Cutaneous Wegener's granulomatosis

Report of a case and review of the literature

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A 32-year-old man with documented Wegener's granulomatosis had papules and pustules on his elbows, hands, and feet and petechiae on his palms and soles. Skin biopsy showed chronic vasculitis and epidermal necrosis. The patient's condition improved markedly after chemotherapy with nitrogen mustard, prednisone, and cyclophosphamide. This case illustrates characteristic clinical and histopathologic findings of cutaneous Wegener's granulomatosis based on a current literature review. Although no one skin change is pathognomonic of Wegener's granulomatosis, certain cutaneous findings are suggestive of the disease. Clinicians should be aware of these skin changes to aid early diagnosis and treatment of a rapidly fatal but potentially treatable disease.

Index term: Wegener's granulomatosis

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Generalized or classic Wegener's granulomatosis is characterized by necrotizing granulomas in the upper and lower respiratory tracts, disseminated necrotizing vasculitis involving small arteries and veins, and focal necrotizing glomerulitis.[1] The etiology is unknown, but the disease may have an autoimmune origin.[2] The mean age of onset is in the fifth decade, with a slight predominance in men.[3] Respiratory tract involvement is the most significant finding in Wegener's granulomatosis, and lung disease is invariably present. The renal manifestations of Wegener's granulomatosis usually occur late in the clinical course. Once functional abnormalities of the kidneys occur, the course is fulminant unless cytotoxic therapy is initiated.[4] Wegener's granulomatosis is treatable. Long-term remissions can occur in most patients treated with cyclophosphamide and prednisone.[5]

Case report

A 32-year-old man was admitted to the Cleveland Clinic hospital with polyarthritis, skin changes on his hands, feet, and elbows, and an elevated serum creatinine level. The patient had a history of episcleritis controlled with low-dose methotrexate (12.5 mg per week) and chronic sinusitis.

Physical examination revealed the following: The vital signs were stable and the temperature was 37.6°C. The skin showed petechiae of the palms and soles with a hemorrhagic bulla on the left medial heel. There were erythematous papules and pustules on the elbows, palms, and soles, and across the dorsa of the metacarpophalangeal joints, many topped with scale and/or crust (*Fig. 1*). The head, eyes, ears, nose, and throat (HEENT) examination was remarkable for bilateral scleral injection, whereas the nose and throat were normal. The lungs were clear to auscultation. The left elbow and knee joints had obvious effusions with increased warmth and tenderness.

Laboratory studies showed that, on admission, the patient had a white blood cell count of 10.3×10^3 cells/μL, platelet count 433×10^3 cells/μL, and Westergren sedimentation rate 131 mm/h. There was a normochromic/normocytic anemia with a hemoglobin level of 10.8 g/dL. The chemistry profile was normal except for elevated BUN (54 mg/dL) and creatinine (3.5 mg/dL) levels. Urinalysis was remarkable for 2+ protein, 3+ hemoglobin, 6–10 white blood cells/dL, more than 25 red blood cells/high-power field, and more

