

Chronic Cutaneous Bacterial Hypersensitivity: A Third Case and Reevaluation of the First Two Cases

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ABSTRACT

We present a third case with similar features of our first two cases of a patient with chronic recurrent indolent inflammatory skin lesions. This is called chronic cutaneous bacterial hypersensitivity. As with the first two cases, the third case had nondiagnostic skin biopsies and laboratory tests with failure to respond to antibiotics. All three cases responded to corticosteroids with the first two cases in remission and off systemic corticosteroids at 9 and 4 years, respectively. All three cases are considered consistent with bacterial allergy because of IgG and or IgE antibodies against common cutaneous bacteria. Either a remission from therapy with prednisone occurs, or control with low dose oral or topical corticosteroids is achieved in this frightening and disfiguring dermatopathy.

INTRODUCTION

THIS REVIEW IS A 9-year and 4-year reevaluation of our first two cases and a recently identified third case of chronic cutaneous bacterial hypersensitivity.^(1,2)

The similar clinical presentations, supportive immunologic studies, and response to therapy of all three cases are reviewed and discussed.

Case report 1

A 43-year-old black female presented with a 6-year history of gradual onset of knee to foot lesions. These lesions were painless, nonpruritic, erythematous macules with palpable, tender subcutaneous nodules that would evolve over a 2-week period to become erosions. These would evolve into pustules and after 4 to 6 weeks resolve to form 1- to 2-cm hyperpigmented macules. Figure 1 shows the active lesions. Except for mild malaise, the patient had no other systemic symptoms and excluding the skin lesions, her physical examination was normal.

Several skin biopsies were reviewed by the Armed Forces Institute of Pathology. The final reports var-

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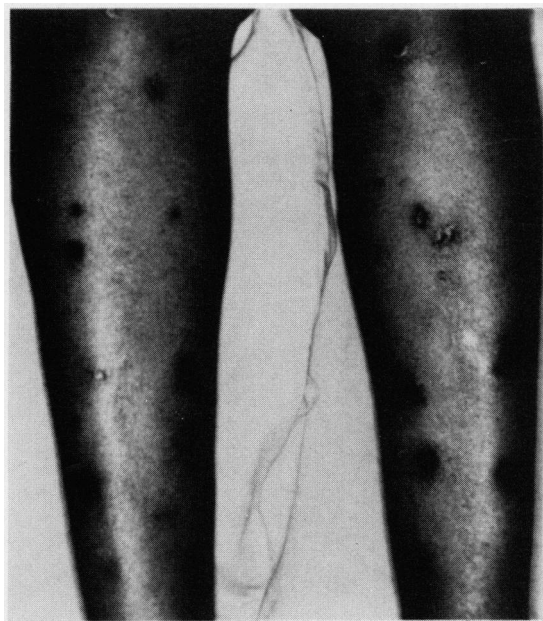


FIG. 1. Case 1.

ied and diagnoses included panniculitis, granulomatous inflammation, and severe lymphocytic vasculitis with a wedge-shaped infarct. An initial diagnosis of malignant atopic papulosis (Degos' disease) was made but later discounted due to the appearance and duration of the lesions with lack of systemic involvement characteristic of this disorder. The differential diagnosis considered is listed in Table 1. To exclude these possibilities the patient had a complete laboratory evaluation including quantitative immunoglobulins, cryoglobulins, sedimentation rate, complete blood count, serum chemistry, and complement levels. All of these tests were within normal limits except a mildly elevated SGOT of 40. She had a positive purified protein

TABLE 1. DIFFERENTIAL DIAGNOSIS CONSIDERED IN
CASE 1^a

Bacterial infection
Tuberculosis and "tuberculoid reaction"
Degos disease (malignant atrophic papulosis)
Collagen vascular disease including vasculitis
Factitious
Drug induced
Leprosy
Syphilis
Sarcoidosis
Erythema nodosum
Erythema induration
Hypersensitivity to bacteria
Immune complex cutaneous reaction
Job's syndrome
Polymorphonuclear leukocyte and lymphocyte dysfunction

^aFrom McGrath KG, et al. Chronic cutaneous granulomatous dermatopathy: Morphologic and serologic evaluation, differential diagnosis and pharmacologic control. *Int Arch Allergy Appl Immunol* 1985;76:318-323. Used with permission.

