

Bilateral low-density lesions in the internal capsule, with confirmed cryptocococcus meningitis and CNS toxoplasmosis in immunocompromised patients

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Case study 1 CNS toxoplasmosis

A 34-year-old known immunocompromised female patient presented with fever of unknown origin and expressive apraxia. She was also on anti TB treatment for pulmonary TB.

On clinical examination she was found to have a fever of 39°C, lymphadenopathy in the right axilla, increased tone in the upper limbs and generally globally increased reflexes.

Investigations

A CT scan done on admission revealed bilateral low-density areas in the internal capsulae. Post-contrast images revealed bilateral ring-enhancing lesions with central enhancing nodules — target lesions (Figs 1 and 2).

Further investigations included: (i) CD4+ cell count 127.5/l; (ii) toxoplasma serology — toxoplasma

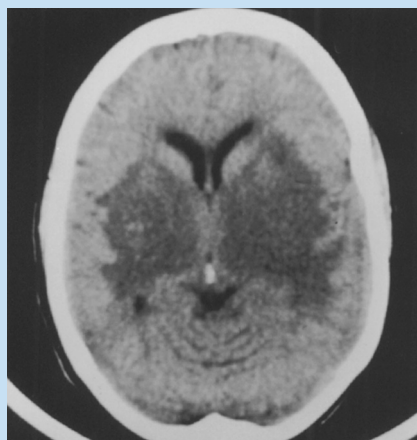


Fig. 1.

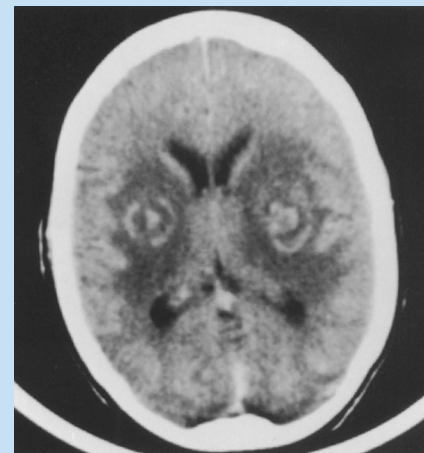


Fig. 2.

enzyme-linked immunosorbent assay (ELISA) immunoglobulin (Ig) 3.84 (normal 0 - 1.0 units); toxoplasma immunofluorescence assay (IFA) polyvalent - positive; and (iii) cerebrospinal fluid test for India ink and antigen studies were negative.

The patient responded to TB treatment. She was put on warfarin for deep venous thrombosis (DVT). The patient was allergic to Bactrim and was given fluconazole and discharged. Three weeks later she deteriorated and died.

Discussion

Toxoplasma gondii is a protozoan organism that is ubiquitous in nature. Its definitive hosts and reservoir are felines, but it can cause acute infection and disease in humans.

The infection is asymptomatic or minimally symptomatic in older children or adults with normal immune function.

Cysts of *T. gondii* persist in the central nervous system (CNS) as well as extra neural tissues after infection, which keep quiescent, but with immune dysfunction as in HIV/AIDS, these cysts may become reacti-

vated and cause disease, the most common of which is toxoplasmic encephalitis, which occurs late in the course of HIV infection when the CD4 cell count has fallen to less than 100 cells/mm³.

Onset of symptoms is usually gradual, with headache, confusion, fear, lethargy or seizures. On examination patients can have an abnormal level of consciousness or focal neurological signs, such as hemiparesis, ataxia or cranial nerve palsies.

Amongst all the CNS infections seen in AIDS patients, toxoplasma encephalitis is the most eminently treatable, because it usually responds to antibiotic therapy. For this reason early identification is important, because treatment leads to rapid clinical improvement. Three types of CNS infection by *T. gondii* have been described. The first consists of a necrotising abscess, characterised by a mixture of free-living tachyzoites and encysted organisms, vascular reaction, inflammation and petechial haemorrhage.

The second type consists of a lesion containing a necrotic cystic centre surrounded by a fibrous capsule, and is usually seen between 2 and 4 weeks of onset of CNS infection.

