Cryptococcosis and sarcoidosis: strange bed-fellows. A report of five cases

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Abstract. Background and Aim: Sarcoidosis is known to predispose to cryptococcal infection. In this case series, variations in presentation, diagnostic dilemmas and responses to treatment are highlighted. Methods: Of several hundred patients referred to the sarcoidosis clinic at The Prince Charles Hospital, Brisbane and to the private clinic of the co-author between 1990 and 2002, five subsequently developed cryptococcal infections as a complication of sarcoidosis. All five subjects were treated by the co-author (RKAA). A review of the literature was also performed. Results: Cryptococcal infection occurred in 4 patients with sarcoidosis being treated with steroids and one patient who was not on treatment. All responded to antifungal therapy. Cryptococcosis was diagnosed by transbronchial (2), bronchial (1) and cutaneous (2) biopsies. Fluconazole was used in those with pulmonary infections but not in cutaneous disease where excision sufficed. One patient with pulmonary cryptococcosis from immunosuppressants also developed a nocardial brain abscess. Conclusions: Our series of patients with sarcoidosis and cryptococcal infections is unique in Australia. Although an unusual infection, cryptococcosis should always be considered in patients with sarcoidosis as it may be overlooked particularly in the lungs and can be fatal if untreated. Further immune dysregulation through steroid use may contribute significantly to the disease manifestations. Understanding why cryptococcosis and not other infections is more common in patients with sarcoidosis may reveal more about the mechanisms of granuloma formation and the nature of sarcoidosis itself. (Sarcoidosis Vase Diffuse Lung Dis 2004; 21; 71-76).

Key Words: Cryptococcosis. Sarcoidosis.

Introduction

Cryptococcus neoformans, a dimorphic fungus, was first described in 1894 as a causative agent of disease [1]. Of the nineteen species within the genus Cryptococcus, most clinical disease is attributable to Cryptococcus neoformans var. neoformans (serotypes A and D) or var. gattii (serotypes B and C) [2]. The association of cryptococcal infection with sarcoidosis has been noted in a number of case reports in the literature [3-13], including larger case series [14-17]. We report five patients diagnosed with sarcoidosis who had infections with Cryptococcus neoformans. All were treated by the co-author (RKAA) at his sarcoidosis clinic at two tertiary referral centres for cardiothoracic disorders between 1990-2002.

Cases

Case One

A 50-year-old Caucasian man presented with stage III biopsy-proven sarcoidosis in 1995 (Fig. 1). He had abnormal lung function and was treated with oral corticosteroids. In
August 1997 he developed a skin lesion on his right arm, which on biopsy was proven to be *Cryptococcus neoformans*. His serum cryptococcal antigen was negative and he was not started on any anti-fungal medications. His steroids were withdrawn and the rash improved. His sarcoidosis reactivated in March 1999 with hypercalcemia, serum calcium of 3.32 mmol/L (reference range 2.25-2.65 mmol/L). He was recommenced on prednisolone 40 mg/day and his serum cryptococcal antigen has remained normal. In 2002 he still had pulmonary infiltrates (sarcoidosis stage III) with mild airflow obstruction and a normal diffusing capacity. His serum ACE was intermittently elevated when he was off prednisolone. There has been no recurrence of the cryptococcal infection.

**Case Two**

In 1989 after the birth of her first child, this 29-year-old Caucasian woman experienced right parotid swelling and erythema nodosum for which she was treated with prednisolone. In 1992, she developed a lump on the right side of her neck and left axilla and chest radiograph showed diffuse pulmonary shadowing for which she was treated with prednisolone after a transbronchial lung biopsy showed histological evidence of sarcoidosis. In 1994 she had mild diffuse infiltrate in her upper zones, which was widespread by mid-1996 with no associated hilar adenopathy. A CT scan showed interstitial shadows and mild mediastinal lymphadenopathy. Her serum ACE was markedly elevated (164 u/L, reference range up to 65 u/L) and her lung function showed a mild restrictive ventilatory defect with mildly depressed diffusing capacity. She was recommenced on corticosteroids in 1996 with the addition of Methotrexate 7.5 mg weekly. In March 1997 she developed a tender lump in her left thigh, which was not associated with trauma. Biopsy of the lesion and subsequent culture showed *Cryptococcus neoformans* (Figs. 2 and 3). Her serum cryptococcal antigen (latex agglutination) titre was 1:64. CT scan of her chest and a lumber puncture were normal. She was treated with Fluconazole 400mg/day for 3 months with a fall in the antigen titre to 1:4 by November 1998. She continued on prednisolone at 10-7.5 mg/daily and in July 2000 remained asymptomatic from her sarcoidosis. She has had no recurrence of the cryptococcal infection.

