

LETTERS TO THE EDITOR

5-Fluorouracil-Induced Reticular Hyperpigmentation

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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 supravenuous 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-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



Figure 1. Reticulate hyperpigmentation in the lumbar region.



Figure 2. Mottled hyperpigmentation on the palms and lines of the hands.

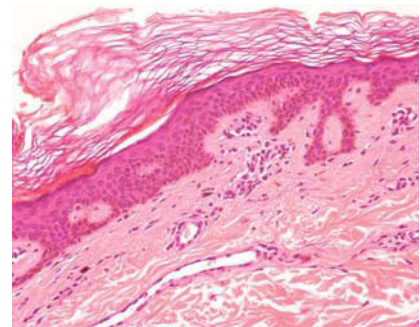


Figure 3. Epidermis with hyperkeratosis and increased basal pigmentation. A small amount of chronic inflammatory perivascular lymphocytic infiltrate was seen in the superficial dermis with occasional melanophages. (Hematoxylin-eosin, ×100).

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.⁵ The reaction could also be provoked by higher concentrations of the drug in areas of skin experiencing greater blood flow.⁹

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 supravenuous hyperpigmentation described in association with 5-fluorouracil—due to subclinical phlebitis induced by the infusion or by localized hyperthermia.^{6,7}

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

1. Vukelja SJ, Bonner MW, McCollough M, Cobb P, Gaule DA, Fanucchi P, et al. Unusual serpentine hyperpigmentation associated with 5-fluorouracil. *J Am Acad Dermatol.* 1991;25:905-8.
2. De Argila Fernández-Durán D, Rivera Díaz R, López Estebaranz L, Guerra Tapia A, Iglesias Díez L. Eritema acral inducido por 5-fluorouracilo en infusión continua. Presentación de un caso y revisión de la literatura. *Actas Dermosifiliogr.* 1993;84:315-8.
3. Jogi R, Garman M, Pielop J, Orenge I, Hsu S. Reticulate hyperpigmentation secondary to 5-fluorouracil and idarubicin. *J Drug Dermatol.* 2005;4: 652-6.
4. Vázquez-Bayo C, Rodríguez-Bujaldón AL, Jiménez-Puya R, Galán-Gutiérrez M, Moreno-Giménez JC. Hiperpigmentación secundaria a capecitabina. *Actas Dermosifiliogr.* 2007;98:491-3.
5. Fukushima S, Hatta N. Atypical moles in patient undergoing chemotherapy with oral 5-fluorouracil prodrug. *Br J Dermatol.* 2004;151:698-700.
6. Jain V, Bhandary S, Prasad GN, Sheno SD. Serpentine supravenuous streaks induced by 5-fluorouracil. *J Am Acad Dermatol.* 2005;53:529-30.
7. Chen GY, Lee JY, Chen WC. Sclerotic and retracted supravenuous hyperpigmentation associated with combination chemotherapy for metastatic breast carcinoma. *Br J Dermatol.* 2005;52:1383-5.
8. Allen B, Parker D, Wright AL. Reticulate pigmentation due to 5-fluorouracil. *Int J Dermatol.* 1995;34: 219-20.
9. Wright AL, Bleeche SS, Campion AE. Reticulate pigmentation due to bleomycin: light- and electron-microscopic studies. *Dermatologica.* 1990; 180:255-7.

Imported Donovanosis in an Adolescent Girl

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To the Editor

Donovanosis or granuloma inguinale is a granulomatous, progressive, ulcerative bacterial infection caused by *Calymmatobacterium granulomatis*.

This infection is rare in children or adolescents.^{1,2} However, we present the case of a 12 year-old girl seen at our hospital, after referral from the Tangiers Hospital, Morocco, with an ulcerative

genital lesion that had been present for 1 year, diagnosed as squamous cell carcinoma. The patient had been raped by a family member some months before the lesions appeared. Examination