Lessons from practice

Paracoccidioidomycosis: an Australian case

Timothy C Badrick[1]
Ella M Meumann[1]
Kathryn Shirley[1]
Peter Simos[2]
Mertya L May[1]
Gary Quagliotto[1]
Evan C Bursle[1]
Nici Leonard[3]
Rodney J McDougall[1]
Jennifer M Robson[1]

1 Sullivan Nicolaides Pathology Central Laboratory, Brisbane, QLD.
2 Gold Coast University Hospital, Gold Coast, QLD.
3 General Practice Market Street Medical Practice, Brisbane, QLD.

timothy.badrick@uqconnect.edu.au

doi: 10.5694/mja2.52300

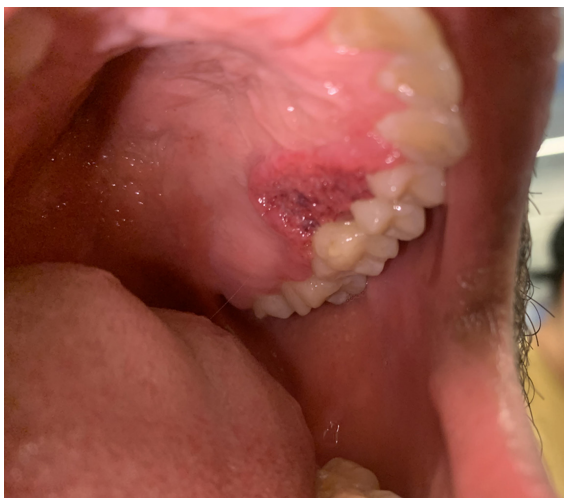
Clinical record

A 34-year-old man, born in Brasília, Brazil, who had been living in Australia for three years with no return travel, presented to his dentist with an eight-week history of a painful, progressively enlarging maxillary, gingival ulcerative lesion (Box 1) with associated occasional cough. Non-tender bilateral cervical and right-sided axillary lymphadenopathy were noted on clinical examination. He had no significant medical background and was not receiving any immunosuppressing agents.

Biopsy was taken to exclude malignancy. Histopathological examination demonstrated pseudoepitheliomatous hyperplasia and active, chronic inflammation with round, yeast-like structures noted in the periodic acid–Schiff (Box 2) and Grocott methenamine silver (Box 3) stains, suggestive of a fungal organism. Calcofluor-white staining of the tissue revealed yeast cells with multiple narrow-based buds resembling "mariner's wheels" (Box 4). Fungal culture results on brain heart infusion (BHI) agar showed thermal dimorphism, with moist, glabrous, white colonies at ten days and 35°C incubation, consistent with a yeast; and suede-like brown colonies with brown reverse on Sabouraud agar at 14 days and 30°C incubation, consistent with a mould. Panfungal polymerase chain reaction (PCR) targeting *ITS1/2* (Institute of Clinical Pathology and Medical Research, Westmead Hospital) confirmed the identification of *Paracoccidioides brasiliensis*.

A diagnosis of chronic progressive adult-onset paracoccidioidomycosis was made based on clinical presentation and findings of investigations. Co-infection with human immunodeficiency virus (HIV) and pulmonary tuberculosis were excluded following negative serology and absence of acid-fast bacilli on smear or culture from three samples of sputum. Plain computed tomography imaging of the chest, abdomen and pelvis reported bilateral axillary lymphadenopathy only (less than 10 mm in short axis diameter) with no other significant positive findings. *Paracoccidioides* spp serology was not performed as this test was not available in Australia. The patient was given oral itraconazole at 150 mg twice daily (suprabioavailable) and completed a total treatment duration of 12 months with therapeutic levels maintained throughout. He had an excellent clinical response to therapy with complete resolution of the ulcerative lesion within two months of initiating antifungal therapy.