**Azathioprine**

The steroids were commenced 1995 and continued weekly. November 1993, the mild restrictive pulmonary function test (Fig. 4) showed mild CSE. The serum c-ANCA titre was normal. There was no clinical evidence of a vasculitis. The chest radiograph showed some interstitial shadowing and a pleural effusion at the right base.

**Case Four**

A 42-year-old woman presented in 1996 for thoracentesis and transbronchial biopsy for a mediastinal mass. She had a history of dyspnoea and a dry cough. She was a non-smoker and a dog breeder. Examination revealed a systolic murmur. Chest radiograph showed a large cardiomegaly with multiple pulmonary nodules. Pulmonary function tests were normal. Her serum ACE was elevated (134 units). CT scan showed a 5 cm in diameter, mediastinal mass that was hyperdense on unenhanced CT scan. The tumour was biopsied and found to be a squamous cell carcinoma.

**Case Five**

A 41-year-old Caucasian woman presented in 1991 with bilateral facial palsy, papilloedema, cingulate neuritis, horizontal oscillopsia and mild bilateral sensory neural deafness. MRI of the brain showed no abnormalities. She also had mild bilateral hilar adenopathy with mediastinal lymphadenopathy, which was proven to be sarcoidosis on mediastinoscopy. She was commenced on intravenous Methylprednisolone at 500 mg/day for 5 days and then 100 mg/day, followed by a gradual reduction in steroid dose.
Azathioprine was introduced (100 mg/day, gradual reduction of the steroid dose) to the regimen and methotrexate was commenced in December 1991 at an initial dose of 10 mg weekly. Methotrexate was withdrawn in July 1992. In February 1993, the patient’s prednisolone dose was 6 mg/day. A ventriculo-peritoneal shunt was inserted (July 1993) for non-resolving gross intracranial hypertension, the persistence of a mild CSF pleocytosis and elevated CSF protein. At that stage there was no radiographic evidence of pulmonary or mediastinal sarcoidosis. She then developed pulmonary infiltrates (Fig. 4 & 5) and a skin lesion on her leg. Biopsy showed both to be Cryptococcus neoformans. She was commenced on Fluconazole 400 mg/day for 6 months and continued on Azathioprine 100 mg/day but no oral Prednisolone. Lumbar puncture excluded neurological involvement with cryptococcus.

Case Four

A 48-year-old Caucasian woman presented in October 1996 for investigation of a mass in the left lung with some mediastinal lymphadenopathy. In April of that year she had developed a non-productive cough with no other symptoms. She had a 12 pack/year history of smoking. Other medical history included removal of two melanomas (level one; no lymph node involvement in either), untreated hypertension and a duplex kidney with renal artery stenosis. Chest radiograph showed an increased density in the left hilum with a soft tissue mass above the left pulmonary artery. HRCT scan of the chest showed a large mass filling the left paravertebral gutter extending anteriorly around the ascending aorta into the posterior mediastinum. The mass was 10 cm in length and 5 cm at its widest with patchy linear enhancement following intravenous contrast. There were two lymph nodes in the aorto-pulmonary window, the largest measuring 2 cm in diameter. Bronchoscopy showed the appearance of a fungating tumour occluding the apical segment of the left lower lobe. Bronchial biopsies showed granulation tissue with abundant yeasts typical of Cryptococcus with no evidence of malignancy, dysplasia or acid-fast bacilli. Her serum Cryptococcal antigen (latex agglutination) was positive (1/16). CT scan of her brain and lumbar puncture were normal. Other investigations were normal. She was treated with Fluconazole 400 mg for 6 months. In August 1997 she developed a dry cough, some lower left-sided chest pain, arthralgias involving shoulders, hands and knees and dry eyes. Her cryptococcal antigen serology was negative. A Gallium 67 scan showed bilateral hilar uptake a little more prominent on the left. Serum ACE and serum immunoglobulins were normal and a formal eye assessment showed only constitutionally dry eyes. Transbronchial biopsies showed non-caseating granulomata consistent with sarcoidosis. Siropiometry showed mild airflow obstruction in September 1998 (FEV1, 2.78 L, FVC, 3.73 L) with no improvement after Salbutamol [predicted 2.71 (3.16 L)]. She received no further immunosuppression and suffers only mild arthralgia.

