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Cryptococcal meningitis complicating sarcoidosis

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Abstract

Background: Cryptococcal meningitis is an uncommon but severe complication of sarcoidosis.

Methods: We present 2 patients with cryptococcal meningitis complicating sarcoidosis and compared findings with 38 cases reported in the literature.

Results: When analyzing our patients and 38 cases reported in the literature, we found that median age of sarcoidosis patients with cryptococcal meningitis was 39 years (range 30–48); 27 of 33 reported cases (82%) had a history of sarcoidosis. Only 16 of 40 patients (40%) received immunomodulating therapy at the time of diagnosis of cryptococcal meningitis. The diagnosis of cryptococcal meningitis was delayed in 17 of 40 patients (43%), mainly because of the initial suspicion of neurosarcoidosis. Cerebrospinal fluid (CSF) examination showed mildly elevated white blood cell count (range 23–129/mm^3). Twenty-nine of 32 cases (91%) had a positive CSF culture for *Cryptococcus neoformans* and 25 of 27 cases (93%) had a positive CSF *C neoformans* antigen test. CD4 counts were low in all patients in whom counts were performed (84–228/mL). Twelve patients had an unfavorable outcome (32%), of which 7 died (19%) and 24 patients (65%) had a favorable outcome. The rate of unfavorable outcome in patients with a delayed diagnosis was 7 of 17 (41%) compared to 5 of 28 (21%) in patients in whom diagnosis was not delayed.

Conclusion: Cryptococcal meningitis is a rare but life-threatening complication of sarcoidosis. Patients were often initially misdiagnosed as neurosarcoidosis, which resulted in considerable treatment delay and worse outcome. CSF cryptococcal antigen tests are advised in patients with sarcoidosis and meningitis.

Abbreviations: ACE = serum angiotensin converting enzyme, CSF = cerebrospinal fluid, CT = computed tomography, HIV = human immunodeficiency virus, MRI = magnetic resonance imaging, PET-CT = positron emission tomography–computed tomography, WBC = white blood cell.

Keywords: autoimmune diseases, cryptococcal meningitis, cryptococcus neoformans, fungal infections, sarcoidosis

1. Introduction

Cryptococcal meningitis is an opportunistic infection caused by the encapsulated yeast *Cryptococcus neoformans*. T-cell immunity is the predominant pathway for protection against cryptococcal infection,[1,2] and a high incidence of cryptococcal infection is reported in HIV-infected patients.[3] A minority of cryptococcal meningitis cases occur in HIV-negative patients and half of these patients have a co-existing immunocompromised state, for instance, due to glucocorticoid treatment, hematologic malignancy, or organ transplantation.[4–6] Cryptococcal meningitis is an uncommon complication of sarcoidosis.[4,6–20] In patients with sarcoidosis T-cell-mediated immunity has been shown to be impaired, which might be explained by a combination of sequestering of CD4-T cells in granulomas and suppression of T-cell proliferation by regulatory CD4 T-cells causing anergy.[21–23] We present 2 patients with cryptococcal meningitis complicating sarcoidosis and performed a meta-analysis of our cases and those identified in the literature.

2. Case reports

2.1. Case 1

A 32-year-old previously healthy white male presented with a 6-month history of headache, which worsened 3 weeks before presentation. Furthermore, he suffered from malaise and weight loss. Over the last 2 weeks, he noticed weakness of the lower limbs and in the last 2 days diplopia, dysphagia, and paresthesia of the hands. He had no specific occupational exposure to toxins. Neurologic examination showed neck stiffness, right-sided third and sixth cranial nerve palsy, and absent tendon reflexes. Lumbar puncture revealed an elevated opening pressure and CSF analysis showed 15 leukocytes per mm^3, CSF glucose concentration of 0.8 mmol/L, CSF protein concentration of 0.59 g/L. Cranial MRI showed no abnormalities. Tuberculous meningitis was suspected and tuberculostatic drugs were initiated. Two days