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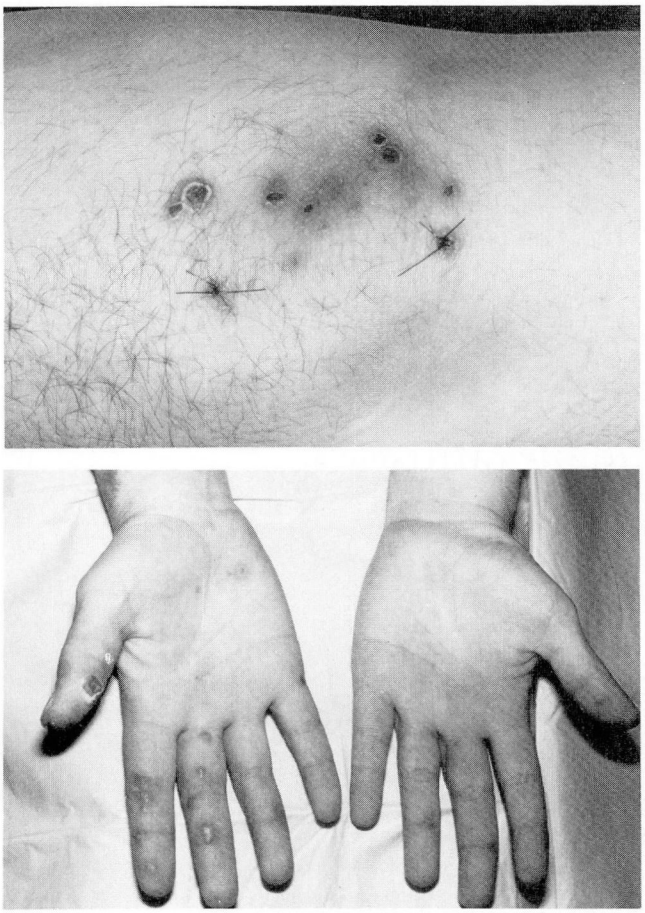

Fig. 1. A. Papulonecrosis of the right elbow.
B. Papules and pustules of the palms.

than 10 granular casts/low-power field. Cultures of blood, urine, and a palmar pustule were negative. A throat culture grew normal flora.

Skin biopsies of the left sole and right elbow showed central epidermal necrosis surmounted by an acutely inflamed crust, beneath which was a mixed acute and chronic inflammatory dermal infiltrate (*Fig. 2a*). Blood vessels within the dermis were surrounded by mononuclear inflammation (*Fig. 2b*). The endothelial walls were markedly thickened, and a phosphotungstic acid-hematoxylin stain for fibrin showed fibrin adhering to and within several vascular walls. Direct immunofluorescent studies of a papule showed focal deposits of fibrin within the dermis. The histopathology was consistent with chronic vasculitis.

Once the patient was hospitalized, his renal function continued to deteriorate. New pulmonary nodules were discovered on a routine chest radiograph, and he complained of a sore throat, despite a negative throat culture. A bronchoscopy with transbronchial lung and nasal biopsies revealed chronic inflammation. There was necrosis of the nasopharyngeal mucosa and the false cords. A diagnosis of Wegener's granulomatosis was based on the constellation of upper and lower airway disease, rapidly progressive renal dysfunction, joint and ocular symptoms, and chronic cutaneous vasculitis.

The patient received 22 mg of intravenous nitrogen mustard administered in divided doses over 10 days. He was also given 60 mg of prednisone daily. Three weeks after receiving the intravenous nitrogen mustard, cyclophosphamide 50 mg per day was added to his outpatient regimen. The patient's serum creatinine level progressively decreased, and his constitutional symptoms abated. The skin disease improved quickly and virtually resolved with chemotherapy.

After approximately six weeks of treatment, fever, cough, and malaise developed, and the patient was re-admitted to the hospital with a depressed white cell count and signs of sepsis. *Staphylococcus aureus* was isolated from the blood. Cyclophosphamide was discontinued; however, within three weeks the vasculitis worsened. Re-treatment with intravenous nitrogen mustard controlled the disease, but staphylococcal sepsis recurred. Because of these infectious complications of the alkylating agents, the patient's disease has been treated with trimethoprim-sulfamethoxazole twice a day and prednisone 40-60 mg per day. His hands, feet, and elbows have remained free of disease.

