Bullous Eruption and Elevated Leukocyte Alkaline Phosphatase in the Course of Busulfan-Treated Chronic Granulocytic Leukemia

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Chronic granulocytic leukemia is characterized by hepatosplenomegaly, a markedly elevated white blood cell count with a spectrum of immature and mature granulocytic elements present, a proliferative granulocytic bone marrow, low levels or absence of leukocyte alkaline phosphatase activity and the presence of the Philadelphia chromosome.1 The patient to be described had chronic granulocytic leukemia and developed an erythema multiforme like rash following busulfan therapy. The leukocyte alkaline phosphatase activity at the height of the rash was markedly increased in association with a normal white blood cell count. The serum vitamin B₁₂ and B₁₂ binding capacity were significantly elevated at this time. The leukocyte alkaline phosphatase activity fell gradually to zero and the white blood cell count increased as the rash subsided. The B₁₂ levels remained elevated.

Case Report

J.Y., a 35-year-old man, first consulted a physician in June 1968 because of a 40-pound weight loss in four months. The spleen was felt 14 cm. below the left costal margin and the liver 5 cm. below the right costal margin. The blood count revealed a hemoglobin of 8.4 Gm. per cent, hematocrit of 26 per cent, platelet count of 254,000 per cu. mm., and a white blood cell count of 200,000 per cu. mm. The differential white blood cell count was one per cent myeloblasts, four per cent promyelocytes, six per cent myelocytes, 10 per cent metamyelocytes, 22 per cent bands, 42 per cent segmented neutrophils, six per cent eosinophils, five per cent basophils, three per cent lymphocytes and one per cent monocytes. The patient was treated with 10 mg. of busulfan daily for one month until the leukocytes count fell to 8000 per cu. mm. and the hemoglobin rose to 12 Gm. per cent. Busulfan was then discontinued. Three months later busulfan was reinstituted because of a white blood cell count of 17,500 per cu. mm. The dose was increased rapidly over the
next three weeks from 2 mg. daily to 12 mg. daily, and was continued at this dose for three more weeks. Busulfan was discontinued when the white blood cell count decreased to 8000 per cu. mm. and the hemoglobin to 9.4 Gm. per cent.

Two weeks later the patient was evaluated by the present authors for the first time because of fever, epistaxis and ulceration of the left knee. The temperature was 105°F. There was an ulcer crater measuring 6 cm. × 8 cm. with a necrotic interior over the lateral aspect of the left knee. The spleen was felt 2 cm. below the left costal margin. The liver was not palpable. The hemoglobin was 6.1 Gm. per cent, hematocrit of 19 per cent, red blood cell count 1.96 million per cu. mm. platelet count 40,000 per cu. mm. reticuloocyte count 1.0 per cent and the white blood cell count 7900 per cu. mm., of which 77 per cent were neutrophils, 16 per cent bands, five per cent lymphocytes, one per cent monocytes and one per cent basophils. A sternal bone marrow aspirate was normocellular with a normal myeloid–erythroid ratio. Leukocyte alkaline phosphatase measured biochemically2 was 162 Bessey-Lowry units per 10 polymorphonuclear neutrophils (normal range for men is 10–40). The serum vitamin B12 and vitamin B12 binding capacity measured by the radioactive charcoal method3,4 were: vitamin B12, 1632 picograms per ml. (normal range 150–1000) and the binding capacity 4582 picograms per ml. (normal range 500–1900). The patient was given cephalothin intravenously, 5 Gm. daily and kanamycin intramuscularly 1 Gm. daily. The temperature ranged between 103–105°F, although the blood and the ulcer crater were sterile.

In the course of the next two weeks, bullae formed and progressed to ulcers over all of the extremities (Fig. 1) and the original ulcer enlarged (Fig. 2). There were no lesions on the trunk or on the mucous membranes. The clinical impression was erythema multiforme. Skin biopsy revealed a subepidermal bulla with a large degree of inflammation and necrosis and polymorphonuclear leukocytes predominating. The epithelial layer was relatively intact. The histology above was felt to be characteristic of erythema multiforme. The leukocyte count reached a nadir of 1200 per cu. mm. two-and-one-half weeks after admission. Bone marrow aspirate at this time was hypocellular. Karyotyping of the hypoplastic bone marrow performed by the direct method revealed the Philadelphia chromosome in all evaluable mitoses. Peripheral blood culture in the presence of phytohemagglutinin revealed chromosome and chromatid breaks, exchange figures, fragments, translocations and a minority population with the Philadelphia chromosome. Prednisone 100 mg. daily was given by mouth and within 48 hours the patient was afebrile. The skin lesions began to heal and recovery from the pancytopenia ensued. Skin grafting was necessary to cover...
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Fig. 2.—Large ulcer crater on left knee two weeks after hospitalization.

