Case Report

Protein-losing enteropathy and hypogammaglobulinaemia as first manifestations of disseminated histoplasmosis coincident with Nocardia infection

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Disseminated histoplasmosis and nocardiosis typically affect immunocompromised hosts. We report a case of gastrointestinal and adrenal histoplasmosis, presenting as protein-losing enteropathy and hypogammaglobulinaemia, coincident with Nocardia infection, in a HIV-negative patient in whom a specific immunological defect could not be identified. Clinicians in areas of non-endemicity should be vigilant for rare manifestations of histoplasmosis.

Introduction

Histoplasma and Nocardia are ubiquitous, environmental pathogens. In endemic areas such as the Midwest of the United States, the fungus Histoplasma capsulatum most commonly causes localized pulmonary disease whilst disseminated histoplasmosis (DH) typically occurs in patients with HIV/AIDS or other immunodeficiencies (Kauffman, 2007; Suh et al., 2001). DH has also been reported in persons with inherited humoral and cellular immunodeficiencies, including defects in the interferon gamma (IFN-\(\gamma\)) receptor–interleukin 12 axis and the hyper-IgM or hyper-IgE syndromes (Antachopoulos et al., 2007; Zerbe & Holland, 2005). Symptomatic gastrointestinal (GI) histoplasmosis is uncommon (3–12% of patients), although autopsy series have shown that GI tract involvement is frequent in HIV/AIDS patients (Kauffman, 2007; Wheat et al., 1990). The manifestations of GI infection in other patient groups are not well defined.

Nocardia species cause opportunistic infections in the lungs and central nervous system, but also affect individuals without immune-compromise. Common pathogenic species include Nocardia farcinica, Nocardia nova and Nocardia brasiliensis. In Australia, localized cutaneous disease is most frequently due to N. brasiliensis, though any species may cause disseminated infection (Georghiou & Blacklock, 1992; Brown-Elliott et al., 2006).

We report an unusual case of DH, coincident with cutaneous nocardiosis, with first manifestations of hypogammaglobulinaemia secondary to protein-losing enteropathy. Typically associated with immune-compromise, the two entities arose in an apparently healthy host. Clinicians should be alert to atypical manifestations of histoplasmosis, and exclude the possibility of underlying immunodeficiency.

Case report

A 40-year-old white male was admitted to hospital with a 5-month history of recurrent left thigh abscesses, fever and anorexia. Despite broad-spectrum antibacterial therapy and multiple surgical debridements, the abscesses failed to resolve. No pathogen was isolated from surgical specimens. Five years earlier, the patient was extensively investigated for diarrhoea and post-prandial bloating associated with protein-losing enteropathy and hypogammaglobulinaemia.
A diagnosis of primary intestinal lymphangiectasia was made, based on a small bowel series demonstrating ‘flocculation’ of barium in the ileum, in the absence of any abnormality on upper and lower GI endoscopic examination. Medium-chain triglyceride supplementation was commenced with little clinical response. The patient worked as a landscaper, pursued recreational caving but had not travelled outside Australia. There was no family history of immunodeficiency or previous infections, nor of consanguinity.

The patient was cachectic and febrile, and had marked lower limb oedema. There were multiple, large suppurative abscesses in the left thigh associated with inguinal lymphadenopathy. Physical examination was otherwise unremarkable.

Laboratory studies included: total protein, 57 g l$^{-1}$ (normal range 63–84 mg l$^{-1}$); albumin, 18 g l$^{-1}$ (35–53 g l$^{-1}$); and 25-hydroxy-vitamin D, 11 nmol l$^{-1}$ (37–131 nmol l$^{-1}$).

