Acta Dermatovenerol Croat 2010;18(2):107-113 CASE REPORT

Cutaneous Granulomas in Common Variable Immunodeficiency: Case Report and Review of Literature

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Received: October 19, 2009
Accepted: January 8, 2010

SUMMARY Common variable immunodeficiency (CVID) is a heterogeneous disease characterized by recurrent infections, autoimmunity, malignancies, and granulomatous inflammation. Granulomatous lesion is one of the important manifestations of CVID, which continues to be unknown to many clinicians. While noncaseating granulomatous lesions can be detected in lungs, liver, spleen or conjunctiva of CVID patients, there are only few reported cases with skin granuloma. This report presents a 27-year-old female with multiple persistent cutaneous granulomatous lesions on both hands. The patient had been well until age of 20 years, when she developed these skin lesions and frequent upper respiratory infections and bacterial pneumonia. Also, she experienced recurrent diarrhea (more than 10 episodes). Laboratory evaluation showed decreased serum levels of all immunoglobulin isotypes and low specific antibody responses. The diagnosis of CVID was based on clinical and laboratory findings. Intravenous immunoglobulin therapy at a dosage of 400-500 mg/kg monthly was introduced and improved skin lesions. In conclusion, taking history of recurrent infections and measuring immunoglobulin levels can be suggested in patients with granulomatous lesions instead of other expensive tests.

KEY WORDS: common variable immunodeficiency, noncaseating cutaneous granulomatous lesions, immune dysregulation

INTRODUCTION

Common variable immunodeficiency (CVID) is the most prevalent symptomatic primary antibody deficiency with an incidence estimated at 1:10000-1:50000 (1). CVID is characterized by low levels of IgG and IgA and/or IgM, and impaired antibody response, leading to recurrent infections, mostly in

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the respiratory and gastrointestinal tracts (2,3). A significant proportion of CVID patients also manifest features of immune dysregulation, including autoimmune/malignant diseases and granulomatous inflammation of the lymphoid organs or the skin (4). Typical histology shows noncaseating granulomatous (sarcoid-like) lesions without evidence of infection (5). The prevalent sites of noncaseating granulomatous lesions reported were the lungs, liver, spleen or conjunctiva in CVID (6), while only few CVID cases have been reported in combination with skin granulomas (7).

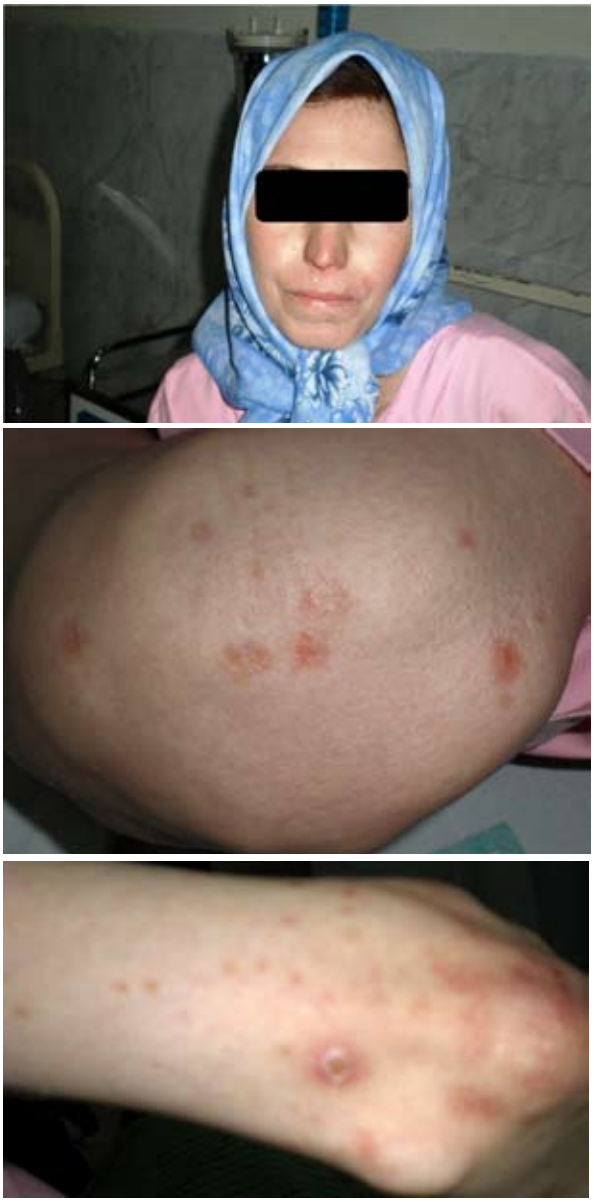

Figure 1. Clinical photograph of the skin granulomatous lesion rash of the patient's face and extensor surface of the elbows and forearms.

