

Sarcoidosis in Chronic Granulomatous Disease

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ABSTRACT

In addition to increased susceptibility to infections in patients with chronic granulomatous disease (CGD), a higher incidence of sterile inflammatory disorders in these patients has been noted. However, sarcoidosis has not been reported previously in CGD. In this report, we describe two patients who have CGD and a disorder consistent with sarcoidosis on the basis of unequivocal clinical-radiographic presentations, their responses to treatment, and serum angiotensin-converting enzyme levels. Serum angiotensin-converting enzyme levels were measured in 26 other patients with CGD to establish an appropriate reference range. A possible relationship between CGD and sarcoidosis is discussed.

CHRONIC GRANULOMATOUS DISEASE (CGD) is a rare primary immunodeficiency with an incidence of 1 in 200 000 to 250 000 live births.¹ Mutations in any 1 of the 4 genes (CYBB, CYBA, NCF-1, or NCF-2) encoding the subunits (gp91^{phox}, p22^{phox}, p47^{phox}, and p67^{phox}, respectively) of the phagocyte nicotinamide adenine dinucleotide phosphate oxidase complex result in defective production of microbicidal reactive oxidant species.² Patients with CGD therefore are more susceptible to recurrent suppurative infections. Granulomas, typically caseating, in the setting of infections are a hallmark of CGD. The mechanism for granuloma formation remains unclear and may be related to factors such as increased susceptibility to infections and poor clearance of microorganisms. In addition, a significant subset of patients with CGD have noninfectious inflammatory problems that are often autoimmune in character. The reason for this association is poorly understood.

Sarcoidosis, a multiorgan granulomatous disease, occurs at a frequency of 1 to 50 per 100 000 individuals with a cause that remains unknown despite its first description >100 years ago.³ The pathognomonic finding of sarcoidosis is noncaseating epithelioid granulomas, although necrosis is occasionally seen.⁴ Clinically, sarcoidosis can have a spectrum of presentations and severity.⁵ Pulmonary involvement is the most common, occurring in ~90% of the patients, mostly including bilateral hilar lymphadenopathy.⁶ Extrathoracic localizations include peripheral lymph nodes, skin (erythema nodosum, and lupus pernio), eyes (uveitis, iridocyclitis, and keratoconjunctivitis), joints, liver, and spleen. Neu-

rosarcoidosis is a serious and much more rare complication that is seen in 5% to 15% of patients.³ In the absence of specific tests for sarcoidosis, it is essentially a diagnosis of exclusion. However, in addition to typical clinical-radiographic findings and histopathologic evidence of noncaseating granulomas, diagnosis can be supported by raised serum angiotensin-converting enzyme (ACE) levels.

To date, we have been unable to identify a report of sarcoidosis in patients with CGD. Here we report a diagnostic dilemma in 2 patients with CGD and features that are compatible with sarcoidosis and not explainable by their underlying CGD and discuss possible relationships between CGD and sarcoidosis.

CASE REPORTS

Patient 1 is a black female who is from North Carolina and received a diagnosis of autosomal recessive CGD at 4 years of age after recurrent infections of her skin, liver

Key Words: chronic granulomatous disease, sarcoidosis, neurosarcoidosis, angiotensin-converting enzyme

Abbreviations: CGD, chronic granulomatous disease; ACE, angiotensin-converting enzyme; CT, computed tomography; ESR, erythrocyte sedimentation rate; SLE, systemic lupus erythematosus; TNF- α , tumor necrosis factor α ; Th1, helper type 1 T cells

