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Case Report Open Access

Blue Man: Melaninophagia Secondary to Imatinib

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Abstract

Gastrointestinal Stromal Tumors (GIST) is the most frequent sarcoma of the gastrointestinal tract. In metastatic disease or locally advanced (inoperable) imatinib is the standard therapy, even in situations where the patient has already received adjuvant treatment with the same drug and has not presented disease progression in that period. This case report exemplifies a rare adverse effect secondary to the use of imatinib. Most of the published reports describe a greater frequency of hypopigmentation of the skin, but the patient presented bluish hyperpigmentation of the oral mucosa and over extensive areas of the skin.

Keywords: Gastrointestinal Stromal Tumors (GIST); Imatinib; Hyperpigmentation

Introduction

Gastrointestinal Stromal Tumors (GIST) are rare mesenchymal malignancies whose incidence is approximately 1.5/100,000 people per year. However, it is important to emphasize that there are limitations to estimate the true incidence, because only recently it has been considered a distinct clinical-pathological disease [1,2]. The first description occurred in 1960 and until the 1990s it was classified as a smooth muscle tumor [3,4]. At the beginning of the 21st century, Tyrosine Kinase Inhibitors (TKI) was identified, generating knowledge about the tumor pathogenesis involving TKI and the Platelet-derived Growth Factor Alpha Receptor (PDGFRA) [5]. GIST corresponds to the most frequent sarcoma of the gastrointestinal tract (TGI), affecting the stomach more frequently (60%) followed by the small intestine (30%) [6]. Some conditions predispose the onset of this disease, such as Carney-Stratakis hereditary syndrome (GIST associated with Familial Paraganglioma), Carney's triad (GIST associated with pulmonary chondromas and extra-adrenal paragangliomas) and Neurofibromatosis type 1 [7-9]. Pathologically, the diagnosis of GIST is based on its morphological and immunohistochemical evaluation, the latter being positive for CD 117 and/or DOG1. A proportion of GIST, about 5%, are CD 117 negative [10,11]. Stromal tumors of TGI are known to be resistant to cytotoxic chemotherapies. In metastatic or locally advanced disease (inoperable), imatinib is the standard therapy, even in situations where the patient has already received adjuvant treatment with imatinib and has not presented disease progression in that period [12-15]. The mechanism of action of imatinib is related to the ability to inhibit BCR-ABL tyrosine kinase, a fusion protein created by an abnormality of the Philadelphia chromosome that characterizes chronic myeloid leukemia. Competitive inhibition by the ATP binding site of the enzyme leads to tyrosine phosphorylation inhibition of the proteins involved in the BCRL-ABL signal transduction [16]. This inhibition is not completely selective because imatinib also inhibits the platelet-derived growth factor receptor and c-KIT tyrosine kinase receptor [17]. Thus, with the use of this drug, cells expressing BCR-ABL inhibit their growth or their apoptosis, but normal cells are not affected. Treatment with imatinib is generally well tolerated and the frequency of severe adverse events is very low. Among the most common side effects are water retention, nausea and vomiting, diarrhea, muscle cramps and skin rash. Elevation of liver enzymes and myelosuppression may occur less frequently and there is resolution following discontinuation of therapy [18]. Hypopigmentation of the skin has often been described and its emergence during treatment with Imatinib seems to be a predictor of better response. On the other hand, there are rare reports of skin hyperpigmentation secondary to the use of this drug, and among them, the majority occurred in oral mucosa [19-21].

Case Report

A 64 years older male patient, retired, previously hypertensive, cardiopath (dilated cardiomyopathy), with neurofibromatosis, complained about syncope with a fall of his own height and rapid recovery of consciousness. In the moment of the medical consultation he referred about 4 episodes of syncope during the last 8 months. The assistant cardiologist began clinical investigation for pheochromocytoma and abdominal tomography showed a large liver injury. He was submitted to laparoscopic liver biopsy with intraoperative peritoneal implant findings. Biopsy showed Gastrointestinal Stromal Tumor (GIST) with positive immunohistochemistry for CD 117, CD34 and Protein DOG1. Staging exams showed lesions close to the duodenum measuring 25.0 × 10.6 × 22.0 cm. In addition to peritoneal dissemination, that was secondary hepatic lesions and masses in iliac fossa. With the diagnosis of high-risk small intestine GIST, clinical stage IV, the patient was referred to the Clinical Oncology team of the General Hospital of the Medical School of Ribeirão Preto of the University of São Paulo for specific treatment, and imatinib 400 mg/day was started. After 9 months with evidence of stable disease, the patient complained of darkening of some neurofibromas in the face, oral mucosa (Figure 1) and around the shoulder (Figure 2). The oncology team proposed the skin lesion biopsy. The result showed melaninophagy in the superficial dermis and the pathologist suggested that this hyperpigmentation was secondary to the use of imatinib (Figure 3). The biopsy result was discussed with

the patient and he agreed to keep on the treatment. As expected, there was a progressive increase in hyperpigmented areas.

