (OCT) scans of both eyes indicate resolutions of macular thinning OU two months after beginning treatment.

revealed significant thinning of the macula, probably due to a reversible macular cyst or hole, as has been reported in other leukemic cases (Figure 2).¹¹

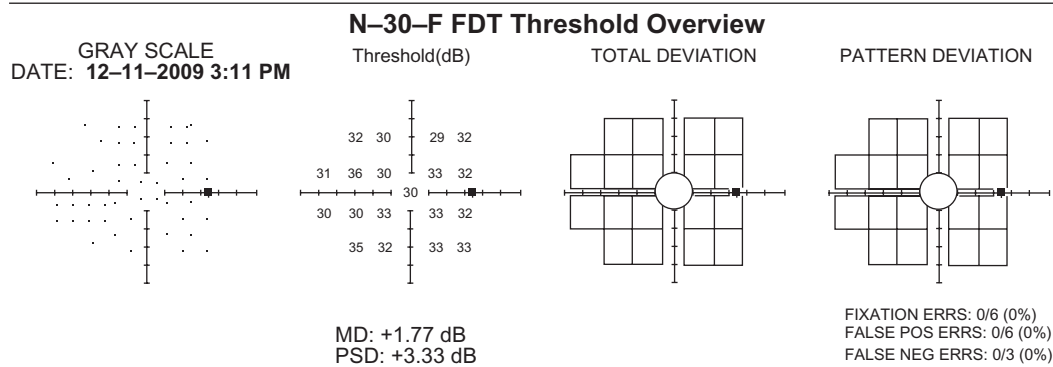
Treatment

The treatment of CML is based upon specifics of the three disease phases: chronic stable phase, accelerated phase, and blast crisis. Chronic phase CML is managed by BCR-ABL tyrosine kinase inhibitors (TKIs) such as imatinib (Gleevec), interferon alpha, cytotoxic agents such as hydroxyurea (Hydrea®), and allogeneic hematopoietic cell transplantation (HCT). Although allogeneic HCT is the only curative therapy, Gleevec is the initial treatment of choice for all patients with chronic phase CML.¹² The majority of patients

with initial chronic phase CML treated with Gleevec showed no disease progression and remained on treatment for years.⁸ Our patient was treated initially with hydroxyurea with allopurinol, which was then followed by imatinib treatment. During imatinib treatment for two months, her vision in the left eye had improved as did the retinal findings as evidenced in recent fundus photography (Figures 3A, 3B) and OCT (Figure 4).

Imatinib treatment is generally well tolerated, the most common side effects in patients with chronic CML are superficial edema, muscle cramps, diarrhea, nausea and musculoskeletal pain. Neutropenia, thrombocytopenia and anemia are rare, but more severe, adverse events in patient with advanced disease.¹³ Ocular side effects of cystoids

Right Eye



Left Eye

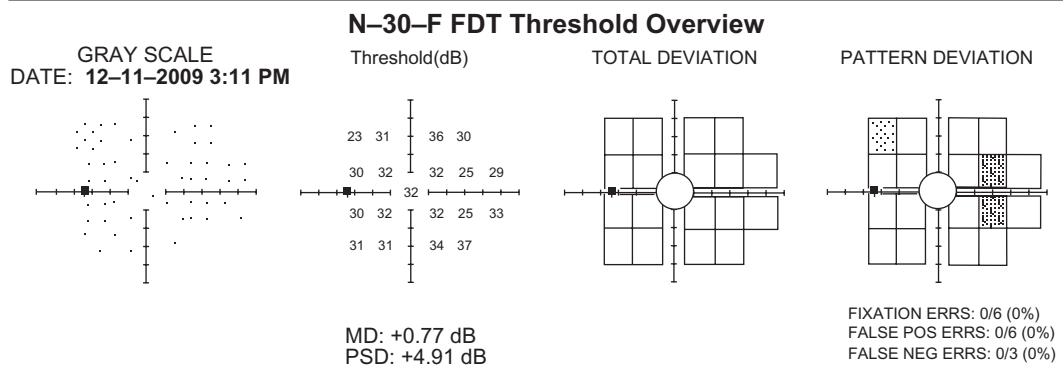


Figure 5 Frequency Doubling Technology (FDT) Visual Field Tests showed normal VF OD and a few areas of loss OS two months after beginning treatment.

macular edema and macular ischemia had been reported in patients treated with Imatinib that resembled the signs of active disease and could complicate the differential diagnosis of visual disturbances.^{14,15}

A number of studies have focused on the prognosis of CML and found the strongest single predictor of outcome is the stage of disease at the time of diagnosis. Patients with chronic phase at the time of diagnosis have the best long-term prognosis with treatment.¹⁶ The overall prognosis for patients with retinopathy is no different from those without retinopathy. The retinopathy typically resolves with treatment of the underlying disease, as seen in this case. An update from the International Randomized Interferon study versus the STI571 (IRIS) study revealed an overall survival rate of 86% with imatinib versus less than 50% at 5 years for those who discontinued imatinib (due to intolerance or lack of efficacy).¹⁷ This confirmed the effectiveness of imatinib in controlling the disease. However, the treatment must be maintained chronically or the disease will relapse.⁸ Furthermore, some patients do not respond to or tolerate imatinib, thus second generation TKIs (nilotinib, dasatinib, bosutinib) have been developed and shown efficacy in some of these patients.¹⁸

A more severe ophthalmic manifestation worthy of noting is optic nerve leukemic infiltration, which causes decreased vision. This is an ophthalmic emergency and requires prompt radiation therapy to preserve vision. Magnetic resonance imaging, B-scan ultrasonography, and lumbar puncture with cerebrospinal fluid analysis are helpful diagnostic tools in determining the presence and extent of infiltration.¹⁹

Conclusion

In conclusion, CML is a relatively asymptomatic disease in up to 50% of patients. However, approximately 50% or more of all leukemias have some form of ocular manifestations. Eye care professionals are amongst the first health care providers to detect the disease, work with internists and refer to oncologists for timely management. A thorough case history is crucial in identifying some of the systemic symptoms such as fatigue, weight loss and excessive sweating. A thorough dilated eye examination is required for detection of retinal abnormalities. Every patient with retinal infiltrates requires a systemic and central nervous system workup.¹⁸ The patient in this case was fortunate to discover her CML early in the chronic phase. Her prognosis is good as she continues with medical management.

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