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Spontaneous unilateral hyphema presenting after imatinib treatment for gastrointestinal stromal tumors

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Abstract

Imatinib, a first-generation tyrosine kinase inhibitor, is the standard of care for the treatment of metastatic and/or unresectable malignant gastrointestinal stromal tumor. Bleeding complications, although rare, have an incidence of 5% with imatinib therapy. The most reported site of imatinib-associated bleeding is along the gastrointestinal tract near the surrounding mass. Although the ocular bleeding complications of retinal and subconjunctival hemorrhages have been reported, there have been no reports of hyphema. This case presents a report of anterior segment bleeding presenting as a spontaneous unilateral hyphema without predisposing neovascularization, surgery, or trauma.

Keywords

Imatinib; Tyrosine kinase inhibitor; Hyphema; Gastrointestinal stromal tumor.

Introduction

First-line chemotherapy for advanced gastrointestinal stromal tumor (GIST) is imatinib mesylate (Gleevec®, Novartis, Basel, Switzerland), a BRC-ABL, c-kit, PDGF-R tyrosine kinase inhibitor [1]. Imatinib was first approved in 2001 for the treatment of chronic myelogenous leukemia and has since been approved for the treatment of acute lymphoblastic leukemia, chronic eosinophilic leukemia, gastrointestinal stromal tumors, as well as other KIT-positive diseases [1]. Second-generation tyrosine kinase inhibitors have been developed and approved, such as bosutinib (Bosulif®, Pfizer, New York, USA), dasatinib (Sprycel®, Bristol Myers Squibb, New York, USA) and nilotinib (Tasigna®, Novartis, Basel, Switzerland), yet imatinib remains the gold standard for first-line treatment. Imatinib is generally well-tolerated in the treatment of GIST. However, less common systemic side effects of imatinib include pancytopenia, neutropenia, cardiac toxicity, renal failure, pancreatitis, hypogammaglobulinemia, and hepatotoxicity [2]. Reported ocular side effects of imatinib include periorbital edema, epiphora, increased intraocular pressure, glaucoma, recurrent retinal hemorrhage, conjunctival hemorrhage, optic neuritis, and cystoid macular edema [3].

This case report describes a 66-year-old Caucasian male who presented with a spontaneous unilateral hyphema following the treatment of gastrointestinal stromal tumors. There is a singular report of a second-generation tyrosine kinase inhibitor, dasatinib, causing a bilateral hyphema in a 66-year-old male with chronic myelogenous leukemia [4]. However, there are no reported cases of spontaneous hyphema without previous neovascularization associated with any first- or second-generation tyrosine kinase inhibitors.

Case Report

A 66-year-old Caucasian male with a past medical history of benign essential tremor, chronic obstructive pulmonary disease, diabetes mellitus, hypertension, and osteoarthritis, was diagnosed with GIST in 2019 and had a resection of the tumor in January of 2020. He was started on oral imatinib therapy in March of 2020 on a dosage of 400 mg per day. Two months later, the dose was increased to 800 mg per day for Monday through Friday and 400 mg on Saturday and Sunday. The patient tolerated the medication well and remained on the medication due to a high risk of tumor recurrence.

In September of 2021, the patient presented to his oncologist with the complaint of left-sided periorbital edema and excessive bleeding when shaving his face. Imatinib toxicity was suspected, however the medical regiment was continued until one month later, when the patient presented to the emergency department (ED) after being referred by urgent care. The patient described that he woke up that morning with painless blurring of his vision in the left eye as if looking through "white fog." He stated no trauma to the eye or previous eye surgery. The patient's past ocular history was significant for keratoconjunctivitis sicca. The patient was found to have 20/20 self-corrected visual acuity (VA) in both eyes and intraocular pressures (IOP) of 15 and 18 mmHg in his right and left eye, respectively. The anterior segment ocular exam was otherwise determined to be normal other than an inferior hyphema in the left eye (Figure 1). No fundus examination was performed. The patient was discharged and scheduled for ophthalmology for follow-up the next day.

The following day, the patient presented for ophthalmology evaluation where he reported that the blurring of vision in his left eye had completely resolved. Self-corrected VA was determined to be 20/25 in both eyes. Bilaterally, pupils were 5 mm and constricted to 4 mm with direct light. No relative afferent pupillary defect was noted. The anterior segment examination was normal other than a microhyphema seen inferiorly on gonioscopy in the left eye. No other abnormalities were found on the rest of the gonioscopic exam. The dilated fundoscopic exam and anterior segment optical coherence tomography (OCT) did not reveal any neovascularization, mass, or other abnormalities that would cause a hyphema. The patient returned for a one-month follow-up at which time the hyphema was resolved and other ocular exam findings were unchanged.

