Learning Objectives

- Cryptococcal infections are rare in immunocompetent hosts, however a relatively new species, *C. gattii*, has been characterised which is pathogenic in otherwise healthy patients.
- This organism is endemic in Australia and has been diagnosed in New Zealand patients who have spent time in Australia.
- The disease presents with non-specific pulmonary disease. MR appearances of cerebral lesions are characteristic.
- The diagnosis should be considered in patients with atypical pulmonary or neurological symptoms, and there should be a low threshold for fungal culture when biopsy specimens are obtained.
Background

Cryptococcus is a genus of fungus with two pathogenic species, *C. neoformans* and the more recently isolated *C. gattii*. *C. neoformans* typically causes pulmonary and cerebral infection in immunocompromised hosts, and is a significant pathogen in transplant recipients and patients with AIDS[1]. However it is a rare entity in immunocompetent hosts.

Recently *C. gattii* has come to attention due to outbreaks of disease in immunocompetent patients in the US and Australia. It has not been well-reported in New Zealand populations.

Case 1

A 20 year old Polynesian male resident in Wellington presented with a short history of confusion, headache, vomiting and right upper limb weakness. He had no significant medical history. He admitted occasional marijuana use, but no other significant drug use. He had recently spent several months resident in Melbourne, where he worked as a tree mulcher. HIV antibody testing was negative, and CD4+ and CD8+ lymphocyte counts were normal.

Contrast-enhanced CT of the head demonstrated multiple ring-enhancing mass lesions within both cortical hemispheres and the cerebellum. These were thought most likely to be multiple cerebral metastases, with a differential of septic emboli. There were no systemic signs of sepsis, and the neurological symptoms responded to corticosteroid therapy.

Workup for malignancy including testicular ultrasound and CT of the chest and abdomen revealed a large left lower lobe lung mass and a subcutaneous nodule within the lower back.

Core biopsy of the pulmonary lesion demonstrated *C. neoformans* complex and no evidence of malignancy; unfortunately a microbiological specimen was not obtained from this biopsy. Subsequent sputum and CSF culture revealed *C. gattii*. MRI of the brain demonstrated multiple lesions with features typical of CNS cryptococcoma.
He was initially well on antifungal therapy, although developed symptomatic intracranial hypertension following cessation of corticosteroid therapy and required ventriculoperitoneal shunting.

Case 2

A 39 year old woman presented with a 6 month history of mild respiratory symptoms, pleuritic chest pain, and a 6 week history of occipital headache. She had previously lived in the Gold Coast region of Australia for an extended period, but had returned to New Zealand 3 years prior to presentation.

A large left-sided pulmonary mass was detected on plain radiography. CT of the chest revealed an 8cm cystic lesion in the left lower lobe. CT of the head was unremarkable. CT-guided percutaneous aspiration of the pulmonary lesion and CSF culture revealed *C. gattii*.

A course of IV and antifungal agents was initiated, resulting in CSF sterility. The lung mass underwent minimal reduction in size; consequently left lower lobectomy was performed, which was complicated by a postoperative air leak. This settled and she remains well on antifungals.

Microbiology

Cryptococcus is an environmental fungus comprising at least 30 species. Only two cause disease in humans - *C. neoformans* and *C. gattii*.

The disease-forming yeast form has a lipopolysaccharide capsule - the only eukaryotic organism to produce one. The capsule interferes with dendritic cell processing and consequent T-lymphocyte activation[2]. The fungus grows well at 37°C, and can switch phenotypes *in vivo* to form gelatinous colonies[1].

Cryptococcal production of phospholipase B1 facilitates adherence to lung epithelium and lymphatic dissemination. The organisms are also able to replicate inside pulmonary macrophages and produce antiphagocytic enzymes. It is neurotropic due to melanin production which requires dopamine as a substrate[3].

The primary immune response to cryptococcus involves the activation of cytotoxic CD4+ and CD8 T-lymphocytes. Impairment of this response in HIV-infected patients is responsible for the prevalence of cryptococcal infection in this group. Microglial cells (CNS-resident macrophages) are the main form of immune defence within the CNS.
The fungus is transmitted to humans via spores from rotting plant material. It is endemic in Australia and colonises a number of eucalyptus species[4]. It is also widespread in British Columbia, Canada[5] and the Pacific Northwest region of the US[6].

Diagnosis is generally made from sputum or CSF culture, although positive sputum samples can be misleading in patients with unrelated pulmonary disease who have asymptomatic colonisation. Rapid identification of *C. neoformans* complex can be made using an India ink stain.[7] Histological or cytological appearances are also pathognomonic[8]. *C. gattii* speciation can be performed using canavanine glycine bromothymol media[9].

Antifungal therapy is based on inhibition of fungal biochemical processes. Fluconazole and amphotericin B are the mainstays of treatment in immunocompetent hosts and work by disrupting ergosterol within fungal cell walls[2, 10]. Flucytosine is a cytosine analogue which inhibits fungal RNA synthesis[11].