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(abscess), and lungs. She and, subsequently, her 2 siblings were found to lack p47^{phox} in neutrophils. At 12 years of age, she was referred to the Clinical Center at the National Institutes of Health after prolonged high fevers (>1 month) that were not responsive to numerous antibiotics and antifungals (vancomycin, ceftazidime, sulfamethoxazole-trimethoprim, rifampicin, levofloxacin, and amphotericin B). Imaging studies revealed hepatomegaly and a massive splenomegaly with what was thought to be a splenic abscess. Laboratory tests showed pancytopenia and coagulopathy secondary to hypersplenism, which improved with splenectomy. Although a large granuloma with central necrosis was found, there were also numerous small noncaseating granulomas elsewhere in her spleen without evidence of infection. Six months later, she returned with ongoing fevers, headaches at increasing frequency (daily at presentation), and arthritis of her knees bilaterally. Laboratory examination of her knee effusion did not reveal a specific pathology. She denied any weight change, sweats, cough, dyspnea, or skin manifestations. An ophthalmologic examination revealed interstitial keratitis, conjunctival nodules, lacrimal gland enlargement, and chorioretinitis with vascular sheathing in both eyes, worse in the left eye than in the right. Again, no infective causes were found. Specifically, serology for toxoplasmosis, histoplasmosis, syphilis, tuberculosis, and borreliosis was negative. Analysis of cerebrospinal fluid was consistent with aseptic meningitis (clear fluid with lymphocytosis of 45/ μ l with reactive changes, protein 28 mg/dL, and glucose 47 mg/dL). MRI of her head did not reveal a specific pathology except for swellings in the left frontal sinus, which on biopsy revealed noncaseating granulomas. Bilateral mediastinal lymphadenopathy was evident on chest computed tomography (CT) and chest radiograph. Erythrocyte sedimentation rate (ESR) was 56 mm/hour, serum calcium level was within normal range, and serum ACE level was 70 IU/L (our laboratory reference range: 16–52 IU/L) at this point. She received a diagnosis of neurosarcoidosis in view of her neurologic involvement with uveitis, chorioretinitis, and aseptic meningitis. The patient was treated with prednisone (15 mg/day), which brought relief of symptoms. Her course was complicated further by urinary tract infections, a thoracic paravertebral fungal abscess (T10), and fungal osteomyelitis caused by *Paecilomyces variotii* infection. Eighteen months after her first presentation of neurologic symptoms, at age 14, she relapsed with more high fevers, headaches, and severe arthritis of her right knee such that she was restricted to ambulating only with crutches. Radiographs of her wrists revealed fine bony cysts. Despite maintenance of low-dose prednisone, her sarcoidosis progressed rapidly in the following months with development of bilateral papillitis, impairment of visual acuity, and visual field loss (Fig 1A). An intensified course of pulse steroids (starting dose of

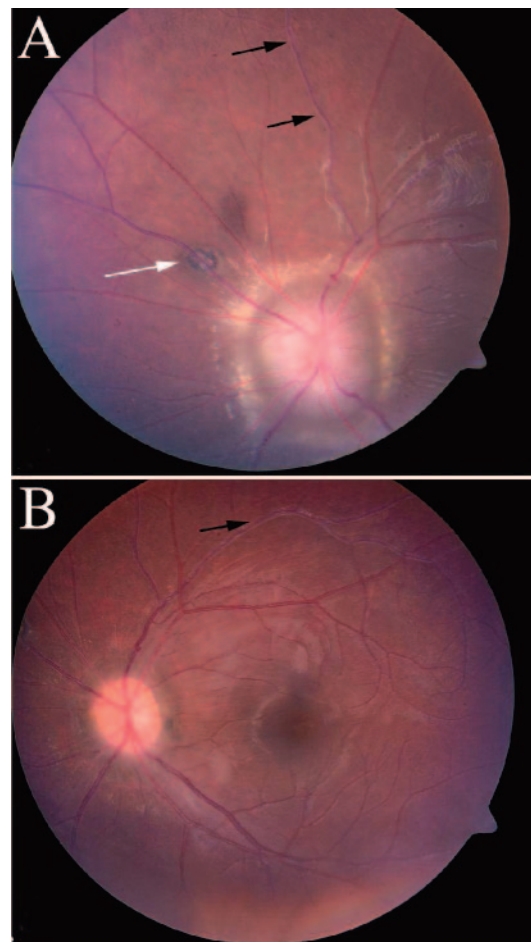


FIGURE 1
 A, Fundus photograph of the left eye of patient 1 showing severe papillitis and perivascular sheathing (black arrows). The patient had preexisting chorioretinal scars (white arrow) present along vessels in both eyes, a common finding in patients with CGD. B, Fundus photograph of the left eye of patient 1 3 months after beginning of intensified corticosteroid therapy showing significant improvement in the papillitis with resolution of the peripapillary exudates. Perivascular sheathing is still present along the superior arcade vessels (black arrow).