Case Five

This 60-year old Caucasian man developed non-productive cough in 1991 followed by bilateral segment inflammation with visual loss panuavitis and vitritis one year later due to sarcoidosis. Chest radiograph showed reticular nodular shadows and a CT scan showed multiple mediastinal lymph nodes. Transbronchial biopsies showed granulomata and he was commenced on prednisolone 40 mg. In 1995, he also developed asymptomatic non-sustained ventricular tachycardia with a dilated cardiomyopathy suspected to be secondary to his sarcoidosis. In 1996, the patient was on 9 mg of prednisolone and azathioprine 25 mg daily when he was diagnosed with cryptococcal pneumonia following deterioration in his condition. Cryptococcus was cultured on bronchial washings and serum cryptococcal antigen was elevated. He was treated with intravenous Amphotericin for a total of 4 weeks in addition to Fluconazole at 400 mg/day. The pulmonary infiltrates cleared considerably after this period but significant residual shadowing on the chest radiograph was attributed to sarcoidosis and improved with initiation of prednisolone (40 mg/day) with Fluconazole cover at 400 mg daily. In 1997, the patient was admitted to hospital with a 4-day history of right upper lobe weakness and inco-ordination. A CT scan demonstrated a large left anterior frontal lobe ring-enhancing lesion, with a smaller left posterior frontal lobe lesion. There was marked peri-lesional oedema. A stereotactic excision biopsy was performed and microbiology established the diagnosis to be that of Nocardia. The patient was treated with Septrin and subsequently ceftazidime and made a good recovery after several months, albeit complicated by grand mal seizures. Chest radiograph remained clear on Fluconazole 400 mg daily and prednisolone 7 mg daily.
Discussion

In conclusion, Cryptococcal meningitis is a disease that is not uncommon in the immunocompromised patient, with a high mortality of 80% in untreated patients with meningitis. The disease can extend to the skin and other organs, as shown in the radiographic lesion of the lung.

Cryptococcal infection is primarily a disease of the nervous system, and meningitis is the most common form of the disease. However, cryptococcal infection can also involve the skin and other organs, as shown in the radiographic lesion of the lung.

Cryptococcus is a fungus that primarily infects the immune system, and TH1 and TH2 responses are crucial in the immune response to this infection. The role of these cytokines is important in the immune response to Cryptococcus, and their role in the response to infection is still not fully understood.

A key player in the immune response to Cryptococcus is the mannose receptor, which recognizes the mannose residues on the capsular polysaccharide of Cryptococcus. This receptor is expressed on the surface of macrophages and dendritic cells, and its interaction with the capsular polysaccharide of Cryptococcus is essential for the phagocytosis of the fungus. The receptor is also expressed on the surface of other immune cells, such as B cells and T cells, and its role in the immune response to Cryptococcus is not fully understood.

The role of the capsular polysaccharide of Cryptococcus in the immune response is crucial, as it is a major antigenic determinant of the fungus, and its interaction with the capsular polysaccharide is essential for the phagocytosis of the fungus. The role of the capsular polysaccharide in the immune response is not fully understood, but it is clear that it is an important determinant of the immune response to Cryptococcus.
Discussion

Inhalation of cryptococcal spores (< 2 μm in diameter) is considered the primary route of host inoculation. This results in pulmonary involvement with the potential of later dissemination to the meninges and less commonly to organs such as bone, skin or prostate [2]. Direct inoculation of the organism has also been documented resulting in skin lesions [6].

Cell-mediated immunity (CMI) is important in protecting against *C. neoformans*. In both clinical and murine models, the clearance of *C. neoformans* from the lung requires the presence of both CD4+ and CD8+T cells [18]. Protection against dissemination, however, is dependent on splenic CD4+ cells [19]. The mechanism of action of both lymphocyte subsets may be direct, or mediated indirectly by the stimulation of the anti-cryptococcal activity of effector cells, including cytotoxic cells and phagocytes such as NK cells, neutrophils and macrophages [18]. Pro-inflammatory cytokines secreted by the TH1 cells (IL-12, IFN-γ, IL-2, TNF-β) are crucial to the anti-cryptococcal response with IFN-γ and IL-2 conferring resistance to *C. neoformans* infection [19]. Other cytokines, which establish resistance to *C. neoformans*, include TNF-α, IL-12 and IL-18 [18,19] of which TNF-α is crucial [20].

