Atypical Pyoderma Gangrenosum With Leukemia

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Pyoderma gangrenosum (PG) has been increasingly reported in association with myeloproliferative disorders. Monoclonal gammopathy, myeloma, myeloid metaplasia, and polycythemia have all been found in association with PG. Recently, seven cases of PG in association with leukemia have been described: three cases with acute myeloblastic leukemia, two cases with chronic myelogenous leukemia, one case with acute lymphoblastic leukemia, and one case with acute leukemia of either plasma cell or myeloblast origin. To these we add two cases of PG with acute myeloblastic leukemia. These patients often have an atypical clinical presentation for PG, with bullae and relatively superficial involvement obscuring the correct diagnosis.

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THE LEUKEMIAS have many known cutaneous manifestations. Some cutaneous lesions result from invasion of the skin by leukemic cellular infiltrates. Among these specific malignant infiltrative lesions, only the chloroma of acute myeloblastic leukemia is considered pathognomonic. Characteristically, red-brown or purple macules, papules, tumors, plaques, and gingival hypertrophy may occur in association with any of the leukemias.1

Skin lesions associated with leukemias, but not specifically due to leukemic infiltration, are collectively termed leuke¬mids. Leukemids include macules, papules, vesicles, wheals, bullae, petechiae, purpura, erythroderma, erythema multiforme, erythema nodosum, herpes simplex, herpes zoster, and vaccinia gangrenosa.2

To these well-known cutaneous manifestations of leukemia, Perry and Winkelmann3 added pyoderma gangrenosum (PG) in a report of three cases in 1972. They distinguished the skin lesions of their patients from typical PG, noting that in the leukemic cases, ulcers were superficial with unusual vesiculobullous borders.

Two instances of atypical bullous PG associated with leukemia were seen within the past year at the Columbia-Presbyterian Medical Center.

REPORT OF CASES

Case 1.—A 42-year-old housewife had been in good health until September 1974, when midepigastic pain, anorexia, nausea, vomiting, loss of taste for cigarettes, and brown-red urine developed. On Sept 19, she consulted a physician and received an injection of an unknown medication into her right buttock. Over the next two days, fever, lassitude, and tenderness at the injection site developed. She came to the Columbia-Presbyterian emergency room and was noted to have a temperature of 39.8 °C, mucous-membrane pallor, scleral icterus, tenderness to palpation of the right upper abdominal quadrant, and tenderness of the right buttock without visible abnormality.

A hemogram showed a hemoglobin level of 6.7 g/dl; the WBC count was 3,400/cumm, with 80% neutrophils, 13% lymphocytes, 3% monocytes, and 4% myeloblasts. The ESR was 156 mm/hr. She was admitted to the hospital. Admission laboratory data included a total bilirubin level of 2.4 mg/dl. Serum protein electrophoresis findings showed a serum albumin level of 2.24 g/dl (normal, 3.5 to 4.8); α1-globulin, 1.92 g/dl (normal, 0.1 to 0.4); α2-globulin, 1.3 g/dl (normal, 0.5 to 0.9); β-globulin, 0.59 g/dl (normal, 0.7 to 1.2); and γ-globulin, 0.51 g/dl (normal, 0.9 to 1.8).

Antinuclear antibodies, Australia antigen, latex fixation, heterophil agglutination, serum iron and iron-binding capacity, direct and indirect Coombs’ test results, and serum B12, serum creatinine, alkaline phosphatase, SGOT, and lactic dehydrogenase levels were all within normal limits. The 50% complement hemolysis (CH50) value was 316 (normal, 160 to 210); glucose-6-phosphate dehydrogenase value was 1.9 units of specific activity per minute per gram of hemoglobin (normal, less than 40); leukocyte alkaline phosphatase was 150...
(normal, 10 to 70 of a possible 400 points). She reacted to mumps and to 5-tuberculin-unit PPD intradermal skin tests with only 2 mm of erythema and induration after 48 hours. Bacterial cultures of blood, urine, and oropharyngeal exudate grew no pathogens. A bone marrow biopsy specimen yielded a highly cellular marrow that was packed with immature cells, with pleomorphic nuclei containing stippled and clumped chromatin. Occasional cells with cytoplasmic granules suggestive of myeloid cells were seen. The only normal marrow elements were the megakaryocytes.

A diagnosis of acute myeloblastic leukemia was made and intravenous (IV) ticarcillin disodium was administered for possible bacterial sepsis. Over the next few days, her buttock became swollen and exquisitely tender, and then erythema and edema developed, spreading diffusely on her posterior thigh. A small central area of necrosis and purpura with a bullous covering developed. This lesion rapidly enlarged, until erythema and edema extended from the hip to below the knee, with a 40-cm central bulla overlying a necrotic base (Fig 1).

Daily elevations in temperature to 39.4 °C continued. The platelet count fell to 20,000/cu mm. The hematocrit reading was maintained at 30% by multiple transfusions, and her WBC count increased to 8,200/cu mm, with 15% lymphoblasts. The administration of IV gentamicin sulfate, ticarcillin disodium, and cephalothin sodium failed to resolve the febrile course or the lesion. Gram stains of the bullous fluid showed no organisms; cultures of the fluid were negative for bacteria, fungi, and mycobacteria. Candida and Aspergillus gel precipitin tests were negative. A coagulation profile including prothrombin time, thrombin time, fibrinogen level, and celite cephalin time failed to demonstrate any coagulopathy.