We report on a female patient with CVID diagnosed at age 27, presenting multiple persistent cutaneous granulomatous lesions on her limbs.

CASE REPORT

A 27-year-old woman born to consanguineous parents had six healthy siblings and had been well until age 20, when she developed frequent upper respiratory infections, pneumonia and recurrent diarrhea. At 26 years of age, the diagnosis of ulcerative colitis and duodenal villous atrophy was made after gastrointestinal endoscopy. Although the patient experienced recurrent episodes of respiratory infections and gastrointestinal manifestations, the diagnosis of CVID was not made until age 27, once she presented skin lesions. She reported the presence of constitutive symptoms such as fatigue, weight loss and fever. In addition, erythematous papules and small plaques that enlarged gradually were noticed on her limbs.

On physical examination, several non-pruritic and indurated papules and small plaques were scattered on her face and limbs, especially on the extensor surface of her both forearms and dorsal hands (Fig. 1). Finger clubbing was also present. Hepatomegaly and splenomegaly were detected and confirmed by ultrasonography. Ophthalmologic, neurologic and cardiologic examinations were normal, and there was no evidence of regional lymph node enlargement.

Laboratory findings were as follows: WBC 7000/mm^3 (64% neutrophils and 26% lymphocytes); hemoglobin level 11.8 g/dL; total serum protein 5.9 g/dL; albumin ratio 54.5% (normal range: 44%-55%); serum IgG, IgM and IgA 77 (normal range: 700-1600) mg/dL, 74 (normal: 40-230) mg/dL and 13 (normal range: 70-400) mg/dL, respectively; and cluster of differentiation markers normal (67% CD3, 33% CD4, 32% CD8, 10% CD16 and 6% CD19). Anti-gliadin antibody, anti-tissue transglutaminase (TTG), angiotensin converting enzyme (ACE), SGOT, SGPT, alkaline phosphate, bilirubin (total/direct) and erythrocyte sedimentation rate (ESR) were normal. Serum calcium, serum phosphate and serum ACE were normal. Anti nucleotide antibody (ANA) and rheumatoid factor (RF) were negative.

Spiral high resolution computed tomography (HRCT) scan indicated bronchiectasis. Pulmonary function test showed mild airway obstruction (FEV1 79%, FVC 94.5%, FEV1/FVC 87% and MMEF 45%) and DLco/VA result of gas exchanging tests was 4.79 mL/mm Hg/min/L (75% of normal).

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Abdominal CT scan revealed multiple hypodensities in the liver and spleen, while fine needle biopsy of the liver showed chronic hepatitis. Tuberculosis infection was excluded by direct smear and culture for acid-fast bacillus (AFB). All repeated microbiological studies failed to isolate any microorganism.

Skin biopsy showed a classic histopathologic pattern of noncaseating granulomatous lesion, frequently identified in CVID patients, with focal infiltration of macrophages, histiocytes, multinucleated giant cells, epitheloid cells, lymphocytic cellular infiltrate and plasma cells surrounded by fibrous tissue and palisading necrotizing granuloma. It is very similar to perforating granuloma annulare (PGA) features that usually present in the dorsum of children's hands (Fig. 2).

The diagnosis of CVID was based on clinical and laboratory findings. Regular intravenous immunoglobulin (IVIg) therapy at a dose of 500 mg/kg every 4 weeks was introduced. Within two months of IVIg initiation, skin lesions resolved completely without any scar formation. The lesions did not aggravate during pregnancy, but her skin lesions recurred during IVIg withdrawal. She is married to her cousin and their two daughters aged 6 and 2.5 years are in good health so far.

