

BRIEF ARTICLES

CVID-associated Granulomatous Dermatitis Resembling Sarcoidosis

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ABSTRACT

Common variable immunodeficiency (CVID) is a disorder of the adaptive immune system predominantly characterized by hypogammaglobulinemia and variable T-cell abnormalities. Patients classically present with recurrent sinopulmonary infections, but interstitial lung disease, autoimmunity, and lymphoproliferative disorders are also common. Approximately 10% of CVID patients are reported to have noncaseating granulomatous disease that is indistinguishable from sarcoidosis on pathology; it most commonly affects the lungs, lymph nodes, and liver. We present the case of a 75-year-old male with known CVID who presented with granulomatous dermatosis on the trunk and extremities in the setting of progressive cognitive impairment, new-onset cough with ground glass opacities on chest computed tomography in the setting of stable mediastinal lymphadenopathy, and the presence of granulomas on prior bone marrow biopsy, initially suggesting the diagnosis of sarcoidosis. Though clinically and histologically similar, it is important to make the distinction between CVID-associated granulomatous disease and sarcoidosis in order to select appropriate treatment.

INTRODUCTION

Our patient is a 75-year-old male former smoker with a past medical history of common variable immunodeficiency (CVID) on weekly subcutaneous human immunoglobulin, hypertension, hyperlipidemia, coronary artery disease, and chronic kidney disease, who presented to the hospital with new-onset weakness and ataxia, as well as urinary and fecal incontinence. He had been diagnosed with CVID four months prior to presentation due to three recurrent episodes of pneumonia over a two month period. He had no prior history of other autoimmune or inflammatory

disease. Review of systems was notable for low-grade fevers and intermittently-productive cough for several months.

Dermatology was consulted for evaluation of a pruritic full-body rash that had been present for approximately one year. Previous treatment with ultrapotent topical steroids did not provide any benefit; however, a seven-day oral prednisone taper resulted in partial improvement of pruritus and mental status. Skin examination was notable for diffuse pink to red papules with overlying fine white scale (Figure 1), as well as isolated linear excoriations on the trunk and extremities. Additionally, there were blanchable red to

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violaceous macules with minimal scale on the bilateral palms and soles.

Skin biopsies were performed on the left arm and back and revealed multiple noncaseating dermal granulomas associated with a sparse cuff of lymphocytes (Figure 2). Given his clinical presentation, immunocytochemical staining against *Treponema pallidum* (monoclonal antibody to *T. pallidum*) was performed to rule out syphilis and was negative. Further staining with CD30 showed scattered reactive CD30-positive cells, thus ruling out clonal lymphoproliferative disorders. Of note, a prior bone marrow biopsy showed noncaseating granulomatous disease with negative fungal and mycobacterial stains (Figure 3). Workup was notable for a normocytic anemia (hemoglobin 10.8 g/dL), thrombocytopenia (platelet count 117 K/mcL), elevated creatinine (1.71 mg/dL), and elevated alkaline phosphatase level (201 IU/L). Erythrocyte sedimentation rate was within normal limits, but C-reactive protein was elevated at 25 mg/L. Prior serum IgG, IgA, and IgM levels were all below detection. Blood and urine cultures were negative. Chest CT revealed prominent mediastinal lymph nodes (unchanged from earlier CTs), in addition to new patchy, nodular parenchymal disease within the right upper lobe. Head CT and non-contrast magnetic resonance imaging showed chronic small-vessel disease, mild generalized cerebral volume loss, and cerebellar atrophy, but no acute intracranial abnormalities or features consistent with sarcoidosis. Cerebrospinal fluid studies were unremarkable and ruled out infectious or inflammatory causes of encephalitis.

The patient was referred to immunology for further management. The patient was started on prednisone 40mg daily and infliximab 5mg/kg intravenous every 6 weeks (following induction with 5mg/kg at weeks 0, 2, and 6)

for suspected neurosarcoidosis. The patient's skin findings improved dramatically with this treatment regimen, while he also became increasingly alert and responsive to stimuli. However, his cough was persistent and his memory remained poor.

Two months after starting the above regimen, the patient was readmitted to the hospital with fevers to 103.3°F and altered mental status. He developed acute respiratory failure and was diagnosed with *Pneumocystis jirovecii* pneumonia, with prednisone and infliximab likely serving as contributing factors. Despite adequate treatment with a 21-day course of trimethoprim-sulfamethoxazole, the patient failed to return to baseline and required close outpatient monitoring. He was readmitted with fevers of unknown origin (temperature 103.1 °F) and altered mental status.

Figure 1. Skin examination was notable for diffuse pink to erythematous papules with overlying fine white scale, as well as isolated linear excoriations on the trunk and extremities.



During this third admission, he underwent repeat bone marrow biopsy and was found to have Epstein Barr virus-positive Hodgkin's lymphoma. He received a course of high dose steroids without improvement. His hospitalization course was further complicated by acute renal failure, hyperbilirubinemia, metabolic encephalopathy, and ultimately acute respiratory failure requiring intubation and leading to his demise.

Figure 2. A) Scanning photomicrograph of a biopsy from the left arm shows an ill-defined infiltrate of histiocytes and lymphocytes in the upper dermis (hematoxylin and eosin, 2x). **B)** Higher power shows a non-caseating granuloma (hematoxylin and eosin, 20x).

