Fungal Infections

INTRODUCTION

Fungal infections (mycoses) of the central nervous system (CNS) are more common than hitherto thought because of ever-increasing populations with compromised immune status and host defences. This is due to the pandemic of HIV disease and, ironically, to advances in medical care.

Fungi are generally saprophytic organisms that live in the soil and buildings. Man is constantly exposed to them, through aerosol and percutaneous implantation, but can usually mount a defence that prevents disease. A few fungi, such as Candida, have become commensals in the mucosae and gut. A larger group cause a primary infection in the lung, which is often non-symptomatic, and induce a latent infection that may reactivate later to cause systemic infection including CNS disease, or remain dormant for the lifetime of the individual.45

LOCATIONS AND ROUTES OF INFECTION

Fungal infections (also termed mycoses) are most easily classified by genus, route and location of infection in man. Considering the latter, there are

- superficial fungal infection – e.g. dermatophytes;
- cutaneous infection – e.g. the tineas;
- subcutaneous infection – e.g. mycetoma;
- systemic infection – e.g. histoplasmosis, acquired via the respiratory tract.

For the CNS, the majority of fungal infections are part of systemic infection; the routes are listed in Box 22.1.

EPIDEMIOLOGY

Fungal infections of the CNS were relatively uncommon until recent decades. In part this is due to improved diagnostics and case recognition. However, four other trends are more important, including healthcare-associated infection transmission:12,15

1. More people with haematological malignancy, solid organ cancers and organ transplants are being treated and surviving longer.
2. Similarly there are more patients with debilitating chronic diseases, such as diabetes, systemic lupus, renal failure, and liver failure.
3. HIV disease emerged as a major factor, causing suppression of the cell-mediated immunity that happens to be the major defence against many fungal infections.
4. There is a rise in injection drug abuse and infections from contaminated syringes and needles.

In haematological malignancy, aspergillosis is the main problem. Because of the association with pandemic HIV, CNS cryptococcosis is the most important of all these infections.

BOX 22.1. The routes of fungal infection into the meninges, brain and spinal canal

- Systemic infection from initial primary pulmonary infection, including reactivation of a latent primary infection
- Systemic infection from cutaneous and visceral mycosis (particularly in immunocompromised hosts)
- Systemic infection from mycosis implanted from the environment – including direct spread from scalp skin
- Direct spread from nasal sinus or mastoid cavity
- Systemic spread from infected heart valve
- Acquired as a healthcare-associated infection (HCAI) – during neurosurgery – from contaminated paraspinal steroid injections
The newer immunosuppressive therapies, such as drugs active against tumour necrosis factor-α (TNF-α), are increasingly reported as risk factors for systemic mycoses such as aspergillosis. In 2012, an outbreak of fungal meningitis occurred in the United States, causing hundreds of cases and many deaths. It resulted from the contamination during manufacture of methylprednisone injectable solutions by Aspergillus spp. and an unusual black mould Exserohilum spp.

CENTRAL NERVOUS SYSTEM CLINICAL PATHOLOGY

The clinicopathological patterns of CNS mycotic infections are varied and include:

- diffuse encephalitis;
- meningitis;
- focal meningoencephalitis of the meninges;
- space-occupying lesion in CNS parenchyma – granulomas and abscesses;
- infarction from vascular invasion and thrombosis causing stroke;
- haemorrhage from mycotic aneurysm and rupture;
- myelopathy;
- epilepsy.

Many of the mycoses can produce several of these disease patterns at the same time.

CLASSIFICATION

The taxonomy of the vast number of fungus species is changing as new entities are recognized in man and other animals, aided by the explosion of molecular DNA technology; it is a confusing area, as names change and genera relationships are reorganized. This is particularly true with the hyphal fungi and moulds; the yeasts are more straightforward. Many species are dimorphic (both yeast and hyphal form) in that they have different forms in nature and in pathological lesions. Confusingly, although Candida is known to all pathologists to be dimorphic in tissues, a few other classic visceral yeast infections may occasionally produce hyphae as well (Histoplasma capsulatum and Coccidioides). There is also a rapidly evolving literature on the pathogenesis of mycotic infections, particularly in terms of fungal secretions and host responses.

The most common fungal infection to affect the CNS in man is cryptococcosis (because of the HIV pandemic). A list of the most frequently encountered agents is in Box 22.2.

<table>
<thead>
<tr>
<th>Neurotrophic colourless fungi</th>
<th>Neurotrophic dematiaceous (brown)</th>
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</thead>
<tbody>
<tr>
<td>Cryptococcus neoformans</td>
<td>Cladophialophora bantiana</td>
</tr>
<tr>
<td></td>
<td>(ex-Cladosporium)</td>
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<tr>
<td>Pseudallescheria/</td>
<td>Exophila dermatitidis</td>
</tr>
<tr>
<td>Scedosporium spp.</td>
<td>Rhinocadiella mackenziei</td>
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<td></td>
<td>(ex-Ramichlodium)</td>
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<td></td>
<td>Ochroconis gallopava</td>
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Some fungi are especially neurotropic, and the CNS can be the only location of disease (irrespective of how the agent arrived there). Visually for pathologists, most fungi are colourless or haematoxyphilic on staining, and known as ‘pale-grain’ if they are moulds; but some are pigmented brown (dematiaceous or melanized). The neurotrophic colourless and dematiaceous genera are listed in Table 22.1.