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after admission the culture and antigen test of the CSF were found positive for *C neoformans*; HIV serology was negative. The patient was started on amphocytericine B and flucytosine. After 3 days, he developed vision loss and a unilateral fixed pupil, followed by a respiratory arrest. He was intubated and cranial CT was normal. Subsequently, a lumbar puncture was performed showing an opening pressure above 50 cm water. After withdrawal of 80 mL CSF, pupillary reaction and cranial nerve palsies improved, and he was transferred to our tertiary referral center. In our center, an external lumbar drain was placed, which was followed by a sudden decline of consciousness (E3M3Vtube). Cranial CT showed a cerebellar hemorrhage with compression of the fourth ventricle and hydrocephalus (Fig. 1). A permanent external ventricular catheter was placed and his neurological condition improved. Cranial MRI showed leptomeningeal enhancement. FDG PET showed hilar and mediastinal lymphadenopathy (Fig. 2) and biopsy of a subcarinal lymph node showed granulomatous inflammation consistent with sarcoidosis. Laboratory investigations showed a CD4-count of 130/mm^3, a CD8-count of 200/mm, and an ACE concentration of 17 U/L (normal 20–70 U/L). The patient was treated with methylprednisolone (1000 mg during 3 days) followed by prednisolone (60 mg daily). Amphocytericine B (0.7 mg/kg daily) and flucytosine (100 mg/kg daily) were continued for 6 weeks after admission, followed by fluconazole (200 mg daily). At discharge, the patient had a severely impaired vision, a diffuse mild paresis of the limbs, and ataxia of the lower limbs.

2.2. Case 2

A 49-year-old white woman presented with a 1 week-history of headache, nausea, and anorexia. Her medical history revealed pulmonary sarcoidosis, for which she received no medication at presentation. She had no specific occupational exposure to toxins. Neurological examination was normal. Because of severe persistent headache and fever, a lumbar puncture was performed showing an opening pressure of 30 cm water, 117 leukocytes per mm^3, glucose concentration of 3.3 mmol/L and protein concentration of 0.36 g/L; blood and CSF culture showed *C neoformans*. HIV-serology was negative and cranial MRI was normal. CD4 count was 200 cells/mm^3 and CD8-count was 290/mm. Amphotericine B and flucytosine were initiated, and a monthly lumbar puncture was performed to monitor the presence of the cryptococcal antigen. She made a full recovery and required no treatment for sarcoidosis as she had few symptoms.

3. Literature review

In a PubMed search using the Mesh terms "Meningitis, Cryptococcal" and "Sarcoidosis," as well as synonyms of these terms (see Fig. 3) and Embase search using the terms "Sarcoidosis" and "Cryptococcal meningitis," 26 of 176 identified articles met our inclusion criteria (Fig. 3 and Supplementary Table 1, http://links.lww.com/MD/B240).[4,7–14,16–20,23–34] Cases were excluded if they had a positive HIV status or immunocompromised status of other cause. Patients treated for sarcoidosis with immunomodulating therapy were included. Articles with neither access to the abstract or full text were excluded. Studies written in English, German, French, and Dutch were included. In a meta-analysis of clinical data, we systematically scored baseline and presenting characteristics, clinical course, and outcome. Outcome was categorized in "favorable" (e.g., no or mild functional disability or complaints) and "unfavorable" (e.g., moderate to severe functional disability or complaints and death). The 2 patients described in the case reports have given informed consent. Because this article includes only case reports, approval from our ethics committee was not necessary. All studies were single case reports, except for 1 study reporting 13 cases. Studies were performed in Europe (12), the USA (9), Canada (1), Iran (1), Australia (1), Japan (1), and South Africa (1).

