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Case Report

Imatinib-induced postoperative periorbital purpura: GASP (Gleevec-Associated Surgical Purpura) in a woman with imatinib-treated chronic myelogenous leukemia

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Abstract

Background: Imatinib mesylate is a selective tyrosine kinase inhibitor used in the treatment of chronic myelogenous leukemia. Ocular side effects of imatinib include periorbital edema, which may become so severe as to obstruct the visual field.

Purpose: The purpose of this case study is to describe the clinical characteristics of imatinib- induced postoperative periorbital purpura.

Materials and methods: We retrospectively reviewed the medical literature using PubMed, searching the terms edema, Gleevec, imatinib, periorbital, postoperative and purpura. Patient reports and previous reviews of the subject were critically assessed and the salient features are presented.

Results: Three patients have undergone surgery to reduce the imatinib-induced periorbital edema; two of these individuals have developed imatinib-induced postoperative periorbital purpura.

Conclusion: We recommend discontinuing imatinib usage one week prior to periorbital surgery and not resuming therapy until the eighth postoperative day.

Keywords: edema, Gleevec, imatinib, periorbital, postoperative, purpura

Introduction

Imatinib mesylate (Gleevec, formerly STI571, Novartis Pharmaceutical AG, East Hanover, NJ) was developed as a selective tyrosine kinase inhibitor [1]. Imatinib selectively inhibits the Bcr-Abl protein tyrosine kinase, an oncogene constitutively expressed in chronic myelogenous leukemia [2]. In addition, imatinib selectively inhibits Kit and platelet derived growth factor receptor tyrosine kinases [1]. Mutations of Kit kinase have been discovered in gastrointestinal stromal tumors. Based on these observations, recent clinical studies have shown promising effects of imatinib usage for patients with advanced gastrointestinal stromal tumor [2]. Platelet derived growth factor receptor has been implicated in malignant soft tissue sarcomas, particularly dermatofibrosarcoma protuberans [2]. Treatment with imatinib slows the growth rate of platelet derived growth factor-transformed cells, both in vitro and in vivo [2]. Recent reports noted response rates approaching 50% for patients with unresectable or metastatic dermatofibrosarcoma protuberans [3]. We describe a 59-year-old woman with imatinib-treated chronic myelogenous leukemia who developed drug-associated periorbital edema and subsequent severe postoperative periocular purpura.

Case synopsis

A 59-year-old woman presented with bilateral ecchymotic periorbital regions one year after blepharoplasty. She had been diagnosed with chronic myelogenous leukemia five years prior; she was successfully treated with imatinib mesylate at a dosage of 400 mg per day.

Several months after initiating treatment, she noted lagging of her lower eyelids and an associated obstruction of her vision. One year prior to presentation, she underwent a bilateral blepharoplasty during which she continued taking her regular dosage of imatinib. Postoperatively, she experienced significant bleeding and severe bruising of the face, jaw, neck, and chest down to her breasts.

The postsurgical periorbital ecchymosis with associated cutaneous discoloration persisted with minimal spontaneous resolution (Figure 1). Two additional surgical procedures were performed in an attempt to remove the discolored areas; the affected areas were excised and replaced with full-thickness skin grafts. Importantly, for the latter two procedures, her imatinib usage was discontinued one week prior to surgery and the drug was not reinstated until the eighth postoperative day. There were no postoperative bleeding episodes.

