Wells’ Syndrome

Recurrent Granulomatous Dermatitis With Eosinophilia

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Two cases of granulomatous dermatitis with eosinophilia (Wells’ syndrome) are reported. With Wells’ original four cases, these two cases define a distinctive dermatosis with onset as cellulitis and formation of solid edema and either final spontaneous resolution or resolution with steroid therapy. Microscopic study showed diffuse tissue eosinophilia and fibrinoid flame figures, evolution of associated focal necrobiosis, and formation of focal microgranulomas associated with eosinophils. Biopsy of muscle and fascia showed comparable fasciitis and eosinophilic myositis. Immunofluorescence in one case disclosed fibrin in the dermis and IgM, IgA, and C3 in the blood vessels of the muscle. Recurrences of the lesions often appeared to be related to drug administration or surgery.

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Recurrent granulomatous dermatitis with eosinophilia was first described by Wells1 in 1971. He described four patients who had a rather unusual clinical presentation of skin manifestations that resembled acute cellulitis and whose biopsy specimens showed distinctive inflammatory and granulomatous features. The clinical eruption usually occurred in two phases: the first phase was an eosinophilic cellulitis, which was described as a localized redness and edema of the skin and which appeared and spread rapidly, with central involu- tion, during a two- or three-day period, occasionally with blistering. The second phase was the appearance of an infiltrative granulomatous dermal and subcutaneous mass, which remained edematous and slate-colored for several weeks while the border was rosy or violaceous. Continued involution produced a pale solid lesion similar to morphea, and eventually the skin recovered completely. All patients had eosinophilia of the blood and marrow during the active phase of the disease.

Wells divided the characteristic histopathologic changes into three stages. The first or acute stage, which he called “eosinophilic cellulitis,” was characterized by dermal edema and masses of leukocytes, predominately eosinophils, throughout the dermis. The second or subacute stage, granulomatous dermatitis, showed masses of dermal eosinophils and histiocytes about angular, focal, fibrinoid flame masses. The flame figures consisted of a core of collagen coated with leukocyte and eosinophil debris surrounded by a palisade of histiocytes and giant cells. The final stage of resolution was characterized by histiocytic necrobiosis, similar to that seen in granuloma annulare, and the persistence of the flame figures.

We wish to report two additional cases of recurrent granulomatous dermatitis with eosinophilia and to report new observations regarding this disease.

REPORT OF CASES

Case 1 — A 56-year-old woman with recurrent skin lesions since 1967 was seen at the Mayo Clinic in 1968. The skin lesions, consisting of tender plaques of “cellulitis” on the trunk and extremities, had been present for months (Fig 1). Flares of the skin lesions occurred after surgical procedures and after the use of various drugs, including antibiotics, anticoagulants, and local anesthetics. The patient never had fever, chills, or night sweats. In 1967, when she was first examined by her local physician, findings on biopsy were consistent with that of granuloma annulare. Levels of immunoglobulins, including IgE, were normal. A stool was negative for ova and parasites. Review of multiple skin biopsy specimens, including those taken elsewhere, all showed a similar histologic pattern that was consistent with Wells’ syndrome. Treatment with corticosteroids temporarily suppressed the skin lesions and shortened the course. Pertinent laboratory data included hemoglobin level, 14.8 g/dL; hematocrit reading, 44%; and leukocyte count, 13,800/mm³, with 46% neutrophils, 5.5% band forms, 21% lymphocytes, 7.5% monocytes, 19.5% eosinophils, and 0.5% basophils. Bone marrow aspiration and biopsy showed eosinophilia.

On the patient’s most recent visit in November 1977, Trichophyton rubrum was cultured from the foot. The patient had had a chronic problem involving her feet and toenails for many years. Results of delayed hypersensitivity skin tests were strongly positive to Candida, Trichophyton, and mumps. Skin biopsy of normal, previously involved skin yielded negative results, as did direct immunofluorescence.

Case 2 — A 66-year-old woman was first seen in June 1977 with a history of cellulitis and erythema of the right arm for one month. Treatment for the cellulitis with penicillin and oxypenbutazone was of no benefit. The patient gave a history of a fixed drug eruption reaction to penicillin, and on admission to the clinic she had several nummular hyperpigmented areas on the upper part of her shoulders and right leg, which were considered to be consistent with a fixed drug eruption. She was also receiving multiple drugs, including thyroglobulin, a mixture of chlordiazepoxide hydrochloride and clidinium bromide (Librax), diazepam, aspirin, acetaminophen, and conjugated estrogens. She gave a history of a purpuric eruption to acetaminophen. Because of the striking clinical presentation resembling acute infective cellulitis, a surgical exploration was performed on her right arm and multiple biopsy specimens were taken for histopathologic study, immunofluorescence study, and culture. All cultures for common and esoteric organisms were negative. Pertinent laboratory data included the following: leukocyte count, 6,800/cu mm; hemo- globin level, 12.5 g/dL; hematocrit reading, 37%; platelet count, 285,000/cu mm; and sedimentation rate, 53 mm in one hour. There were 35% neutrophils, 25.5% lymphocytes, 3.5% monocytes, 34% eosinophils, and 2% basophils. Bone marrow aspiration and biopsy showed a slight increase of eosinophils, with lymphocytosis. Biopsy showed eosinophilic granulomatous disease, and direct immunofluorescence was positive for fibrin in the dermis.

