Megaloblastic Anemia Associated with Psoriasis: Case Report and Review of the Literature

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A 68-yr-old male with severe psoriasis developed megaloblastic anemia due to folate deficiency 3 months after the cessation of low-dose methotrexate therapy. The mechanism of megaloblastic anemia in this case was suggested to be multifactorial. The case report and a review of megaloblastic anemia associated with psoriasis are presented.

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Introduction

Psoriasis is known to be one of the skin diseases which can cause folate deficiency (1–3). However, psoriasis alone rarely produces folate deficiency severe enough to be associated with megaloblastic anemia (1–3). Recently, methotrexate has been widely used as an effective therapy for patients with severe psoriasis who are resistant to conventional agents (4), but such therapy increases the risk of megaloblastic anemia (5–8). As the present case illustrates, megaloblastic anemia associated with psoriasis is often a multifactorial condition.

Case Report

A 68-yr-old male had a 25-yr history of severe psoriasis. His dietary intake had been unbalanced for 6 yr due to his living alone after his wife’s death. Out-patient treatment with low-dose methotrexate (7.5 mg once a week) was instituted by a dermatologist in August 1988. In February 1989, the methotrexate treatment was discontinued because of severe stomatitis, glossitis, and the inability of the patient to eat. However, his symptoms persisted and in March he developed a fever. On May 15, he was admitted to our hospital with severe gingival bleeding, chest tightness, and dizziness. Physical examination revealed erythema, desquamation, pigmentation, and purpura on the trunk and extremities. The oral findings were gingival bleeding, ulcers of the buccal mucosa, and atrophy of the lingual papillae. He also complained of lingual pain. No hepatosplenomegaly was noted. Neurological examination was negative. Examination of the blood showed severe pancytopenia (WBC, $0.8 \times 10^9/l$; Hb, 3.1 g/dl; MCV, 114 fl; MCH, 38.1 pg; MCHC, 33.3 g/dl; reticulocytes, 0%; and platelets, $3.0 \times 10^9/l$). Smears of the peripheral blood showed hypersegmented neutrophils (Fig. 1a), no other pathological cells were detected. The neutrophil alkaline phosphatase (NAP) score was within normal limits. The serum total bilirubin (1.4 mg/dl) and lactic dehydrogenase (435 IU/l) levels were mildly elevated, while total protein (4.7 g/dl), total cholesterol (116 mg/dl), and cholinesterase (0.24 $\Delta$P) levels were all reduced. The serum vitamin B$_{12}$ level was within normal limits (390 pg/ml), anti-intrinsic factor antibody was negative, and a Schilling test showed no disturbance of vitamin B$_{12}$ absorption. Urinary excretion of methylmalonic acid was below 10 mg/day. Methotrexate was not detectable in the serum. Folate levels in both serum (1.0 /g/l) and red blood cells (18 /g/l) were found to be decreased significantly by radioimmunoassay. Bone marrow aspirate revealed mildly hypercellular marrow, but there was no apparent erythroid hyperplasia. The bone marrow smears disclosed dysplastic changes in all the hematopoietic lineages, i.e., megaloblastic change in the erythroid lineage, giant transformation in the myeloid lineage, and micromegakaryocytes or megakaryocytes with multiple small separated nuclei (Figs. 1b–f). Chromosomal analysis revealed a normal karyotype. Since a definite hematological diagnosis could not be made immediately after his
admission, he was treated with only packed red cells and platelet transfusions. After transfusion, the reticulocyte count began to rise on the 6th hospital day and his pancytopenia subsequently made a prompt recovery. In addition, on the 8th hospital day he also received a multivitamin infusion which contained 400 μg of folate. No other specific agent or nutritional supplementation was given during his time in hospital. The stomatitis and glossitis also improved immediately. On the 22nd hospital day, bone marrow aspirate revealed hypercellular marrow with markedly reduced dysplastic changes. The psoriasis showed deterioration in contrast with the hematological improvement. He was discharged on July 10, 1989 with a normal serum folate level and normal hematological findings.

Discussion

The major hematological findings of this case on admission were severe pancytopenia and a mildly hypercellular marrow with dysplastic changes in all the hematopoietic lineages, a picture which was suggestive myelodysplastic syndrome. However, he was eventually diagnosed as having megaloblastic anemia due to folate deficiency because of his low serum and red blood cell folate levels and the prompt recovery of his pancytopenia and dysplastic changes after several transfusions and a single parenteral dose of 400 μg of folate.