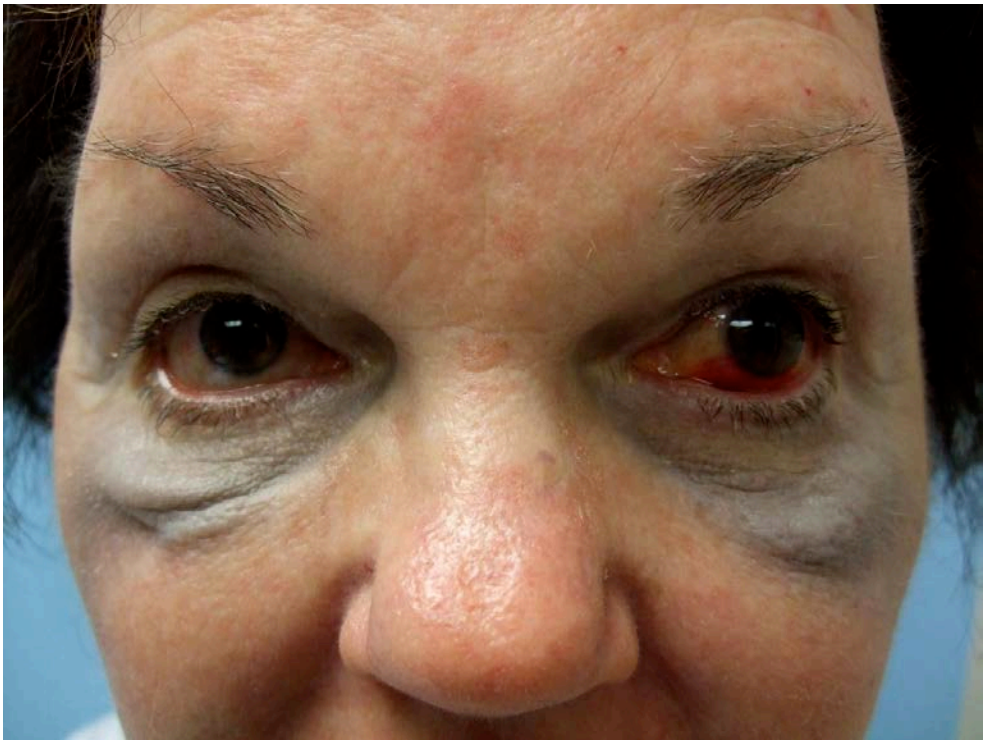

Figure 1. Imatinib-induced postoperative periorbital purpura with subsequent cutaneous discoloration in a 59-year-old woman with chronic myelogenous leukemia. Bilateral blepharoplasty of her lower eyelids had been performed to correct drug-associated periorbital edema while she was receiving 400 mg of imatinib daily.

Follow-up cutaneous examination showed improvement of discolored areas beneath the eyes. However, purple hyperpigmentation was noted bilaterally on the lateral malar cheeks (Figure 2). Between the hyperpigmentation and the eyelashes there was normal pigmentation from the surgically imparted skin grafts. Subsequent examination two years postoperatively continues to show sustained improvement.

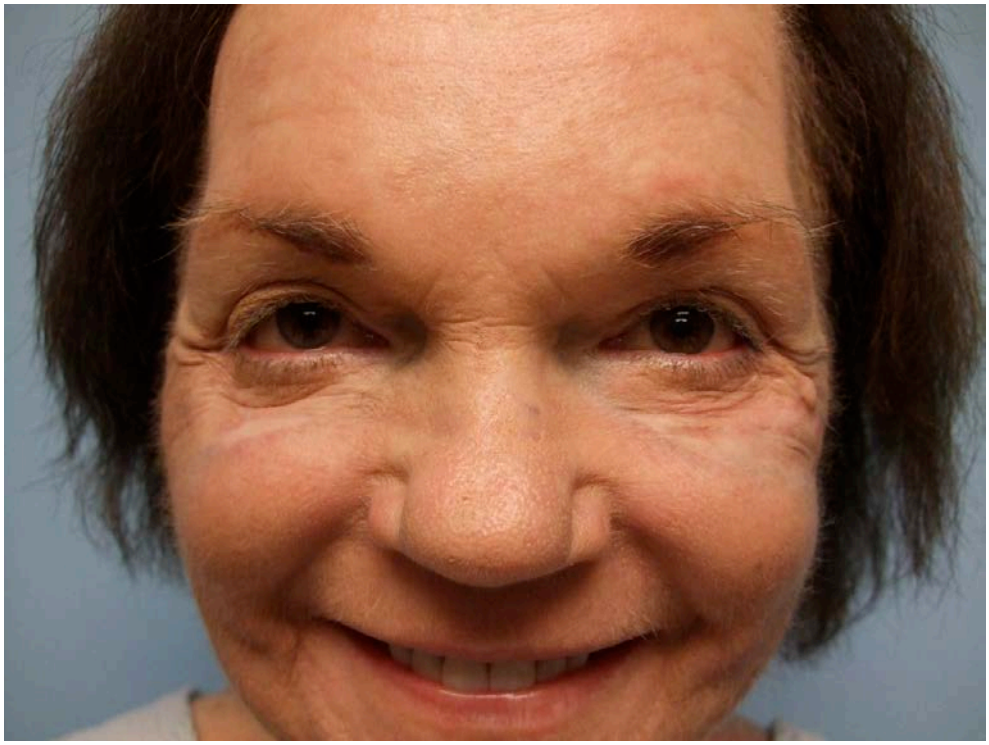

Figure 2. There is sustained improvement of the discolored areas beneath the patient's eyes (between her eyelashes and cheek discoloration) after two additional surgical procedures (excision and skin grafting). However, residual purple hyperpigmentation is still noted bilaterally on the lateral malar cheeks. Imatinib treatment was discontinued one week prior to each surgery and reinstated on the eighth postoperative day.

