

# Cutaneous Granulomas Masquerading as Tuberculoid Leprosy in a Patient with Congenital Combined Immunodeficiency

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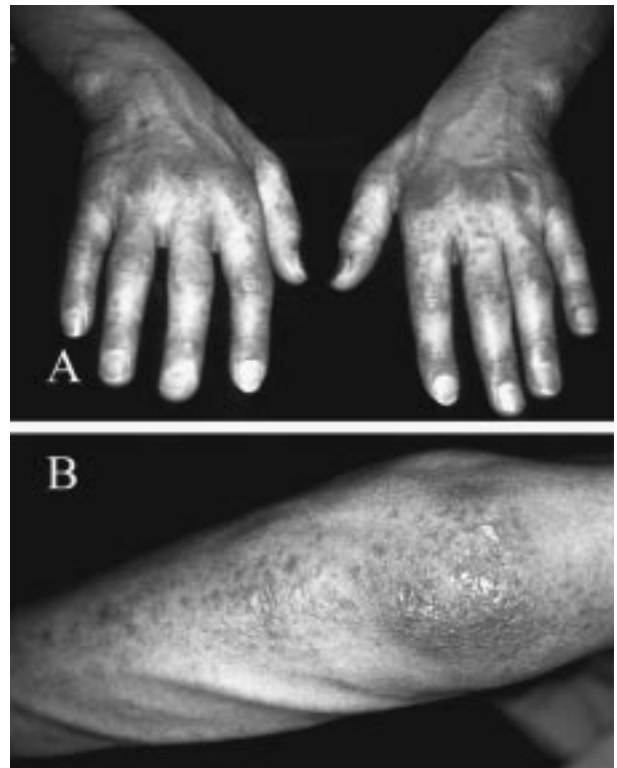
## Abstract

Combined immunodeficiency disorders are characterized by abnormalities in cellular and humoral immunity. This classification includes common variable immunodeficiency (CVI), a primary immunodeficiency disorder characterized by hypogammaglobulinemia, recurrent bacterial infections, and significant T-cell abnormalities. Associated autoimmune diseases include rheumatoid arthritis, pernicious anemia, idiopathic thrombocytopenic purpura, and systemic lupus erythematosus. Granulomatous lesions in lymphoid tissues, solid organs, and skin have been reported. We describe a patient with CVI who developed cutaneous granulomas with perineural invasion; to our knowledge, this is a previously undescribed feature.

**Key Words:** Tuberculoid leprosy, cutaneous granulomas, immunodeficiency.

## Case Report

A 32-YEAR-OLD MAN who had recently arrived in the U.S. from Kuwait was diagnosed with common variable immunodeficiency (CVI) in 1988, based upon subnormal immunoglobulin levels and multiple infections. These infections included herpes zoster, viral warts, purulent knee infections, oral candidiasis, chronic diarrhea, pneumonia and iridocyclitis. In 1996, a skin biopsy specimen of a lesion on the left elbow demonstrated features of a rheumatoid nodule. He had been treated with intravenous immunoglobulin with partial success. He was then referred for evaluation of persistent skin lesions that had been present for the past eighteen months. Examination revealed numerous indurated, erythematous and pink-red macules and papules located over the extensor aspect of the forearms and legs. The distribution of the lesions also included the dorsa of the hands (Fig. 1A) and feet, with particular prominence over the metacarpophalangeal and interphalangeal joints of the hands. A plaque on the left elbow had some central scaling (Fig. 1B). There was decreased sensation to pain and light touch in the C5–C6 and L3 distribution. On abdominal examination, there was splenomegaly.



**Fig. 1.** (A) Macules and papules on the dorsa of the hands, with particular prominence over the joints. (B) Multiple, indurated, erythematous and pink-red macules on forearm and a plaque with superimposed scaling on the elbow.

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The patient's lymphocyte screen, shown in Table 1, reveals a generalized lymphopenia with a low B-cell population.