Magnetic resonance imaging (MRI) of the left leg confirmed an abscess 3 × 2.3 cm in diameter in the inguinal region and two similar-sized abscesses in the quadriceps muscles. A thoracic CT scan revealed multiple nodules up to 25 mm in diameter in both lung fields and reactive mediastinal lymphadenopathy. MRI of the brain was normal. Microscopy of abscess material collected at open biopsy of the leg lesions revealed thin, branching, Gram-positive rods. Culture grew an aerobic actinomycete identified as *Nocardia* sp. by standard phenotypic-based methods (Brown-Elliott et al., 2006). DNA sequence analysis of the 16S rRNA gene also assigned the isolate as ‘*Nocardia* sp.’ since its 16S rDNA sequence yielded 99% similarity to those of multiple species of *Nocardia* in the GenBank database (BLASTN 2.2.10; http://www.ncbi.nlm.nih.gov).

Investigations were undertaken to reassess the diagnosis of ‘intestinal lymphangiectasia’. Protein-losing enteropathy was confirmed by an elevated stool alpha-1-antitrypsin level of 51 mg l$^{-1}$ (normal range <1.5 mg l$^{-1}$) and technetium-99m dextran scan demonstrating focal concentration in distal small bowel loops consistent with GI protein loss. Push enteroscopy showed macroscopically dilated lacteals in the jejunal mucosa (Fig. 1).

Histopathological examination of duodenal and jejunal biopsy specimens revealed villi distended with well-formed granulomata and sheets of foamy macrophages containing ovoid, budding yeast forms 2–4 μm in diameter which stained with methenamine silver (Fig. 2). *H. capsulatum* was cultured from these specimens. Histoplasmin ‘H’ and ‘M’ antigens (Fungal Immunodiffusion System; Meridian Bioscience) were detected, but blood cultures were negative for the fungus and bone marrow examination revealed no granulomas or organisms. An abdominal CT scan revealed bilateral homogeneous adrenal masses (6.2 cm diameter) consistent with infiltration by *Histoplasma*, but specimens obtained by fine needle aspiration were negative on culture and nucleic acid testing (Lau et al., 2007). A normal cortisol response was observed with adrenocorticotropic hormone stimulation.

Investigations for possible immunodeficiency were unfruitful. Serum IgG level was low at 3.06 g l$^{-1}$ (normal range 6.1–15.5 g l$^{-1}$) consistent with protein-losing enteropathy, but IgM and IgE levels were normal, whilst IgA levels were above normal at 6.32 g l$^{-1}$ (0.8–5.3 g l$^{-1}$). Total lymphocyte count was mildly reduced at 900 cells μl$^{-1}$ (1000–4000 cells μl$^{-1}$). Total monocyte count, determined by CD14 expression on a single layer flow cytometry analysis platform, was 194 cells μl$^{-1}$, within the lower limit of the normal range. The CD4 count was 344 cells μl$^{-1}$.

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**Fig. 1.** Endoscopic images showing dilated lacteals in the jejunum.

**Fig. 2.** Diffuse sheets of small (2–4 μm diameter) ovoid, yeast-like organisms in jejunal tissue visualized by methenamine silver staining. Original magnification ×40.
(380–1390 cells μl⁻¹), representing 39% (37–63%) of total lymphocytes, but CD3 and CD8 proportions were unremarkable. The B-cell proportion was initially low at 0.7%, but this normalized following treatment. The NK cell fraction was normal and HIV antibody test was negative. The following conditions were excluded: chronic granulomatous disease (normal neutrophil oxidative metabolism as measured by dihydrorhodamine reduction); X-linked hyper-IgM syndrome (normal induced CD40 ligand expression on T cells, and raised IgA levels); Mendelian susceptibility to mycobacteria disease (normal expression of IFN-γ receptor I on monocytes, normal phosphorylated STAT-1 response of T cells to IFN-γ stimulation, normal phosphorylated STAT-4 response after interleukin 12 signalling of activated T cells); X-linked agammaglobulinemia (DNA sequencing of the Bruton’s tyrosine kinase gene); hyper-IgE syndrome (lack of other manifestations, normal IgE level).