Although *C. neoformans* does not elaborate any known exotoxins, there are a number of factors, which determine its virulence. These include the capsule, melanin and mannitol production and the soluble extracellular constituents of *C. neoformans* (glucuronoxylomannan, galactoxylomannan and mannanproteins) [20]. They act through a variety of processes to reduce production of inflammatory cytokines, reduce leukocyte migration, inhibit CMI and reduce protection against oxidative injury. The immunological deficits in sarcoidosis [21] and the effects on the immune system by steroids have been extensively described previously [22] and sarcoidosis on its own can predispose to fungal infections [23].

The role of steroids in *C. neoformans* infection has been extensively studied by Goldmann *et al* [24] using a rat model. Cortisone treatment of rats has been shown to decrease the capsular specific antibody response of rats immunised with capsular polysaccharide in complete Freund’s adjuvant [25] as well as decrease antibody titres against cryptococcal proteins [24]. Goldmann *et al* [24] have shown that steroids administered to rats early in the course of pulmonary infection resulted in partial abrogation of granulomatous inflammation and were associated with increased lung fungal burden, change in organism location from primarily intracellular to extracellular, reduced inflammation and extrapulmonary dissemination. Rats infected with *C. neoformans* who were then treated with steroids showed smaller effects with respect to lung fungal burden and extrapulmonary dissemination. Similar findings have been made by Gadebusch and Gikas [25]. The results of these studies suggest that the late stages of infection may be relatively resistant to steroid immunosuppression and that the reactivation of latent infection may require the use of additional immunosuppressive agents. This is a pertinent finding in that human exposure is common on serological evidence, but cryptococcosis is relatively rare among individuals on steroid therapy [26]. A further consideration is recent evidence for increased numbers of CD4+/CD25 bright T-lymphocytes (Treg cells) in active sarcoidosis [27]. These cells mediate a transferable immunologic tolerance by suppressing T-lymphocyte reactivity against infectious agents and further studies aimed at whether they could play a role in the development of fungal infections in sarcoidosis should be pursued.

Apart from the immunological considerations raised, our cases highlight the need for the rapid diagnosis of cryptococcal infections in patients with sarcoidosis using a variety of diagnostic modalities. In the HIV-negative host, the chest radiograph can reveal a number of patterns including discrete masses, lobar/segmental heterogeneous opacities, a diffuse bilateral nodular or reticulonodular pattern [28,29]. Air bronchograms and cavitation of masses, adenopathy and pleural effusions also occur. More than one radiological feature may present on a single radiograph [17,29] and one report has suggested there may be diagnostic confusion in interpreting chest radiographs in the context of sarcoidosis [10]. If there is concurrent meningitis, lumbar puncture and CT head or MRI of the head should be performed [30].

Four of our five cases received antifungal treatment with complete resolution of disease. There are no randomised-controlled trials evaluating the various treatment regimens in HIV-negative patients but the recognition of fungal drug resistance makes
the choice of two or more agents as initial therapy an attractive proposition in significant disease. However, Fluconazole (fungistatic) alone has been shown to be equally efficacious as first line treatment as other regimens in the HIV-positive population [31]. The Mycoses Study Group Cryptococcal Subproject [30] has recently proposed practice guidelines for the management of cryptococcal disease in a variety of settings, typically based on level 4 and 5 evidence.

In summary, our series of patients with sarcoidosis and cryptococcal infection substantially contributes to the body of cases currently available in the medical literature. We highlight the variability of the clinical presentation and disease course as well as the uniformly good responses to various antifungal regimens available. Although an unusual infection, cryptococcosis should always be considered in the context of sarcoidosis from which it may be difficult to distinguish and in which it may be fatal especially in the presence of additional immunosuppression. Currently, the precise mechanism whereby sarcoidosis per se (without immunosuppressive therapy) confers reduced resistance to this fungal infection is unknown and would represent a challenging area of research.

References