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Review

# The spectrum of opportunistic diseases complicating sarcoidosis

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ABSTRACT

Sarcoidosis is an inflammatory disease marked by a paradoxical immune status. The anergic state, which results from various immune defects, contrasts with the inflammatory formation of granulomas. Sarcoidosis patients may be at risk for opportunistic infections (OIs) and a substantial number of cases have been reported, even in untreated sarcoidosis. It is not clear how OIs in patients with sarcoidosis are different from other groups at risk. In this review, we discuss the most common OIs: mycobacterial infection (including tuberculosis), cryptococcosis, progressive multifocal leukoencephalopathy, and aspergillosis. Unlike peripheral lymphocytopenia, corticosteroids are a major risk factor for OIs but the occurrence of OIs in untreated patients suggests more complex predisposing mechanisms. Opportunistic infections presenting with extrapulmonary features are often misdiagnosed as new localizations of sarcoidosis. Aspergillomas mostly develop on fibrocystic lungs. Overall, physicians should be aware of the possible occurrence of OIs during sarcoidosis, even in untreated patients.


**Contents**



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## 1. Introduction

Sarcoidosis is a systemic disease of unknown cause that is characterized by the formation of immune granulomas in various organs, mainly the lungs and the lymphatic system [1,2]. The persistence of an as-yet unidentified poorly degradable antigen in genetically susceptible hosts is thought to trigger the typical Th1 cellular immune response, leading to formation of granulomas. Sarcoidosis is characterized by a paradoxical immune status. Indeed, the exaggerated immune response within granulomas contrasts with various immune defects that manifest by anergy to tuberculin test and by the possible occurrence of opportunistic infections (OIs).

Several situations can be observed. First, OIs may occur in untreated patients or reveal sarcoidosis. This is mainly described for cryptococcosis and progressive multifocal leukoencephalopathy (PML). Second, corticosteroid (CS) therapy [3–5] and the use of immunosuppressive agents or anti-tumor necrosis factor (TNF)-α [6] in severe or refractory sarcoidosis may, like in other systemic diseases, predispose patients to OIs. Third, OIs in sarcoidosis patients may only depend on epidemiologic or geographic factors. This is mostly true for tuberculosis and histoplasmosis. Finally, anatomic changes, such as parenchymal fibrocystic lesions in advanced pulmonary sarcoidosis, can predispose to aspergillosis.

Seven studies have focused on the risk of OI in the setting of sarcoidosis and have reported an incidence of 0–10% (Table 1) [4,7–12]. These studies were heterogeneous in terms of purpose, studied populations, sarcoidosis definition, and follow-up periods. Thus, it is not possible to conclude in an increased risk of OI during sarcoidosis.

Although the medical literature contains a substantial number of reports of OIs during sarcoidosis, only one focused review has been published in French, ten years ago [13]. Girard et al. reported on 65 cases of OIs complicating sarcoidosis, between 1966 and 2004. Cryptococcosis was the most frequently reported infection (59%) followed by mycobacterial infections (13%), nocardiosis (11%), histoplasmosis, pneumocystosis (9% each), and aspergillosis (7%). However, no newer reviews have been undertaken despite several new case series and case reports becoming increasingly available. Notably, two recent studies of our group have reported on several cases of cryptococcosis or PML complicating sarcoidosis [14,15]. Mycobacterial infections are also increasingly reported. Given these data, we performed an exhaustive literature review with the aim of determining how sarcoidosis predisposes to OIs.

## 2. Literature-search strategy and selection criteria

### 2.1. Search strategy

Searches were conducted in PubMed database (including Medline, National Library of Medicine, and PubMed Central), for the time period between January, 1974 and March, 2014, using strategies recommended by the Cochrane handbook [16]. The review strategies consisted of a exhaustive search using the terms “sarcoidosis”, “opportunistic infection”, “tuberculosis”, “mycobacteria”, “aspergillosis”, “cryptococcosis”, “nocardiosis”, “toxoplasmosis”, “mucormycosis”, “zygomycosis”, “histoplasmosis”, “pneumocystosis”, “blastomycosis”, “strongyloidiasis”, “leishmaniasis”, “coccidioidomycosis”, “bartonellosis”, “*Rhodoccocus*”, “sporotrichosis”, “candidiasis”, “cryptosporidiosis”, “microsporidiosis”, “isosporiasis”, “cyclosporiasis”, “JC virus”, “progressive multifocal leukoencephalopathy”, “BK virus”, “Epstein–Barr virus”, “papillomavirus”, “herpes zoster”, and “cytomegalovirus” as keywords. These different keywords were used in three different ways; as a *Mesh Term*, a *Sub Heading*, or an *All Field Term* and associated with “AND”, or separately.

### 2.2. Eligibility criteria

All potentially relevant abstracts were retrieved and reviewed by one of the two main investigators (YJ). We only selected cases where tuberculosis was diagnosed after or simultaneously with sarcoidosis, and we excluded tuberculosis cases occurring during end-stage pulmonary sarcoidosis. Mycobacterial infection and cryptococcosis are prototypic chronic granulomatous infections that may clinically mimic sarcoidosis. When sarcoidosis and such infections coexist, it can be difficult to be sure whether one condition has preceded the other. To avoid this pitfall, we only included patients with 1) a histologically-proven granulomatous disease and clinical manifestations compatible with sarcoidosis; 2) a clinically detectable deterioration that punctuated the onset of an infection; and 3) an improvement of these manifestations under specific antimicrobial therapy. For cryptococcosis and PML, the methods of literature search were similar and have been described previously [14,15]. Only well-described cases of *Aspergillus*-related lung diseases were included [17].

When there was doubt, the abstract was reviewed by the second main investigator (PS), who made the final decision regarding eligibility. Reference lists of original studies were hand-searched and relevant articles were extracted. The manuscripts of all potentially relevant studies identified during the search of abstracts were then retrieved and reviewed. Articles published in English, French, and Spanish were included.

## 3. Sarcoidosis and immunodepression

### 3.1. Sarcoidosis

Sarcoidosis affects people from all racial/ethnic origins and occurs at any time of life. Its incidence is estimated at between 4.7 and 64/100,000 and its prevalence varies from 1.0 to 35.5/100,000 per year, with a particular proclivity for young adults [1,18–20]. Diagnosis is established when compatible clinico-radiological features are supported by histological evidence of a non-caseating epithelioid granuloma [21]. Histological confirmation should be obtained whenever possible, except in patients presenting with Löfgren's syndrome [21].

Spontaneous resolution occurs in as many as 60%. However, the disease can be chronic or progressive and ~20% of patients have permanent clinical symptoms mainly because of significant fibrosis lesions in the lung or other organs. Mortality has been reported to be up to 7.6% [1] and is mostly associated with advanced pulmonary fibrosis, and less frequently to cardiac or central nervous system involvement. CSs are the mainstay treatment for sarcoidosis and are always required in severe