Sarcoidosis in Chronic Granulomatous Disease
Suk See De Ravin, MD, PhD, Nora Naumann, MD, Michael R. Robinson, MD, Karyl S. Barron, MD, David E. Kleiner, MD, PhD, Jean Ulrick, RN, Julia Friend, PA-C, Victoria L. Anderson, MS, Dirk Darnell, MS, Elizabeth M. Kang, MD, Harry L. Malech, MD

*National Institute of Allergy and Infectious Diseases, †National Eye Institute, and ‡National Cancer Institute, National Institutes of Health, Bethesda, Maryland

The authors have indicated they have no financial relationships relevant to this article to disclose.

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 (gp91phox, p22phox, p47phox, and p67phox, 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 supplicative 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.3 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. Neurosarcoidosis 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...
(abscess), and lungs. She and, subsequently, her 2 siblings were found to lack p47phox 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/µl 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 70 mg/day) and methotrexate 25 mg subcutaneously weekly was commenced. During the next month, her visual acuity and funduscopic 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 p47phox CGD with a GT deletion at start of exon 2 as noted in most p47phox 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 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 is currently 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. 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 limitations and is not specific for sarcoidosis. It can be...
elevated in other diseases, for example, diabetes mel-
itus, histoplasmosis, hyperthyroidism, amyloidosis, Blau’s syndrome, and myeloma. Most elevations in se-
rum ACE levels in patients with sarcoidosis range be-
tween the upper limit of normal and up to a 2-fold
increase compared with the reference levels for normal
control subjects. 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), in-
cluding 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 es-
tablished CGD reference, patient 2’s was markedly ele-
vated (Fig 4), even compared with the CGD reference,
providing additional support for the diagnosis of sarcoid-
OSIS.

**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 con-
sistent with sarcoidosis and distinct from their underly-
ing CGD. Although granulomas are characteristically
seen in both CGD and sarcoidosis, there are salient fea-
tures that weigh more heavily in one disease than the
other. In general, noncaseating epithelioid granulomas
are the pathologic hallmarks of sarcoidosis and reflect
the inflammatory character of the disease but are not
specific for this disease. They are found in other condi-
tions, for example, Crohn’s disease and malignant dis-
eases such as lymphomas. 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 noncaseat-
ing granulomas as well as some with necrotic areas in
her spleen.

Patient 1 presented with significant fevers and head-

---

**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.

**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.
aches with cerebrospinal fluid findings of aseptic menin
gitis typical of neurosarcoidosis. Her conjunctival
nodules, chorioretinitis, papillitis, and perivascular
sheathing are representative of the inflammation seen in
ocular sarcoidosis and not in CGD. Unlike the chronic
type of optic nerve involvement in sarcoidosis, the acute
form responds well to corticosteroid therapy, 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 postmor-
tem findings, all reported cases to date are related to
fungal infections. The prevalence of chorioretinal le-
sions in CGD is 23% to 35%, but they typically appear
“punched out” and are associated with pigment clump-
ing. However, papillitis and sheathing of retinal ves-
sels, 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.

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. However, se-
rum ACE is still the only serologic marker in sarcoidosis
recommended by the World Association of Sarcoidosis
and Other Granulomatous Disorders 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 ele-
vated, further supporting this difficult diagnosis.

Making clear distinctions between CGD and sarcoid-
osis is important to understand better the pathologic
mechanisms of different diseases and the potential in-
creased susceptibility to autoimmune or other inflam-
atory disorders in CGD and for making optimal man-
agement decisions. The diagnosis of a sarcoidosis-like
disorder in patient 2 allowed implementation of a man-
age strategy for this patient that no longer in-
cludes invasive biopsies in pursuit of identification of
infective organisms in the face of waxing and waning
pulmonary lesions. Aggressive therapy for acute deter-
oration of visual and neurologic symptoms from pro-
gressive sarcoidosis is indicated in patients such as pa-
tient 1 with the use of immunosuppressives. Although
many patients with sarcoidosis are not treated systemi-
cally, there are subgroups of patients who have chronic
diseases or patients who have ocular, neurologic, car-
diac, 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. Among these drugs are phosphodiesterase inhibitors
and thalidomide (blocking the release of TNF-α from alveolar
macrophages) as well as monoclonal antibodies that
are directed against either the receptor or the ligands
themselves, such as infliximab and etanercept.

Polymorphisms in a number of host defense genes,
including genes for myeloperoxidase, Fcγ receptors,
and mannose-binding lectin, may influence the frequency
and the severity of sterile inflammatory complications in
patients with CGD. Furthermore, recent reports have
highlighted a hyperresponsiveness of neutrophils on
stimulation that leads to an excessive release of proin-
flammatory cytokines (including TNF-α) in CGD. Studies have also demonstrated a skewing of cytokine
production toward helper type 1 (Th1) in stimulated T
cells from gp91phox- and p47phox-deficient mice. It is
interesting that there has been evidence that sarcoidosis
may be expressed more frequently in hosts with in-
creased Th1-skewed responses to stimulation, suggest-
ing an increased risk for developing sarcoidosis in pa-
tients 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 sarcoid-
osis. Blockers of TNF-α synthesis and TNF-α inhibitors
have been used increasingly in therapy of both sarcoid-
osis 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. There-
fore, 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 es-
cential in making the diagnosis and in treatment of such
patients with multisystem involvement from both dis-
eases. A better understanding of underlying inflamma-
tory mechanisms will enable better guided therapeutic
options.

ACKNOWLEDGMENT
This research was supported by the Intramural Research
Program of the National Institutes of Health, National
Institute of Allergy and Infectious Diseases.
REFERENCES


Sarcoidosis in Chronic Granulomatous Disease

Pediatrics 2006;117;e590; originally published online February 1, 2006; DOI: 10.1542/peds.2005-1349

Updated Information & Services
including high resolution figures, can be found at:
/content/117/3/e590.full.html

References
This article cites 29 articles, 1 of which can be accessed free at:
/content/117/3/e590.full.html#ref-list-1

Citations
This article has been cited by 1 HighWire-hosted articles:
/content/117/3/e590.full.html#related-urls

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Hematology/Oncology
/cgi/collection/hematology:oncology_sub

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
/site/misc/Permissions.xhtml

Reprints
Information about ordering reprints can be found online:
/site/misc/reprints.xhtml
Sarcoidosis in Chronic Granulomatous Disease
Pediatrics 2006;117:e590; originally published online February 1, 2006;
DOI: 10.1542/peds.2005-1349

The online version of this article, along with updated information and services, is located on the World Wide Web at:
/content/117/3/e590.full.html