Discussion

Therapeutic effects of imatinib were initially observed in chronic myelogenous leukemia secondary to effects on Bcr-Abl protein [2]. Clinical studies subsequently found imatinib to be an effective inhibitor of ABL-related gene protein, Kit and platelet derived growth factor receptor kinases [2]. In addition to therapy for chronic myelogenous leukemia, imatinib has demonstrated activity clinically against Kit-associated advanced gastrointestinal stromal tumors as well as platelet derived growth factor receptor-related dermatofibrosarcoma protuberans [3,4].

Frequently reported adverse side effects from imatinib include diarrhea, dyspepsia, edema, fatigue, myalgias, and mild to moderate nausea [4]. Several mucocutaneous adverse effects to imatinib have been reported (Table 1) [5,6]. Ocular side effects are common in chronic myelogenous leukemia patients undergoing therapy with imatinib. The most commonly reported side effect is periorbital edema, which has also been observed in gastrointestinal stromal tumors treated with this drug [7,8,9].

Table 1: Mucocutaneous side effects of imatinib

Mucocutaneous side effect	Reference
Benign tumors	
Hyaline cell syringoma	14
Malpighian epithelioma	14
Generalized eruptions	
Acute generalized exanthematous pustulosis	15
Stevens Johnson syndrome	16
Toxic epidermal necrolysis	17
Lichenoid eruptions	
Graft versus host-like eruption	14
Lichen planus	18
Oral lichenoid eruption	19

Miscellaneous conditions	
Follicular mucinosis	20
Gynecomastia	21
Herpes zoster	22
Hypopigmentation	23
Porphyria cutanea tarda (reactivation)	24
Malignant neoplasms	
Epstein BarrVirus-positive cutaneous B-cell lymphoproliferative disease	25
Squamous cell carcinoma	26
Neutrophilic dermatosis	
Neutrophilic eccrine hidradentitis	27
Sweet's syndrome (acute febrile neutrophilic dermatosis)	28
Vasculitis (purpura)	14
Ocular conditions	
Blepharoconjunctivits	9
Edema (periorbital)	9
Epiphora	9
Glaucoma/increased ocular pressure	9
Photosensitivity	9
Ptosis	9
Purpura (postoperative periorbital)	11
Retinal hemorrhage	9
Vision abnormality	9
Papulosquamous conditions	
Erythema nodosum	14
Panniculitis	29
Pityriasiform eruption	30
Pityriasis rosea	31
Psoriasis vulgaris	14

Epiphora is the second most commonly reported ocular adverse effect in chronic myelogenous leukemia patients [10]. Other less frequently associated side effects include abnormal vision, blepharoconjunctivitis, and ptosis [9]. Rarely, increased intraocular pressure, photosensitivity, and retinal hemorrhage have been observed [9].

Imatinib-induced postoperative periocular purpura occurred in a woman with chronic myelogenous leukemia after four years of treatment. In addition to our patient, this unusual adverse effect was also observed in another individual receiving treatment with imatinib: a 70-year-old man (Table 2) [11]. Both of these patients had chronic myelogenous leukemia. Each patient experienced drug-associated periorbital edema and visual field defects. However, neither developed an ectropion. Our patient's imatinib dosage was 400 mg daily, whereas the other patient had been treated at a higher daily dose of 600 mg.

The investigators who reported the imatinib-induced postoperative periorbital purpura in the 70-year-old man interpreted his appearance as having "returned to normal" as reflected by their description of his face 17 months postoperatively. However, careful inspection of a published follow-up photograph shows a bluish purple tinge of his lower eyelids [11]. Our patient's purpura did not resolve spontaneously, but after two additional surgeries she achieved partial improvement and considered the results to be cosmetically acceptable.