70 mg/day) and methotrexate 25 mg subcutaneously weekly was commenced. During the next month, her visual acuity and fundoscopic changes improved markedly (Fig 1B) and her papillitis resolved gradually over a 6-month period, allowing gradual tapering of prednisone to 10 mg/day. Currently, her other maintenance therapy includes methotrexate 25 mg subcutaneously weekly and prophylactic antibiotics and antifungals (moxifloxacin and itraconazole).

In summary, patient 1 received a diagnosis of progressive sarcoidosis with complications of neurosarcoidosis in view of the following features: uveitis, papillitis, interstitial keratitis, chorioretinitis, aseptic meningitis, bilateral mediastinal lymphadenopathy, extensive joint involvement, cystic bony lesions of her wrists, noncaseating granulomas evident in sinus and spleen, moderately elevated serum ACE level, good response to prednisone and methotrexate, and associated risk factors (racial origin and originated from North Carolina).

Patient 2 is a 17-year-old male of African American and Korean descent who also is from North Carolina and has autosomal recessive p47^{phox} CGD with a GT deletion at start of exon 2 as noted in most p47^{phox} CGD. The diagnosis of CGD was made at 7 months of age after a severe pneumonia, and interferon γ therapy was commenced. At 6 years of age, he presented with fever, lethargy, and a productive cough. CT imaging of his chest revealed fluffy infiltrates. For determination of the infective agent(s) for the pulmonary infiltrates, fiberoptic bronchoscopies, bronchoalveolar lavages, and CT-guided needle aspirates were performed. All samples were negative on acid-fast stain (regular or modified) and Gram stain or cultures for bacterial, fungal, or viral microorganisms. He was treated with various antibacterial and antifungal agents, all of which failed to achieve any improvement, either clinically or on imaging studies. Finally, a wedge resection was performed, which showed small, well-formed, noncaseating granulomas with giant cells (Fig 2). However, an improvement was seen after oral prednisone was started (10 mg on alternate days). Over the next few years, this patient presented on multiple occasions (at ages 8, 9, 11, 13, and 14 years) with similar symptoms of cough and lethargy, usually without fever, and occasionally with pleuritic chest pain. Chest CT would demonstrate these fluffy infiltrates, which, when observed over time, demonstrated a distinct and unusual pattern. The lesions were well circumscribed, rim enhancing, and enlarged over time to involve extensive areas of the lungs (Fig 3A). This wax-and-wane pattern of his pulmonary disease and lesions on CT scans was thought to correspond to his erratic compliance with his prescribed oral prednisone, with marked improvement during renewed compliance with his medication (Fig 3B). After a period of noncompliance at 14 years of age, he presented again with acute

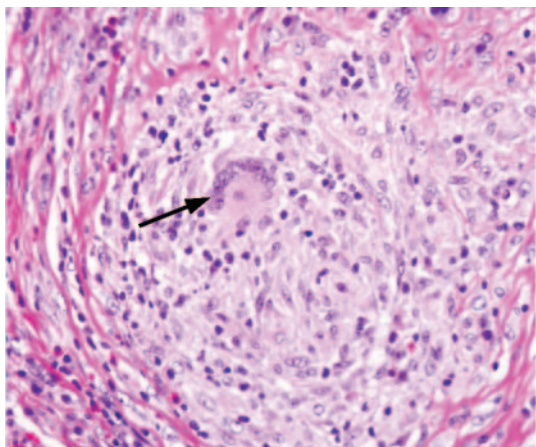


FIGURE 2
Photomicrograph from patient 2's lung wedge resection showing a nonnecrotizing, sarcoid-like granuloma with epithelioid histiocytes and a Langhans-type giant cell (black arrow). Magnification: $\times 400$, hematoxylin and eosin.