DIAGNOSTIC TECHNIQUES AND RESOURCES FOR MYCOTIC INFECTIONS

Historically, morphological diagnosis – fixed-tissue histopathology and direct microbiological examination – has dominated the identification of fungus infections, with fungal culture as desirable confirmation. The standard special stains – PAS and Grocott silver stains – are usually more definitive than haematoxylin and eosin (H&E) evaluation alone. In fact, comparative evaluation of biopsies with formal culture has demonstrated that histomorphology is not totally reliable, even in experienced hands. Candida/Cryptococcus/Histoplasma can be confused, as can Cryptococcus/Coccidioides; Aspergillus versus Mucorales genera is a standard confusion; and there are many non-pigmented mould hyphae in human disease that are not Aspergillus. These infections matter because drug sensitivities vary between genera, and many fungal infections are virulent and require rapid diagnostic confirmation.

Specification of the yeast infections is aided by their relative sizes – see Box 22.3.

**BOX 22.2** The most frequent fungal infections of the central nervous system

- Aspergillus spp.
- Blastomyces dermatitidis
- Candida spp.
- Cryptococcus neoformans
- Histoplasma capsulatum
- Mucorales genera (including Rhizopus, ex-Mucor)
- Chromomycotic (pigmented) fungi
- Other mould infections (e.g. Scedosporium)

Under treatment, some fungi alter their shape and shrink, e.g. Cryptococcus can lose its capsule and appear smaller.

**BOX 22.3** Relative size of yeast infections in the brain, as an aid to diagnosis

- Small yeasts (3–5 µm diameter) – Candida spp., Histoplasma capsulatum, Pneumocystis jiroveci, Penicillium marneffei
- Medium-sized yeasts (5–15 µm diameter) – Cryptococcus neoformans, Blastomyces dermatitidis, Paracoccidioides brasiliensis, Sporothrix schenckii
- Large yeasts (15–100 µm diameter) – Coccidioides immitis, Rhinosporidium seeberi
Immunohistochemistry for fungus infections has a limited role because the reagents are not widely available or standardized – the exception here is Pneumocystis, where the labelled antibodies used for cytological confirmation in bronchial aspirates work well on formalin-fixed paraffin-embedded tissue (FFPE).

Serological antibody and antigen detection has a major role in diagnostic pathways, however, apart from cryptococcal antigen body fluid tests, they are not widely available. The major growth area is in fungal molecular diagnostics with polymerase chain reaction (PCR). This is becoming the gold standard alongside culture. The test systems, originally for fresh tissue analysis of yeasts and moulds, increasingly reliably work with FFPE. Central public health institutes include PCR in the repertoire for reference diagnostics (e.g., in the UK, the Bristol Mycology Reference Centre).

There is no current comprehensive clinical pathology text for fungus infections. Mandell’s classic infectious disease text contains much clinical and diagnostic information. A good, illustrated review of most aspects of the histopathological differential diagnosis of mycoses can be found in Guarner and Brandt. This also includes a comparative overview of the relative diagnostic powers of histopathology, immunohistochemistry, in situ hybridization and PCR technology in the assessment of fungal infection.

Diagnostically, most patients with CNS mycoses will have neuroimaging; the radiological differential diagnosis of brain tumour, tuberculosis, pyogenic abscess and meningitis, and mycosis is often not specific, but contributes to the multimodality work-up of patients. The fungal causes of intracerebral haemorrhage are those that destroy blood vessels: Aspergillus, Candida and Coccidioides.

In the following sections, the more common CNS fungi are considered alphabetically and in clinicopathological groups. Because antifungal chemotherapy is now specialized and complicated, references to drug treatment are minimized.

**SPECIFIC FUNGAL INFECTIONS**

**Aspergillosis**

Aspergillus spp. are ubiquitous globally. Of the hundreds of known species, the most common pathogens in man are A. fumigatus (the majority of cases), A. flavus, A. terreus and A. niger. The organisms are found in soil and decaying vegetation and the infective conidia are inhaled into the lung.

People with intact immunity and host defences rarely acquire aspergillosis, although occasional cases of isolated CNS infection are recorded in intravenous drug injectors. The major risk factors for infection are:

- neutropenia (<100 neutrophils/µL of blood);
- haematological malignancies;
- solid organ and bone marrow transplantation, with immunosuppressive treatment;
- corticosteroid therapy;
- HIV disease;
- alcoholism;
- collagen diseases and their treatment;
- chronic granulomatous disease in childhood.

