Disappearance of Lentigines in a Patient Receiving Imatinib Treatment for Familial Gastrointestinal Stromal Tumor Syndrome

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Background: Gastrointestinal stromal tumors (GISTs) harbor gain-of-function mutations of the c-kit tyrosine kinase receptor. Imatinib mesylate is an inhibitor of c-kit and is indicated in the treatment of chronic myeloid leukemia and GISTs. Reported adverse effects of imatinib include hypopigmentation, depigmentation, and hyperpigmentation. Although the exact mechanism by which these occur is unclear, it is likely that inhibition of c-kit leads to downstream inhibition of the tyrosinase gene promoter and thus to inhibition of pigment production.

Observations: A 45-year-old woman with a history of multiple dysplastic nevi and lentigines was diagnosed as having familial GIST syndrome. Treatment with imatinib mesylate was started in an attempt to decrease the tumor load. Three months after treatment initiation, the patient noted a decrease in the number of pigmented lesions, lightening of the skin in her genital area, and graying of her terminal hair.

Conclusions: The potential association between a specific genetic mutation and pigmentation changes secondary to imatinib therapy may account for the variety in presentation of this potential side effect. Further genetic studies paired with melanocyte-specific or c-kit–specific stains of affected tissue are warranted to better understand the relationship between the genetic mutation and the effect of imatinib on pigmentation.


Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract and originate from the interstitial cells of Cajal. Interstitial cells of Cajal are part of the autonomic nervous system found in the wall of the gastrointestinal tract and are the “pacemakers” of the human digestive tract. Symptoms of GISTs include abdominal discomfort, pain, and bleeding into the gastrointestinal tract that can manifest as melena and anemia. The patient described herein has been documented to have familial GIST syndrome, an extremely rare autosomal dominant condition that predisposes the patient to developing GISTs throughout her lifetime. With only 24 families reported to date, patients who carry the mutation in familial GIST syndrome have a greater than 90% lifetime risk of developing 1 or more GISTs. Despite the tendency for multiple tumors to develop in the gastrointestinal tract, patients with familial GIST syndrome may have less of a tendency for metastasis, and the clinical course has been described as relatively indolent. Some cases of familial GIST syndrome exhibit anticipation, meaning that the syndrome manifests earlier with each consecutive generation.

Most GISTs—both sporadic and familial types—harbor gain-of-function mutations of the c-kit tyrosine kinase receptor. Those who do not harbor this mutation have a mutated PDGF receptor alpha (PDGFRα) gene or an unknown mutation. Both c-kit (location 4q12; OMIM *164920) and PDGFRα (location 4q12; OMIM *173490) are tyrosine kinase receptors for growth factors that are activated in normal tissues. C-kit and its ligand stem cell factor (SCF) regulate the development and survival of melanocytes, interstitial cells of Cajal, and many other types of cells. The c-kit mutation in exon 11 causes most GISTs because it promotes continued activation of the receptor, which can lead to an increased cellular proliferation, decreased apoptosis, and ultimately neoplasia.

It is currently believed that c-kit and its ligand SCF regulate the development and survival of melanocytes. Through a series of kinase activation and phosphorylation reactions, the combination of c-kit...
and its ligand SCF activates the tyrosinase gene promoter and thus initiates pigment production. Specific hypopigmentary disorders, such as vitiligo and piebaldism, have been known to be associated with c-kit mutations. One patient reported that her vitiligo became more extensive after being treated for chronic myeloid leukemia with the c-kit inhibitor imatinib. This association suggests that altering the function of c-kit may be responsible for impaired pigment production.

**REPORT OF A CASE**

A 45-year-old woman with a history of multiple dysplastic nevi and lentigines presented to the dermatology clinic at Rush University Medical Center in 2001 for a full skin examination. On physical examination she was found to have medium brown flat macules that were too numerous to count and that were generalized to the entire cutaneous surface with involvement of the palms and soles (Figure 1 and Figure 2). Also of significance was a diffuse darkening of her labia minora pudendi. There was no oral or anal pigmentation. Since then, she has been followed up by photographic surveillance every 6 months for dysplastic nevi.

In November 2005, the patient had a 6.2-cm mass removed from her colon and was diagnosed as having a GIST. Regional lymph node biopsy specimens taken at the time of surgery were negative for malignancy. Two months after the tumor resection, she underwent endoscopic ultrasonography and endoscopy and was found to have 3 additional small gastric tumors consistent with GIST. Because of a family history significant for GIST in her mother and multiple intestinal "sarcomas" in her maternal grandmother, genetic studies were performed and confirmed a c-kit mutation on exon 11. She was subsequently diagnosed as having familial GIST syndrome.