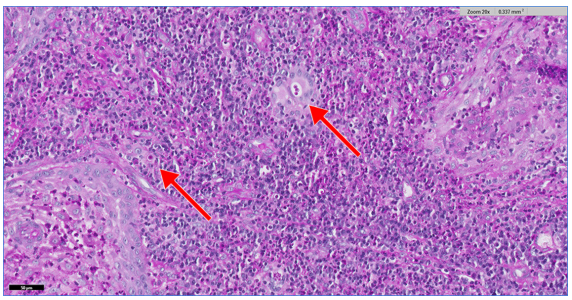
1 Presenting maxillary gingival ulcerative lesion



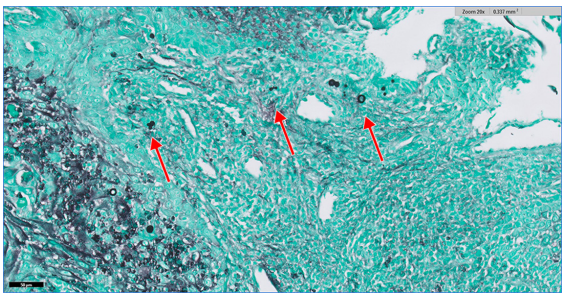
Discussion

Paracoccidioidomycosis is a systemic mycosis caused by thermodimorphic fungi from the genus *Paracoccidioides*; they exist in mould form in the environment and when cultured at 25–30°C, and yeast form in human tissues and when cultured at 35–37°C. These organisms are endemic to South and Central America with up to 80% of cases occurring in Brazil.[1] Cases are predominantly seen in rural farming areas and are likely under-reported due to reduced access to health care and diagnostics. Imported cases have previously been reported on every continent other than Australia and Antarctica. This may be due to the unfamiliarity among Australian clinicians with the diagnosis. With increased international migration, and changing climatic conditions, infections with more unusual pathogens, such as *Paracoccidioides* spp, may become

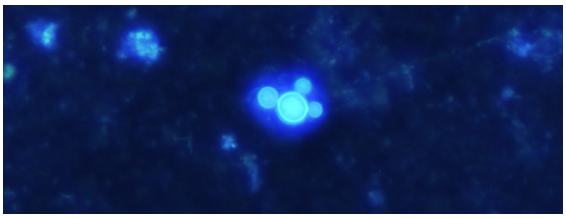
2 Periodic acid–Schiff stain of tissue showing round yeast-like structures (arrows) (200 × magnification)



3 Grocott methenamine silver stain of tissue showing round yeast-like structures (arrows) (200 × magnification)



4 Calcofluor-white staining of the tissue revealing yeast cells with multiple narrow-based buds resembling "mariner's wheels" (40 × magnification with further digital image zoom)



more frequently seen in non-endemic areas such as Australia.[2] Paracoccidioidomycosis has been recognised as a neglected tropical disease and a medium risk mycosis by the World Health Organization; however, global surveillance systems for this condition remain inadequate and the true global burden is unknown.

Paracoccidioides spp are soil saprophytes, with infection occurring via inhalation of spores; however, only 1–2% of exposed individuals will develop clinical manifestations.[1] Acute and subacute presentations of paracoccidioidomycosis develop weeks to months after exposure and include rapid progression of polymorphic skin lesions, lymphadenopathy, fever and anorexia. The chronic form occurs in 80–90% of symptomatic cases. The disease develops over years, with pulmonary involvement including cough, dyspnoea, pulmonary fibrosis, bullae and pulmonary hypertension being the most common presentations. Other manifestations include lesions of the oral mucous membranes, which may be painful with areas of contact bleeding and surrounding tooth loosening,[3] and lesions of the skin, adrenal and central nervous system. A mixed acute and chronic presentation often occurs in immunocompromised patients, particularly those with HIV infection.[1] Overall mortality is low but morbidity is high, with chronic sequelae, such as pulmonary fibrosis and emphysema, narrowing of the oral cavity, glottic stenosis, and sensory and motor neurologic manifestations,[4] occurring in up to 50% of patients despite appropriate treatment.[1] Those with immunocompromising conditions are at higher risk of poor outcomes.[4] Smoking is a risk factor for the development of chronic disease and is present in up to 90% of cases.[5] The described clinical manifestations may be mistaken for tuberculosis, leishmaniasis, histoplasmosis or syphilis given the crossover in geographic endemism.

