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Generalized hypopigmentation due to imatinib: A fairness boon?

Sir,

Imatinib (STI571, Glivec©) is a new selective tyrosine kinase inhibitor that is very useful in the treatment of chronic myelogenous leukemia (CML) and gastrointestinal stromal tumors (GIST). More side effects are being reported with its increasing use. We report generalized hypopigmentation with the use of this drug.

The majority of CML and GIST patients on imatinib mesylate experience some undesirable side effects that involve many organ systems in the body, including the skin. The most common dermatological side effects are periorbital edema and dermatitis. Facial edema, pruritus, erythema, dry skin, alopecia, night sweats and photosensitivity reaction are infrequently reported.[1]

Over 120 patients of CML or GIST are being treated with imatinib at our institute since 2001. For the last one year, during routine outdoor visits, many patients have been reporting that their skin was becoming fairer while on imatinib. We interviewed 26 patients regarding this side effect; 22 of the patients and their relatives confirmed this experience at varying durations of treatment (median 2 months; range 2 to 8 months). Three patients in whom the drug had to be discontinued because of different reasons reported that their skin complexion had reverted to the original one.

Skin biopsies were performed on seven of these 'fair' patients. On H and E staining, even though melanin pigment was seen in all of these biopsy specimens, low melanin content was observed in two of them. In the absence of a pretreatment biopsy, quantification of the melanin pigmentation was not possible. Currently, we are doing electron microscopy and tyramine based tyrosinase assay on the skin biopsies performed pre- and post-imatinib treatment for quantification of the melanin deposition in melanosomes.

The exact mechanism for this generalized hypopigmentation with imatinib is not known. Apart from inhibiting a tyrosine kinase, the BCR-ABL oncoprotein, imatinib also inhibits platelet-derived growth factor receptors (PDGFRs) and c-KIT receptor tyrosine kinases.[2] The latter two kinases have important roles in normal pigmentation.[3] Certain hypopigmentary disorders like piebaldism and vitiligo are associated with mutations in the c-KIT gene causing alteration in the respective tyrosine kinases.[4] Tsao et al recently reported a similar finding.[5] However, we found hypopigmentation to be much more common than they did, possibly because it is more apparent in Blacks or Indians because of their otherwise dark skin complexion. Based on our observation, we hypothesize that inhibition of melanocyte c-KIT receptor tyrosine kinase by imatinib leads to generalized hypopigmentation. The long-term implications of this observation need to be studied. Meanwhile, it will be interesting to see whether topical use of imatinib is possible in the future.

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Amiodarone-induced angioedema: Report of two cases

Sir,

Amiodarone, a class II long-acting anti-arrhythmic, capable of blocking both α and β -adrenoceptors is an iodine-containing highly lipophilic benzofuran derivative.[1,2] Adverse reactions are common and are duration-dependent. Frequent reactions include nausea and other GI symptoms. Ten percent of patients may develop photosensitization (possibly due to phototoxicity) and bluish skin pigmentation, but allergic skin reactions are rare.[3-6] The most serious side-effect related to amiodarone is pulmonary alveolitis and fibrosis.[4] Only a single case of amiodarone-induced angioedema has been reported in the literature.[2] We came across two unrelated cases of angioedema triggered by the use of amiodarone in the last couple of years.

A 65-year-old lady was admitted with pericardial effusion and after a positive pericardial tap antitubercular drugs (ATD) were started (isoniazid 300 mg, rifampin 600 mg, ethambutol 800 mg and pyrazinamide1500 mg). She developed atrial fibrillation and an alteration in the ventricular rate. She was put on amiodarone 800 mg twice daily for 15 days and then the dose was tapered to once daily. Facial angioedema appeared within a couple of weeks and she complained of anorexia. Chest roentgenogram was done and was non-contributory. Laboratory evaluation was normal (blood analysis and serum chemistry, stool examination for parasites, IgE, thyroid tests (T3, T4 and TSH), and urinalysis). Liver function tests yielded a mild rise in liver enzymes like ALT, AST and serum alkaline phosphatase; which were 93, 97 and 371 respectively. She was anicteric. Fundoscopy was normal. Symptoms of angioedema were unrelated to any physical activity, stress or ingestion of any particular food. She was not an atopic and had no clinical history of nasal polyps, chronic rhinitis, sinusitis, asthma or chronic and chronically relapsing dermatitis. After another four weeks ATD were stopped. Then they were again started one by one. No improvement was noticed. Angioedema persisted. All medicines were stopped and she was put on prednisolone in a reducing dosage. Within another four weeks that was also completely tapered off. She improved dramatically and was completely symptom-free within 10 days. ATD were started again. No angioedema was noticed then but it appeared within a day when she was given a single dose (400 mg) of oral amiodarone. Again this symptom improved when amiodarone was taken off. Now she is without any symptoms since the last two years.

The second patient was a 73-year-old woman with a history of recurrent episodic facial swelling since one year. This was treated with oral steroids, resulting in clinical improvement. However, facial swelling reappeared after discontinuation of the steroids for which steroids were continued for a year. She presented to our clinic with typical cushingoid habitus. A complete clinical history was taken, and she was carefully questioned about past history and recent symptoms. Symptoms of angioedema were found to be unrelated to any food ingestion, activity, or stress. She had no clinical history of nasal polyps, chronic rhinitis, sinusitis, or asthma. It was found that she was taking oral corticosteroids and amiodarone 200 mg/day. This last drug had been started by a general practitioner 3 years back for cardiac rhythm abnormalities and had never been discontinued. Her chest radiograph was normal and all the laboratory tests (including blood analysis and serum chemistry, stool examination for parasites, IgE, thyroid profile and urinalysis) were within range except mild hyperglycemia and low ACTH level. Suprarenal glands were normal. A diagnosis of iatrogenic Cushing's syndrome was made. Complete physical examination, ECG and echocardiography were non-contributory. Skin patch tests with common allergens were done and found to be negative. In view of the patient's previous history, the diagnosis of amiodarone-induced angioedema was considered. Amiodarone was discontinued, and the symptoms disappeared with the reduction of steroids, which were finally discontinued. In order to confirm that amiodarone was the cause of the patient's reaction, a double-blind oral challenge with amiodarone was undertaken. Within 30 min of receiving the dose (200 mg), she began to experience facial flush and facial