Author/s:
MacIsaac, MB;Fehily, SR;Muhi, S;Yang, L;McKelvie, PA;Jeremiah, CJ;Demediuk, B

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

Date:
2019-09-01

Citation:
MacIsaac, M. B., Fehily, S. R., Muhi, S., Yang, L., McKelvie, P. A., Jeremiah, C. J. & Demediuk, B. (2019). Disseminated histoplasmosis in a patient with Crohn's disease on dual immunosuppression. Medical Journal of Australia, 211 (5), pp.206-207.e1. https://doi.org/10.5694/mja2.50298.

Persistent Link:
https://hdl.handle.net/11343/286253

Article begins on page three of this document.

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

Authors:

	Title	First name	**Mid inits**	Last name	Postnom (eg, PhD)	Position1	Address1	Position2	Address2	Tel	Email
1	Dr.	Michael	B	MacIsaac	MD, BBiomed		1			03 9231 2211	michaelmacisaac11@gmail.com
2	Dr.	Sasha	R	Fehily	MBBS, MPH		1				fehilysasha@gmail.com
3	Dr.	Stephen		Muhi	BSc, BMedSc, MBBS, MPHTM	Infectious Diseases Registrar	1			(03) 93427000	steve.muhi@gmail.com
4	Dr.	Linda		Yang			1				linda.yang@svha.org.au
5	Dr.	Penelope	A	McKelvie		Anatomical Pathologist	1				penny.mckelvie@svha.org.au
6	Dr.	Cameron	J	Jeremiah	MBBS, FRACP	Infectious Diseases Physician	1				cameron.jeremiah@svha.org.au
7	Dr.	Barbara		Demediuk		Gastroenterologist	1				barbara.Demediuk@svha.org.au

Number of corresponding author:	1
Number of alternative corresponding author:	

Addresses:

	Institution		City	State		
1	St Vincent's Hospital		Melbourne	VIC		
2						
3						
4						
5						

Postal address of first corresponding author (if different from the institutional address given above)	

Primary Keywords [Office use only]	Infectious diseases; Digestive system diseases; Diagnostic techniques and procedures; Immune System Diseases
Secondary keywords [Office use only]	Inflammatory bowel diseases; Histoplasmosis; Histopathology; Gastrointestinal diseases; Immunosuppression; Immunotherapies; Microbiology
Notes:	

Article details (press ctrl – 9 to enter details):

Article type	Lessons from practice
Blurb	With increasing use of anti-TNF-α therapy, clinicians should be aware of histoplasmosis when investigating for opportunistic infections

Office use

Ms. Number	mja19.00258.R2
Medical editor	Geoffrey Thompson/Christine Gee
Medical editor email	cgee@mja.com.au
Structural editor	Graeme Prince
Structural editor email	gprince@mja.com.au
Section/Category	Medical education/Lessons from practice
Strapheading	Medical education
Substrap	Lessons from practice

Elsevier – file data:

Filename for copyediting	mac_mja19.00258_ms
Accompanying graphics	mac_mja19.00258_gr1; mac_mja19.00258_gr2; mac_mja19.00258_gr3
Stock images	
Appendices	

Office use – history:

Event	Date
Original submission received	18/03/2019

Event	Date
Accept	14/05/2019

Proof sent to author	
Proof returned by author	
Published (date format xx/xx/xx)	02/09/19
Issue	5
Vol	211
DOI	10.5694/mja19.00258
Journal	The Medical Journal of Australia
Original article DOI (for response)	

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.

Competing interests: No relevant disclosures.
Provenance: Not commissioned; externally peer reviewed.

Author details

Michael B MacIsaac
Sasha R Fehily
Stephen Muhi
Linda Yang
Penelope A McKelvie
Cameron J Jeremiah
Barbara Demediuk
St Vincent's Hospital, Melbourne, VIC.
michaelmacisaac11@gmail.com
doi: 10.5694/mja19.00258

References

1 McLeod DS, Mortimer RH, Perry-Keene DA, et al. Histoplasmosis in Australia: report of 16 cases and literature review. *Medicine* 2011; 90: 61-68.
2 Muhi S, Crowe A, Daffy J. Acute pulmonary histoplasmosis outbreak in a documentary film crew travelling from Guatemala to Australia. *Trop Med Infect Dis* 2019; 4: 25.
3 Culter JE, Deepe Jr GS, Klein BS. Advances in combating fungal disease: vaccines on the threshold. *Nat Rev Microbiol* 2007; 5: 13-28.
4 Kauffman CA. Histoplasmosis: a clinical and laboratory update. *Clin Microbiol Rev* 2007; 20: 115-132.
5 Dussouil AS, Allardet-Servent J, Dunogeant L, et al. Disseminated histoplasmosis partially mimicking a dermatomyositis in a patient with rheumatoid arthritis. *Br J Dermatol* 2015; 173: 797-800.

[Boxes]

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

[mac_mja19.00258_gr1]

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

[mac_mja19.00258_gr2]

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

[mac_mja19.00258_gr3]