shortness of breath and oxygen desaturation in room air. Repeat fiber-optic bronchoscopies and CT-guided needle aspirates again failed to reveal an infective cause. A second wedge resection of his right lower lobe showed similar pathology of chronic inflammatory aggregates as seen in earlier sections, increased eosinophilic infiltrations, and some areas of calcification. After exclusion of identifiable infective causes and failure to improve on aggressive antibiotic and antifungal treatment, he again was treated with increased doses of prednisone (15 mg/day), which resolved his symptoms and infiltrates that were evident on chest CT scans. He has also had fleeting complaints of arthralgia during the course. However, after 1 week of omitting prednisone recently, in addition to chest CT changes (Fig 3C), he had significant generalized arthralgia that caused difficulty in walking, and effusions were noted in both knees. His laboratory parameters mostly have been unremarkable, with serum calcium of 2.2 to 2.38 mmol/L and ESR ranging from 15 to 35 mm/hour, except for this most recent exacerbation whereby ESR was 100 mm/hour. However, it is of note that he had a significantly elevated serum ACE level of 93 IU/L during an episode of "flare," which dropped to 80 IU/L on improvement and was 86 IU/L with this most recent episode of symptoms. He currently is receiving maintenance oral prednisone (7.5 mg/day).

Thus, patient 2 received a diagnosis of sarcoidosis in view of the combination of the following features: recurrent granulomatous pulmonary disease marked by noninfective infiltrative lesions, which respond to corticosteroids; joint involvement; histopathologic evidence of well-demarcated, noncaseating, epithelioid granulomas with giant cells; elevated serum ACE levels; and the same associated risk factors as in patient 1 of racial and geographic origin.

It is interesting that patient 2 recently developed lupus-like skin lesions, ulcerative oral mucosal lesions, and polyarthritis involving mainly nonaxial joints. Skin biopsies and blood tests (elevated antinuclear, anti-double-stranded DNA, anti-Smith/ribonucleoprotein, anti-extractable nuclear antigens, and anti-soluble substance A nuclear antigen antibodies) suggest that he now may have developed disease features that overlap with those of systemic lupus erythematosus (SLE). Although rare, the association between features of both sarcoidosis and SLE is well reported, and it has been suggested that this association may relate to a common pathogenesis.⁷⁻⁹ This recent evolution of the clinical condition of patient 2 strengthens the case for a diagnosis of sarcoid accounting for his respiratory problems but with clear features also of SLE.

RESULTS OF SERUM ACE MEASUREMENTS

Serum ACE level is raised in many patients with sarcoidosis. However, it has diagnostic and prognostic limitations⁶ and is not specific for sarcoidosis. It can be



FIGURE 3

A, Chest CT scan of patient 2 at age 14 showing distinct nodular infiltrates with air bronchograms in the right lower lobe. B, Much improved chest CT scan of patient 2 when compliant with oral prednisone. C, His chest CT during a recent deterioration after 1 week off prednisone shows extensive rim-enhancing, circumscribed lesions in both right and left lower lobes.

elevated in other diseases, for example, diabetes mellitus, histoplasmosis, hyperthyroidism, amyloidosis, Blau's syndrome, and myeloma. Most elevations in serum ACE levels in patients with sarcoidosis range between the upper limit of normal and up to a 2-fold increase compared with the reference levels for normal control subjects.¹⁰ Raised serum ACE levels (70 IU/L and 93 IU/L, respectively) were noted in both patients 1 and 2 compared with a range of 16 IU/L to 52 IU/L in normal control subjects (our laboratory reference using the method of Holmquist). To date, the range of serum ACE levels in patients with CGD has not been established. To ascertain serum ACE levels specifically in patients with CGD, we measured ACE levels in 26 other age-matched patients with CGD (CGD reference, age >8 years), including those with or without significant intercurrent infections at time of measurement. The levels of serum ACE ranged from 16 IU/L to 73 IU/L (overall mean: 44.4 ± 16.6 IU/L; Fig 4). The majority (69.2%) of the levels from these patients with CGD were within the range of those of normal control subjects, and no correlation between infection-related inflammation activity and ACE level was evident. Although the serum ACE level from patient 1 clearly exceeded the range from normal control subjects and was in the upper range of the established CGD reference, patient 2's was markedly elevated (Fig 4), even compared with the CGD reference, providing additional support for the diagnosis of sarcoidosis.