Combining these data with our 2 patients, we found that the median age of cryptococcal meningitis patients with sarcoidosis was 39 years (range 30–48) and 28 of 38 cases (74%) in whom sex was reported were male (see Table 1). Twenty-seven of 33 cases (82%) had a medical history of sarcoidosis before presenting with symptoms of cryptococcal meningitis. In the remaining 6 cases, sarcoidosis and cryptococcal meningitis were diagnosed simultaneously. In 16 of 40 patients (40%) immunomodulating therapy at the time of diagnosis was reported, consisting of prednisolone in 15 cases, hydrocortisone in 1 case, methotrexate in 1 case, and cyclophosphamide in 1 case. None of the patients using prednisolone were using dosages exceeding 50 mg daily, and the mean dosage was 20 mg per day. Frequently

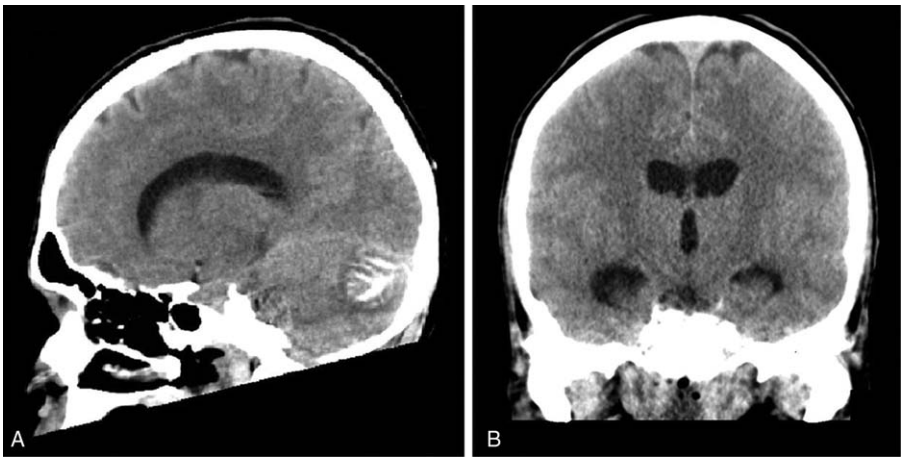

Figure 1. Cranial CT of case 1 showing cerebellar hemorrhage (A) and hydrocephalus (B). CT = computed tomography.