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derivative (PPD-tuberculin) skin test. The chest roentgenogram, cultures, and special stains of the skin biopsies for acid fast organisms, including leprosy, were negative.

Initial therapy included several trials of antibiotics in addition to topical and intralesional injections of corticosteroids, all of which were ineffective. The lesions progressed becoming more disfiguring and a 6-week course of antituberculosis therapy did not reduce the total lesion count. Cutaneous hypersensitivity to bacteria was considered and a dramatic response to oral prednisone occurred. The regimen consisted of prednisone 30 mg for 7 days and then 30 mg on alternate days for 3 weeks. No new lesions were observed during the alternate day prednisone therapy and the dose was subsequently tapered to 5 mg every other day for several months. Several attempts to discontinue prednisone over the next 6 years resulted in a recrudescence of her skin lesions. The lesions abated upon resumption of low-dose alternate day prednisone. At 9 years the patient has been off prednisone for 1 year and is lesion free.

Concomitant investigations into the immunologic mechanism of this dermatopathy were inconclusive. These included skin testing to available specific bacterial antigens, ELISA antibody determination and inhibition, lymphocyte transformation, and polymorponuclear leukocyte function tests.

Case report 2

A 56-year-old oriental male had a 6-month history of scattered pruritic hyperpigmented macules on his arms, legs, and trunk. A dermatologists's initial impression was spider bites. A skin biopsy was obtained and the patient was empirically administered a 2-week course of prednisone. The lesions subsided and the biopsy revealed mild acanthosis with perivascular lymphocytic infiltrates and intact vascular walls consistent with either insect bites or a toxic eruption.

After termination of prednisone, the patients lesions progressively returned. A travel and environmental history was unrevealing. He denied symptoms of malaise, fever, chills, nightsweats, anorexia, or weight loss. His medical history was significant for allergic and nonallergic asthma and allergic rhinitis. He was otherwise healthy.

Examination of his skin revealed 4–6 mm brownish red macular papular lesions at different stages of evolution. They were located primarily over his arms, legs, and abdomen. The newer lesions were erythematous, raised, and pruritic. The older resolving lesions were lighter brown, macular, and nonpruritic. New lesions were noted to reappear at sites of previously healed areas. Figure 2 shows the active lesions.

Due to the progressive nature of these lesions, another skin biopsy was performed. The differential diagnosis included insect bites, venereal disease, leukocytoclastic vasculitis, and malignancy. Screening blood



FIG. 2. Case 2.

work was normal except for a mildly elevated triglyceride level and SGOT. A VDRL was nonreactive. Quantitative immunoglobulins demonstrated an elevated IgE of 520 (90–450), a low normal IgM, and a normal IgG level.

Biopsies of two skin sites were different. Both sites showed dense perivascular infiltrates of lymphocytes without necrotizing vascular changes. One specimen showed considerable cellular pleomorphism suggesting premalignant cutaneous disease, lymphomatoid papulosis. Based on the patient's clinical presentation the conclusion with Mucha-Habermann syndrome or acute pityriasis lichenoides, speculated to be virally transmitted.⁽³⁾ The patient was treated with tetracycline, shown to be effective in several of these cases. Six months of tetracycline was administered and the total lesion count of 92 remained unchanged as new lesions appeared and older ones faded.

Because of the similarity to the index case, the possibility of a cutaneous bacterial allergy was suggested. On July 19, 1989, almost 1 year after the initial presentation, prednisone 20 mg every morning was initiated for 1 week followed by 20 mg on alternate days. Within the first 2 weeks of therapy all the lesions had faded or resolved, and no new lesions were observed. The patient was tapered off prednisone over the next 2 months. Four years later he still has occasional lesions, which respond to topical corticosteroids.

