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Title	Disseminated histoplasmosis in a patient with Crohn's disease on dual immunosuppression: an under-recognised opportunistic fungus endemic to Australia

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Disseminated histoplasmosis in a patient with Crohn's disease on dual immunosuppression

Clinical record

A 76-year-old man from rural Victoria presented with 4 months of difficulty swallowing due to a painful, large, non-healing tongue ulcer (Box 1). He was diagnosed with Crohn's disease 20 years earlier, requiring previous small bowel resections and currently managed with azathioprine and infliximab. Associated symptoms included fatigue, fevers, night sweats and 5 kg weight loss. There was no relevant travel history or exposure to bird or bat guano.

Before admission, biopsies had been performed on the tongue lesion on two occasions, showing ulcerated mucosa with granulomatous inflammation and occasional fungal hyphae, but there was no evidence of malignancy and no organisms had been cultured (extended fungal culture was not performed due to a lack of diagnostic suspicion). A fluorodeoxyglucose positron emission tomography (FDG-PET) scan demonstrated intense metabolic uptake of the left tongue, with extension into the sublingual space and cervical and retropharyngeal lymph nodes.

On examination, he was febrile with a large, ulcerated lesion on the left lateral tongue, crusted cutaneous lesions over his face, scalp and chest and a heliotrope rash around his eyelids. Blood analysis on admission revealed pancytopenia, with a haemoglobin level of 85 g/L (reference interval [RI], 130–180 g/L), white cell count of 3.0×10^9/L (RI, 4.0–11.0×10^9/L) and platelet count of 125×10^9/L (RI, 150–400×10^9/L). Inflammatory markers were raised, with a C-reactive protein concentration of 170 mg/L (RI, < 5 mg/L) and erythrocyte sedimentation rate of 43 mm/h (RI, < 13 mm/h). Creatinine kinase concentration was normal (20 U/L; RI, < 170U/L). Antinuclear antibody was weakly positive (speckled). Myositis-specific antibody panel was positive for anti-Mi-2β and anti-nuclear matrix protein 2 antibodies.

There was a strong suspicion of a primary oral cancer with associated paraneoplastic dermatomyositis. Neck to pelvis computed tomography showed an ill defined irregular region in the left tongue, enlarged cervical lymph nodes bilaterally (maximum size, 6 mm), and focal consolidation and centrilobular nodules throughout both lungs. A repeat FDG-PET scan was again suspicious for a primary oral cancer. A further tongue biopsy was performed, with periodic acid–Schiff (PAS) and silver methenamine staining (Box 2) showing intracellular organisms in the cytoplasm of macrophages, suggestive of microsporidia. Retrospective review of other biopsy sites (periorbital rash, duodenal ulcer) also revealed PAS-positive intracytoplasmic organisms. Although therapy with

albendazole was commenced, the patient died shortly thereafter.

Posthumous examination of electron microscopy samples revealed no internal features of microsporidia. Microsporidium polymerase chain reaction (PCR) testing was negative. Further evaluation with panfungal PCR was positive for *Histoplasma capsulatum*. A final diagnosis of disseminated histoplasmosis was supported by the clinical presentation and subsequent molecular investigations (Box 3).

Discussion

Histoplasma capsulatum is a dimorphic soil fungus that is endemic to Northern and Central America, parts of Europe and South-East Asia, but is rarely observed in Australia.[1] Less than 70 cases have been reported in Australia, with only four cases described in Victoria — one locally acquired and three imported.[1,2] This is therefore the second reported case of histoplasmosis acquired in Victoria and the first Australian case in a patient receiving anti-tumour necrosis factor (TNF)-α therapy.

Most immunocompetent patients exposed to *H. capsulatum* are asymptomatic, although a mild, self-limiting pneumonitis may occur with greater inoculation. Disseminated disease is more frequently seen in immunosuppressed patients, particularly those with human immunodeficiency virus (CD4 count < 150/μL).[1] Disseminated disease is increasingly recognised in patients receiving anti-TNF-α therapy, due to the critical role of TNF-α in the host immune response to *H. capsulatum*.[3]

Disseminated histoplasmosis manifests with a broad range of symptoms including fever, cough, weight loss, hepatosplenomegaly, lymphadenopathy and pancytopenia.[4] Oropharyngeal ulceration is well recognised, particularly in immunosuppressed patients. Although our patient was pancytopenic, a bone marrow biopsy was considered to be of low diagnostic yield and therefore not performed. Liver enzyme levels were mildly raised, but there was no demonstrated liver or spleen involvement on imaging.

Few reports exist of disseminated histoplasmosis in patients with dermatomyositis, with most already receiving immunosuppressive therapy at the time of presentation.[5]

Diagnosis of histoplasmosis is difficult, requiring a combination of fungal culture and histopathology. Fungal culture can take up to 6 weeks and must be specifically requested. Extended culture was not done in this case but should be considered in similar cases in the future. Histopathological identification requires methenamine silver or PAS stains.[4] Newer diagnostic techniques including serology and PCR may be helpful but are available at reference laboratories only, and serology is unreliable in immunocompromised hosts. Urinary antigen is unavailable in Australia. Treatment is indicated for disseminated disease in immunosuppressed patients with intravenous amphotericin followed by oral itraconazole in severe cases, or itraconazole alone for mild manifestations.

Disseminated histoplasmosis is rare and has a broad range of clinical manifestations, and culture requires a long incubation period. With increasing use of anti-TNF-α therapy, clinicians should be aware of histoplasmosis when investigating for opportunistic

infections.

Lessons from practice

- *Histoplasma capsulatum* is endemic to Australia. Despite clinical infection occurring infrequently, it is an important opportunistic pathogen to recognise.
- Patients with progressive disseminated histoplasmosis present with diverse clinical features, hindering early diagnosis and timely initiation of therapy.
- Oropharyngeal infection has been well described as a manifestation of disseminated histoplasmosis, particularly in immunocompromised patients.
- Anti-tumour necrosis factor-α therapy is increasingly used for a range of autoimmune and inflammatory conditions and is associated with an increased risk of opportunistic infections, including histoplasmosis.

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[Boxes]

1 Clinical photograph showing left-sided tongue ulceration, following biopsies performed as part of the diagnostic evaluation

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2 Silver methenamine stain (magnification × 600) showing numerous intracytoplasmic organisms within macrophages (arrows), later revealed to be *Histoplasma capsulatum*

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3 Electron microscopy showing morphological features of *Histoplasma capsulatum* at magnification × 30 000 (A) and × 10 000 (B)

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