Aspergillus spreads haematogenously and locally. The most common origin site is lung infection, but maxillary sinusitis can be the source: this is noted particularly in India where working in a ‘mouldy environment’ is considered the root cause. The fungus typically invades through vessel walls and obliterates vascular lumens, so contributing to the necrosis. Cerebral aspergillosis has the highest mortality (90 per cent) of the invasive aspergillosis syndromes, and is usually associated with concomitant pulmonary infection. The risk of cerebral infection depends on the underlying condition of the patient, and is overall 10–20 per cent of all cases with invasive aspergillosis. Patients with leukaemia and organ transplants have the highest risk. In contrast with cryptococcosis, it is less common in HIV-infected patients. In transplantation, it often develops months after the transplant and is associated with extensive immunosuppression, such as treatment for graft-versus-host disease.

Other sources of CNS infection are the gastrointestinal tract, ear and orbit, and skin following head injury. Diffuse myelitis is also recorded as an indirect immunopathological consequence of treated aspergillosis.

**Pathology**

Brain infection usually presents as a single or multiple abscesses, but may also be granulomatous and solid. Grossly the abscess lesions are necrotic haemorrhagic lesions, with much surrounding oedema. They are located usually in the territories of the anterior and middle cerebral arteries, but cases of subdural location around the thoracic cord are noted.

Histologically, the abscess lesions depend on the underlying immune status of the patient and the chronicity of the lesion. There may just be proliferating pale (hyaline) fungal septate hyphae, about 5 µm in diameter, branching typically at 45 degrees, arranged in a star-burst pattern from a vessel with local necrosis and no inflammation (Figure 22.1); or neutrophils may be present and the lesion is more purulent.

Granulomatous lesions with large giant cells, fibrosis and no necrosis are seen in more chronic lesions and in immunocompetent people, when cell-mediated immunity is more preserved; the hyphae are more scanty and broken up, and the histology is parallel to that of chronic fibrosing paranasal aspergillosis. Eosinophils may also be present in these lesions. Mycotic aneurysms can develop from disseminated aspergillosis infection, with thrombosis and subarachnoid haemorrhage.

Importantly, *Aspergillus* spp. are not the only pale fungal hyphae that infect the brain. The differential diagnosis includes *Pseudallescheria/Scedosporium* (see later), *Paecilomyces* and *Fusarium* species – all of which can look similar to *Aspergillus*. It is here that PCR diagnostics plays an increasing role. The distinction morphologically from the Mucorales (see later) is vital since the treatment is different; the latter are much wider than the other hyphae, with thinner walls and more bizarre morphology and without septa.

**Blastomycosis**

Blastomyces dermatitidis is endemic in the southern United States, Africa, India, the Middle East, and Central
and South America. It is not indigenous to Europe, but can be imported in travellers. The fungus resides in the soil. Infection is via the lung, with dissemination to many organs, including the CNS.45

In the normal host, CNS disease is uncommon, reported in less than 5 per cent of cases.14 HIV is a particular predisposing factor, with 40 per cent of those with advanced HIV disease and blastomycosis having CNS lesions.54 The presentation is with meningitis, meningoencephalitis, single or multiple abscesses, or dural abscess. The spinal cord may also be affected with radiculopathy. Hydrocephalus resulting from cranial osteomyelitis and obstructive meningal infection are also recorded, as is hypopituitarism.1

Histopathologically, the reaction is primarily granulomatous but may also include acute inflammatory cells.23 In abscesses, the centre is caseous, and in the brain and elsewhere blastomycosis and tuberculosis may be indistinguishable clinicopathologically.37 Sometimes, blastomycotic meningitis is very suppurative, mimicking pyogenic infection.23 The fungi are medium-sized yeasts 8–15 µm in diameter, with a thick refractile cell wall. In contrast to Cryptococcus, the yeasts have a more solid-appearing body, and cell division is by budding with a typically broad base (Figure 22.2). The fungi are seen within macrophages.

### Candidiasis

There are more than 150 species of Candida genus, but only nine are regarded as frequent human pathogens, the most common being C. albicans. C. veronae is also noted as a CNS infection. As well as living in soil, food and hospital environments, Candida is a normal commensal on skin, in the gut and airways and in the vagina. The infection is globally distributed.45

CNS infection is very uncommon unless the host defences are abnormal. The major risk factors for this are:

- neonatal intensive care,47 particularly in premature babies;
- HIV infection;
- diabetes;
- haematological malignancy and lymphoma;
- intravenous drug injection;
- ventricular shunt infection, neurosurgery and lumbar puncture.19

Clinically, the signs are those of meningitis and single or multiple parenchymal lesions. Usually, patients with CNS candidiasis also have other organ infection, including kidney and heart, from candidaemia. Grossly, the lesions may
resemble those of aspergillosis, being haemorrhagic necroses (Figure 22.3). In more chronic cases, they are solid and granulomatous.

Diagnosis in life is made by lumbar puncture and direct examination of cerebrospinal fluid (CSF) and culture. Histopathologically, there is a very variable mixture of necrosis, acute inflammation, granulomas and vasculitis with thrombotic obstruction. The fungi are characteristically dimorphic in tissues: there are budding yeasts (3–5 µm diameter) and pseudohyphae (strings of budding cells, often elongated and thus resembling true tubular hyphae) together (Figure 22.3). On H&E, the fungi are rather basophilic, and they stain well with PAS and silver stains.