A systemic work-up was conducted to determine a potential cause for the hyphema. Laboratory tests performed included a complete blood count (CBC) with differential which demonstrated mild leukopenia (WBC 4.4 – reference range 4.6-10.2 K/mcL), macrocytic anemia (RBC 3.12 – reference range 4.30-5.70 M/mcL, Hemoglobin 10.4 – reference range 13.5-17.5 g/dL, and MCV 99.8 – reference range 80.0-97.0 FL), and eosinophilia (Eosinophils 8.7 – reference range 0.0-7.0%). Additional hematological diseases were ruled out based on normal iron and TIBC, ferritin, protein S activity, protein C activity, vitamin B12, thyroid

stimulating hormone (TSH), B-type natriuretic peptide (BNP), prothrombin time, and negative sickle cell screening. A complete metabolic panel demonstrated an elevated glucose (Glucose 101 – reference range 70-99 mg/dL) and hemoglobin A1c confirmed hyperglycemia (Hemoglobin A1c 6.8 – reference range > 6.5% diagnostic for diabetes mellitus). Overall, diagnostic testing results were inconclusive in determining a possible cause for the spontaneous hyphema in our patient.

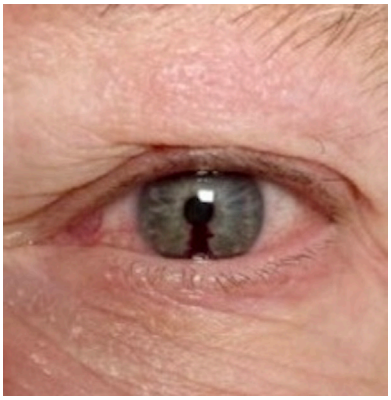

Figure 1: External photograph showing an inferior hyphema of the anterior chamber of the left eye.

Conclusion

Following 2001 European and United States Phase II trials, imatinib, a first-generation tyrosine kinase inhibitor, has become the standard of care for the treatment of metastatic and/or unresectable malignant gastrointestinal stromal tumors [1]. Imatinib is a potent inhibitor of BCR-ABL, as well as other kinases such as c-kit, platelet-derived growth factor receptor (PDGF-R) and SRC family kinases [1]. While uncommon, bleeding has been associated with imatinib, with an incidence of 5%, most often in the GI tract near the primary tumor [1]. A proposed mechanism is local tumor lysis leading to tumor necrosis and rupture of vessels invading the tumor. Additional sites of bleeding peripheral to the GIST that have been noted to include gingival, vaginal, and nasal [1].

Spontaneous or nontraumatic hyphema have been reported in hematological diseases such as hemophilia, sickle cell disease, von Willebrand disease, and acute leukemia [5]. In addition, certain medications have been reported to increase the risk of hyphema, such as aspirin, warfarin, and ethanol [5]. In the case of this patient, he had no history of hematologic disease nor was he prescribed or using any known medications that would increase his risk of hyphema. A 2019 case report noted a non-traumatic hyphema in a 45-year-old male with type 2 diabetes, uncontrolled neovascular glaucoma, and chronic myeloid leukemia following the initiation of both bevacizumab and imatinib simultaneously [6]. An additional case report from 2013 noted a hyphema secondary to neovascular glaucoma in a 64-year-old female with type 2 diabetes and chronic myeloid leukemia following the initiation of imatinib [7]. In contrast to these reports, our patient did not have a previous history of or any evidence of neovascularization on ocular exam.

The mechanism by which imatinib can lead to peripheral bleeding in patients being treated for GIST remains poorly understood. Yet, there are a few potential associations. One possible cause for worsened bleeding with imatinib could be due to decreased platelet function and aggregation. In addition, imatinib is

known to inhibit PDGF-R which is essential in vascular smooth muscle proliferation and angiogenesis regulation [1]. Interestingly, second-generation tyrosine kinase inhibitors, such as dasatinib (Sprycel®, Bristol Myers Squibb, New York, USA), ibrutinib (Imbruvica®, AbbVie, Illinois, USA), and gilteritinib (Xospata®, Astellas, Illinois, USA) have been found to have associated spontaneous hyphema [4,8-10]. Spontaneous or nontraumatic hyphema are thought to be a result of conditions such as rubeosis iridis, neovascularization, intraocular neoplasms, blood dyscrasias, severe iritis, fibrovascular membranes in the retrolental or zonular area, and vascular anomalies of the iris [5]. However, none of these conditions correlate with the history or clinical exam findings in this patient. Thus, we recommend that patients on imatinib therapy should be made aware of the potential side effects of hyphema and other types of ocular bleeding, even if the patient does not have any other predisposing causes of hyphema.

Declarations

Patient consent: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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