A biopsy specimen from the left forearm revealed noncaseating granulomata in the superfi-

**TABLE 1**  
*Patient's Laboratory Data*

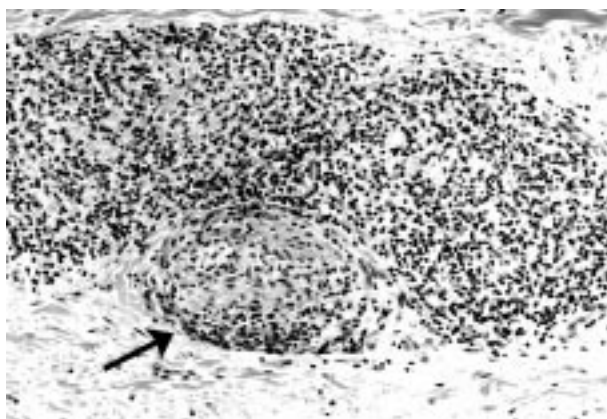
	Cells per mm <sup>3</sup>	Normal range (cells per mm <sup>3</sup> )
T total	570	750–2500
T helper	380	480–1700
T suppressor	190	200–1200
NK cells	50	135–525
B cells	10	75–375
% total B cells	1	5–15

NK = natural killer

cial and deep dermis, with prominent perivascular inflammation (Fig. 2). An unusual feature was the variable infiltration of small nerves by mononuclear cells, illustrated in the deep margin of the biopsy, which is not shown in Fig. 2. The immunohistochemistry of the mononuclear cells was positive for CD45RO, CD43, and CD68, supporting a predominantly T-cell infiltrate with occasional histiocytes. No polymorphs or eosinophils were noted. Special stains for acid-fast bacilli (including Fite and AFB) polymerase chain reaction assay revealed no evidence of mycobacterial infection. Culture for leishmaniasis was negative. Bacteria and fungi were not seen in or cultured from the biopsy specimen. A culture for echovirus was negative.

### Discussion

Granulomatous lesions in lymphoid tissues, solid organs, and skin are well-recognized manifestations of chronic immunodeficiency disorders, including chronic granulomatous disease (CGD) and CVI (1). In patients with CGD,



**Fig. 2.** Skin biopsy specimen showing mononuclear cells, primarily lymphocytes, which are focally organized into poorly formed granulomas (arrow) [hematoxylin-eosin stain; original magnification x200].

granulomas occur in the lung, liver, and gastrointestinal tract, and rarely in the skin (2). In contrast, there have been reports of cutaneous, as well as visceral and lymphoid, granulomas in patients with CVI, although the incidence rate is not known (3–27). Fasano et al. (20) described the development of noncaseating granulomas in individuals with CVI as a “sarcoid-like” syndrome. They found 8 cases among 80 patients with CVI who had clinical findings, including multiple noncaseating granulomas, consistent with sarcoidosis (20). Two other reports tell of granulomas developing prior to the diagnosis of CVI (3, 13). Cutaneous granulomas were present in 9 of the 25 reported cases describing granulomas in association with hypogammaglobulinemia.

Twelve previous reports (3–11, 25–27) described 15 patients with CVI who developed cutaneous lesions (Table 2). Our patient shared many clinical features with these cases. The mean age at presentation was 33; our patient was 32. Along with indurated and erythematous lesions, there were red macules and papules. Seven of the 15 patients demonstrated scaling, which had previously received little attention (3–5, 9, 11). The most common anatomic sites were the extremities for 12 of the 15 (3–5, 8–11, 25, 26). Granulomatous skin disease in an acral pattern may be a manifestation of early immunodeficiency (3). In two reports, the lesions were noted to be prominent over the joints of the dorsal hands, similar to our case (8, 10).

The histopathologic features of this case are also similar to those seen in previously reported cases. Nine of the 15 patients demonstrated noncaseating granulomatous inflammation (3, 4, 6, 7, 9, 10, 25, 27). Three of the remaining 6 had characteristics of palisading granulomas (3, 26). This histologic picture can be associated with rheumatoid nodules, as well as with granuloma annulare and necrobiosis lipoidica (24). Interestingly, rheumatoid arthritis is a commonly encountered autoimmune disease in patients with CVI. An infectious etiology is ruled out when bacteria, acid-fast bacilli (AFB) and fungi are not found. Our patient's specimen revealed no evidence of AFB by Ziehl-Neelsen stain (3).

