CASE REPORT

5-Fluorouracil-induced bilateral persistent serpentine supravenuous hyperpigmented eruption, bilateral mottling of palms and diffuse hyperpigmentation of soles

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SUMMARY

A 42-year-old woman being treated with 5-fluorouracil for carcinoma of the sigmoid colon developed persistent serpentine supravenuous hyperpigmented eruption (PSSHE), bilateral mottling of the palms and diffuse hyperpigmentation of the soles. To the best of our knowledge, such a combination of findings has not been reported earlier. Recognition and knowledge of this side effect are important as the dose of the drug need not be altered nor is there a need to replace the drug on worries about a serious adverse effect. However, changing the peripheral venous route to the central line can be useful in management of PSSHE.

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CASE PRESENTATION

A 42-year-old woman with carcinoma of the sigmoid colon was being treated with a FOLFOX-6 regimen consisting of oxaliplatin, folinic acid and 5-fluorouracil (5-FU) through the peripheral venous route. She presented on the 10th day after the second treatment cycle with a serpentine arbourising eruption over her left forearm acquired after the first treatment cycle and a similar but smaller lesion on her right forearm after the second treatment cycle. The lesions appeared to follow the course of upper limb veins. There was mild itching without systemic symptoms. The patient had given a history of the lesions having started on the second day of chemotherapy; they were in both arms as erythematous seriginous eruptions associated with intense itching and subsided in a span of 10–14 days, evolving into hyperpigmented streaks with mild scaling, without any treatment. Examination revealed linear branched hyperpigmented, serpentine skin plaque approximately 1–1.5 cm in diameter along the superficial venous network of both forearms (L>R) with lesions in the left upper limb extending from the wrist to the antecubital fossa (figure 1A). The recently involved right forearm showed some erythema along the linear plaque while the left arm had hyperpigmented plaque only. The right forearm lesion also showed two flaccid bullae with the larger measuring 2 cm in diameter approximately at the site of insertion of the venous catheter. On tying a

BACKGROUND

5-Fluorouracil (5-FU) is a cytotoxic agent used alone or in combination to treat a variety of malignant disorders. Hyperpigmentation is a rare side effect occurring with 5-FU infusions; it has been reported in 2–5% of patients.¹ Various types of pigmentary abnormalities have been reported with 5-FU use such as diffuse hyperpigmentation of the face and palms, macular pigmentary changes on the palms and soles, hyperpigmentation overlying the superficial venous network also called serpentine supravenuous hyperpigmentation (SSH) and persistent supravenuous erythematous eruptions (PSEE).^{2–4}

We report a case of a 42-year-old woman being treated with 5-FU for carcinoma of the sigmoid colon who developed serpentine supravenuous erythematous eruptions, bilateral mottling of the palms and diffuse hyperpigmentation of the soles. To the best of our knowledge, such a combination of findings has not been reported earlier. Recognition and knowledge of this side effect are

Figure 1 (A) Both forearms showing serpentine supravenuous hyperpigmentation. Right forearm plaque showing erythema and bullae at the site of venous catheter. (B) Both palms showing hyperpigmented macules. (C) Both soles showing diffuse hyperpigmentation.

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tourniquet the pigmentation was seen to follow the superficial venous network on both the forearms. No thrombophlebitis was seen and the veins were patent.

Both palms showed multiple brownish macules, which were non-scaly and non-tender (figure 1B). Both the soles showed diffuse hyperpigmentation (figure 1C). There were no other mucocutaneous lesions or regional lymphadenopathy. The patient had received a total cumulative dose of 8.6 g of 5-FU at the time of presentation.

Her blood counts and biochemical tests were normal. Biopsy of one of the lesions was performed on day 4 of the patient presentation. Histopathological examination revealed sparse superficial perivascular infiltrate predominantly of melanophages with a few lymphocytes. There was slight flattening of rete ridges and the papillary dermis showed mild fibroplasia (figure 2).

INVESTIGATIONS

Skin biopsy.

DIFFERENTIAL DIAGNOSIS

- ▶ Thrombophlebitis
- ▶ Linear lichen planus

TREATMENT

The peripheral venous route was changed to a central venous route for drug infusion.