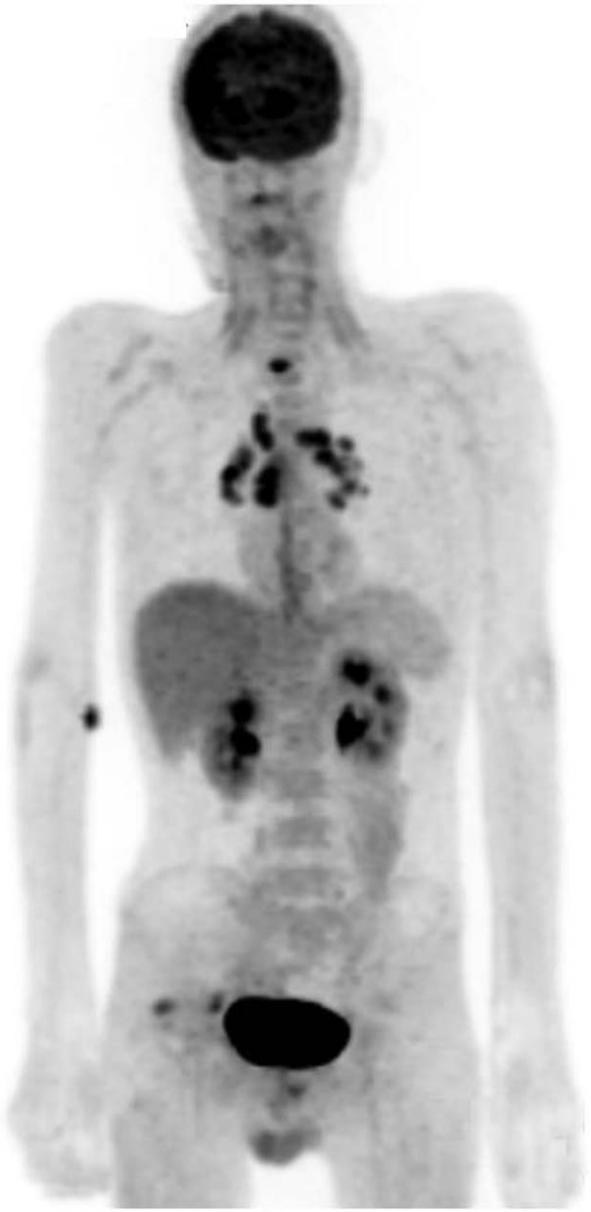

Figure 2. PET-CT scan of case 1 showing hilair and mediastinal lymphadenopathy. PET-CT = Positron emission tomography–computed tomography.

involved organs in sarcoidosis were the lungs in 31 of 38 cases (82%), the skin in 5 cases (13%) and the central nervous system in 5 cases (13%).

Presenting features were reported in 35 cases and included headache in 16 cases (46%), fever in 22 cases (63%), neck stiffness in 20 cases (57%), and altered consciousness in 12 cases (34%). Other frequently reported features were weight loss and nausea in 9 cases (26%), focal neurologic deficits in 8 cases (23%), and fatigue in 7 cases (20%).

White blood cell count (WBC) in the CSF was reported in 12 cases and showed a median of 63 cells per mm^3 (range 23–129), CSF protein level was reported in 14 cases and showed a median of 1.5 g/L (range 0.6–3.1), and the median glucose level was 2.2 mmol/L (range 1.3–2.8, reported in 10 cases). Lumbar puncture opening pressure was reported in 8 cases and was raised in 7 of them (88%).

Twenty-nine of 32 cases with available CSF culture results were positive for *C neoformans* (91%), 25 of 27 cases had a positive *C neoformans* antigen test (93%), and India ink staining of the CSF was positive for *C neoformans* in 14 of 23 reported cases (61%). In 1 case both antigen and culture were negative for *C neoformans* and India ink staining was the only positive test. In all cases with available test results, 1 of the 3 tests (antigen, culture, or India ink staining) was positive for *C neoformans*. In 5 patients culture or antigen of *C neoformans* was only positive in a repeated sample, or became positive after >1 week.

Results of blood culture of *C neoformans* were reported in 8 cases and positive in 4 (50%) and serum antigen was reported in 20 and positive in 15 cases (75%). In 5 cases antigen for *C neoformans* was negative in the serum and positive in the cerebral spinal fluid (CSF). In 20 cases, the CD4 count was reported and showed a median of 137/mm^3 (range 84–228). 13 of these patients (65%) had a CD4 count below 200/mm^3.

Cranial magnetic resonance imaging (MRI) was reported in 13 cases and showed meningeal enhancement in 5 cases (33%), focal abnormalities in 6 cases (33%)—consisting of ring-enhancing nodules or masses in 4 and parenchymal lesions or masses not further specified in 2 cases—hydrocephalus in 3 cases (23%), and no abnormalities in 6 cases (46%). Cranial computed tomography (CT) was reported in 11 cases and abnormalities consisted of cortical inflammation typical for neurosarcoidosis in 1 case (9%), a calcified lesion in the cerebellum in 1 case (9%), hydrocephalus in 2 cases (8%), and in 8 cases (73%) no abnormalities were reported.

Pulmonary or lymph node sarcoidosis was detected by chest x-ray (22 of 26 [85%]), chest CT (8 of 9 [89%]) or positron emission tomography (PET)-CT (1 of 2). Sarcoidosis was histopathologically confirmed in 15 of 18 cases (83%) during life and in 3 cases at autopsy.