Discussion

The scattered focal vasculitis in Wegener's granulomatosis affects many organs, including the joints, ears, eyes, nervous system, heart, and skin.[2,5] The incidence of skin disease in generalized Wegener's granulomatosis is consistently reported as 40–50%.[2,5–8] Skin changes are nonspecific and can assume many forms. Papules,[2,5–11] ulcers,[2,4,5,7,8,11–14] purpura,[4–7,11,15] and subcutaneous nodules[2,5,7,8,10–12] are frequently reported. Of 118 cases of Wegener's granulomatosis in the world literature reviewed by Reed et al,[6] papulonecrotic changes of the extremities were the most common type of skin involvement after abnormalities associated with terminal uremia were excluded. Other authors[8,9,11] have also reported papulonecrotic skin disease as a manifestation of generalized Wegener's granulomatosis, as was the case in our patient. Fauci and Wolff[8] reported ulcers as the most common cutaneous findings in 18 patients with Wegener's granulomatosis. Less frequently, vesicles,[2,5–8] pustules,[4,9,16] petechiae,[6,7] and ecchymoses[7] are present. Pyoderma gangrenosum has also been noted in some patients.[6,16] The skin findings in our patient were entirely consistent with those previously reported. He exhibited papules, pustules, and petechiae on the extremities.

Skin involvement can be part of the initial clinical presentation of Wegener's granulomatosis and may be the only initial sign, preceding other evidence of disease by several months.[3] In the series of Reed et al[6] six of the 118 patients had cutaneous disease as the first sign of Wegener's granulomatosis, each having ulcers characteristic of pyoderma gangrenosum. Other reports have described pyoderma gangrenosum,[16] skin ulcers,[13,14] and painful induration of postoperative scars[9] as the sole presenting features of Wegener's granulomatosis. Two cases of skin dis-

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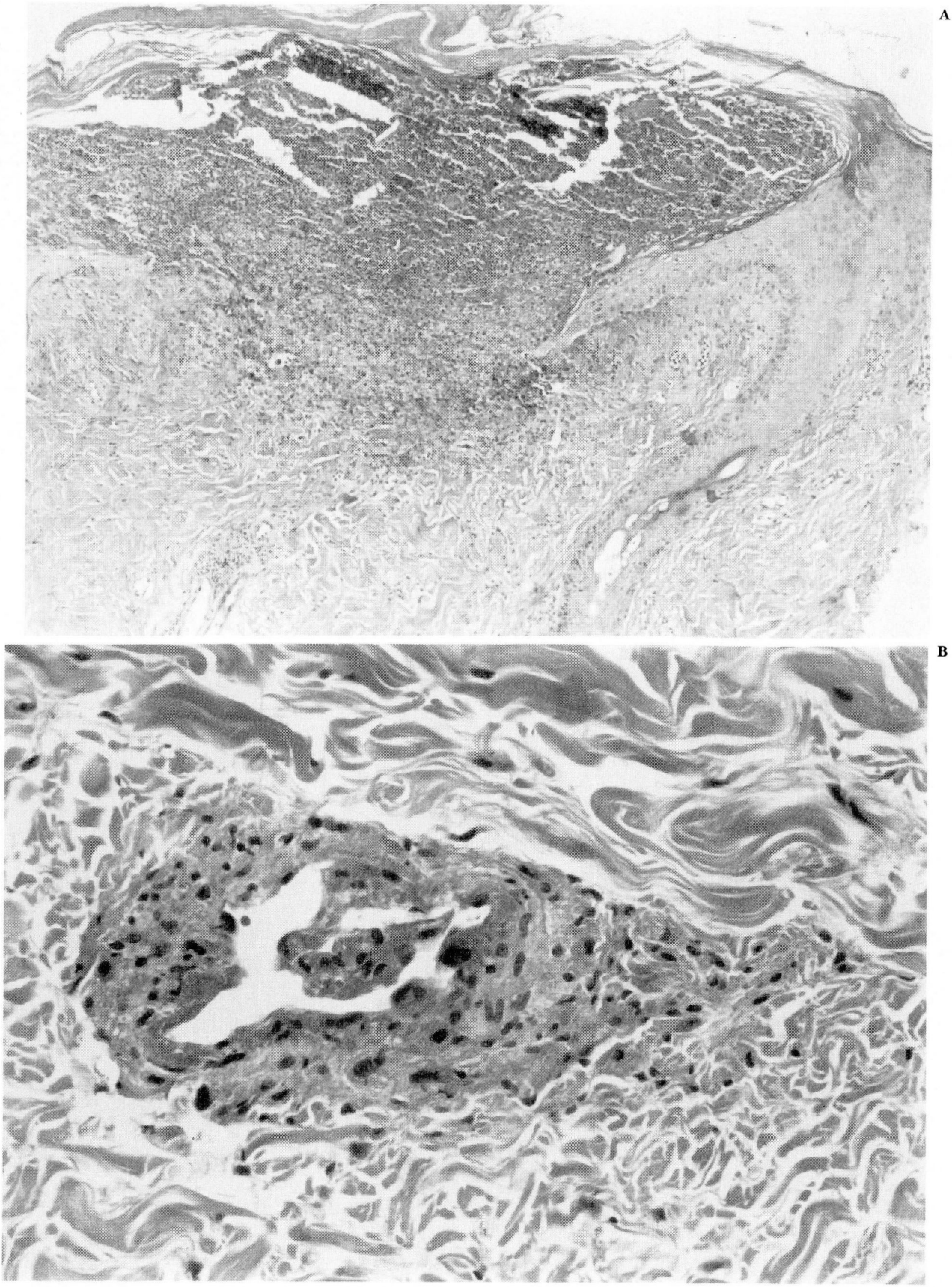