the denuded area over the left knee. The white blood cell count rose to a high of 59,000 per cu. mm. and has remained in the range of 30,000–50,000 per cu. mm. Serial determinations of leukocyte alkaline phosphatase activity revealed a gradual decrease to zero, while the serum vitamin B₁₂ concentration and vitamin B₁₂ binding capacity remained elevated (Fig. 3).

DISCUSSION

Erythema multiforme has been reported in association with many drugs and some malignant disorders, but not with chronic granulocytic leukemia or following administration of busulfan. The most common known dermatologic toxicity of busulfan is diffuse hyperpigmentation resembling Addison's disease. Erythema nodosum, urticaria, and porphyria cutanea tarda have also been reported. Skin lesions in chronic granulocytic leukemia are uncommon, consisting of herpes zoster, nonspecific rashes and leukemic infiltrates. Lesions indistinguishable from erythema multiforme have been reported rarely in acute myelogenous leukemia, but not in other leukemias. In the present case the histologic and clinical appearance were characteristic of erythema multiforme. The beneficial response to withdrawal of busulfan and administration of corticosteroid drugs suggest that the syndrome represented a hypersensitivity response to busulfan. The alternative possibilities, that the erythema multiforme was a manifestation of the underlying chronic granulocytic leukemia or a coincidental occurrence, appear less likely.

Leukocyte alkaline phosphatase activity is below normal in chronic granulocytic leukemia in relapse, but may occasionally return to normal in the remission phase. Increased levels have been found in childhood chronic granulocytic leukemia when overwhelming infection and severe ulcerative colitis were also present, dropping to very low levels with healing of the infection or inflammatory process. The present report illustrates the ability of
the leukocytes of a young adult patient with classical chronic granulocytic leukemia to respond to an intercurrent illness (erythema multiforme) by a marked rise in alkaline phosphatase activity in the presence of severe leukopenia. The etiology of the elevated leukocyte alkaline phosphatase activity is not clear in this case. Elevation of this enzyme might be due to an outpouring of normal cells while the decrease later might reflect replacement by the leukemic cell line. This explanation seems implausible, since a bone marrow chromosome preparation performed at a time when the leukocyte alkaline phosphatase was markedly elevated showed the Philadelphia chromosome in all evaluable mitoses. Thus, all the granulocytes present in the peripheral blood at the time when the leukocyte alkaline phosphatase activity was 122 Bessey–Lowry units and the white blood cell count was 1200 per cubic millimeter were probably derived from the leukemic cell line.

In contrast to the increased leukocyte alkaline phosphatase activity, the serum vitamin B₁₂ and B₁₂ binding capacity were markedly elevated on admission and remained at comparable levels throughout the course of the illness, as expected in chronic granulocytic leukemia. An increased number of granulocytes or an increased turnover of granulocytes is considered to be responsible for the increased levels of vitamin B₁₂ found in chronic granulocytic
leukemia. It is unlikely that either of these conditions was present early in the acute phase of this patient's illness, as there was a pancytopenia and a hypocellular bone marrow, and an explanation for the increased levels is lacking.

In conclusion, the case reported here illustrates the development of a bullous eruption, pancytopenia, bone marrow hypoplasia and an elevated leukocyte alkaline phosphatase activity following treatment with busulfan in a patient with classic chronic granulocytic leukemia.

**Summary**

A 35-year-old man presented with a bullous eruption similar to erythema multiforme following the administration of high doses of busulfan therapy for chronic granulocytic leukemia. There was pancytopenia, hypoplasia of the bone marrow, elevation of serum vitamin B₁₂ and B₁₂ binding capacity and a paradoxical elevation of the leukocyte alkaline phosphatase level. Discontinuation of the busulfan and the administration of prednisone were followed by gradual healing of the skin lesions, reversal of the pancytopenia and reduction of the leukocyte alkaline phosphatase activity to zero. This case illustrates an unusual and previously unreported untoward response to busulfan and is another example of the capacity of the leukocytes in some patients with chronic granulocytic leukemia to develop high alkaline phosphatase activity in response to inflammation.

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