The diagnosis of cryptococcal meningitis was not recognized at initial presentation in 17 of 40 cases (43%). Initial diagnoses in these cases consisted of neurosarcoidosis (n = 7), side effects of steroids (n = 1), migraine (n = 1), ocular toxoplasmosis (n = 1), tuberculous meningitis (n = 1), cerebellar metastasis (n = 1), and an undefined psychiatric diagnosis (n = 1). Three cases were diagnosed after >2 weeks after presentation, and in 1 case a definite diagnosis could only be made during autopsy.

In 36 cases treatment measures were reported, which consisted of amphotericin in 31 cases (86%), flucytosine in 23 cases (64%), and fluconazole in 21 cases (58%). Fifteen cases were treated with amphotericin and flucytosine as induction therapy in the acute phase and received fluconazole as consolidation therapy. Of the 16 cases receiving immunomodulating therapy at presentation, prednisolone was discontinued in 2 cases (13%), tapered in 2 cases (13%), and continued in 1 case (6%), and in the remaining cases treatment for sarcoidosis was not reported. Five cases developed hydrocephalus of which 3 required a ventricular drain.

Seven of 40 patients (18%) died due to cryptococcal meningitis. Four of these cases received adequate antifungal treatment, in 1 case the diagnosis was made post-mortem, 1 case died due to a subsequent *Staphylococcus aureus* infection, and 1 case was reported in 1957, prior to availability of adequate antifungal treatment.[7,18] Outcome could be classified as favorable (complete recovery or mild functional disability or complaints) or unfavorable (deceased or sequelae) in 27 patients. Twenty-four patients (65%) had a favorable outcome and 12 patients (32%) had an unfavorable outcome. Unfavorable