In February 2006, the patient started treatment with imatinib mesylate (Gleevec; Novartis Pharmaceuticals Corp, East Hanover, New Jersey), 400 mg/d, in an attempt to decrease the tumor load. Three months after treatment initiation, the patient noticed a decrease in the number of pigmented lesions on both palms (Figure 3), lightening of the skin in her genital area, and graying of her pubic hair, eyebrows, and scalp hair. She also experienced some nausea, weight loss, and periorbital edema. Physical examination results showed a decreased number of brown macules on her trunk (Figure 4). Her palms, soles, and face had very few pigmented lesions, and there was diffuse lightening of her labia minora pudendi.

Biopsy specimens were taken from her right deltoid and right lower back, where lentigines had been previously. Hematoxylin-eosin and Melan-A immunohistochemical staining of both specimens showed underactive melanocytes at the basal layer (Figures 5), which were identified with the help of a dermatopathologist. Fontana-Masson staining revealed only subtle focal melanin pigmentation (Figure 6). Unfortunately, Melan-A and hematoxylin-eosin cannot stain the activity of melanocytes. Immunostaining with anti–TRP-1 (antityrosinase antibodies) would have been more informative; however, that stain was unavailable.

For the first 2 years after her diagnosis, the patient underwent computed tomography every 3 months, endoscopic ultrasonography every 4 months, positron emission tomography every 6 months, and colonoscopy every 8 months. At her last follow-up visit, the patient reported continuing treatment at the Dana-Farber/Brigham and Women’s Cancer Center in Boston, Massachusetts, where she receives counseling, monitoring, and treatment and is involved in clinical trials for famil-
GIST syndrome. The patient seemed to be doing very well with imatinib therapy and stated that the graying of her terminal hair, the lightening of the skin in her genital area, and the decrease in the number of pigmented lesions had stabilized. The patient had no evidence of new GIST foci or metastasis.

**COMMENT**

Imatinib is one of the treatments currently available for GISTs. Imatinib is a tyrosine kinase inhibitor that inhibits bcr-abl tyrosine kinase (the constitutive abnormal tyrosine kinases encoded by the Philadelphia chromosome abnormality in chronic myeloid leukemia). In addition to bcr-abl, imatinib has inhibitory effects on the PDGF receptor and c-kit. In familial GIST syndrome, imatinib induces apoptosis, and imatinib is currently indicated for the treatment of c-kit–positive GISTs that cannot be removed surgically and/or have spread to other parts of the body. Although the effectiveness of imatinib in the treatment of GISTs has yet to be defined, our interest in this drug lies in its potential role to induce pigment changes.

As stated herein, imatinib has been shown to have inhibitory effects on c-kit, the receptor believed to play a regulatory role in melanocyte development and survival. In vitro studies have shown that the number of melanocytes with high tyrosinase activity (an indication of high pigment production activity) decreases after treatment with imatinib. Parallel in vitro studies of fibroblasts have shown a 50% decrease in melanocyte proliferation after treatment with imatinib. Because fibroblasts secrete SCF, it is thus thought that imatinib may...
inhibit pigment production through direct inhibition of c-kit–mediated gene activation and indirect inhibition of SCF production.\textsuperscript{11} 

There have been many reports of patients developing pigmentedary abnormalities after imatinib therapy. Specifically, patients have experienced localized, patchy, or diffuse hypopigmentation and depigmentation\textsuperscript{12} that appears to be dose dependent and generally reversible on discontinuation of therapy.\textsuperscript{13,14} Although less common, patchy hyperpigmentation has also been reported secondary to treatment with imatinib.\textsuperscript{15,16} However, not all patients experience pigmentedary changes in response to imatinib, and not all experience it to the same degree. The effect of imatinib on cellular response may be specific to the c-kit mutation in the individual. In a study of patients with c-kit–positive melanocytic tumors, it was found that mere expression of c-kit does not make a tumor susceptible to imatinib.\textsuperscript{17} However, in a study of 126 patients with GISTs, in vitro response rates and clinical outcomes after imatinib treatment were different, and this difference was based solely on the type of c-kit mutation present. Specifically, patients with activating mutations of c-kit on exon 11 showed increased in vitro and clinical response to imatinib compared with patients harboring different mutations.\textsuperscript{18}

Further genetic studies paired with melanocyte-specific or c-kit–specific stains of affected tissue would be beneficial to our understanding of the pathogenesis behind imatinib-induced pigment changes. Specifically, the dopa reaction would provide information as to the density and distribution of epidermal melanocytes, and the c-kit monoclonal antibody stain would help identify tissues that are c-kit positive.

Our patient is unique in that hypopigmentation specifically targeted her lentigines in addition to generalized hypopigmentation. Because little is known about familial GIST syndrome and imatinib’s role in this disease, the molecular basis for the disappearance of pigment remains elusive. One theory is that the lentigines are part of her familial GIST syndrome and therefore harbor the same mutation that makes both interstitial cells of Cajal and melanocytes susceptible to imatinib therapy via the c-kit pathway. Furthermore, it is possible that the diverse variation in pigmentedary response for those treated with imatinib can be explained by the presence of different c-kit mutations in different patients.

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