Untreated, the mortality is very high, in part because of multiorgan disease.

**Coccidioidomycosis**

*Coccidioides immitis* is endemic in the semi-arid soils of the southern United States, central America and many countries in South America. Travellers visiting these regions can bring the infection to anywhere in the world and present clinically. In endemic areas, up to 50 per cent of people may be infected, mostly subclinically, but the lung lesion is a latent infection that can reactivate.

Coccidioidomycosis is primarily a pulmonary infection, and the common lesion is a pulmonary granulomatous fibro-necrotic nodule that resembles tuberculosis. In about 0.5 per cent of those infected, there is extrapulmonary spread, of which meningeal infection is the most serious. The risk of such spread is greatly augmented by certain risk factors:

- HIV infection;
- transplantation and associated immunosuppression;
- lymphoma;
- steroid therapy;
- pregnancy.

The main CNS diseases are basal meningitis, spinal cord compression by a paravertebral abscess, and intracerebral lesions including cerebellar abscess; one third of cases do not have meningitis. The meningitis may cause hydrocephalus and is fatal unless treated.

The histological reaction to *Coccidioides* is typical of many fungal infections: mixed granulomatous with acute inflammatory foci, and a surprising amount of eosinophils. More chronic lesions are nodular with a caseous-type necrosis with surrounding granulomas and fibrosis. In HIV-positive patients, the reaction is less granulomatous. A vasculitis is frequent, causing arterial obstruction and infarctive necrosis. Occasionally, it causes dural and cerebral venous thrombosis resulting in haemorrhagic infarction.

*Coccidioides immitis* is a dimorphic fungus, with mycelial hyphae in the soil, but in man the yeast form is seen. The fungi are highly characteristic histologically because they can be large yeasts 10 µm up to 100 µm in diameter (the largest common yeast infection seen in man). When they also contain numerous tiny 2–5 µm endosporcs (Figure 22.4), there is no differential diagnosis. Special centres may have specific antibodies that can support the diagnosis. Rarely, hyphae are also encountered as a reversion to the saprophytic form. This appears to be associated with inserted plastic CNS devices, and has obvious implications for diagnosis of the infection. Culture is diagnostic in these cases.

**Cryptococcosis**

*Cryptococcus neoformans* and the less common *C. gattii* are fungi harboured in the soil and the faeces of birds. The distribution is global. CNS infection follows infection via...
the respiratory tract (i.e. systemic infection), although the initial lung focus is not usually apparent and may have resolved long before the CNS becomes involved. The infection is borne haematogenously to the brain and cord.

The great majority of patients with CNS C. neoformans are immunocompromised. The HIV pandemic currently accounts for most such cases. C. gattii can infect both immunocompetent and compromised hosts. The other associations are:

- cirrhosis;
- lymphoproliferative diseases;
- transplantation;
- immunosuppressive steroid and cancer chemotherapy;
- sarcoidosis;
- malnutrition.

Early on, cryptococcal meningocenephelitis was made an AIDS-defining condition, and without treatment is always fatal in such patients. However, with treatment, the mortality of cryptococcal meningitis is similar in both HIV-infected and non-infected people, at about 30 per cent. The proportion of HIV-infected patients developing the infection varies according to geography and the availability of antiretroviral therapy. It usually develops only after the blood varies according to geography and the availability of antiretroviral therapy. However, immunocompetent individuals are also affected by cryptococcal CNS infection, in whom it has a more benign course. The syndrome of HIV-negative idiopathic CD4+ T-cell lymphopenia can also present with CNS cryptococcosis.

Clinically, CNS cryptococcosis presents with headache, confusion and dementia, cranial nerve palsies, coma and sometimes focal neurological signs. Imaging abnormalities are often subtle: because of lack of meningeal inflammation, the infiltration may not be very evident on computed tomography (CT) or magnetic resonance (MR) imaging (Figure 22.5). Cryptococcal masses in the parenchyma show as non-enhancing hypodensities or hypointensities on CT and MR.

Pathogenesis

Because of its importance in HIV/AIDS, much work continues on the pathogenesis of this infection. From a cryptococcal meningitis perspective, the fungus appears to cross the blood-brain barrier by passing through endothelial cells. The unique cryptococcal capsular material, composed of glucuronoxylanmannan, is the major virulence factor and can inhibit host defence responses. It is striking, histologically, how in severe immunodeficiency there is essentially no host reaction to the fungus; whereas in the immune competent and in HIV-positive people who are reconstituting their cell-mediated immunity on antiretroviral treatment (see below), the host reaction is granulomatous. CD4+ T-cells are critical in determining this outcome.

Pathology

The location of infection is usually a meningitis, affecting brain and spinal cord together. Sometimes purely spinal infection or a lumbosacral polyradiculitis may develop. The gross pathology is characteristic in fatal untreated cases. In the immunosuppressed, there is a granular milky texture to the meninges over the brain surface. The brain may be swollen, related to hydrocephalus from blockage of the arachnoid villi by infection.

