To the Editor

5-fluorouracil, a fluorinated analogue of pyrimidine, is an antineoplastic drug used to treat tumors, especially those of the digestive tract.

Many cutaneous side effects have been described in association with this drug, including lesions similar to lupus erythematosus, outbreaks of seborrheic dermatitis, photosensitivity, folliculitis, palmar keratoderma, periungual ulceration, nail deformities (Beau lines), inflammation of actinic keratosis, palmar plantar erythrodysesthesia, and changes in pigmentation.1,2

We present the case of a patient with reticular and mottled hyperpigmentation associated with the systemic administration of 5-fluorouracil.

The patient was a 75-year-old man, with a history of high blood pressure and diabetes mellitus, diagnosed with stage III cecal carcinoma in February 2006. He underwent right hemicolectomy followed by neoadjuvant cycles of chemotherapy with 5-fluorouracil, oxaliplatin, and folinic acid. Following the fifth infusion, he reported the rapid appearance of asymptomatic pigmentation on his back and the palms of his hands. He reported no skin lesions prior to hyperpigmentation.

A physical examination revealed a brownish, macular, reticular hyperpigmentation in the lumbar region, mottled coloring on the palms of the hands, and hyperpigmentation in the lines on the hands (Figures 1 and 2).

A biopsy was taken of the reticular hyperpigmentation on the back. The histological study showed an epidermis with hyperkeratosis and increased basal pigmentation. A small amount of chronic inflammatory perivascular lymphocytic infiltrate was seen in the superficial dermis with occasional melanophages (Figure 3).

The patient continued to receive cycles of chemotherapy, with no observed increase in pigmentation, until completing the treatment after 11 infusions.

Five months after the last cycle of chemotherapy and 8 months after the appearance of the hyperpigmentation, no pigmentation was seen on the palms of the hands, and the reticular pigmentation still present on the back had decreased in intensity.

Hyperpigmentation of the skin is a side effect associated with various chemotherapy drugs including bleomycin, cyclophosphamide, etoposide, carboplatin, hydroxyurea, capecitabine, melphalan, and 5-fluorouracil.3,4 This hyperpigmentation can affect the skin, mucosa, and nails. Systemic administration of 5-fluorouracil has been associated with various patterns of pigmentation, most commonly in areas exposed to sunlight. Hyperpigmentation has also been described in irradiated areas, along with diffuse and mottled pigmentation on the hands and feet, melanonychia, and pigmentation of the oral mucosa.1-3,5

Less common cases of serpiginous supravenous hyperpigmentation have been reported, where pigmentation was seen in the skin overlying the veins through which the drug was injected.6,7

The reticular or serpiginous pattern has been associated with 5-fluorouracil only in exceptional cases.1,3,9 Although the clinical presentation suggests 5-fluorouracil-induced pigmentation in this case, the phenomenon may have other causes. A similar pattern was first described in association with bleomycin9 and later with idarubicin infusion.3

Our patient was being treated with 2 antineoplastic agents (oxaliplatin and 5-fluorouracil), and we attribute the reticular pigmentation to 5-fluorouracil on the basis of cases described previously.
in the literature, even though it is an exceptional side effect. However, an association with oxaliplatin cannot be ruled out, despite the absence of published case reports.

The cause of this drug-related hyperpigmentation is unknown, although there may be a mechanism common to all the cited chemotherapy drugs. These substances could increase pigmentation by means of melanocyte-stimulating hormone or by direct stimulation of melanocytes themselves. The reaction could also be provoked by higher concentrations of the drug in areas of skin experiencing greater blood flow.

This pigmentation is clinically reminiscent of erythema ab igne, which has been related to long-term exposure to heat below the burn threshold. Such exposure to heat would cause erythema followed by postinflammatory pigmentation with this cutaneous vascular pattern. In our patient, as in the cases described in the literature, the hyperpigmentation did not recur in later cycles, although the drug was maintained and the dosage remained unchanged. It is therefore possible that the patient presented hyperpigmentation due to local toxicity of the drug, resulting from increased blood flow to this location, as would occur, for example, with an increase in ambient temperature.

This would be interpreted as postinflammatory pigmentation of the overlying skin taking a cutaneous vascular pattern—similar to the supravenous hyperpigmentation described in association with 5-fluorouracil—due to subclinical phlebitis induced by the infusion or by localized hyperthermia.

We conclude that this case of reticular hyperpigmentation was an exceptional side effect of 5-fluorouracil, even though the same symptom has also been associated with the infusion of other antineoplastic agents. We suggest it was produced by a higher concentration of the drug in areas of skin that experienced greater blood flow. It occurred as an asymptomatic and persistent cutaneous reaction that did not require any modification of the prescribed oncological treatment.

References