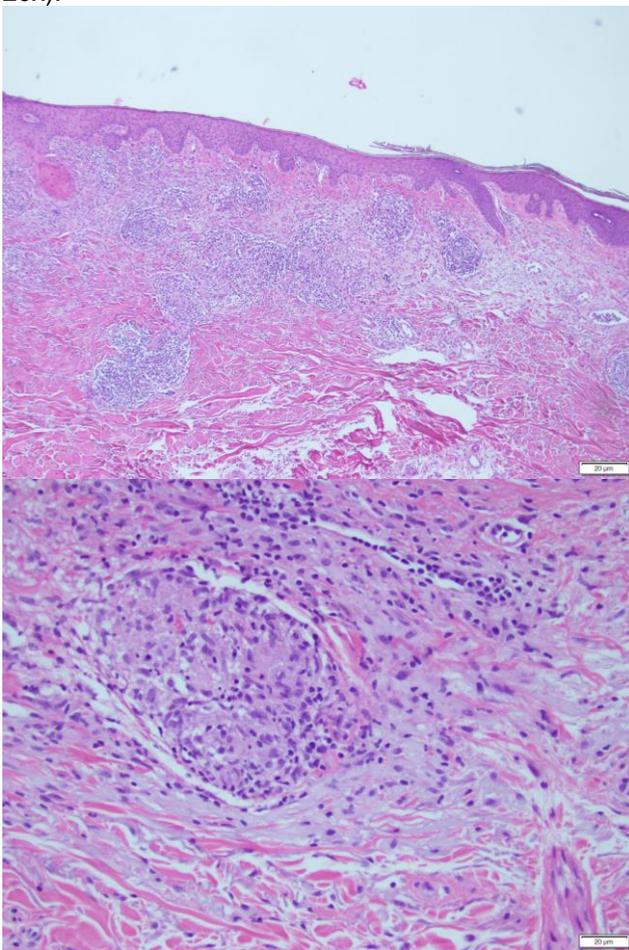
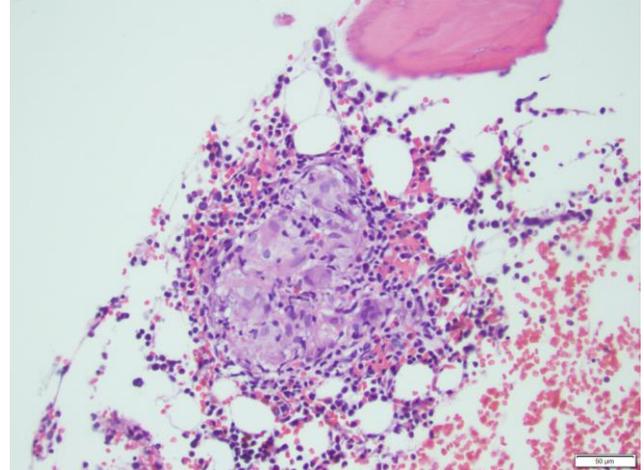


Figure 3. Bone marrow biopsy shows a non-caseating granuloma (hematoxylin and eosin, 20x)



DISCUSSION

CVID is the most common primary immunodeficiency, with an annual incidence between 1:50,000 and 1:200,000. Patients typically present with recurrent sinopulmonary infections, though clinical phenotype is highly variable. Initial clinical manifestations are relatively nonspecific, often resulting in delayed diagnosis and treatment with subsequent increased risk of serious complications including chronic otitis media, deafness, pulmonary fibrosis, bronchiectasis, and cor pulmonale. CVID is also associated with autoimmune disorders and malignancy, with lymphoma being the most common cause of death, primarily of B-cell origin and non-Hodgkin type¹.

Our patient was initially presumed to have sarcoidosis given the presence of noncaseating granulomas on skin pathology and prior bone marrow biopsy, in the context of new-onset cough and neurologic symptoms. Granulomatous disease is observed in approximately 10% of CVID patients. Of those CVID patients with granulomatous disease, the most commonly affected sites are lung (50%), lymph nodes (40%), and liver (30%). Granulomatous

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involvement of the skin or bone marrow is less common, seen in approximately 20% and 5% of CVID patients, respectively^{2,3,4}. Cutaneous involvement in sarcoidosis is more common, with some reports citing up to 35% prevalence, whereas osseous bone involvement is seen in 10-15% of sarcoidosis patients^{5,6}. Cases of sarcoid involving the bone marrow have been reported, although very rare^{7,8}.

Our patient's neurological symptoms were initially attributed to neurosarcoidosis. Though neurosarcoid-like granulomas in the setting of CVID have been reported⁹, this diagnosis was ruled out with normal findings on magnetic resonance imaging of brain and cerebrospinal fluid analysis. Ultimately it was proposed that his progressive cognitive impairment may be explained by an underlying frontotemporal dementia leading to acute decompensation in mental status, secondary to recurrent infections and newly diagnosed lymphoma.

Sarcoidosis and CVID-associated granulomatous disease may be indistinguishable based on clinical and histological features^{2,10,11}. The two entities, however, can be distinguished based upon immunoglobulin levels. Low immunoglobulin (Ig) levels are typical of CVID. A study of 224 CVID patients reported mean IgG, IgA, and IgM levels at initial diagnosis as 258 mg/dL (reference range 768 to 1728 mg/dL), 28 mg/dL (reference range 99 to 396 mg/dL), and 40 mg/dL (reference range 38 to 266 mg/dL), respectively¹². In contrast, sarcoidosis typically presents with polyclonal hypergammaglobulinemia¹⁰.

Finally, it is important to distinguish between the two clinical entities as the management highly differs. While sarcoidosis is typically steroid-responsive, CVID patients with granulomas are treated with IVIG to address their primary immunodeficiency. Treatment

with IVIG allows for an immunosuppressive-sparing option in these patients with baseline immunosuppression, thus potentially avoid some of the complications seen in our patient. Based on some case reports, treatment with IVIG may improve the granulomas as well¹⁰. In some refractory cases, however, TNF-alpha inhibitors have been shown to improve the CVID-associated granulomas¹³.

Foot Note: Authors Jeanette R. Zambito and Pooja R. Shah contributed equally to this work.

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