On cutting the brain, the meninges are perceptibly thickened by pale exudates. The parenchyma is usually also involved, although this may only be evident microscopically. In gross cases, there is a ‘Swiss cheese’–like appearance, often around the basal ganglia, caused by gelatinous accumulations of fungi (Figure 22.5). Microscopically, the fungi are characteristic. They are budding oval yeasts, sized 5–10 µm with typically empty cell contents (Figure 22.5). The walls stain well with H&E, Grocott and PAS stains. The yeast cells are surrounded by a polysaccharide capsule up to 5 µm thick, which does not stain with H&E, although it is coloured by mucicarmine and, to a lesser extent, by Alcian blue stains. Thus, on H&E, the infection often appears rather hypocellular, in a sea of pale vacuoles. The walls stain well with H&E, Grocott and PAS stains. The yeast cells are surrounded by a polysaccharide capsule up to 5 µm thick, which does not stain with H&E, although it is coloured by mucicarmine and, to a lesser extent, by Alcian blue stains. Thus, on H&E, the infection often appears rather hypocellular, in a sea of pale vacuoles. As well as the meninges, the fungus infiltrates along the Virchow–Robin spaces and spreads laterally into the parenchyma. In advanced HIV disease, there is virtually no cellular reaction in the meninges; only a few macrophages are seen containing yeasts. There is also little astrocytic or microglial reaction.

In immunocompetent patients, the meningeal reaction may be granulomatous, simulating tuberculosis, both grossly and microscopically, with Langhans giant cells containing the yeasts. The infection load is markedly lighter than in the non-reactive pattern. This inflammatory reaction is also seen in some HIV patients with usual non-reactive cryptococcal meningitis, who have recovered cellular immunity through treatment with antiretroviral therapy – the so-called IRIS phenomenon (immune reconstitution inflammatory syndrome). In such patients,
the presentation can be abrupt with seizures, neurological signs, increased intracranial pressure and even rapid death (Figure 22.6). The differential diagnosis between IRIS and progressive infection may be difficult, but quantification of infection load and assessment of the cellular response assist the distinction.

Localized granulomatous lesions – cryptococcomas – were described in the brain in the pre-HIV era, often with no associated meningitis or fungi detectable in the CSF. Intramedullary and intraspinal cord location of a cryptococcoma is even more rare.62

**Diagnosis and Treatment**

The diagnosis is usually made on CSF samples by direct vision using, classically, India ink background contrast (Figure 22.5). Cryptococcal antigen detection methods (the CrAg test) are supplanting this, in both CSF and
blood samples, because they are more sensitive.

Culture of CSF or biopsy material provides further confirmation. Morphologically, the diagnosis is usually straightforward because of the capsule, unique to this fungus. Corpora amylaceae can be mistaken for cryptococci, being of similar size and staining characteristics, and also perivascular, although usually more solid and haematoxyphilic in appearance, and without a capsule. CSF cytological preparations may lack an inflammatory component, and sometimes abundant yeasts may be mistaken to be washed-out erythrocytes.

CNS cryptococcosis is treated with antifungal agents and, in HIV patients, antiretroviral therapy. HIV patients require long-term chemoprophylaxis against recurrence or reactivation of infection unless their blood CD4+ count rises >200/µL, at which point the prophylaxis can usually be stopped.

**22.6 Cryptococcosis and immune reconstitution inflammatory syndrome (IRIS).** A human immunodeficiency virus (HIV)-positive patient with cryptococcal meningitis who developed an immune reconstitution reaction on receiving anti-HIV therapy. (a) Magnetic resonance scan showing irregular meningeal enhancement and ventricular dilation. (b) Granulomatous meningitis. (c) Giant cell granulomatous reaction, with yeasts visible in the macrophages. (d) Cryptococcus yeasts, varying in size and including some crenated, collapsed forms. Untoned Grocott silver impregnation.

**Ocular Cryptococcosis**

Eye involvement by Cryptococcus is frequent in HIV patients, causing loss of vision. The fungi can infiltrate the retina and under the cornea. Infiltration of the optic nerve is probably the main pathogenesis of blindness.

**Histoplasmosis**

There are two species of Histoplasma that affect man. The smaller yeast form, Histoplasma capsulatum, is the more frequent and important; the African form, Histoplasma duboisii infection, has not been recorded to affect the CNS. Histoplasma capsulatum is widely distributed globally in the soil of all continents, but not in northwestern Europe. It is associated with bird and bat guano. Cases of histoplasmosis in the U.K. are all imported. In highly endemic areas,
up to 25 per cent of the population will acquire a primary pulmonary infection, asymptomatic in >90 per cent, which leaves a lung lesion as latent infection.22

The risk factors for progressive disseminated infection or later reactivation with dissemination are:

- HIV infection;
- haematological malignancies and lymphoma;
- old age per se.

Between 10 and 20 per cent of those with disseminated infection develop CNS disease. However, even in HIV disease, only 1–2 per cent of those with histoplasmosis develop CNS lesions.