Treatment for DH was initiated with liposomal amphotericin B for 2 weeks, followed by oral itraconazole, with the intention of continuing for a minimum of 2 years (Wheat et al., 2007). The nocardiosis was initially treated with a combination of merozosan and oral trimethoprim/sulfamethoxazole for 2 weeks, followed by trimethoprim/sulfamethoxazole as a single agent. After 6 months of combined antibacterial and antifungal treatment, the patient’s skin abscesses completely resolved, the diarrhoea and post-prandial bloating significantly improved and he reported a weight gain of 5 kg. Repeat CT scans showed the persistence of only a single small pulmonary nodule and substantial reduction in size of both adrenal lesions. Examination of subsequent jejunal biopsy specimens demonstrated normal villous architecture; however, Histoplasma organisms were still visualized within the villi although cultures were negative. Repeat technetium-99m dextran images showed substantial improvement in protein-losing enteropathy. Serum albumin improved to 29 g l⁻¹; however, IgG has remained at pre-diagnosis levels.

**Discussion**

The patient described herein is notable for having two opportunistic infections in the absence of an identifiable immune deficiency; both DH and nocardiosis typically affect immunocompromised patients (Kauffman, 2007; Brown-Elliott et al., 2006). Furthermore, he presented with a highly unusual form of GI histoplasmosis – protein-losing enteropathy and hypogammaglobulinaemia. Histoplasmosis is rare in non-endemic countries such as Australia (Hunt et al., 1984; Smith et al., 2006), and clinicians should be aware of its varied non-specific presentations.

A key feature of this patient’s illness was the presentation of long-standing protein-losing enteropathy as the first manifestation of chronic DH. This is notable not only because protein-losing enteropathy is a most unusual form of GI histoplasmosis, but since GI tract disease is rarely symptomatic; even when present, symptoms are often non-specific (Kahi et al., 2005). GI histoplasmosis is typically associated with inflammatory lesions or ulcers in the intestine (Cappell et al., 1988), which were absent in our patient. In HIV-positive individuals, diarrhoea, fever and abdominal pain are common and large-bowel disease is characteristic (60% of cases) (Kauffman, 2007; Suh et al., 2001). In contrast, small-bowel disease with protein-losing enteropathy or malabsorption are rare complications of GI histoplasmosis (Bank et al., 1965; Orchard et al., 1979; this study). In support of GI histoplasmosis as the cause of the enteropathy in this case is the symptomatic improvement and biopsy-proven reversal of abnormal villous morphology following antifungal treatment. The persistence of hypogammaglobulinaemia is probably due to incomplete reversal of the longstanding pathological process, although persistence of infection is not excluded as Histoplasma organisms were still seen in the repeat jejunal biopsy samples.

Given the propensity for both *Histoplasma* and *Nocardia* to cause disseminated infection, investigation of other anatomical sites for disease is essential for effective patient management. In our patient, the pulmonary lesions could be due to either histoplasmosis or nocardiosis. A respiratory specimem, which was not obtained, may have identified the causative infective agent. Pulmonary nocardiosis though seems more likely, due to the lack of calcification in the lung nodules and the propensity for pulmonary 'histoplasmomas' to persist despite treatment (Kauffman, 2007; Goodwin & Snell, 1969). Despite negative microbiological and histopathological results from adrenal biopsy, adrenal involvement is common in DH, and the CT appearances of the adrenal glands in this patient (bilateral organ enlargement, hypoattenuation with rim enhancement and low-density foci of necrosis) support the diagnosis of adrenal histoplasmosis (Grover et al., 2005). In contrast, adrenal nocardiosis is rare and typical CT scan findings comprise contrast-enhanced heterogeneous appearances with internal septations (Midiri et al., 1998).

The development of two unusual opportunistic infections in this patient strongly suggested a cellular immunodeficiency, although thorough investigation failed to define any known genetic or functional defect. His CD4 count was only slightly below the lower limit of the normal range, and since the CD4 proportion of lymphocytes was always normal, this simply reflected his persistent lymphopenia, itself most likely due to lymphangiectasia. In the absence of a family history, it is difficult to further investigate this and other similar cases of undefined cellular immunodeficiency.

Of interest, we were unable to identify the pathogenic *Nocardia* organism to species level. It was not surprising that phenotypic-based methods including antimicrobial susceptibility profiles were not able to identify the organism since these methods are insensitive (Brown-


References