On Oct 6, wide surgical debridement of the necrotic area was performed with placement of a porcine xenograft. Histologic examination of tissue from the margin of the necrotic area showed massive infiltration of the dermis and subcutaneous fat with neutrophils, extravasation of RBCs, and necrosis of the upper dermis. There was no evidence of vasculitis. Special stains and cultures of biopsy material for bacteria, mycobacteria, and fungi showed no growth of organisms. Within hours of debridement, the widespread erythema and edema subsided. Her fever temporarily abated only to recur one day later and to continue daily with shaking chills.

On Oct 14, the xenograft was replaced by a split-thickness autograft. Only a small border of erythema and edema surrounded the debrided area; however, the autograft became necrotic and sloughed. The patient could not be supported beyond a hematocrit reading of 25% and a platelet count of 10,000/cu mm, despite multiple transfusions of platelets and packed RBCs. On Oct 21, she began to pass tarry stools and died on Oct 24, 1974. Postmortem examination confirmed the cause of death to be massive...
gastrointestinal hemorrhage.

Case 2.—A 32-year-old woman came to the Columbia-Presbyterian emergency room on July 20, 1975, complaining of a tender nodule on her left scapular area that had been present for four days, and a nodule on the pretibial area of each leg that had been present for two days. She claimed good health and denied feeling ill or sustaining trauma or insect bites. Her only medications had been birth control pills, which had been taken for ten months. Each nodule was approximately 5 cm in diameter. A complete blood cell count showed a hemoglobin level of 9.2 g/dl, and the WBC count was 7,900/cu mm, with 71% neutrophils, 3% band cells, 21% lymphocytes, and 5% monocytes. The ESR was 65 mm/hr. A chest roentgenogram was normal. The clinical diagnosis was erythema nodosum. Mumps and 5-tuberculin-unit PPD intradermal skin tests were applied. She was given aspirin for analgesia and was instructed to return to the clinic for follow-up.

Three days later, she returned with complaints of fever, chills, and progression of the skin lesions; she was admitted to the hospital. She again denied other symptoms of illness including arthralgias, myalgias, diarrhea, bloody stools, or weight loss. Positive physical findings were a temperature of 38.4 °C and several soft, freely movable axillary lymph nodes; 10-mm induration of the mumps skin test and no induration of the PPD skin test were present. The three nodular lesions had progressed to exquisitely tender, bluish-black, necrotic, indurated plaques, with erythematous halos and central bullae (Fig 2 and 3). The scapular lesion measured 9×12 cm and the pretibial lesions were 8 cm each, with 4-cm central bullae. Microscopic examination of bulla fluid showed only an occasional neutrophil. Bacterial and fungal cultures of the fluid grew no organisms. A Gram-stained smear of the fluid was negative for organisms.

Admission hematologic profile showed a hemoglobin level of 8.4 g/dl, and a WBC count of 12,200/cu mm, with 50% neutrophils, 3% band cells (some with nucleoli), 10% monocytes, and 28% lymphocytes. The platelet count was 248,000/cu mm and the reticulocyte count was 0.8%. A biopsy specimen was obtained from the scapular lesion. Administration of IV cephalothin sodium and gentamicin sulfate for possible sepsis was then initiated. The skin biopsy specimen showed the epidermis to be partially absent and, where present, to be invaded by inflammatory cells. The cutis and subcutis contained heavy neutrophilic inflammatory infiltrates. No vasculitis was seen (Fig 4). This severe inflammatory process was considered to be consistent with PG. A bone marrow biopsy specimen on July 25 showed a cellular marrow with predominance of myelomonocytic blast cells.

Daily temperature elevations continued with repeatedly negative cultures of skin, blood, and urine. The biopsied lesion rapidly improved with decreasing erythema and tenderness and progressive healing. The pretibial lesions ulcerated and continued to enlarge to 15 cm in diameter, with wide bullous overhanging borders.

On July 29, chemotherapy was begun with cytarabine and daunorubicin hydrochloride for treatment of acute myeloblastic leukemia. Within two days, her WBC count had decreased to 8,700/cu mm. The erythematous halo about the leg lesions disappeared and the lesions ceased to enlarge (Fig 5). One week later, she received an additional course of cytarabine and daunorubicin for persistence of blast cells in her bone marrow, and, on Sept 4, a five-day course of cytarabine and thioguanine was started. She was discharged in remission Sept 9, 1975. She has since received intermittent outpatient maintenance chemotherapy. All ulcerations were healed by Nov 5, 1975, and had not recurred as of May 10, 1976.

COMMENT

The term pyoderma gangrenosum was originally used by Brunsting et al" in 1930 to describe a characteristic progressive skin lesion that begins as a tender erythematous nodule, then forms a pustule, which rapidly ulcerates with edematous, dusky, overhanging borders and a surrounding margin of erythema. These ulcers typically enlarge to 10 cm or more, persist for weeks to months, heal with scarring, and may recur over a period of years. The "postoperative progressive gangrene" of Meleney is now considered to represent PG.