Psoriasis is known to be one of the skin diseases which can cause folate deficiency. Touraine et al (3) reported reduced serum and red blood cell folate levels in 22 out of 50 patients with psoriasis. Similar observations have also been reported by Shuster and Marks (1) and Fry et al (2). They attributed the folate deficiency mainly to the increased utilization of folate by the rapid turnover of epidermal cells in psoriasis. The malabsorption of folate first proposed to occur in psoriasis by Shuster and Marks (1) has since been noted only in rare cases by Touraine et al (3). Folate deficiency due to excessive loss in exfoliated skin was suggested by Hild (9), but was ruled out by Fry et al (2).

In contrast to the reduced folate levels, serum vitamin B₁₂ levels are reported to be normal in most psoriasis patients (1, 10, 11) and no evidence of impaired vitamin B₁₂ absorption has been detected despite abnormal Schilling test results in some cases (11, 12). In addition, there is no increased incidence of pernicious anemia in psoriasis patients to our knowledge. These findings suggest that vitamin B₁₂ deficiency is unlikely to be a contributory factor in the megaloblastic anemia in psoriasis.
However, it is unusual for psoriasis alone to produce severe folate deficiency and megaloblastic anemia (1–3), which suggests the existence of other contributing factors.

The first possibility in this patient is inadequate dietary intake. Folate stores in the body are not very large from the standpoint of daily requirement when compared with those of vitamin B₁₂. Herbert (13) reported that a folate-deficient diet caused severe folate deficiency followed by megaloblastic anemia in only 4 months in a healthy young volunteer. In the present patient, the dietary intake had been unbalanced for years due to his single life, and his intake of raw vegetables was particularly poor. Moreover, stomatitis and glossitis had made him almost unable to eat for 3 months before admission.

The second possibility is the administration of methotrexate, which is an inhibitor of intracellular folate metabolism. It has been reported that there is a potential for intracellular folate depletion during long-term methotrexate therapy in psoriasis patients (14). In fact, megaloblastic anemia associated with low-dose methotrexate therapy has been reported in both patients with rheumatoid arthritis (15–17) and psoriasis (5–8, 18–22). However, low-dose methotrexate alone rarely causes severe megaloblastic anemia without the presence of other contributing factors that exaggerate its hematopoietic toxicity: renal impairment, hypoalbuminemia, and interactions with other protein-bound or weakly acidic drugs (salicylates, NSAIDs, trimethoprim-sulfamethoxazol) are all reported to possibly act as such contributing factors (5, 6, 15–17, 22). Enteropathy due to methotrexate can also potentially cause folate deficiency (23). On the other hand, Ellegaard et al (24) reported moderately decreased levels of serum vitamin B₁₂ in 3 out of 7 psoriasis patients on methotrexate therapy, and attributed the decreased vitamin B₁₂ level to vitamin B₁₂ malabsorption due to enteropathy secondary to methotrexate or folate deficiency. However, serum vitamin B₁₂ levels have been reported to be normal in other patients on methotrexate therapy (1, 7, 19, 20). In the case of the present patient, methotrexate was discontinued 3 months before his admission. However, it is still possible that methotrexate had a role in the development of the folate deficiency and megaloblastic anemia, and it was probably also associated with the occurrence of his stomatitis.

A hematological malignancy, especially myelodysplastic syndrome (MDS), may present with psoriasis in rare cases (25). Although no increased incidence of hematological malignancies had been recognized in psoriasis patients (26, 27), more attention should be paid to the possibility of such hematological malignancies developing in relation to some types of treatment (25, 28–30).

Previous reports of megaloblastic anemia in patients with psoriasis are summarized in Table 1. As is shown in the table, psoriasis alone rarely causes megaloblastic anemia, and recently the mechanism has been recognized to be multifactorial. In the presence of other contributing factors, patients with psoriasis are prone to develop severe folate deficiency and megaloblastic anemia, especially those on low-dose methotrexate therapy.

In light of the course of this patient, it is recommended that serum folate levels are analyzed and the possibility of megaloblastic anemia is kept in mind when treating any patient with psoriasis, especially those individuals on low-dose methotrexate therapy.

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References

3) Touraine R, Revuz J, Zittoun J, Jarret J, Tullies M. Study

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MTX, methotrexate