Table 2: Characteristics of patients with imatinib-induced postoperative periorbital purpura [a]

C	Age Race Sex	HM	PE	Ect	VFD	Imatinib: dose, duration	Tx	Comment	Ref
1	59y Ca W	CML	+	-	+	400 mg, 4y	2 additional surgeries	Residual purple	CR
2	70 Ca M	CML	+	-	+	600 mg, NS	Observation	Residual blue tinge at 17 months	11

[a] Abbreviation: +=present, - =absent, C=case, Ca=Caucasian, CML=chronic myelogenous leukemia, CR=current report, Ect=ectropion, HM=hematologic malignancy, M=man, NS=not shared, PE=periorbital edema, Tx=treatment, Ref=reference, VFD=visual field defect, W=woman, y=years

The pathogenesis of imatinib-induced postoperative periocular purpura remains to be elucidated. The extensive postoperative bleeding in the 70-year-old man was attributed, by his physicians, to leukemia-associated thrombocytopenia [11]. Indeed, imatinib-induced thrombocytopenia has also been observed in another chronic myelogenous leukemia patient [12]. Interestingly, not only first but also second generation tyrosine kinase inhibitors have recently been associated with severe thrombocytopenia [12]. Our patient's platelet counts were normal.

Our patient also experienced severe hemorrhage postoperatively in spite of her normal platelet counts. Hence, we speculate that her imatinib-related postoperative bleeding episode was not mediated by insufficient platelets. Nevertheless, we cannot exclude the possibility of a drug-induced abnormality of platelet function.

Table 3: Mechanism of action of common treatments that prolong bleeding [a]

Treatment	Mechanism of action	SG	Reference
Aspirin	Acetylates cyclooxygenase causing irreversible inhibition of arachidonic acid production	7-10; 1	[35]
Coumadin	Inhibits clotting factors II, VII, IX and X	5; 1	[35]
Fragmin	Inhibition of coagulation factor Xa and thrombin (factor IIa) by binding to antithrombin III	1; 1	[35]
Heparin	Increases rate of thrombin – antithrombin reaction; causes inhibition of factors IXa and Xa	1; 1-3	[36]
NSAIDs	Reversible blockade of platelet cyclo-oxygenase affecting platelet thromboxane A2 activity	1; 1	[35]

[a] Abbreviations: NSAID=Non-steroidal antiflammatory drugs, SG=Surgical Guidelines(number of days discontinued prior to surgery;when therapy can be reinstated after surgery)

We hypothesize that imatinib may affect either platelets or clotting factors, resulting in prolonged bleeding. Other medications that can affect coagulation are presented in Table 3. The duration of time required for correction of medication-induced abnormalities range from 1-7 days depending on the drug. Therefore, we recommended discontinuation of imatinib for one week prior to our patient's subsequent surgeries and for the drug to be held until the eighth postoperative day before restarting treatment.

Imatinib-associated periorbital edema is typically mild to moderate in severity. Several management interventions, of variable success, have been described: low salt diet, elevating the head of the bed, decreasing fluid intake, oral diuretics, and topical corticosteroids [11,13]. In addition to the two aforementioned patients with imatinib-induced postoperative periocular purpura, we are only aware of one additional patient whose drug-induced periorbital edema was surgically excised without any adverse sequella [7]. Because it is impossible to predict whether adverse effects will happen and in which patients they will occur, we conservatively recommend that imatinib be held one week prior to and one week after surgery. Based on these recommendations, our patient did not experience bleeding during her subsequent periocular surgeries.

Conclusion

Imatinib mesylate is a selective tyrosine kinase inhibitor used in the treatment of chronic myelogenous leukemia. Periorbital edema is one of the possible side effects experienced by patients undergoing imatinib treatment. Owing to the severity of the edema, three patients have undergone surgery to reduce the imatinib-induced swelling; two of these individuals have developed imatinib-induced postoperative periorbital purpura. We hypothesize that imatinib may affect either platelets or clotting factors, resulting in prolonged bleeding. In comparing imatinib with other drugs that affect bleeding, we found that the duration of time required for correction of medication-induced abnormalities ranges from 1-7 days. Therefore, we recommended discontinuation of imatinib for one week prior to our patient's subsequent surgeries and for the drug to be held until the eighth postoperative day before restarting treatment. Also, based on the dramatic clinical presentation of imatinib-induced postoperative periorbital purpura, we suggest GASP an appropriate eponym for this drug-associated adverse event: Gleevec-Associated Surgical Purpura.

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