Diffuse histoplasmosis in a patient with sarcoidosis

PS Badesha, MG Saklayen, N Hillman

Summary
A case is presented of a woman with a long history of sarcoidosis who developed diffuse histoplasmosis. Although association between these two entities has been described before, there are only a few case reports of histoplasmosis among sarcoid patients. Diagnosis was finally established by bone marrow biopsy which saved the patient’s life.

Keywords: histoplasmosis, sarcoidosis

Histoplasma capsulatum, a dimorphic fungus and a soil saprophyte, is distributed throughout the world. Although histoplasmosis occurs worldwide, endemic regions in the US are in the Ohio-Mississippi River Valley, with microfoci in other areas. It is usually asymptomatic or self-limiting, except in patients who have a predisposing immunodeficiency.

Disseminated histoplasmosis predominantly affects the lungs and reticuloendothelial system, but it may affect any part of the body. The diagnosis becomes particularly difficult when systemic diseases such as tuberculosis or sarcoidosis predispose to dissemination of histoplasmosis. We report a case of diffuse histoplasmosis that developed in a patient with sarcoidosis.

Case report
A 29-year-old black woman had presented to the hospital with fever and cough of several weeks duration. Pulmonary sarcoidosis was diagnosed by mediastinal lymph node biopsy in 1987, followed by progressive renal failure. A percutaneous renal biopsy revealed focal glomerulosclerosis. The patient’s pulmonary symptoms were successfully treated with corticosteroids, but renal function soon deteriorated to end-stage renal disease requiring haemodialysis. She received a one-haplotype-identical living renal transplant from her mother in 1989. Her graft was functioning well two years post-transplant, when she moved from Boston to Dayton, Ohio. During the second year after her transplant, she inadvertently stopped taking azathioprine for several weeks. Her renal function deteriorated and a renal biopsy revealed severe acute and chronic rejection with prominent eosinophils in the interstitium. No granuloma was visible. Despite pulse solumedrol therapy her graft kidney could not be salvaged and she was started on ambulatory peritoneal dialysis.

Two months later she developed persistent fever with night sweats, chills, diarrhoea and weight loss. There was no evidence of infection or recurrence of sarcoidosis despite an extensive work up that included blood cultures, chest X-rays and gallium scan. The transplanted kidney was thought to be the source of infection and she underwent transplant nephrectomy with complete resolution of her symptoms. She was switched to haemodialysis after the surgery. The patient remained off corticosteroids and immunosuppressive agents for more than a year.

While on haemodialysis, she had a recurrence of high-grade fever with night sweats, weight loss and nonspecific diarrhoea. Physical examination was unremarkable. All infectious work up, including chest X-rays, blood cul-

Figure 1 Histological appearance of bone marrow with noncaseating granuloma (short arrow) of Histoplasma capsulatum infection, bone marrow biopsy material from posterior iliac crest, before steroid therapy. Long arrow indicates granuloma (Hematoxylin, Eosin X 11)

Figure 2 Intracytoplasmic appearance of Histoplasma capsulatum in a mononuclear cell within bone marrow aspirate smear preparation, after initiation of steroid therapy (Wright & Giemsa, X 700)
Figure 3 Histological appearance of bone marrow aspirate with rare microgranuloma (−) of *Histoplasma capsulatum* infection, after initiation of steroid therapy (Hematoxylin, Eosin, X 230)

Figure 4 Intracytoplasmic appearance of *Histoplasma capsulatum* within a mononuclear cell in the peripheral blood smear,uffy coat preparation (Wright & Giemsa, X 700)

tures, stool studies, HIV and Mantoux test were negative. Gallium scan revealed no activity in the lung or any other organ. Bone marrow aspiration and biopsy revealed multiple noncaseating granulomas (figure 1). No organisms were seen. Mycobacterial and fungal cultures were done and she was started on high dose steroids for presumed recurrence of sarcoidosis.

She showed improvement, but within a week, fever and night sweats recurred, accompanied by hepatomegaly and abnormal liver function tests. Disseminated tuberculosis was suspected and, pending mycobacterial culture report, she was started on triple drug antituberculosis therapy. In the ensuing week her condition deteriorated; she developed leucopenia and thrombocytopenia with worsening liver function. Cultures remained negative. A repeat bone marrow aspirate and biopsy revealed numerous *Histoplasma capsulatum* within the reticuloendothelial cells (figure 2). There was rare granuloma (figure 3). A peripheral blood smear stained with Wright stain also showed *Histoplasma* within monocellular nuclei (figure 4). The patient was given intravenous amphotericin B for three months (total cumulative dose 1.5 g) followed by oralitraconazole. She responded dramatically within a few days and recovered completely after four months of antifungal therapy.