Ergosterol is also contained in mammalian cell walls; this is considered to be the primary mechanism of drug toxicity from these agents[12]. Fluconazole has a relative affinity for fungal cytochrome P-450, which is responsible for a more favourable side-effect profile.

The Infectious Diseases Society of America (IDSA) recommends amphotericin B in combination with flucytosine for induction of therapy, and transferring to fluconazole after at least 6-8 weeks and CSF culture is negative[13].

There is some debate over the significance of isolation of cryptococcus from the lung in an asymptomatic patient, as pulmonary colonisation is common in patients with occupational or other exposure to the fungus. However, only 10% of patients with disseminated cryptococcosis have symptomatic pulmonary disease on presentation[14], and the IDSA recommend fluconazole therapy for immunocompetent patients with isolated mild or moderate pulmonary infection.
Fig. 1: Caffeic acid agar plate. The dark colonies are of Cryptococcus producing melanin. The control culture on the left is Candida albicans.

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Fig. 2: CSF specimen from Case 1 demonstrates marked lymphocyte pleomorphism.

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Fig. 3: Haematoxylin and eosin stain of the biopsy specimen from Case 2 reveals *C. neoformans* complex within a dense lymphcytic infiltrate.

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Both patients in our series had large pulmonary cryptococcomata at presentation with CNS involvement, taking the form of intracranial mass lesions in the first patient and cryptococcal meningitis in the second.

**Pulmonary disease**

Pulmonary cryptococcosis disease patterns are relatively non-specific, and range from ground-glass airway change, to multiple small nodules, to solitary or multiple nodular mass lesions. Cavitation, lymphadenopathy and pleural effusions are seen more commonly in immunocompromised hosts.[15]

**CNS disease**

Cerebral cryptococcosis typically manifests as fungal meningitis or mass-like cryptococcomata. Meningeal enhancement on post-contrast MRI is generally only a feature of infection in immunocompetent hosts, as a diminished immune response in immunocompromised patients results in a weaker immune response with minimal enhancement.[15]

Alternatively cryptococcomata form via perivascular extension within dilated Virchow-Robin spaces. These lesions appear on CT as low-density foci with or without ring-enhancement post-contrast. Vasogenic oedema is typically only a feature of infection in immunocompetent hosts, again relating to a preserved immune response. CT typically underrepresents the extent of lesions.

Cryptococcomata have a characteristic MRI appearance. This comprises well-circumscribed rounded lesions isointense to CSF within the basal ganglia, cortical grey/white matter interfaces, and within the cerebellum.[15, 16]

Contrast enhancement of these lesions post-gadolinium is variable and may be absent. The reason is thought to be twofold: the lesions lie outside the blood-brain barrier in the perivascular space; and the CNS immune response is variable depending on immune status.[17]
Fig. 4: Frontal radiograph from Case 1 shows a large mass projecting over the left lung base.

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**Fig. 5:** Lateral radiograph from Case 1 redemonstrates a large inferoposterior pulmonary mass.

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Fig. 6: Axial CT slice through the lower chest of Case 1 reveals a well-circumscribed low density mass.

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**Fig. 7:** Case 2. Contrast-enhanced CT of the head shows multiple enhancing intracerebral lesions with minimal vasogenic oedema.

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Fig. 8: MRI of the brain in Case 2. T1-weighted sequence demonstrates multiple low-signal lesions at the grey-white interface and within the basal ganglia, consistent with cryptococcomata.

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**Fig. 9:** MRI of the brain in Case 2. Lesions are T2-intermediate to high signal suggesting the presence of complex or proteinaceous fluid.

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**Fig. 10:** MRI of the brain in Case 2. FLAIR sequence documents the presence of minimal vasogenic oedema.

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**Fig. 11:** MRI of the brain in Case 2. DWI demonstrates a lack of diffusion restriction.

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**Fig. 12:** MRI of the brain in Case 2. There is no significant post-contrast enhancement, again characteristic of *C. gattii.*

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Conclusion

Cryptococcus is a significant pathogen in patients with impaired cell-mediated immunity. More recently *C. gattii* infection in immunocompetent hosts has been documented. The lung and CNS are the two sites most commonly involved, due to respiratory exposure and neurotropic microbial factors. MRI appearances within the CNS are characteristic and are typically more florid in immunocompetent patients due to the presence of a strong inflammatory response.

The diagnosis should be included in the differential of patients who present with intracerebral mass lesions or meningitis, particularly in young patients or those with an atypical history. Consideration to sending specimens for microbial as well as histological analysis in these cases should be made, as this allows rapid speciation and guides therapy.
Personal Information

Dr Walklin is a third-year Radiology Registrar at Wellington Regional Hospital.

Dr Entwisle is the Clinical Director of the Radiology Department and a Consultant Radiologist at Wellington Regional Hospital.

Dr Raymond is an Infectious Diseases and General Physician at Wellington Regional Hospital.
References