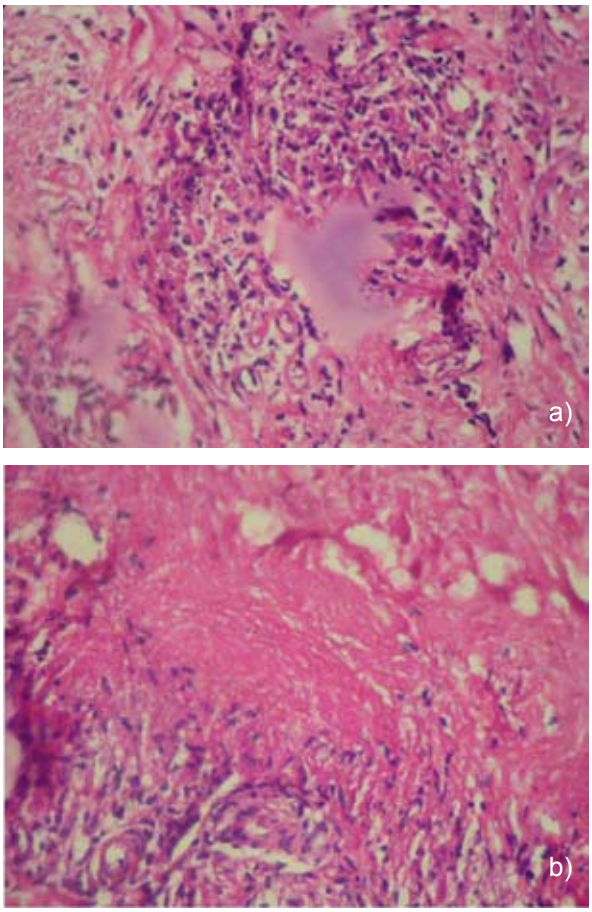

Figure 2. Skin biopsy: (a) small granulomatous lesion with a central pink area surrounded by inflammatory cells in the dermis (X400, H&E); (b) central amorphous area surrounded by inflammatory cells in the dermis (X400, H&E).

DISCUSSION

CVID is a heterogeneous group of disorders with a wide variety of clinical and immune manifestations, which could be due to heterogeneity of the underlying mechanisms (1-4,8,9). Patients with CVID are more susceptible to recurrent infections, especially those caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* in the respiratory and gastrointestinal tracts. Some patients develop autoimmune and malignant diseases, as well as granulomatous inflammation (2,3).

Granulomatous lesions have been reported in 5.4% to 22% of CVID patients (6,10), involving the lungs, liver, spleen or conjunctiva (6) and rarely the skin (7). Our patient had several episodes of respiratory infections and recurrent diarrhea requiring hospital admission since age 20. At age 27, when she was diagnosed with CVID, the scattered skin lesions appeared on dorsum of her both hands and nose as the most common sites of granuloma formation in CVID (Table 1) (5,10-16).

In 14 of 15 cases reported, cutaneous granulomatous lesions occurred at a mean of 4 (range 1-34) years after CVID diagnosis, whereas in only one case reported by Sidwell *et al.* (15) skin lesion was detected before the diagnosis of CVID. In male CVID patients, the rate of granulomatous skin lesions is about twofold that recorded in female CVID patients. Cutaneous granulomatous manifestation of CVID includes generalized persistent infiltrated erythematous plaques which usually are scaly and atrophic. Lesions are often found in association with visceral granulomatous lesion (5,10-12,17) rather than isolated cutaneous lesion (13,18,19).

In our patient, liver biopsy for hepatomegaly suggested chronic hepatitis rather than granulomas. Histopathologic features of cutaneous granulomas have been reported as caseating (tuberculoid) (20) or noncaseating (sarcoid as the most prevalent feature) (13), and necrobiotic (non-tuberculoid non-sarcoid) (21). Our case highlighted the distinguishing difficulties in differential diagnosis of granulomatous lesions between sarcoidosis and

Table 1. Previous case reports on cutaneous granulomatous lesions in common variable immunodeficiency patients