The CNS manifestations of disseminated infection are meningitis, mass cerebral lesions and diffuse encephalitis; chronic basal meningitis is the most frequent. Clinically, there is headache, cranial nerve palsy, altered mentation and focal neurological signs. Hydrocephalus is frequently a feature, particularly in those who are not immunocompromised.59

Grossly, the meningitis is a grey-yellow exudate. The histopathology of histoplasmosis is determined by its pathogenesis, which is cell-mediated immunity. Granulomas, with giant cells, are typical. In the larger intracerebral lesions, there is caseous necrosis and surrounding fibrosis. Occasionally, a lesion may be so large as to mimic a tumour. As with tuberculous meningitis, there is endarteritis obliterans, with local ischaemic necrosis of brain in severe cases; and with treatment and resolution, there is fibrosis. In immunosuppressed patients, the reaction may be less granulomatous and more of diffuse macrophage infiltration.

The fungi are obligatory intramacrophage infections. They are small ovoid yeasts 2–4 µm in diameter, which divide by budding.23 On H&E, they appear as small fried eggs, the grey nucleus occupying much of the cell. PAS stains highlight the cell wall, and they appear larger and most distinctive with silver stains (Figure 22.7). The differential diagnosis lies with penicilliosis and pneumocystis, both of which are uncommon in the CNS. Occasionally, Histoplasma capsulatum can present with rather larger yeast forms and so cause confusion with Cryptococcus and Blastomyces.

**Paracoccidioidomycosis**

Paracoccidioides brasiliensis is endemic in Latin America from Mexico to Argentina.45 It is primarily a lung infection, with dissemination to other organs, including uncommonly to the CNS. It causes intracerebral mass lesions, most commonly meningitis, and eye infections, and it is associated with HIV infection.19,20 The organism is histologically characteristic, with multiple small yeasts, 4–5 µm in diameter, budding from a central medium-sized yeast (up to 60 µm), so resembling ‘Mickey Mouse ears’ (Figure 22.8).23

**Penicilliosis**

Of the many species of *Penicillium* genus, *P. marneffei* has become clinically important because it is an opportunistic infection associated with HIV infection. It is restricted geographically to Southeast Asia and China, but will be encountered in people who have acquired the infection there and travelled to anywhere else.45 Visceral infection (all organs) and meningitis are reported in HIV-infected patients. The small fungus is very similar to *Histoplasma capsulatum* in size and shape, but divides by splitting instead of budding (Figure 22.9).

There are case reports of other *Pencillium* spp. causing brain abscess in HIV-negative people.50

**Pneumocystosis**

*Pneumocystis jirovecii* (ex-*carinii*) infection is one of the prototypical opportunistic diseases that became clinically prominent with the HIV pandemic.45 Normally it affects just the lungs, but about 2 per cent of patients in the era
before modern antiretroviral therapy developed extrapulmonary pneumocystosis as a late complication. Rarely, it spreads haematogenously to the brain. Clinically, it causes focal neurological signs, and all cases were diagnosed only post mortem. The sites infected include the cerebral cortex, the meninges, the basal ganglia and the pituitary. The organisms cluster around blood vessels, and are small yeasts similar to *Histoplasma capsulatum* in size; but they are characteristically often crenated and have a silver-positive dot-like thickening on the cell wall (Figure 22.10). Unlike for most other fungi, there are available specific monoclonal antibodies for confirmatory immunocytochemistry.

**Pseudallescheriasis/Scedosporiosis**

The hyphal mycoses caused by *Pseudallescheria boydii* (anamorph: *Scedosporium angiospermum*) have clinical pathology similar to that of phaeohyphomycosis (see later under Chromomycosis), but are not dematiaceous.

Infection occurs by inhalation, contamination of nasal mucosa and inoculation through the skin. Risk factors for infection include HIV infection with low CD4+ T-cell count, transplantation, diabetes, ventriculoperitoneal shunt and intravenous drug injection. CNS infection is a noted feature: for example, half of solid-organ transplant recipients with pseudallescheriasis had CNS involvement. Another particular clinical subset includes the survivors of drowning. CNS infection is via the lung or nose and the clinical course is prolonged, but with a 70 per cent mortality even in the immunocompetent. The brain is the main organ affected, with multiple abscesses, but there is often visceral dissemination as well.

The cerebral disease is meningitis and cerebral abscess. Pathologically, around the septate non-pigmented hyphae and necrosis is a mixed neutrophilic and granulomatous reaction. Vascular obstruction and local cerebral infarction is common. Another pathological form of CNS pseudallescheriasis is the intraspinall mycetoma (see later).

**Sporotrichosis**

*Sporothrix schenckii* infection is global, from the soil and mainly a cutaneous infection that can slowly extend proximally via lymphatics to cause so-called ‘sporotrichoid’ nodules. Less commonly, there is pulmonary infection that can spread to all parts of the body, including the CNS. Risk factors for such dissemination include HIV infection and organ transplantation with immunosuppression.

This infection causes a chronic meningitis and sometimes encephalitis with small abscesses and granulomas. Histologically, the fungi are 3–6 µm ovoid yeasts that bud. Formal diagnosis requires culture or PCR proof.