The association of PG with ulcerative colitis is well recognized, with 40% to 60% of PG patients having ulcerative colitis and 1% to 5% of all patients with ulcerative colitis having PG. The skin lesions may precede active colitis. Similar skin lesions have occurred preceding or concomitant with regional enteritis and rheumatoid arthritis. The severity of the PG may parallel the severity of the associated disease.

The first reported association of PG with leukemia was by Maldonado et al, who described a 7-year-old boy in whom, following mercaptopurine therapy for PG, acute leukemia of either plasma cell or myeloblast type developed.

Perry and Winkelmann reported three cases of atypical PG and leukemias. Two patients had chronic myelogenous leukemia and the third had acute myelomonocytic leukemia. These cases were considered atypical because of the superficial nature of the lesions as well as their bullous margins.

Subsequently, Tay, Fayolle et al, and Goldin each reported cases of PG with acute lymphoblastic leukemia, acute myeloblastic leukemia, and chronic myelogenous leukemia, respectively.

Our two cases are consistent with these previous descriptions of PG with leukemia. Our first patient's lesions were atypical, with surrounding erythema that was far more extensive than in the usual case of PG. The large central necrotic bulla did not rupture early and ulcerate as in classical PG, but progressed similarly to that observed by Goldin. Evolution of the PG in our second patient was similar to that described by Perry and Winkelmann because the lesions remained superficial, formed early central bullae that ruptured, and continued to enlarge with wide, bullous overhanging edges.

The typical histopathologic characteristics of PG are not diagnostic. Absence of epidermis with necrosis of upper dermis is seen, acute inflammatory infiltrates may occur in the upper dermis with more chronic infiltrates in the lower dermis. There may be vascular proliferation and epidermal hyperplasia at the periphery. The cases with associated leukemia that were reported by Goldin and two reported by Perry and Winkelmann had infiltrates consisting almost entirely of polymorphonuclear leukocytes that were so dense as to be abscess-like. Our two patients' histologic pictures correspond with those of these three cases.

Various approaches to therapy for PG have been taken. Since PG often worsens with exacerbation of the associated disease, medical control of ulcerative colitis, regional enteritis, or rheumatoid arthritis, when associated, have proved beneficial. Systemic corticosteroid therapy has produced rapid clinical improvement in many cases. Sulfone derivatives, eg, salicylazosulfa-pyrinidine used alone or with steroids, have apparently been beneficial in some cases, as have several antime-tabolites. Our second patient showed immediate cessation of extension and rapid healing of the lesions following...
the initiation of the cytarabine and daunorubicin therapy.

A curious observation was the beneficial effect of surgical excision in our two patients. The first patient had rapid resolution of previously extensive erythema, edema, and intense local tenderness following excision of necrotic tissue. Our second patient had a similar rapid resolution of one lesion from which a large partial biopsy specimen was taken, while untreated lesions enlarged to enormous size. Observation of two cases at our medical center within one year suggests that the association of PG with leukemia may be more common than previously thought, and that surveillance of leukemias should be maintained in new or atypical cases of PG to enable early diagnosis and appropriate treatment.

Nonproprietary Names and Trademarks of Drugs

Cephalothin sodium—Kefin.
Daunorubicin hydrochloride—Cerubidine.
Gentamicin sulfate—Garamycin.
Salicylsalicylic acid—Accuel, Asulfidine, Rocscal.
S.A.S.-500, Sulcolon, W-T Saap Oral.
Ticarcillin disodium—Ticar.

References


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past, to the right, the future. In the left midground, for example, the graceful masts of an abandoned sailing ship are set off by the right by the squat, steam-powered tugboat. In the left foreground grown men, cold with age and idleness, gather around a bonfire. In contrast, the young boys to the right are in the heat of a sandlot baseball game. Meanwhile, the sun is at the horizon, about to switch day to night. Even the world itself stands momentarily still, at the solstice of December. Behind is autumn; ahead is spring. And high above, spanning the entire scene, is the strong horizontal of the bridge, perhaps a link between worlds for those who can find its approach.

A contemporary artist, Mahonri Sharp Young, has recently described the painting and a second similar painting, which hangs in the Toledo museum, thus: "In Paris, tramps sleep under bridges; in New York, you could put a cathedral under a bridge, with room left over for parking lots, second-hand cars, and apartment houses. . . . The Queensborough is no mere slip of a bridge, even by today's standards. . . . And it's still the best way to get to the airports. . . . Work is still going on at this site; they are digging a new subway tunnel, and the tugs still chuff and chatter back and forth. New York makes any other American City except Chicago look dead on its feet" (Young, The Paintings of George Bellow, 1973).

George Bellow's artistic career lasted just a bit longer than the usual athletic career. He died in 1925, aged 42. Cause of death: appendicitis.

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(The Lone Tenement, 1909. Canvas. 91.8 x 122.3 cm. Courtesy of the National Gallery of Art, Washington, DC.)