Number of cases studied	Sex	Age (yrs)	Type	Location	Histopathology	Treatment	Reference number
1	-	37	Scaly papules and nodules	Extremities + sternum + eyelid	Epithelioid noncaseating tubercles	Prednisone	10
1	-	51	Scaly brown-red macules, papules and plaques	Extremities + trunk + scalp	Mixed (sarcoid + tuberculoid) (nonspecific inflammatory process and caseating epithelioid granulomas)	Prednisone	11
1	-	45	Excoriated papules + ulcer	Buttocks	Nonspecific noncaseating granulomas	-	17
1	-	77	Macular skin rash	(not reported)	Noncaseating granulomas	Prednisone	32
6		5-15	Papules + dermatitis		Sarcoid like	Corticosteroids and IVIg	18
3	-	2	Indurated erythematous/scaly papules	Face + Extremities	Granulomatous dermatitis with necrobiosis	Prednisone	31
		9	Indurated erythematous/scaly papules	Face + Extremities	Granulomatous dermatitis with elastic fiber degeneration	IL-2 and Prednisone	
		3	Firm erythematous plaques with ulcerated crusted center	Extremities	Noncaseating granulomas	Prednisone	
1	-	43	Plaques + Gottron violaceous papules	Extremities + face	Necrotizing granulomas	Systemic corticosteroids	12
2	F	42	Maculopapular rash	Extremities	Noncaseating epithelioid granulomas	Cyclosporine and antibiotic	38
	-	49	Maculopapular rash	Extremities + face	Noncaseating epithelioid granulomas	Systemic corticosteroids	
5	-	Child	Plaques + nodule + ulcer (4 erythema/1 erythematous nodule)	Extremities + face	Necrobiotic palisading granuloma	Corticosteroids, antibiotics and anti-TB	5
1	M	9	Erythematous papules + atrophy	Extremities + face	Caseating (tuberculoid) without germ	Prednisone and IVIg	13
1	M	37	Papular eruption + chronic dermatitis	Extremities	Lymphohistiocytic perivascular infiltrate with epithelioid granulomas	Prednisone	19
1	-	18	Violaceous firm papules	Extremities	Noncaseating epithelioid granulomas	-	29
1	F	17	Erythematous plaque/plaque	Cheek + Extremities	Noncaseating granulomas	Spontaneous regress	30
1	M	64	Erythematous papules+ pustule/ Papulonodular ulcerative	Extremities	Necrobiotic palisading granuloma	IVIg	14
1	M	32	Erythematous papules and maculae	Extremities	Noncaseating granulomas	Interleukins, cyclosporine and corticosteroids	34
1	M	21	-	Scalp	Noncaseating epitheloid granulomas	Etanercept	20
1	F	8	Pityriasis lichenoides	Face + Extremities	Noncaseating granulomas	Erythromycin	24
1	M	22	Furunnculosis	Extremities	Noncaseating granulomas	IVIg	15
1	M	60	Violanus plaque + nodules	Extremities	Necrotizing granulomas	Tetracycline	21
1	M	66	Reticulate rash + psoriatic	Extremities	Noncaseating granulomas	Oral steroid and Azathioprine	25
1	M	18	Multiple nodular granulomatous	Extremities	Noncaseating granulomas	Etanercept	26
1	M	29	Vitiligus patch + warts	Extremities + chin	Non-sarcoidal non-tuberculoid granuloma	IVIg and PUVA	27
1	F	8	Erythema + crustae + hyperkeratosis	Extremities	Necrotizing granulomas without germ	Anti-TB	16

F: Female; M: Male; IVIg: intravenous immunoglobulin

sarcoidal (noncaseating) manifestation of CVID, while skin involvement is present in 20%-35% of sarcoidosis patients, but is unusual in CVID (7,22). Long-term delay in diagnosis and inappropriate use of steroid therapy could lead to end-organ damages, whereas awareness of this presentation of CVID may result in early diagnosis.

In the case presented, there were some key points to distinguish CVID from sarcoidosis, such as a history of recurrent infections, low immunoglobulin levels, and disability to produce antibody against specific antigens such as pneumococci, *Haemophilus influenzae* and tetanus toxoid. Also, presentation of bronchiectasis only six months after the diagnosis, the cytotoxic T cells (CD8) outnumbering the T-helper cells (CD4) with a counted CD4/CD8 ratio below 1, and failure of the lesions to respond to oral glucocorticoids (23) assisted in the diagnosis of CVID.

Autoimmune disease (ulcerative colitis found in our patient) in association with CVID granulomatous lesion is indicated in other reports (24-27) and may have a common pathogenesis pathway. Granulomatous lesions may arise from unregulated sterile inflammation (7) and altered cell mediated and humoral immune responses (28).

It is important to emphasize that we started administration of IVIG therapy for recurrent infections and systemic manifestation like inflammatory bowel disease, while it has also a beneficial effect on the regression of granulomatous lesions. The management for cutaneous granulomatous lesions may not be necessary in localized lesions (29). Low doses of topical (30) or systemic (5,31,32) corticosteroids alone (33,34) or with the addition of other immunosuppressants such as cyclosporine (35) proved successful for cutaneous granulomatous lesions in association with CVID, and so did anti-TNF agents, infliximab (mAb against TNF-alpha) (36,37), etanercept (20), cyclosporin with interleukin (20,31) and IVIG (15) when the process is progressive (25). Interleukin therapy (24), antituberculous agents and broad-spectrum antibiotics (38) and cyclosporin therapy have been suggested to be effective in altering the clinical course (5,14), as well as dapsone and hydroxychloroquine (37).

CONCLUSION

Granulomatous lesions are one of the manifestations of CVID in patients presenting with recurrent infections and immunoglobulin abnormality. The best message is to take thorough history for recurrent infections and to measure immunoglobulin levels routinely instead of other expensive tests in all patients with features suggesting granulomatous lesions.

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For sunspots – Orizon cream.
(From the collection of Mr. Zlatko Puntijar; year 1930)