HISTOPATHOLOGIC FINDINGS

In both of our cases, there were the characteristic histopathologic changes of recurrent granulomatous dermatitis with eosinophilia, as described by Wells.1 In our first case, no abnormal-
Fig 1.—Erythematous plaque on right thigh (case 1).

Fig 2.—Focal flame granuloma in right lower dermis with surrounding infiltrate of eosinophils (case 1, hematoxylin-eosin, original magnification ×64).

Fig 3.—Focal flame granuloma shows central fibrinoid mass with surrounding histiocytic cells and peripheral eosinophils (case 1, hematoxylin-eosin, original magnification ×100).

Fig 4.—Diffuse infiltrate of eosinophils and edema showing flame figures (case 2, hematoxylin-eosin, original magnification ×63).

Fig 5.—Fascia inflammation and granuloma formation with eosinophilia (case 2, hematoxylin-eosin, original magnification ×64).

Fig 6.—Muscle shows eosinophilic myositis. Note normal-appearing vessels (case 2, hematoxylin-eosin, original magnification ×64).

Fig 7.—Direct immunofluorescence of muscle shows IgM in vessel wall (case 2, original magnification ×275).
ity of the epidermis or upper dermis was seen. However, low-power view of the lower dermis (Fig 2) demonstrated a diffuse infiltrate of eosinophils and histiocytes and a focal palisading microgranuloma. A higher-power view (Fig 3) of the granuloma showed that the infiltrate consisted of a dense eosinophilic core of collagen with histiocytes and giant cells palisading around it. Surrounding this characteristic lesion was a dense infiltrate of eosinophils. In case 1, there were many focal microgranulomas scattered in the dermis. There was no evidence of vasculitis on numerous skin biopsy specimens. Necrobiosis and fibrinoid change with eosinophils were seen, which we believe represent an early phase of the microgranulomas.

A more acute onset was seen in case 2. There was a more diffuse infiltrate of the upper dermis, with eosinophils and edema formation. High-power view (Fig 4) showed the flame figures (a mixture of fibrin and eosinophil debris). This histologic pattern was in transition between Wells' stage 1 and stage 2. Mild perivascular inflammation was seen (Fig 4), but there was no true vasculitis with destruction of vessels, hemorrhage, or hyalinization of the vessel wall. Review of specimens of fascia and muscle taken at surgical exploration demonstrated the same diffuse infiltration with eosinophils and histiocytes (Fig 5 and 6). There was no inflammation or destruction of vessels in the muscle biopsy specimen.

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Direct immunofluorescence was performed on biopsy specimens taken at surgical exploration in case 2. The skin showed diffuse fibrin deposition in the dermis. Properdin was observed in the vessel walls. IgG, IgM, IgA, C3, or C4 was not found. The subcutaneous tissue showed scattered deposits of fibrin within inflammatory infiltrates. The fascia was essentially negative. The muscle showed IgM, IgA, and C3 within the vessel walls (Fig 7) and fibrin within inflammatory tissue. Nonspecific immunofluorescence of the eosinophils with immunoglobulin and complement was observed. Direct immunofluorescence of normal, previously involved skin in case 1 was negative.

**COMMENT**

The patients in Wells' report and our patients had similar clinical and histologic presentations. All of the patients had a clinical pattern of recurrent, acute, erythematous inflammation through a solid infiltrative edema phase to healing (Table). The duration of the disease ranged from a relatively short time to approximately ten years. One patient had onset three weeks after penicillin was given for a sore throat, and there was associated mild purpura, asthma, and joint pains. Laboratory data in all cases showed increased blood and cutaneous eosinophilia. Bone marrow eosinophilia was noted in both of our patients and in two of the four described by Wells. Steroid therapy produced resolution of the lesions in three patients. One patient of Wells had a gradual spontaneous improvement over eight years.

The striking histopathologic changes in these cases suggest a relationship to Churg-Strauss allergic granulomatosis, particularly in the one in which case disease developed three weeks after a course of penicillin for a sore throat. The typical Churg-Strauss granulomas of the skin consist of palisading extravascular granulomas, basophilic collagen necrobiosis, leukocytoclasis, and variable vasculitis. However, neither the patients described by Wells nor ours had evidence of vasculitis on histopathologic study, and none showed the massive leukocytic and basophilic connective tissue necrobiosis of the Churg-Strauss lesion.

On the basis of histopathologic findings, we believe that recurrent granulomatous dermatitis with eosinophilia is a distinct disease and is part of the eosinophilic syndromes involving skin. The hypereosinophilic syndrome on biopsy of the skin shows only perivascular eosinophils without any evidence of vasculitis. The Churg-Strauss allergic granulomatosis shows a palisading extravascular granuloma similar to the lesion described by Wells, but there may be evidence for vasculitis. Periarteritis nodosa in a significant percentage of patients can be associated with peripheral and cutaneous eosinophilia and rarely with cutaneous granulomas. Recurring granulomatous dermatitis may represent an additional disease of the hypereosinophilic spectrum of vasculitis-granulomatosis involving the skin and shows similar palisading extravascular granulomas, as seen in Churg-Strauss allergic granulomatosis. Although cutaneous vasculitis is not seen on histopathologic study, the finding of vessel immunofluorescence of muscle in our case 2 suggests that, throughout the course, a search be made for vascular inflammation. We believe that Wells described a distinctive hypersensitivity syndrome of the skin and in a recent abstract summarized additional cases and that our two cases confirm his descriptions.

**Nonproprietary Name and Trademarks of Drug**

**Thyroglubulin—Endothyrin, Proloid, Thyraclin, Thyroidin, Thyroprotein.**

**References**