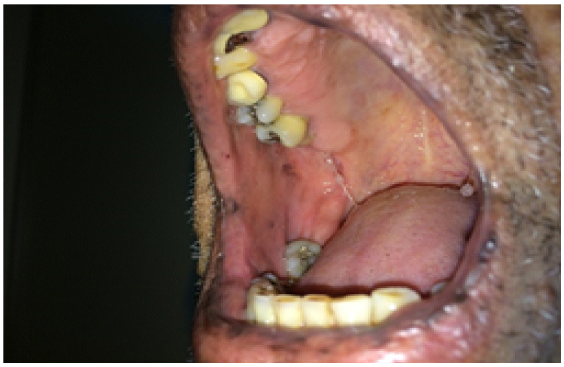

Figure 1: Hyperpigmentation in oral mucosa and libs.

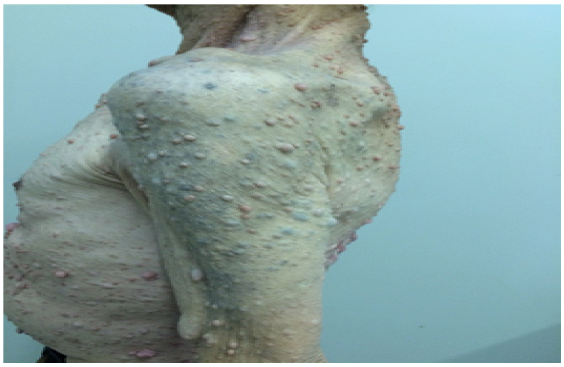

Figure 2: Bluish areas affecting upper limbs and trunk.

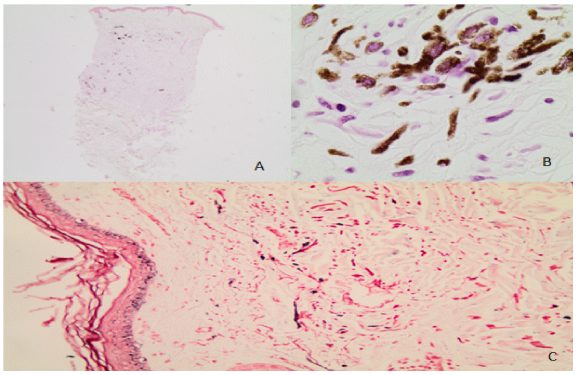

Figure 3: A: 20X H&E-showing melanin deposits; B: 1000X H&E-showing melanin deposits in neurofibromas cells; C: 200X Fontana-Masson-showing melanin inside of neurofibromas cells. Note the presence of melanin in a usual amount for the patient's phototype in the basal layer of the epidermis.

Discussion

The case report illustrates a rare adverse effect secondary to the use of imatinib. Most of the published reports describe a greater frequency of hypopigmentation of the skin, exactly the reverse of what happened with the patient in this article. One of the studies that demonstrated this benign collateral effect of cutaneous depigmentation, is the work published by Tsao et al. in which they describe 6 patients on treatment of chronic myelogenous leukemia with imatinib that developed hypopigmentation of the skin. In addition, all these patients had other toxicities: 5 developed myelosuppression, 4 had diarrhea, 4 reported muscular cramps, 3 reported nausea and vomiting, and 5 had periorbital edema. Some of them needed to suspend or reduce the dose of the medication due to gastrointestinal symptoms and myelosuppression and in 2 of these individuals, it was observed darkening of the skin during those times of interruption and/or reduction of the treatment [22].

After extensive review of the literature, we found 3 case reports that describe melaninophagy secondary to imatinib. The first one was published by Alexandrescu et al. on a male patient with a diagnosis of metastatic GIST, as well as our patient, who after 8 weeks of treatment developed erythema and generalized edema with extensive pruritic hyperpigmentation areas intense extremities, scapulae, trunk and neck [20].

The other 2 cases described, involved women diagnosed with CML. The first one was receiving Imatinib for at least 8 years and only after this long period was identified hyperchromia in palate and blue pigmentation in temporal region bilaterally [23]. The third case, published more recently, involves elderly patients who presented extensive brownish macules compromising the skin of the malar and frontal region and mandible. In this last report, the author highlighted the fact that the oral mucosa and palmar and plantar region were spared [24].

Although it does not represent a case report, two other patients developed hyperpigmentation of the skin in a study whose main objective was to identify factors that could be related to the response to treatment with Imatinib in patients diagnosed with LMC. Thus, there is no detailed description of this adverse effect in the two patients cited in the article [25].

Conclusion

The case report described a very rare adverse effect related to the use of imatinib; hyperpigmentation of the skin and, unlike the other clinical cases found in the literature, the cutaneous involvement was very extensive. There are not drugs that can be aid in the prevention and/or management of this adverse reaction, but discontinuation of the drug seems to lead to hyperpigmentation regression.

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