DISCUSSION

Sarcoidosis has not been reported previously in patients with CGD. This may be related in part to the lack of definitive diagnostic criteria for sarcoidosis, and it has been a diagnosis of exclusion. Patients 1 and 2 reported here have clinical and laboratory features that are consistent with sarcoidosis and distinct from their underlying CGD. Although granulomas are characteristically seen in both CGD and sarcoidosis, there are salient features that weigh more heavily in one disease than the other. In general, noncaseating epithelioid granulomas are the pathologic hallmarks of sarcoidosis and reflect

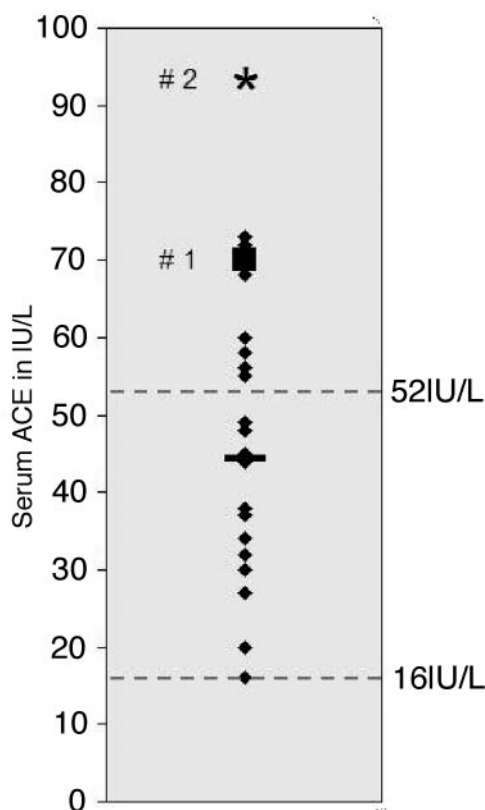


FIGURE 4

Diagram showing serum ACE levels obtained from 26 patients with CGD (◆) with a mean of 44.4 IU/L and levels from patients 1 (■) and 2 (*). The lower and upper limits of the reference for normal control subjects are indicated by dashed lines.

the inflammatory character of the disease but are not specific for this disease. They are found in other conditions, for example, Crohn's disease and malignant diseases such as lymphomas.¹¹ Granulomas that are seen in CGD often have areas of necrosis with a mixture of epithelioid as well as inflammatory cells and are not as well circumscribed as sarcoid-like granulomas. Although granulomas from lung biopsies of patient 2 were clearly noncaseating and sarcoid-like, patient 1 had noncaseating granulomas as well as some with necrotic areas in her spleen.

Patient 1 presented with significant fevers and head-

aches with cerebrospinal fluid findings of aseptic meningitis typical of neurosarcoidosis.³ Her conjunctival nodules, chorioretinitis, papillitis, and perivascular sheathing are representative of the inflammation seen in ocular sarcoidosis^{12,13} and not in CGD.¹⁴ Unlike the chronic type of optic nerve involvement in sarcoidosis, the acute form responds well to corticosteroid therapy,¹⁵ as seen in patient 1. In contrast, central nervous system inflammation unrelated to infections is rare in CGD, and other than 1 report of brain lesions from postmortem findings,¹⁶ all reported cases to date are related to fungal infections.¹⁷ The prevalence of chorioretinal lesions in CGD is 23% to 35%, but they typically appear “punched out” and are associated with pigment clumping.^{14,18} However, papillitis and sheathing of retinal vessels, as seen in patient 1, have not been reported in CGD. Both patients 1 and 2 share 2 associated epidemiologic risk factors for sarcoidosis: black racial background and originating from a highly associated region of North Carolina.¹⁹