Fig. 2. A. Epidermal necrosis with acute and chronic inflammation (hemotoxylin-eosin, original magnification × 40). **B.** Mononuclear inflammation of a dermal blood vessel with fibrin plug within lumen (hematoxylin-eosin, original magnification × 400).

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eases initially misdiagnosed as cystic acne with pustules[5] and acne fulminans with cysts, nodules, and ulcers[12] have been reported in which the teenagers subsequently manifested the characteristic signs and symptoms of Wegener's granulomatosis. In the case described by Chyu et al,[4] the pustular areas eventually broke down to form necrotic ulcers.

The cutaneous histopathology in generalized Wegener's granulomatosis varies. The skin changes in our patient were vasculitic; however, in the clinical series of 18 at the National Institutes of Health,[8] several histologic patterns were present among the patients with skin findings. These included vasculitis (corresponding to vesicles and ulcers), necrotizing vasculitis (ulcers), chronic inflammation (ulcers), granulomatous inflammation (papules, ulcers), necrotizing granuloma (papules, subcutaneous nodules), and necrotizing granulomatous vasculitis (papules), i.e., necrotizing granulomas with necrotizing vasculitis.[3] Hu et al[7] evaluated the histology of the skin changes in a series of 67 patients with generalized Wegener's granulomatosis at the Mayo Clinic. Nine had nonspecific inflammation, whereas 19 patients could be divided into four distinct histologic subgroups. These subgroups were distinguished by necrotizing vasculitis, necrotizing palisading granuloma, granulomatous vasculitis, and lymphomatoid granulomatosis. The patients with necrotizing vasculitis had purpura and hemorrhage. The presence of vesicles and ulcers correlated with the severity of onset and extent of disease. The remaining patients had papules and nodules. Patients with necrotizing vasculitis and lymphomatoid granulomatosis had a worse prognosis than those with a predominantly granulomatous reaction. In general, it appears that the cutaneous pathologic features of Wegener's granulomatosis cover a wide range of histologic entities; they may show the characteristic pattern of the disease (necrotizing granuloma and vasculitis), may only suggest the diagnosis, or may be totally nonspecific.[3]

The skin disease in generalized Wegener's granulomatosis rarely dominates the clinical picture and is usually a minor part of the multisystem involvement. Skin changes parallel disease activity in other organ systems and generally respond promptly to therapy.[5] The case described here exemplifies these points. The clinical and histologic findings in our patient were characteristic of the skin involvement in generalized Wegener's granulomatosis.

Once a rapidly fatal disease, Wegener's granulomatosis can be effectively treated with early intervention with cytotoxic agents. It is important for the clinician to be aware of and to recognize the various cutaneous manifestations of the disease as potential aids in early diagnosis and treatment.

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