**MUCORACEOUS MOULD INFECTIONS**

The causative agents are several members of the order Mucorales; the genera most often encountered are *Rhizopus, Rhizomucor, Mucor, Cunninghamamella, Absidia*.
and Apophysomyces, with Rhizopus the most common.\textsuperscript{17,45} The fungi are ubiquitous, being found in the soil, manure and decaying vegetable matter. Morphologically, they are distinctive in being the largest hyphal fungal forms to affect man. They can affect all organs of the body, including the CNS, and are angioinvasive and angio-obstructive, thus causing considerable tissue destruction.

Although CNS infection is reported in previously healthy people,\textsuperscript{60} the great majority of those affected have compromised host defenses, from various underlying conditions.\textsuperscript{45} The most important ones are:

- diabetic ketoacidosis – strongly associated with rhino-orbito-cerebral disease;
- haematological malignancies;
- transplantation and associated immunosuppression;
- intravenous drug injection;
- HIV disease;
- head trauma (particularly noted with Apophysomyces infection).\textsuperscript{41}

The two distinct clinicopathological patterns of infection are rhino-orbito-cerebral mucormycosis and CNS mucormycosis.

Rhino-orbito-cerebral infection commences with invasion of the palate and orbital cellulitis, then invasion across bone into the basal meninges and brain (Figure 22.11). Cranial nerve palsies are frequent. Grossly, there is black necrotic ulceration of mucosa and bone below the brain. Because the infection causes carotid artery and cavernous sinus thrombosis, there is regional infarction of brain, as well as meningitis.\textsuperscript{6}

Cerebral mucormycosis usually develops from a pre-existing focus, most frequently a skin or visceral infection, or following open head injury. Multiple focal neurological signs and cranial nerve palsies are the clinical manifestations. Occasionally, cerebral mucormycosis can develop without any apparent extracerebral focus.\textsuperscript{21}

Histopathologically, the inflammatory reaction to the fungi is neutrophilic and necrotizing, and there is invasion through the vessels with secondary thrombosis.\textsuperscript{23} Sometimes numerous giant cells, but not true granulomas, are observed. The hyphae are broad and twisted, about 10 μm thick, irregularly branching and non-septate. On H&E, they may be seen only as ill-defined empty holes in the tissues, but silver stains highlight them well (Figure 22.11).

The outcome of these infections is usually rapidly progressive and poor. Surgical debridement of necrotic tissue,
treatment of the underlying condition and amphotericin B are employed, but the overall mortality is 50 per cent or more, depending on the severity of the underlying condition.

**Chromomycoses and Mycetoma**

Chromomycosis is a term encompassing infections caused by a heterogeneous group of dematiaceous fungi, i.e. those producing a brown melanin pigment, which is distinctive under the microscope as well as grossly if the fungus produces grain colonies. They are generally distributed in soil and decomposing plant material. The genera are numerous and include *Alternaria, Bipolaris, Cladophialophora, Curvularia, Exophiala, Fonsecaea, Madurella, Ochroconis, Phialophora, Rhinocladiella* and *Wangiella* spp. Histologically, some of these are yeast infections (e.g. classical chromoblastomycosis caused by, inter alia, *Cladophialophora* spp.), but most are morphologically hyphae, resembling *Aspergillus* in structure. Within these descriptions, the infections look similar microscopically, so to precisely diagnose the infection, culture or PCR is necessary; histopathology alone cannot do this.

Clinicopathologically, they cause a wide range of subcutaneous and visceral diseases, in both immunosuppressed and immunocompetent people, the main patterns being:

- phaeohyphomycosis;
- chromoblastomycosis;
- eumycotic mycetoma.

**Phaeohyphomycosis and Chromoblastomycosis**

Phaeohyphomycosis indicates the presence of pigmented hyphae in tissue, both extracellular and within macrophages; however, yeast-forming fungi are sometimes also included within this description. Strictly speaking, chromoblastomycosis means the presence of the sclerotic muriform brown yeast forms that divide by splitting, not budding; these are seen within macrophages. Chromoblastomycosis, by this definition, is rarely encountered in CNS infection, because it is mainly a subcutaneous disease. Thus, the majority of the non-mycetoma chromomycoses are phaeohyphomycotic.

Infection is usually from implantation through the skin. The CNS infections can develop in immunocompetent people, with no evidence of extraneural infection, presumably by haematogenous spread. Debilitating conditions associated with CNS infections include:

- fungal endocarditis;
- intravenous drug injection;
- HIV infection;
- renal failure with transplantation or peritoneal dialysis catheterization.

The CNS clinical pathology includes meningitis, cerebral abscess in any part of the brain and diffuse encephalitis. Grossly, the meningitis and abscess lesions are no different from their counterparts caused by bacterial infections. Histologically, the reaction is mixed acute inflammation and granulomas, with surrounding reactive gliosis and fibrosis. Vascular occlusion may also occur with secondary ischaemic lesions. In the diffuse encephalitis pattern, there is cerebral swelling without a visible focal lesion (Figure 22.12). Microscopically, the fungal hyphae are seen around vessels eliciting a variably granulomatous macrophage reaction with giant cells. Acute inflammation is also present (the ‘mixed granulomatous’ inflammatory reaction typical of many mycoses).

