

Serpentine Supravenous Hyperpigmentation Following Cisplatin and Pemetrexed Chemotherapy

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PRACTICE POINTS

- A variety of dermatologic complications have been reported with cisplatin chemotherapy, including serpentine supravenous hyperpigmentation (SSH); however, pemetrexed has not been associated with SSH.
- Although discontinuing the offending agent would certainly prevent further development, due to the benign nature of the reaction, modifying therapy based on cutaneous findings alone is not recommended.

To the Editor:

Serpentine supravenous hyperpigmentation (SSH) is a rare phenomenon characterized by linear hyperpigmentation of the skin overlying veins secondary to intravenous antineoplastic therapy. The term was first suggested by Hrushesky¹ in 1976 as an uncommon side effect of administering intravenous 5-fluorouracil (5-FU). Although 5-FU is the most frequent offending agent, cases involving treatment with actinomycin, cyclophosphamide, docetaxel, fotemustine, nitrogen mustard, nitrosoureas, taxanes, and triazine, as well as various combinations of chemotherapeutic agents, also have been observed.^{2,3} We present the case of SSH following a cisplatin and pemetrexed chemotherapy regimen.

A 52-year-old man with newly diagnosed inoperable adenocarcinoma in the left upper lung lobe received 2 cycles of treatment with cisplatin 138 mg and pemetrexed 920 mg 21 days apart. The

first cycle of chemotherapy was delivered intravenously through the left forearm and the second cycle through the right forearm. Each infusion was followed by a 20-cc 0.9% saline flush. The patient developed nausea, vomiting, diarrhea, and hyperpigmentation tracing the path of infusion on the right arm as well as a slight darkness on the left arm that were noted by medical staff. At that time, cisplatin was discontinued from the chemotherapeutic regimen.

A port-a-cath was inserted into the patient's right upper chest 4 weeks later and was used for subsequent infusions. Carboplatin 450 mg was initiated with pemetrexed thereafter. The patient was seen in the dermatology clinic 3 weeks after the insertion of the port-a-cath for evaluation of diffuse tinea versicolor of the trunk. Further examination of the arms revealed asymptomatic serpiginous hyperpigmentation overlying the superficial venous network tracing from the prior intravenous access points in the bilateral forearms to the upper arms (Figure). There was no evidence of extravasation or phlebitis prior to the hyperpigmentation. The patient was continued on pemetrexed and was subsequently lost to follow-up.

Cisplatin was the first member of the platinum-based chemotherapeutic agent class and is now one

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Serpentine supravascular hyperpigmentation of the superficial venous network in the bilateral forearms to the upper arms.

of the most potent and widely used in the treatment of solid malignancies. The cytotoxic mode of action is primarily mediated through interaction with DNA to form intrastrand cross-link adducts leading to aberrant mitosis and culminating in the activation of apoptosis. A variety of dermatologic complications have been reported with cisplatin chemotherapy including melanonychia, oral mucosal hyperpigmentation, hypersensitivity reactions, extravasation,⁴ Raynaud phenomenon, and flushing.⁵

Two cases of SSH have been reported following combination chemotherapy with cisplatin included in the regimen. A 61-year-old man with inoperable esophageal squamous cell carcinoma received cisplatin and 5-FU in addition to concurrent radiotherapy.⁶ After worsening renal function, cisplatin promptly was replaced with leucovorin. The patient developed SSH after the eighth infusion of 5-FU–leucovorin delivered through a peripheral catheter over a 24-hour period. The cutaneous side effect was attributed to the use of intravenous 5-FU.⁶ The second case involved a 48-year-old woman diagnosed with Paget disease of the breast who received adjuvant therapy with 12 courses of once-daily 5-FU and docetaxel for 5 years as well as 2 courses of vinorelbine and 1 course of cisplatin and etoposide for lung metastases.⁷ Serpentine supravascular hyperpigmentation lesions slowly developed over approximately 6 months. Based on the literature, the

authors speculated that 5-FU and vinorelbine were most likely to be responsible. They noted, however, the inability to clarify the relationship between the onset of skin lesions and the time course of the chemotherapy.⁷ Although these cases do not directly implicate cisplatin as the cause of SSH, the possibility of a delayed reaction or augmentation of another drug's effect cannot be excluded.

Pemetrexed, on the other hand, has not been associated with SSH. Several cutaneous adverse reactions have been reported, including acute generalized exanthematous pustulosis, alopecia, pityriasis lichenoides, radiation recall dermatitis, toxic epidermal necrolysis, and urticarial vasculitis.⁸ Three cases of pemetrexed-induced skin hyperpigmentation including the palms of the hands and soles of the feet as well as diffuse hyperpigmentation sparing only the palms and soles have been reported.⁸⁻¹⁰

Similar cases of SSH have demonstrated histopathologic findings with increased basal melanin synthesis and occasional melanophages in the papillary dermis without inflammatory changes.^{7,11} Although the unique serpentine pattern of hyperpigmentation is instantly recognizable, clinical differential diagnosis may include thrombophlebitis, cutis marmorata, erythema ab igne, livedo reticularis, and lichen planus.^{2,12}

The exact mechanism of SSH has not been conclusively elucidated. Several studies postulate that direct cytotoxic damage causes loss of endothelial integrity permitting the extravasation of the agent to the overlying epidermis and interfering with melanogenesis.^{2,6,11} Other hypotheses include direct stimulation of melanocytes, depletion of reduced thioredoxin leading to tyrosinase stimulation, hyperthermia-related changes including reduced cytokine production and/or increased expression of melanocyte-stimulating hormone receptor, subclinical phlebitis leading to postinflammatory hyperpigmentation, or hyperpigmentation secondary to increased blood flow in certain areas and therefore increased drug deposition.^{12,13}

Currently, there is no specific therapy recommended for SSH and the pigment may persist anywhere from a few months to more than a year after completing chemotherapy.^{2,7} Although discontinuing the offending agent would certainly prevent further development, due to the benign nature of the reaction, modifying therapy based on cutaneous findings alone is not recommended.¹² Several authors have suggested avoiding peripheral infusions of chemotherapeutic agents known to cause SSH or have recommended using a permanent central venous catheter.^{6,7} Another option, which needs further investigation, is the administration of an

abundant flush following chemotherapy. This technique was described in a case report of a 47-year-old man who developed persistent SSH in the right forearm following docetaxel injection.¹³ Copious venous washing with 1000 mL of isotonic saline solution following the second infusion in the unaffected arm prevented discoloration. The lack of subsequent reaction may support the theory that direct toxic effect on the vascular endothelium results in hyperpigmentation of the supravenuous skin.¹³

Serpentine supravenuous hyperpigmentation is an uncommon cutaneous reaction secondary to antineoplastic therapies. Given the widespread use of chemotherapeutic regimens, dermatologists should be aware of the reaction. Additional studies are warranted to better elucidate the pathogenesis and investigate how infusion techniques might aid in the prevention of skin discoloration. Although this side effect originally was described in relation to 5-FU, subsequent observations have included other chemotherapeutic agents. In light of the findings presented in this report, cisplatin and pemetrexed should be considered on the list of offending agents. Ultimately, patients should be reassured that the lesions are benign, self-limiting, and gradually resolve on their own in most cases.¹²

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