**Discussion**

The clinical spectrum of histoplasmosis includes a self-limiting influenza-like syndrome, pneumonia, mediastinal and pleural fibrosis, chronic lung cavities, histoplasmomas, miliary disease and disseminated, often fatal illness.4 Histoplasmosis may mimic sarcoidosis clinically or histologically but fungal superinfection is rare.4 The relationship of sarcoidosis and histoplasmosis was well described by *Wheat et al*6 in their review of 11 patients with sarcoidosis accompanied by laboratory evidence of histoplasmosis. They concluded that sarcoidosis and histoplasmosis are similar in many respects, clinically as well as radiographically. Noncaseating granulomas, the hallmark of sarcoidosis, are also seen in tissues from patients with histoplasmosis.6 Cases misdiagnosed as sarcoidosis have been described in which *Histoplasma capsulatum* was subsequently identified in tissues.1,4,7,8

Disseminated histoplasmosis is usually chronic or subacute. The subacute form occurs in apparently healthy individuals with mild parasitization. The histopathologic lesion is a well-formed noncaseating granuloma without any organism (figure 1). This kind of presentation can disguise as sarcoidosis. Sharma described an oriental man with granulomatous disease of the liver that mimicked sarcoidosis.1 The patient actually had histoplasmosis, which was finally diagnosed after eight weeks, with a culture of biopsied liver tissue.

Our patient is an excellent example of histoplasmosis masquerading as sarcoidosis. The bone marrow finding of noncaseating granuloma in the absence of any visible organisms in a patient with a previous history of sarcoidosis prompted a quick diagnosis of a recurrence of sarcoidosis. Since cultures of fungi and mycobacteria usually take weeks, the correct diagnosis was delayed. The continued deterioration in the clinical condition of the patient with development of progressive hepatosplenomegaly and pancytopenia while undergoing steroid therapy raised the spectre of a missed infection, which led to the repeat bone marrow biopsy. This provided the correct diagnosis and saved the patient’s life. However, as it turned out, a careful review of Wright-stained peripheral blood smear or buffy coat (figure 4) would have yielded the diagnosis without any other invasive procedure.

Although most of the immunological para-

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<th><strong>Pulmonary histoplasmosis: clinical spectrum</strong></th>
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<tr>
<td><strong>Acute</strong></td>
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<tr>
<td>• asymptomatic</td>
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<tr>
<td>• self-limiting influenza-like syndrome</td>
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<tr>
<td>• severe dyspnea</td>
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<td>• pneumonia</td>
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<td><strong>Chronic</strong></td>
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<tr>
<td>• granulomas</td>
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<tr>
<td>• mediastinal and pleural fibrosis</td>
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<td>• chronic lung cavities</td>
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<tr>
<td>• histoplasmomas</td>
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<tr>
<td>• ‘Buckshot’ calcifications</td>
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<tr>
<td><strong>Chest X-ray</strong></td>
</tr>
<tr>
<td>• normal</td>
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<tr>
<td>• one or two patchy infiltrates</td>
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<tr>
<td>• mediastinal or hilar adenopathy</td>
</tr>
<tr>
<td>• diffuse miliary opacities</td>
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<td>• pleural effusion and cavitation are uncommon</td>
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**Box 1**
Learning points

- sarcoidosis may be misdiagnosed in patients with histoplasmosis
- histoplasmosis may be a concomitant infection in patients with sarcoidosis
- histoplasmosis may induce a chronic inflammatory illness such as sarcoidosis

Box 2


Selenium-induced thyroid dysfunction

Lorenz C Hofbauer, Christine Spitzweg, Roland A Magerstädt, Armin E Heufelder

Summary

Administration of the anti-oxidative trace element selenium is currently being evaluated for its benefits in patients with inflammatory diseases. However, little is known about the risks of selenium. We report on a patient in whom, along with standard therapy, administration of large intravenous doses of selenium for sepsis secondary to pneumonia resulted in development of marked hypothyroidism. In addition, severe iodine deficiency was noted, and supplementation with iodine led to normalisation of thyroid function.

Keywords: selenium, iodine deficiency, hypothyroidism, euthyroid sick syndrome

Case report

A 66-year-old man with chronic glomerulonephritis and no history of thyroid disorder was admitted for treatment of severe pneumonia following removal of a tongue cancer. Laboratory results showed an elevated white blood cell count of $15 \times 10^9$/l with a left shift, and elevated creatinine (309.4 $\mu$/mol/l) and blood urea nitrogen (29.6 mmol/l) levels. Thyroid function tests revealed serum levels of thyroid-stimulating hormone (thyrotropin) of 2.0 mIU/l (normal 0.4–4.0), free T3 of 1.7 ng/l (2.3–4.2), and free T4 of 0.5 mg/l (normal 0.8–1.8), consistent with euthyroid sick syndrome. Thyroid auto-antibodies were negative. Shortly

The clinical benefit of selenium, an essential trace element with anti-oxidative effects, is currently under investigation.\(^\text{12}\) Target compounds containing selenium include the anti-oxidative enzyme glutathione peroxidase and type I deiodinase which catalyzes hepatic thyroxine (T\(_4\)) to triiodothyronine (T\(_3\)) conversion.\(^\text{3}\) We report on a patient who developed marked hypothyroidism following administration of large doses of selenium. Supplementation with iodide effectively restored normal thyroid function.

Side-effects of selenium

- odour of garlic on the breath
- fatigue, nausea
- diarrhoea, abdominal pain
- red discolouration at the base of the nails
- alopecia
- pulmonary oedema
- polyneuropathy
- increased T3/T4 ratio, hypothyroidism (in the presence of iodine deficiency)
- infertility

Box 1
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