The third type is that of chronic abscess formation, in which necrosis and free organisms constitute most of the lesion. On CT the diagnosis is made when there are typical ring-enhancing lesions in the presence of serum antibodies to *T. gondii*.

The most common regions of involvement are the cortico-medullary junctions (possibly representing haematogenous dissemination), basal ganglia and thalamus. Lesions are typically supratentorial (possibly reflecting the dominant distribution

of blood flow) but cerebellar lesions are also relatively common. On occasion the brain stem, hypothalamus and subthalamic regions are involved. Rarely intraventricular lesions can be seen. Ventricular enlargement is common, which can be present on the basis of atrophy (often itself secondary to HIV encephalitis) or hydrocephalus due to infective meningitis, or partial obstruction of the ventricular outlet, by a toxoplasma lesion. Multiple bilateral lesions are usually seen, but a solitary lesion can occur. Pre-contrast CT toxoplasma lesions appear as rounded masses that are relatively isodense compared with grey matter and they can often be detected on pre-contrast CT due to the adjacent oedema and mass effect. Lesions that appear hyperdense are thought to be due to haemorrhagic necrosis.

Post-contrast enhancement is either nodular or ring-like in appearance. Enhancement can be mild or absent if severely diminished cellular mediated immunity does not allow much of an inflammatory response. The lesions can be very small or as large as several centimetres in diameter, simulating neoplasms such as lymphoma. Following therapy lesions are replaced by areas of encephalomalacia and glial scars that are seen on CT as foci of calcification. MR imaging is more sensitive than CT showing more lesions and sometimes revealing lesions when the CT is normal. On MR imaging lesions are typically hypo- or iso-intense to grey matter on non-contrast T1-weighted images, and iso-intense or hyper-intense on T2-weighted images.

Some lesions remain the same or increase in size, while others decrease in response to treatment, multiple co-existent processes (e.g. toxoplasma

infection, and another entity, e.g. lymphoma) may be present.

Discrimination of toxoplasma encephalitis from cerebral lymphoma is a common diagnostic problem, since both can be solitary or multiple, nodular or ring-enhancing, and associated with oedema, often making the lesion indistinguishable on CT or MR.

Subependymal spread by a periventricular lesion is seen in lymphoma, but not toxoplasma encephalitis, and is one finding that can be helpful in distinguishing the two entities, but is uncommonly seen. Failed response to treatment is another feature suggestive of lymphoma. On MR spectroscopy, toxoplasma lesions have markedly increased lipid and lactate peaks with a decrease in other metabolites, while lymphoma has only a mild or moderate increase on lactate and lipids, but a substantial increase in the choline peak (thought to be due to increased cellularity).

The diagnosis is confirmed by response to therapy. Toxoplasmosis serology is negative in 5 - 10% of cases. If the patient fails to respond to therapy within 10 - 14 days, other diagnoses such as primary CNS lymphoma or bacterial abscess should be entertained. A definitive diagnosis should be sought by stereotactic brain biopsy.

Case Study 2 — cryptococcus meningitis

A 23-year-old woman was admitted in December 2001 with the diagnosis of an acute salpingo oophoritis grade II, as well as an ectopic pregnancy on the right side, diagnosed by a pelvic ultrasound examination. A laparotomy confirmed the ectopic pregnancy. She looked chronically ill

and complained of headache. On examination she had diffuse lymphadenopathy.

After the neurological consultation a lumbar puncture was performed which revealed clear cerebrospinal fluid with slightly raised proteins at 524 mg/l (normal range 150 - 450 mg/l). Chloride, glucose and adenosine deaminase (ADA) were normal.

The TB culture, the gram stain and capsular antigen tests for bacterial meningitis were negative. The India ink and *Cryptococcus neoformans* agglutination tests were positive. The patient's renal function was normal. The white cell count was $4.1 \times 10^9/l$. Wasserman Reaction (WR) test as well as the toxoplasma IFA polyvalent test were negative. She was then started on cryptococcus meningitis treatment with Diflucan from December 2001 to February 2002.

The patient was suspected to be immunocompromised but she initially refused testing. The CD4 count at this stage was 85/l (normal range $560 - 2700 \times 10^6/l$).