Concomitant investigations into an immunologic mechanism of this dermatopathy included skin testing to specific bacterial antigens and ELISA antibody determinations.⁽²⁾

The patient demonstrated by intradermal technique a large immediate wheal-and-flare reaction at a 1:100 dilution of staphage lysate (Delmont Laboratories, Strathmore, PA; *Staphylococcus aureus* serologic types I and III with polyvalent staphylococcus bacteriophage). He was nonreactive to intradermal mixed respiratory vaccine (Hollister-Stier, Spokane, WA; *Staphylococcus aureus*, *Streptococcus viridans*, non-hemolytic streptococcal pneumonia, *Brahmella catarrhalis*, *Klebsiella pneumonia*, and *Haemophilis influenza*).

Antibody determinations by ELISA technique demonstrated significant elevations of IgG and IgE antibodies to *Staphylococcus aureus* at 2 times that of control. IgG and IgE levels were consistently higher than the control for mixed respiratory vaccine antigen but did not reach levels of significance.

Case report 3

A 7-year-old Turkish male in previous good health presented in July of 1993 with a gradual onset of tender, mildly pruritic palpable lesions on his legs, arms, and trunk. The lesions evolved over 10 days into erosions with pustular formation, especially on the legs (Fig. 3). The physical examination was associated with multiple oral aphthous ulcers and hepatosplenomegaly. Routine blood chemistries, complete blood count, chest roentgenogram, and blood, throat, and urine cultures were all within normal limits. The erythrocyte sedimentation rate was elevated at 60 mm/M and serum antibody screening was positive to hepatitis B and C surface antibodies and negative to hepatitis B and C surface antigen. Serum IgG antibodies to cytomegalovirus and Epstein-Barr virus were positive with IgM to both viruses negative. Quantitative immunoglobulins and serum complement levels were normal.

The differential diagnosis included insect bites, atypical varicelliform eruption, papular urticaria, and cutaneous bacterial hypersensitivity.

The treatment initially consisted of a 2-week course of 300,000 IU/kg penicillin G, 15 mg/kg Amikacin, and 3 mg/kg hydroxyzine hydrochloride. The erythrocyte sedimentation rate returned to normal, however, the old skin lesions evolved into 1–2 cm hyperpigmented macules and new erythematous macules with palpable subcutaneous nodules appeared.

A skin biopsy was performed that revealed panniculitis with vasculitis. A decline of the erythrocyte sedimentation rate and regression of individual lesions did not support a diagnosis of vasculitis. Although some lesions regressed, new lesions appeared until therapy with prednisone was initiated for a presumptive diagnosis of chronic cutaneous bacterial hypersensitivity. The regimen was 300 mg prednisolone iv monthly and oral alternate day 10 mg daily therapy for 3 months. Now, the patient is symptom free without medication.

Concomitant investigations into the immunologic mechanism was limited due to the patient being in Ankara, Turkey and the investigators located in Chicago, Illinois. Skin testing with bacterial antigens was

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FIG. 3. Case 3.

not done. Serum, however, was collected and sent for study. The following studies were carried out on Case 3.

MATERIALS AND METHODS

Enzyme-Linked Immunosorbent Assay (ELISA)

ELISA assays for the detection of IgG and IgE to bacterial antigens were performed using the methods of Voller et al.⁽⁴⁾ and Sepulveda et al.⁽⁵⁾ Using Immulon polystyrene micro ELISA plates (Greiner and Sons, Nurtigen, West Germany) and the appropriate washes and incubation periods, the following reagents were added in sequence: Staphage lysate (Delmont Laboratories, Inc., Swartzmore, PA) or mixed respiratory vaccine (Miles Inc., Elkhart, IN) both at 1:1000 dilutions, serial dilutions of the patient or control sera, rabbit antihuman IgG (Accurate Chemical & Scientific Corp., Westbury, NY) or goat antihuman IgE (Sigma Chemical Company, St. Louis, MO), alkaline phosphate-conjugated goat antirabbit IgG (Sigma Chemical Co., St. Louis, MO) or alkaline phosphate-conjugated rabbit antigoat IgG (Sigma Chemical Co., St. Louis, MO), and phosphatase substrate (Sigma Chemical Co., St. Louis, MO) 1 mg/ml in 10% diethanolamine buffer. The optical density of each well was read at 405 nm on a Biotek automated microplate reader model EL 312 (Biotek Instruments Inc., Winooski, VT).