Currently, there are no definitive diagnostic blood, skin, or radiologic imaging tests specific for sarcoidosis. Sensitivity of an increase in serum concentrations of ACE has been found to be highly variable and can range from 24% to 76% in neurosarcoidosis.²⁰ However, serum ACE is still the only serologic marker in sarcoidosis recommended by the World Association of Sarcoidosis and Other Granulomatous Disorders²¹ and is a helpful adjunct in making a difficult diagnosis. We established a range of serum ACE levels in 26 patients with CGD to evaluate better the levels determined for the 2 patients reported here. We found that ACE levels in 69% of our patients with CGD were within the range of those of normal control subjects. However, the levels in patient 1 and, more significant, in patient 2 were notably elevated, further supporting this difficult diagnosis.

Making clear distinctions between CGD and sarcoidosis is important to understand better the pathologic mechanisms of different diseases and the potential increased susceptibility to autoimmune or other inflammatory disorders in CGD and for making optimal management decisions. The diagnosis of a sarcoidosis-like disorder in patient 2 allowed implementation of a management paradigm for this patient that no longer includes invasive biopsies in pursuit of identification of infective organisms in the face of waxing and waning pulmonary lesions. Aggressive therapy for acute deterioration of visual and neurologic symptoms from progressive sarcoidosis is indicated in patients such as patient 1 with the use of immunosuppressives. Although many patients with sarcoidosis are not treated systemically, there are subgroups of patients who have chronic diseases or patients who have ocular, neurologic, cardiac, or serious respiratory involvement and are usually offered some form of treatment with corticosteroids, anti-malarial agents, and/or cytotoxic agents. More re-

cently, various agents that either block the release or inhibit the action of tumor necrosis factor α (TNF- α), a proinflammatory cytokine that is secreted extensively by macrophages in the case of sarcoidosis, have been used.²² Among these drugs are phosphodiesterase inhibitors and thalidomide (blocking the release of TNF- α from alveolar macrophages)^{23,24} as well as monoclonal antibodies that are directed against either the receptor or the ligands themselves, such as infliximab and etanercept.²⁵

Polymorphisms in a number of host defense genes, including genes for myeloperoxidase, Fc γ receptors, and mannose-binding lectin, may influence the frequency and the severity of sterile inflammatory complications in patients with CGD.²⁶ Furthermore, recent reports have highlighted a hyperresponsiveness of neutrophils on stimulation that leads to an excessive release of proinflammatory cytokines (including TNF- α) in CGD.^{27,28} Studies have also demonstrated a skewing of cytokine production toward helper type 1 (Th1) in stimulated T cells from gp91^{phox}- and p47^{phox}-deficient mice.²⁹ It is interesting that there has been evidence that sarcoidosis may be expressed more frequently in hosts with increased Th1-skewed responses to stimulation,²¹ suggesting an increased risk for developing sarcoidosis in patients with CGD. It would be of interest to investigate further proinflammatory cytokine levels and assess for certain polymorphisms in patients who have CGD with inflammatory or autoimmune features to investigate a potential susceptibility to other diseases such as sarcoidosis. Blockers of TNF- α synthesis and TNF- α inhibitors have been used increasingly in therapy of both sarcoidosis and CGD, suggesting at least a common mechanistic pathway for these diseases if not shared susceptibility.

CONCLUSIONS

We argue that having CGD does not preclude one from having sarcoidosis and that it is possible that CGD might itself be an associated risk factor for developing immune-based inflammatory disorders such as sarcoidosis. Therefore, a high index of suspicion is necessary and an awareness of supportive features is needed to establish this difficult but important diagnosis of sarcoidosis in patients with CGD. A multidisciplinary approach is essential in making the diagnosis and in treatment of such patients with multisystem involvement from both diseases. A better understanding of underlying inflammatory mechanisms will enable better guided therapeutic options.

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