The skin biopsy specimen from our patient was unique in that there was perineural infiltration by granulomas. This, in conjunction with decreased sensation on physical examination, raised the possibility of tuberculoid leprosy as the underlying etiology. In our case, the biopsy showed a chronic inflammatory process that was

**TABLE 2**  
*Literature Review Summarizing Previously Reported CVI Cases with Cutaneous Granulomas.*

Case	Reference	Age at Presentation (year)	Clinical Features	Location	Biopsy Results	Treatment
1	3	2	Indurated erythematous scaly papules	Face, extremities	Granulomatous dermatitis with necrobiosis	Prednisone
2	3	9	Indurated erythematous scaly plaques	Face, extremities	Granulomatous dermatitis with elastic fiber degeneration	Interleukin 2, switched to prednisone
3	3	3	Firm erythematous plaques with ulcerated crusted center	Legs, arms	Noncaseating granulomas	Prednisone
4	4	37	Scaly papules and nodules	Legs, forearm, sternum, eyelid	Epithelioid noncaseating tubercles	Prednisone
5	5	51	Scaly brown-red macules, papules, and plaques	Extremities, trunk, scalp	Nonspecific inflammatory process and caseating epithelioid granulomas	Prednisone
6	6	45	Excoriated papules	Buttocks	Nonspecific noncaseating granulomas	None
7	7	77	Macular skin rash	(not reported)	Noncaseating granulomas	Prednisolone
8	8	43	Violaceous papules	Joints of dorsal hands, elbows, knees, lumbar region	Necrotizing granulomatous inflammation	Prednisone
9	9	37	Erythematous scaling plaque and erythematous firm papules	Joints of left hand, right hand, wrist, distal arm, knees	Lymphohistiocytic perivascular infiltrate with epithelioid granulomas	Prednisone
10	10	42	Erythematous maculopapules	Legs, arms	Noncaseating epithelioid granulomas	Cyclosporine
11	10	49	Maculopapules	Legs, arms, face	Noncaseating epithelioid granulomas	Prednisolone, topical steroids
12	11	9	Indurated erythematous plaques with scaling and atrophy	Lower leg, face	Lymphohistiocytic granuloma with surrounding caseating necrosis	Prednisone
13	25	18	Reddish-violaceous firm papules	Legs	Noncaseating epithelioid granulomas	None
14	26	64	Papulonodular ulcerative rash	Right leg	Inflammatory infiltrate with central necrosis and palisading granuloma	Intravenous immunoglobulins
15	27	17	Erythematous indurated plaque	Face	Noncaseating epithelioid granulomas	None
Present Case	—	32	Indurated erythematous and pink-red macules and papules	Extremities	Noncaseating granulomas with perineural invasion	None

not highly organized, as is seen in tuberculoid leprosy and sarcoidosis. Further, AFB stains (Kinyoun and Fite) and polymerase chain reaction were negative for leprosy. Therefore, the perineural invasion may represent an extension from the prominent perivascular infiltration.

Although this patient was diagnosed with CVI in 1988 in Kuwait, x-linked agammaglobulinemia (XLA) cannot be ruled out, in view of the low number of circulating B cells. But it is unlikely that this patient has XLA, given the lack of family history, and the presence of significant T-cell abnormalities and granulomatous lesions. One patient with XLA was reported to have developed caseating granulomas (28). Patients with XLA are able to mount normal immune responses to viral infections. Our patient, however, had a past medical history significant for viral warts and herpes zoster. Patients with XLA are occasionally susceptible to enteroviral infections, such as echovirus, which affects many organs, including the skin (29). Ultimately, the distinction between CVI and XLA is made by genetic testing. The diagnosis of CVI in this patient was confirmed.

The pathogenesis of the granulomatous lesions in patients with CVI is not completely understood (3). It is hypothesized that T-cell deficiencies, antigen processing defects and an imbalance in production of cytokines are important factors in their formation (9). Others suggest a genetic mechanism supported by the frequent occurrence of a tumor necrosis factor allele in CVI patients who have had granulomatous disease (30). Granulomas in CVI may regress spontaneously or after treatment with corticosteroids. Our patient was treated with an experimental immunotherapy, interleukin-2 (IL-2), but due to his return to Kuwait, he was followed for only one month after initiation of treatment. At that time his skin lesions had not yet shown satisfactory improvement. Although the patient's histopathology resembled that of tuberculoid leprosy, an infectious etiology could not be conclusively demonstrated in his case.

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