RESULTS

The optical densities reflect the amount of specific IgG and IgE antibodies in the test serum, and elevations 1.5 to 2 times control are considered significant.

In case 3 significant levels of IgG and IgE antibodies were present against mixed respiratory vaccine reacting greater than 1.5–2 times control (see Table 2). IgG and IgE antibodies to staphage lysate did not reach levels of significance.

TABLE 2. SUMMARY OF ELISA RESULTS—CASE 3

ELISA OD ^b (mean)	MRV ^a	
	Controls (mean)	Patient (mean)
IgG (1:10)	0.694	1.48
IgG (1:100)	0.432	0.675
IgE (1:10)	0.174	0.242

^aMixed respiratory vaccine (Miles, Inc., Elkhart, IN).

^bElisa OD, enzyme-linked immunosorbent assay optical density.

DISCUSSION

A third case of cutaneous bacterial hypersensitivity (CCBH) is presented. It fulfills all but 1 of our 5 listed diagnostic criteria (Table 3). All 3 cases considered and excluded a variety of infectious and systemic diseases. By exclusion the most likely explanation is bacterial hypersensitivity. This is known to be a major course of cutaneous lesions seen in leprosy,⁽⁶⁾ and tuberculosis.⁽⁷⁾ Hypersensitivity to common organisms that populate the skin has been subject of other investigations in man^(8–10) and animals.^(11–16)

All 3 patients had several nondiagnostic skin biopsies or a biopsy that did not correlate clinically and lacking laboratory support. The 3 patients did not respond to therapeutic trials of antibiotics but had a dramatic response to moderate doses of prednisone or prednisilone. The first two cases remain disease free off prednisone for 9 and 4 years, respectively. The second case requires occasional topical corticosteroid. The third patient is on a tapering low dose of alternate day prednisilone without recurrence of lesions.

Skin testing results and antibody determinations for specific IgE and IgE to *Staphylococcus aureus* were consistent with our diagnosis in the second patient, but unrevealing in the first. Skin testing could not be done in the third case due to patient location, however IgG was significantly present for mixed respiratory vaccine. The immunopathogenic mechanisms may be multiple in this disease in which few organisms are introduced into the skin with minimal trauma. IgE antibody, IgG immune complex formation, and lymphocyte reactivity may all contribute at some phase in the generation of the progressive lesions that are limited to local involvement. This hypothesis has been suggested for the mechanism of lung damage in allergic bronchopulmonary aspergillosis, which is similarly reversed and controlled with moderate to low dose corticosteroids. Numerous bacteria are present on the skin and any one of these may induce hypersensitivity, varying from patient to patient. This hampers the choice of antigen for skin testing and ELISA antibody determinations. This would explain the variety of bacterial responses in our 3 cases.

TABLE 3. DIAGNOSTIC CRITERIA FOR CCBH^a

1. Chronic indolent recurrent inflammatory lesions
2. Failure to respond to systemic antibiotics
3. Multiple nondiagnostic skin biopsies
4. Exclusion of other possible etiologies
5. Response to oral corticosteroids either as complete remission or control with maintenance low-dose alternate day prednisone

^aFrom Bernstein JA, et al. Chronic cutaneous bacterial hypersensitivity dermatopathy: A second case and six year evaluation of the first case. *Allergy Proc* 1991;12:261–265. Used with permission.

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In summary, the purposes of this report is to alert clinicians to this disfiguring and frightening chronic cutaneous dermatopathy. The treatment appears to be safe, inexpensive, and effective.

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