# Hyperpigmentation of the Flexures and Pancytopenia during Treatment with Folate Antagonists

*Sir,*

Hyperpigmentation of the skin has been described in patients with megaloblastic anemia from vitamin B12 deficiency and, less frequently, from folate deficiency. The mechanism of the hyperpigmentation in these patients is not clearly understood. The pigmentation pattern, distribution, and shade vary from patient to patient but usually the pigmentation is most pronounced in the hands and feet, especially over the knuckles and in the creases of the palmar and plantar surfaces.

We describe a patient who developed folate deficiency secondary to treatment for ocular toxoplasmosis. She presented with thrombocytopenia, anemia, leucopenia and an unusual brown pigmentation of the flexures.

## CASE REPORT

An 18-year-old white woman was admitted to our hospital because of a pancytopenia. Three weeks earlier she had been diagnosed as having toxoplasma chorioretinitis, and therapy was initiated with pyrimethamine 25 mg twice a day, trimethoprim 160 mg + sulfamethoxazole 800 mg every 12 h and prednisone 20 mg daily. Two weeks after treatment was begun, a brownish pigmentation of the flexures was noticed and 3 days later, epistaxis, purpura and hematuria developed. At that time the hemoglobin was 9 g/100ml, the white blood cell count $1{,}000 \times 10^6$/l and the platelet count $16{,}000 \times 10^6$/l. She was admitted to our hospital the same day. Examination revealed a pale young woman with non-palpable purpura on the extremities, secondary to thrombocytopenia, and a symmetrical brown pigmentation affecting the axillae (Fig. 1), sides of the neck and the antecubital fossae. The mucous membranes, nails and hair were normal. A bone marrow study showed a selective hypoplasia of the erythrocytic and megacaryocytic series, with megaloblastic changes. Serum B12 level was normal and serum folate level was decreased, 4 ng/ml (normal 5.5 to 15 ng/ml). A biopsy specimen of the axilla showed a thinned epidermis with hyperpigmentation of the basal layer and scattered melanophages in the papillary dermis. Fontana-Masson stain confirmed that the pigment within the dermal macrophages was melanin. Treatment was discontinued and the patient was treated with folinic acid 9 mg daily. Ten days later the hemoglobin was 8.5 mg/100 ml, the white blood cell count $5{,}200 \times 10^6$/l and the platelet count $182{,}000 \times 10^6$/l. The pigmentation faded within the next 3 months.

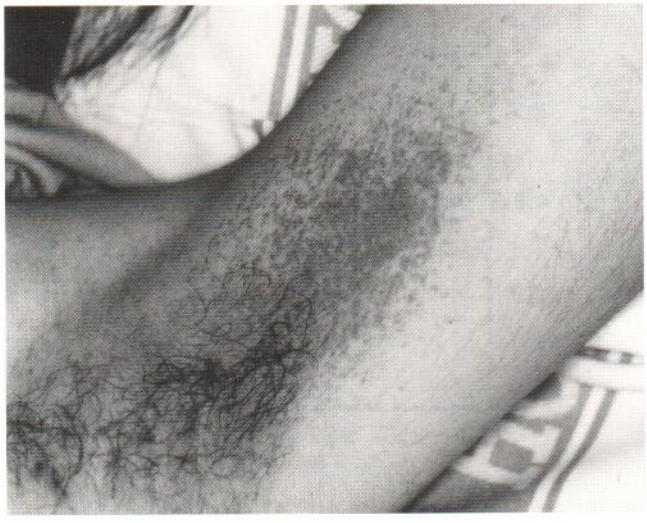

*Fig. 1.* Brown mottled pigmentation on the axilla.

## DISCUSSION

Cutaneous hyperpigmentation secondary to folate deficiency is a much less recognized side-effect than is hematologic toxicity. There are few reports of pigmentary changes secondary to folate deficiency.

Gough et al. (1) described 7 patients with nutritional deficiency of folic acid. They all developed megaloblastic anemia and hyperpigmentation of the skin, particularly of the sun-exposed areas. Baumslag & Metz (2) described 5 women with folic acid deficiency associated with pregnancy and lactation, who developed spotty pigmentation of the palms and soles. Downham et al. (3) reported one case of folate deficiency associated with grayish-brown pigmentation of the skin, not limited to sun-exposed areas. Hyperpigmentation cleared in all patients after treatment with folic acid. The pathogenesis of the pigmentary changes in folic acid deficiency is uncertain. An alteration in the metabolism of glutathione that would lead to inhibition of tyrosinase activity or elevated levels of biopterin, a substance necessary for the hydroxylation of phenylalanine, have been suggested as possible causes of the hyperpigmentation. In our patient the cause of folic acid deficiency was the interference with its utilization by drugs. She was treated with trimethoprim, sulfamethoxazole and pyrimethamine. All these drugs are folate antagonists; when they are concurrently administered, as in our patient, synergism occurs, and it is attributed to the inhibition of tetrahydrofolate production at two sequential steps in its biosynthesis.

Although hematologic toxicity secondary to the use of folate antagonists is a frequently reported adverse effect, we have found only 2 reports of pigmentation and folic acid deficiency due to drug administration. TenPas & Abraham (4) described one patient who developed anemia, thrombocytopenia and a generalized diffuse hyperpigmentation 2 months after treatment with pyrimethamine and sulfadiazine had been started for ocular toxoplasmosis. The patient responded quickly to treatment with packed red cell transfusions, folic acid and prednisone. Greenspan et al. (5) described cutaneous hyperpigmentation resembling acantosis nigricans in 2 patients with malignant brain tumors following chemotherapy with triazinate, a folic acid antagonist. The pattern of hyperpigmentation in these patients was predominantly on the flexures, as in our patient. One of them had a decreased serum folate level that returned to normal as the hyperpigmentation resolved.

In our patient cutaneous hyperpigmentation was the first manifestation of her folate deficiency, before clinical signs of hematologic toxicity appeared. The development of cutaneous hyperpigmentation in a patient treated with folate antagonists should lead to the diagnosis of folic acid deficiency being considered.

## REFERENCES

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