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Halo nevi related to treatment with imatinib in a dermatofibrosarcoma protuberans patient

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Imatinib mesylate is a selective inhibitor of PDGFbeta and Bcr- Abl oncogene, indicated in the treatment of chronic myelogenous leukaemia (CML), gastro-intestinal stromal tumours (GIST), gliomas and small cell carcinomas,1 but also of unresectable or relapsed dermatofibrosarcoma protuberans (DFSP).2 This rare fibrohistiocytic tumour shows frequently chromosomal abnormalities; in particular, the translocation leading to the fusion of the 17q22 and 22q13 results in the expression of a COLIA1-PDGFbeta protein, that is processed into mature PDGF and interacts with the PDGFbeta receptor exposed on the DFSP cell surface. Imatinib treatment is generally well-tolerated, with mild to moderate haematological and gastrointestinal toxicity. Oedema is a common drug-related reaction and cutaneous adverse effects such as dose-dependent rash, pruritus, maculopapular eruptions and exfoliative dermatitis have been recently described.3 Treatment related hypo- and hyper-pigmentation are infrequent and have been reported mainly in ethnically pigmented patients.3

Herein, we report our experience regarding the treatment with imatinib of a Caucasian male 46-year-old patient with multiple papulo-nodular lesions merging into a wide plaque at left groin. DFSP diagnosis was confirmed by histology and immunohistochemistry; surgical approach was excluded because of tumour extension and risk of unacceptable aesthetic defects without effective chances of cure. Imatinib mesylate was started at 400 mg⁄m2 daily; clinical improvement began after 3 weeks, with a significant reduction in thickness, infiltration and tumour size. Treatment was subjectively well-tolerated; blood counts, liver and renal function were in normal range. However, after 8 weeks, patient developed a facial oedema, mainly on the peri-ocular region. Furthermore, at the subsequent follow-up visit, we noted depigmentation areas around some nevi; at first this phenomenon was limited to the back, but in a few weeks, halo nevi developed diffusely (fig. 1); histology documented signs of regression, associated with infiltration by lymphocytes, occasional macrophages and neutrophils. Anamnesis excluded previous halo nevi, or vitiligo; thyroid hormone levels were in normal range and screening for autoimmune disease was negative. Imatinib was discontinued after 9 months, when tumour became surgically treatable. Oedema promptly resolved, whereas halo nevi persist at the time of writing, 3 months after suspension.

Some pigmentary changes during imatinib therapy have been recently described, consisting of hyperpigmentation of skin and hairs4 or localized repigmentation of vitiligo areas in a Chinese man affected by GIST.5 Localized or diffuse hypopigmentation was noted especially in ethnically pigmented CML patients.3,6 In Caucasian subjects, increased photosensibility3 and, in two cases, vitiligo-like lesions7 have been reported. To the best of our knowledge, this is the first case of halo nevi related to imatinib treatment described. Halo nevi represent the clinical result of a lymphohistiocytic inflammatory infiltrate against melanocytes, arising more frequently in children and young adults.

Imatinib can inhibit c-kit tyrosinase kinase function in melanocytes or reduce indirectly melanocytes proliferation decreasing melanogenic molecules secretion by cutaneous fibroblasts.8

Although, Alexeev et al. reported that constitutive signalling from the cKit receptor did not stimulate melanogenesis and proliferation, but significantly promoted migration of the melanocytes both in vitro and

in vivo; thus, activation of the cKit receptor tyrosine kinase may antagonize proliferation and melanogenesis.9
On the other hand, kit activation initiates a signalling cascade that results in the phosphorylation of microphthalmia-associated transcription factor and in a concomitant increase in its transcriptional activation activity.10 All these mechanisms can be implicated in STI-571 related skin depigmentation, even if it does not fully explain the onset of vitiligo or halo nevi in these patients.
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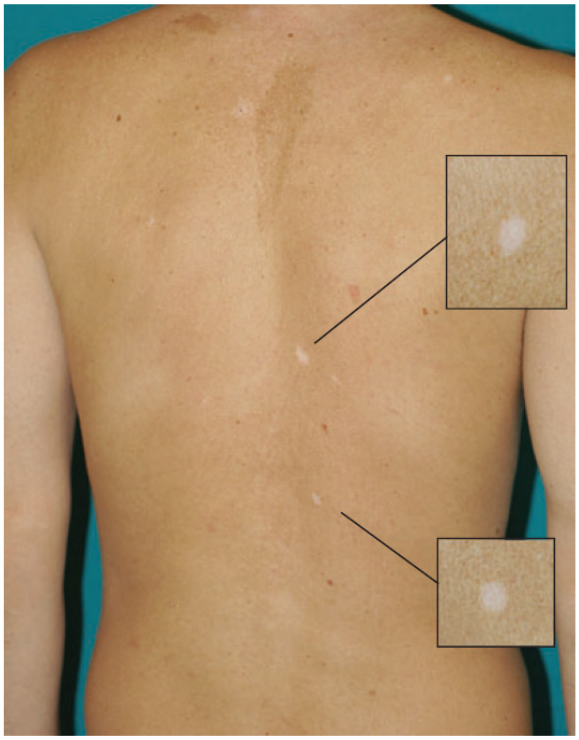

Figure 1 Halo nevi developed on the back of the patient during the treatment with imatinib mesylate.