The patient was discharged and then readmitted on 16 March 2002 after complaining of malaise for 2 days as well as neck stiffness, vomiting, headache and flank pain.

On examination she was drowsy and had severe fundus abnormalities diagnosed by the neurologist as gross papilloedema or severe papillitis or retinitis. The macula and eye movements were normal.

There was no weakness of the limbs and sensation on light touch was intact. She had generalised adenopathy. The chest X-ray was normal. The white cell count at this stage was $6.9 \times 10^9/l$ with 84% neutrophils (40 - 75%), and 9.8% lymphocytes (20 - 45 %).

A CT scan was done on an emergency basis and revealed low-density ill-defined lesions in the basal ganglia. The ventricles were slightly prominent. After contrast administration no enhancement of the low-density lesions was detected (Figs 1 and 2).

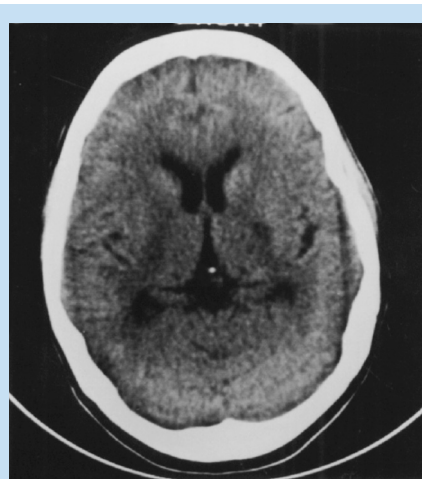


Fig. 1. Pre-contrast brain scan showing oedema involving internal capsule bilaterally with faint hyperdensities.

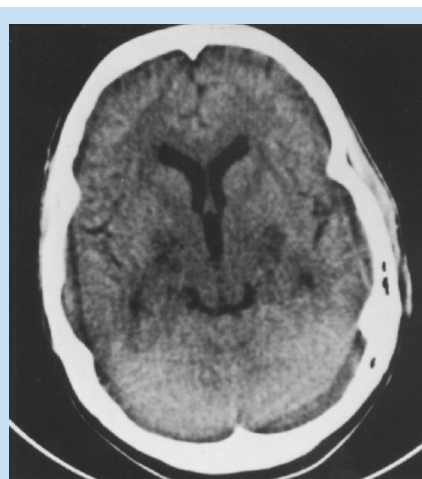


Fig. 2. Contrast-enhanced image, showing bilateral enhancing lesions in the internal capsule.

A repeat lumbar puncture was performed which again revealed clear cerebrospinal fluid with slightly lower but still elevated protein, namely 472 mg/l (normal 150 - 450 mg/l). Chloride, glucose and ADA were nor-

mal. Gram stain and capsular antigens for bacterial meningitis were again negative.

The cell count included 143 erythrocytes/mm³, 44 neutrophils/mm³, and 0 lymphocytes.

India ink cryptococcus and *C. neoformans* agglutination were positive. Again she was put on anticryptococcal meningitis treatment and on 08 April 2002 her Glasgow coma scale dropped to 12/15.

Another CT brain scan was requested which showed the low-density lesions in the basal ganglia more pronounced than on the original scan (Fig. 3).

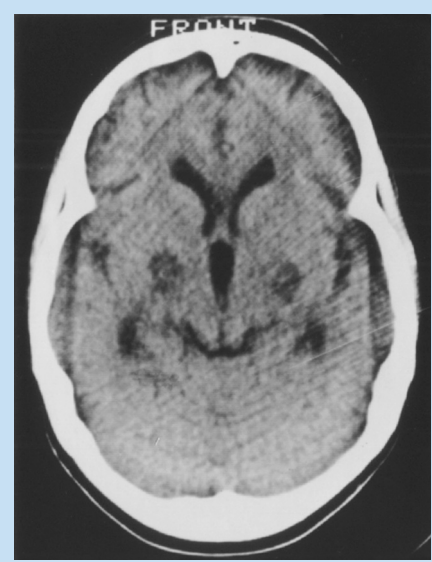


Fig. 3.

Discussion

C. neoformans is the most common fungus involving the brain in immunocompromised patients. The prevalence of the infection has been reported as 6 - 7%.