Diagnosis of paracoccidioidomycosis requires an appropriately equipped laboratory with experienced scientific staff. Tissue biopsy, abscess fluid, skin scrapings, cerebrospinal fluid (CSF) or respiratory samples, including sputum, bronchial washings and bronchoalveolar lavage, are appropriate for diagnosis. Microscopy is the gold standard for identification of pathognomonic narrow-based budding yeast forms using potassium hydroxide (KOH) or calcofluor-white staining. The size of the cells and multiple budding nature allows differentiation from other fungi. Despite this, isolates may be mistaken for other dimorphic fungi or *Cryptococcus* spp.

Culture is usually slow with an average of three to six weeks required for growth on fungal media. Given the risk of laboratory-acquired infection, care must be taken to ensure laboratory staff are not exposed to mould forms. Notification of clinical suspicion to the laboratory is critical to reduce this risk.

Histopathology is also key to diagnosis with organising granulomas or mixed granulomatous and suppurative inflammation commonly seen with yeast forms as described in our patient. Haematoxylin/eosin, Grocott methenamine silver and periodic acid–Schiff stains are commonly used.

Molecular technologies may also be used for diagnosis with specific targeted PCRs being developed, although not currently available in Australia. We used a panfungal PCR from a reference laboratory to confirm the diagnosis from tissue.

Paracoccidioidomycosis is managed with long term (six to 12 months) antifungal therapy. Itraconazole is most commonly used in mild to moderate presentations with high response rates. This therapy may require therapeutic drug monitoring and should be guided by an infectious diseases physician or medical microbiologist.

This case highlights the importance of collaborative diagnosis between clinicians and several pathology disciplines to facilitate prompt diagnosis of paracoccidioidomycosis.

Lessons from practice

- *Paracoccidioides* spp infection may produce a broad range of symptoms and should be considered in patients who have lived in or spent considerable time in South or Central America.
- Chronic infection, although typically presenting with pulmonary manifestations, may also manifest with extrapulmonary symptoms.
- Collection of tissue samples, abscess fluids, cerebrospinal fluid (CSF) or respiratory samples for histopathological examination, culture and polymerase chain reaction is integral for diagnosis.
- To reduce risk of laboratory-acquired infection, the laboratory should be notified of a suspected diagnosis.

Patient consent: The patient provided written consent for publication.

Acknowledgement: We extend our thanks to the patient for allowing publication of his medical history and images.

Competing interests: No relevant disclosures.

Provenance: Not commissioned; externally peer reviewed. ■

1 Peçanha PM, Peçanha-Pietrobom PM, Grão-Velloso TR, et al. Paracoccidioidomycosis: what we know and what is new in epidemiology, diagnosis, and treatment. *J Fungi (Basel)* 2022; 8: 1098.

2 Ashraf N, Kubat RC, Poplin V, et al. Re-drawing the maps for endemic mycoses. *Mycopathologia* 2020; 185: 843-865.

3 Saldanha KFD, Penteado BKC, Siqueira IV, et al. Dental disorders and self-perception of oral health in patients with paracoccidioidomycosis. *Res, Soc Dev* 2021; 10: e11010111557.

4 Hahn RC, Hagen F, Mendes RP, et al. Paracoccidioidomycosis: current status and future trends. *Clin Microbiol Rev* 2022; 35. https://doi.org/10.1128/cmr.00233-21

5 Queiroz-Telles FV, Pietrobom PMP, Júnior MR, et al. New insights on pulmonary paracoccidioidomycosis. *Semin Respir Crit Care Med* 2020; 41: 53-68. ■