Topical application of 4% hydroquinone and clobetasol propionate 0.05% was administered.

OUTCOME AND FOLLOW-UP

The patient was regularly followed every month. 5-FU in the same dose was continued through the central port every 21 days. There was significant decrease in hyperpigmentation at the end of fourth month (figure 3).

DISCUSSION

5-FU is an antimetabolite chemotherapeutic agent that acts as a pyrimidine analogue and causes impaired DNA replication.⁵ 5-FU is the most common drug reported to cause pigmentary abnormalities such as persistent serpentine supravenuous hyperpigmentation (PSSH),¹ PSEE, diffuse palmar, facial pigmentation, transverse pigmented bands over the interphalangeal joints, and pigmented macules of the palms, soles, nails and oral mucosa.²⁻⁴

Figure 2 Biopsy showing superficial perivascular infiltrate of melanophages and a few lymphocytes.

Figure 3 Follow-up image at 4 months showing significant resolution of supravenuous hyperpigmentation.

PSSH presents as asymptomatic linear or serpentine hyperpigmentation along the superficial venous network following injection of chemotherapeutic agents.² PSEE is characterised by linear or serpentine erythematous streaks or red-to-violaceous plaques in the vicinity of injection sites or following the superficial venous network. The lesions develop between 24 h and 15 days after intravenous drug infusion and subside after 1–3 weeks after leaving residual hyperpigmentation.³ Rarely, vesicles and bullae have been reported, as in our patient.⁶ They have also been reported in locations other than in the vicinity of infusion sites.⁷ The presence of an initial erythematous inflammatory phase differentiates PSEE from PSSH. Persistent serpentine supravenuous hyperpigmented eruption (PSSHE) is a more encompassing term to describe the hyperpigmented streaks that follow the superficial venous network in a linear or serpentine pattern. It may or may not be preceded by erythema.^{4, 8}

Our patient showed a combination of serpentine supravenuous hyperpigmented eruptions in both forearms, mottling of palms and diffuse hyperpigmentation of soles. The left forearm vein was used for the first cycle of chemotherapy and had developed erythematous eruptions immediately after infusion; in the second cycle, the patient's right forearm vein was chosen for the infusion because of the earlier skin reaction. Since the patient presented to us on the 10th day after second chemotherapy the lesions on the left forearm had already become hyperpigmented. Some erythema was seen along the right side but the majority of the supravenuous streaking was hyperpigmented. Although the different findings seen in our patient have been reported in isolation, a combination of such findings has probably not been reported within an individual case. Another rare finding in our case is the presence of bullae at the infusion site in a case of PSSHE.

Numerous chemotherapeutic agents causing PSSHE include 5-FU, docetaxel, broxuridine, fotemustine, vinorelbine and some combinations of actinomycin, methotrexate, daunorubicin, 6 mercaptopurine, cyclophosphamide, bleomycin, vinblastine, dacarbazine, vincristine and prednisone.²⁻⁹

The mechanism of the serpentine supravenuous hyperpigmented eruption is because of loss of endothelial integrity of the blood vessels due to 5-FU causing leakage of the drug into the epidermis, thereby damaging the packing of melanosomes within the keratinocytes.² There is literature to suggest that adequate venous washing may mitigate or prevent the PSSHE by reducing the toxic load in the veins.⁸ Cytotoxic damage and

hypersensitivity reaction have both been proposed to cause pigmentary changes.³ Hypersensitivity reaction may explain the hyperpigmentation, which does not follow the superficial venous network, in the palms and soles in our patient.

Learning points

- ▶ Physicians must learn to recognise this rare side effect of this commonly used chemotherapeutic agent.
- ▶ No alteration in drug dose or type is required to alleviate this side effect.
- ▶ Change from the peripheral to central venous line is required to protect the skin from damage.
- ▶ Sufficient venous washing after instillation of the chemotherapeutic agent may prevent persistent serpentine supravenuous hyperpigmented eruption even when using the peripheral venous route.

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Competing interests None.

Patient consent Obtained.

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