Patients with underlying chronic illness such as diabetes mellitus, collagen vascular disease, chronic renal disease, alcoholism, malignancy and

those on immunosuppressive drugs are also more susceptible to cryptococcosis. After HIV and toxoplasmosis it is the third most common infection involving the CNS in AIDS patients.

C. neoformans is an encapsulated yeast-like fungus found in mammal and bird excrement, especially pigeon droppings, and is transmitted to humans through inhalation.

The lung is the primary site of involvement and spread is via the haematogenous route to other organs.

Cryptococcus spreads haematogenously to the CNS. The CNS manifestations may be meningeal or parenchymal. The organism penetrates the meningeal vessel walls as well as colonising the perivascular Virchow-Robin spaces and cerebrospinal fluid, producing meningitis.

After colonising the cerebrospinal fluid, the organisms may extend along the perforating arteries within the perivascular subarachnoid space. The production of voluminous mucoid material may enlarge the perivascular spaces giving rise to small cysts, termed gelatinous pseudocysts. These lesions are non-enhancing because the blood-brain barrier is not disrupted and the patient's immunosuppression may decrease the ability to mount an inflammatory response. On CT these lesions are of a low density similar to cerebrospinal fluid. They follow the expected location of the Virchow-Robin spaces, mainly in the basal ganglia, thalami, substantia nigra and periventricular regions. Large perivascular spaces are also present in the choroid plexus. These lesions are more easily visualised on magnetic resonance imaging, where they have hypointensive signal on T1-weighted images and hyperintense signal on T2-weighted images. The signal intensity is essentially similar to

cerebrospinal fluid, although it is often slightly higher than CSF on T1.

Cerebral oedema rarely occurs. In patients with AIDS dilated perivascular spaces should raise the possibility of cryptococcosis, however diagnosing cryptococcosis on the basis of dilated perivascular spaces should be done with caution because generalised cerebral atrophy, the most common CNS imaging finding in AIDS, can also cause this appearance.

In the more fulminant form of cryptococcosis or if the disease is not treated, the blood-brain barrier is disrupted and parenchymal seeding occurs. Neurovascularity is recruited by meningeal or parenchymal seeds and these may enlarge to manifest as multiple enhancing nodules or a milary pattern. These lesions can be scattered throughout the parenchyma, usually predominating in areas near the Virchow-Robin spaces and the choroid plexus as well as the subarachnoid spaces. These lesions usually have a similar appearance on non-contrast CT and MR imaging. Smaller parenchymal lesions may be covert on non-contrast imaging. They become quite apparent, however, following administration of contrast on CT and MR.

When the organisms extend from the perivascular space into the parenchyma, a collection of organisms, inflammatory cells and gelatinous mucoid material forms. This is considered a cryptococcoma. This may possibly occur from invasion of other meningeal or ependymal surfaces. The most frequent location is adjacent to the perivascular spaces, including the choroid plexus although they can occur anywhere in the parenchyma. Cryptococcomas have a variable degree of surrounding vasogenic oedema on CT or MR.

Cryptococcomas are usually larger masses, which have a variable but often intense enhancement.

Obstructive hydrocephalus can occur from the choroid plexal masses.

Other findings that have been described are gyriform enhancement, and punctate calcifications in the leptomeningeal spaces and brain parenchyma.

CNS cryptococcosis commonly presents with manifestations of meningitis and encephalitis such as headache, nausea, staggering gait, dementia, irritability, confusion and blurred vision. Fever and neck stiffness are mild or absent. The course of the disease may be fulminant or chronic and insidious. Lumbar puncture is the single most important investigation. CSF pressure may be increased and may show mild to moderate leucocytosis, decreased glucose and elevated protein levels. India ink smears demonstrate the yeast. Increased cryptococcal antigen may be found in the CSF or serum.

The differential diagnosis on imaging includes infectious causes such as toxoplasmosis, cytomegalovirus, tuberculoma, pyogenic abscess as well as lymphoma and metastatic disease.

Cryptococcosis is usually treated with intravenous amphotericin B. Surgical drainage of large pseudocysts has been reported.

Acknowledgement

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