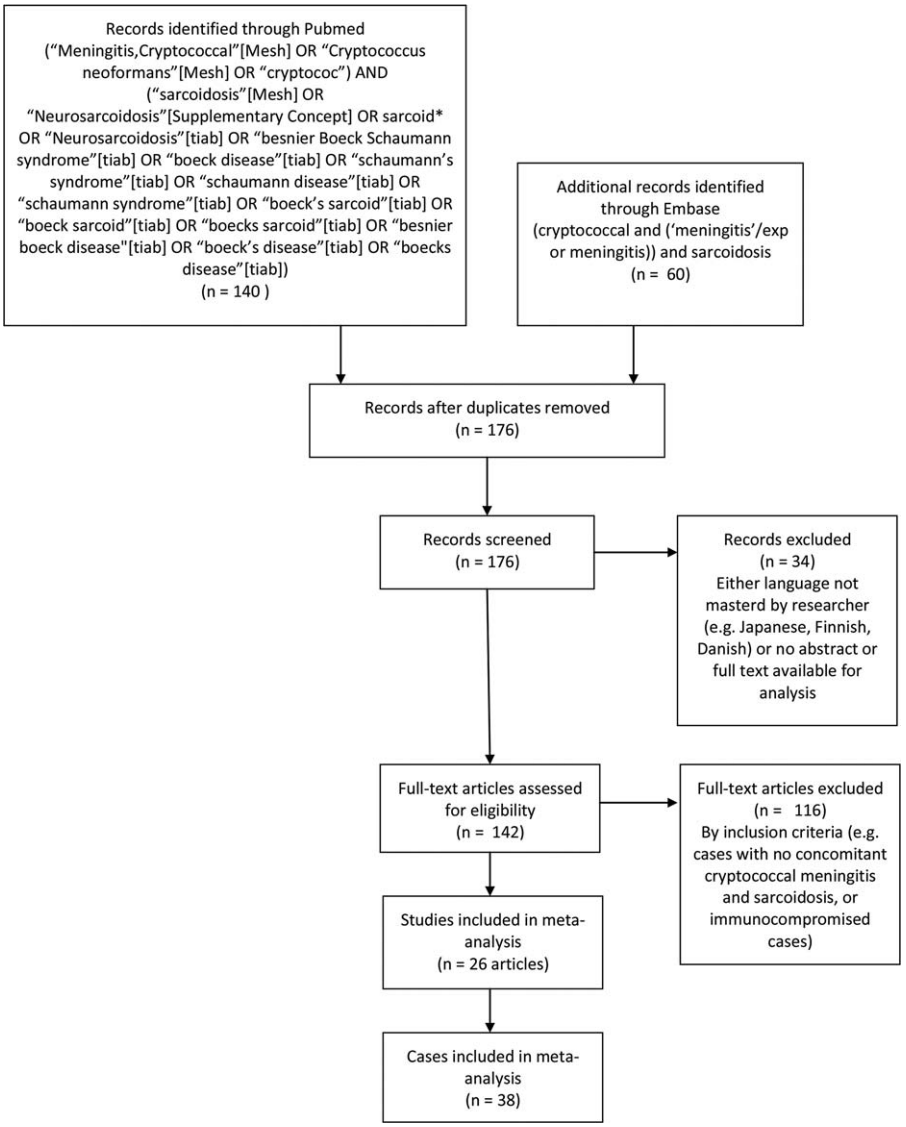

Figure 3. Flowchart of reviewed articles for cryptococcal meningitis in sarcoidosis patients.

outcome occurred in 7 of the 17 patients (41%) in whom the diagnosis of cryptococcal meningitis was missed, versus 5 of 23 (21%) in whom the diagnosis was made shortly after admission (Fisher's exact test $P = 0.29$).

4. Discussion

Cryptococcal meningitis is a rare complication of sarcoidosis. We found that 18% of reported cases die as a consequence of the disease and in 43% of cases the diagnosis was delayed. It is important to recognize cryptococcal meningitis in sarcoidosis patients in an early stage of disease so adequate treatment can be started.

Diagnosis of cryptococcal meningitis complicating sarcoidosis is often difficult, as clinical and diagnostic features can be nonspecific. In 18% of cases, cryptococcal meningitis was the initial presentation of sarcoidosis. India ink staining of the CSF was negative in 39% of patients, *C neoformans* serum antigen was negative in 25% of cases, and in 5 patients culture or antigen of *C neoformans* in the CSF was positive only in a repeated sample, or became positive after >1 week. This often resulted in initial misdiagnosis and delay of treatment.

As demonstrated in our first case, differentiation between cryptococcal meningitis and neurosarcoidosis can be challenging as both diseases can present simultaneously. They both often present with symptoms of chronic meningitis and can be complicated by hydrocephalus.[35,36] CSF abnormalities can be similar, with a mild pleiocytosis and elevated protein.[36–38] We also found that in patients previously diagnosed with neurosarcoidosis, symptoms of cryptococcal meningitis were mistakenly attributed to a relapse of neurosarcoidosis. Presenting symptoms of fever and neck stiffness were more common in cases with cryptococcal meningitis than in reported neurosarcoidosis cases in literature, and focal neurological deficits are more frequently reported in neurosarcoidosis.[39,40] Clinical characteristics and findings on physical examination such as the absence of fever or neck stiffness, however, do not exclude cryptococcal meningitis, and CSF culture or antigen of *C neoformans* remains the only decisive differentiation between the 2 diseases. Repeated CSF analysis may be needed to confirm the diagnosis of

Table 1

Presenting features, ancillary investigations, and clinical course in both our patients and patients described in the literature.