**Intracranial and Intraspinal Mycetoma**

Mycetoma – a disease process where the infective agent forms large, often visible clumps or colonies in the tissue – is...
a chronic granulomatous slowly progressive infection of the skin and subcutis that can spread locally to involve muscle and bone. It is caused by both true fungi of many genera ('eumycetoma') and certain Gram-positive bacilli; the latter includes Actinomyces, Nocardia and Streptomyces spp. and is commonly termed ‘actinomycetoma’. Both types can rarely cause intraspinal infection and very rarely intracranial mycetoma.

The pathogenesis of such fungal infections is often obscure in individual cases. Mycetoma infection is typically implanted through the skin, the saprophytic agent being on a sharp plant or other contaminated object. Local progressive spread is usual, and metastatic spread, e.g. to lymph nodes, is uncommon. Intracranial mycetoma following infection of facial or scalp skin and invasion through skull bones is recorded. Intraspinal mycetoma is noted following spinal surgery and intrathecal injections, and episodes of near-drowning in contaminated fresh waters. The former implies contamination during medical interventions, and the latter suggests infection via the oropharyngeal mucosal route. However, many patients with intraspinal mycetoma have no such history and the infection is exclusively intraspinal.

Clinical presentation is usually with paraplegia, sphincter malfunction and paraesthesia. At surgery, the infection may be extradural or involve the dura, which is grossly thickened, and can be local to a few vertebrae or extend the length of many. Grains of the infectious agent may be seen, especially if it is caused by a black-grain fungus (e.g. Madurella mycetomatis).

Histologically, the mycetoma colonies are surrounded by acute inflammation within a granulomatous reaction, and there is much local fibroplasia. If it is a eumycetoma, the colonies or grain is pigmented dark brown or may be non-pigmented, depending on the genus (Figure 22.13). Hyphae comprise the grain, with often expanded club-shaped forms (chlamydospores) at the periphery. The fungi that cause this include Madurella mycetomatis (black-grain) and Pseudallescheria boydii (anamorph: Seecosporium angiospermum – pale-grain).

‘Actinomycetoma’ infections have a similar presentation. Pathologically, they differ because the infection grain is not a fungus but a bacterium. Streptomyces somaliensis has been described.45 The bacteria are Gram-positive filamentous bacilli. A Grocott silver method will stain both eumycetoma and actinomycetoma, but fungal hyphae are >5 µm thick and are usually septate, whereas the bacilli are 1 µm thick and often beaded.

**Other CNS Mycoses**

There are thousands of other fungal species in nature and, not surprisingly, almost any of them can rarely affect the CNS of man under special conditions of exposure,
medical interventions (e.g. infected intravascular cannulae), infective endocarditis or abnormal host defences. When CNS mycoses are encountered diagnostically, most are categorizable to the genus level (e.g. cryptococcosis) or to the disease level (e.g. pigmented mycetoma) on histopathology alone; however, culture, PCR or serological diagnostic support is always recommended, because treatment and other management options vary according to the genus.

When the fungus is not readily identifiable morphologically, then it is either an abnormal form of a common infection (e.g. hyphae in coccidioidomycosis or histoplasmosis) or an unusual fungus, in which case culture and/or molecular diagnostics are the only means of making the true diagnosis. Some examples of these rarer brain infections include Nodulisporium spp.,67 Fonseccaea pedrosii44 and Rhinocladiella mackenziei – the latter appears to be geographically limited to the Middle East, and CNS disease has been diagnosed on cytology.24 The skin infection Trichosporon asahii can cause a meningitis following burns.27

### Fungal Infections of the Eye and Orbit

The most important part of the eye to be infected with fungi is the surface: conjunctiva and cornea. Fungal infections of the eye can happen to anyone, although a particular risk factor is the wearing of contact lenses. Internal vitreous and choroid mycosis may be part of disseminated infection in the immunosuppressed (e.g. cryptococcosis and paracoccidioidomycosis; see earlier). Aspergillosis and Mucorales fungi may involve the eye as part of orbital invasion. Table 22.2 lists the eye mycotic infections.

Fungal keratitis is the most important pathology, with ulceration caused by the fungi. There appears to be an increase in keratitis, presumably associated with increased usage of therapeutic and non-therapeutic soft contact lenses and also more eye surgery, such as penetrating keratoplasty, and application of topical steroids. Over time, the proportion of hyphal infections compared with yeast infections has risen. Non-iatrogenic risk factors include trauma with vegetable matter contamination and agricultural employment.

The pathology is a suppurative ulcerating keratitis, and the diagnosis is usually made on cytology from direct smears and culture. Identification of the genus of fungus is important to determine the best antifungal agent.

### Rhinosporidiosis

Rhinosporidium seeberi is a chronic infection of mucous membranes in cattle and man. Most cases occur in the Indian subcontinent. Previously considered to be fungus, following DNA analysis, it is now known to be a protistan parasite.45 As well as in the nose, polyps form on the conjunctiva, containing large numbers of the infectious agent.55 The histopathology is pathognomonic, with large sporangia containing numerous endospores (Figure 22.14).

### REFERENCES