Characteristic	n/N (%)	Characteristic	n/N (%)
Age*	39 (30–48)	Laboratory investigations	
Male sex	28/38 (74%)	Blood tests	
History of sarcoidosis at presentation	27/33 (82%)	CD4-count (cells/mm^3)‡	137 (84–228)
Affected organ in sarcoidosis		Positive culture *C neoformans*	4/8 (50%)
Lung	31/38 (82%)	Positive antigen *C neoformans*	15/20 (75%)
Skin	5/38 (13%)	Cerebral spinal fluid (CSF)	
Neuronal tissue	5/38 (13%)	Positive culture *C neoformans*	29/32 (91%)
Eye	4/38 (11%)	Positive antigen *C neoformans*	25/27 (93%)
Liver	5/38 (13%)	Positive India Ink staining	14/23 (61%)
Joints	3/38 (8%)	Cranial MRI	
Parotitis	4/38 (11%)	Meningeal enhancement	7/17 (41%)
Heart	2/38 (5%)	Focal abnormalities§	6/17 (35%)
Kidney	3/38 (5%)	No abnormalities	6/17 (35%)
Immunomodulating medication	16/40 (40%)	Treatment	
Presenting features		Amphotericin	31/36 (86%)
Fever	22/35 (63%)	Flucytosine	23/36 (64%)
Neck stiffness	20/35 (57%)	Fluconazole	21/36 (58%)
Headache	16/35 (46%)	Other‖	1/36 (3%)
Altered mental status	12/35 (34%)	Diagnostic delay	17/40 (43%)
Weight loss	9/35 (26%)	Misdiagnosed neurosarcoidosis	7/17 (41%)
Nausea	9/35 (26%)	Outcome	
Focal neurological deficits†	8/35 (23%)	Favorable	24/37 (65%)
Fatigue and general malaise	7/35 (20%)	Unfavorable	12/37 (32%)
		Death	7/37 (19%)

Data are number/number assessed (%) and median (25th–75th percentile).

* Reported in 38 cases.

† Cranial nerve palsy (n = 4), ataxia (n = 1), and vision loss (n = 1).

‡ Reported in 20 cases.

§ Parenchymal lesions or mass not otherwise specified (n = 2), ring-enhancing lesions (n = 4).

‖ Polymyxin B sulfate and nystatine (n = 1).

cryptococcal meningitis and when clinical suspicion is high, treatment for cryptococcal meningitis should be considered pending microbiological examination.

Only 40% of patients were using immunomodulating drugs at presentation, suggesting that sarcoidosis is a risk factor for contracting cryptococcal meningitis independent of the use of these drugs. CD4 T-cell counts were low, ranging from 84 to 228/mm^3, which is the most likely cause of developing cryptococcal meningitis. CD4 lymfocytopenia is relatively common in sarcoidosis patients, but only a small percentage of these patients have a CD4 count $<200/mm^3$, which is reported to correlate with disease severity and not with immunomodulation therapy.[41] Especially in sarcoidosis patients with severe disease, control of CD4 count in sarcoidosis patients should be considered to identify patients at risk for opportunistic infections such as cryptococcal meningitis. Prophylactic antibiotic treatment in patients with CD4 lymphocytopenia should be considered until CD4 counts are back to normal.

This study has several limitations. Most notably we are limited by publication bias of cases with cryptococcal meningitis in sarcoidosis patients, as for example uncomplicated cases or cases with good outcome may have been underreported. Furthermore, we are limited in our analysis by missing data of the reported cases and heterogeneous diagnostic evaluation, year of publication, and treatment. This caused a suboptimal comparison of cases. Importantly, the presented outcome could have been influenced by cases reported before availability of adequate diagnostic modalities and antifungal medication. However, these limitations could not be overcome, as they are inherent to the study design. To overcome the problem of missing data, we gave an overall of n of N (%) in presenting our results. A better overview of clinical features and course of cryptococcal meningitis in sarcoidosis would require a prospective protocolled analysis of a large cohort of patients. The low incidence of this rare complication, however, hinders the feasibility of such an approach.

We conclude that cryptococcal meningitis is a rare complication of sarcoidosis associated with CD4 lymphocytopenia, which is often delayed or missed. Many patients were initially misdiagnosed as neurosarcoidosis, which caused considerable treatment delay. Therefore, CSF antigen testing for *C neoformans* is indicated in patients with sarcoidosis presenting with signs of (sub)acute meningitis.

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