SHORT REPORT

Encephalomyelitis due to *Cryptococcus neoformans* var *gattii* presenting as spinal tumour: case report and review of the literature

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Abstract

A 24 year old immunocompetent German resident is described who developed multifocal encephalomyelitis due to infection with *Cryptococcus neoformans* var *gatti*, commonly considered a disease of tropical regions. In the light of current knowlege on the epidemiology of *C neoformans* var gatti and the travel history of the patient it is assumed that the infection was aquired outside Europe. As exclusive intramedullary involvement is an outstandingly rare manifestation in spinal cryptococcosis, the particular diagnostic procedure and the therapeutic stratagies are discussed

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With the advent of AIDS and the institution of new immunodepressant drugs cryptococcal disease has received considerable attention. Mycological research has disclosed substantial differences in the epidemiology and clinical course of cryptococcosis seen in infections with *C neoformans* var *neoformans* (serotypes A, D, and AD) and *C neoformans* var *gattii* (serotypes B and C). So far *C neoformans* var *gattii* is found mainly in tropical and subtropical regions[1 2] as opposed to *C neoformans* var *neoformans, which is* encountered worldwide. *C neoformans* var *neoformans* tends to infect, yet not exclusively, immunodeficient people, leading to acute diffuse meningitis or meningoencephalitis. On the contrary, infection with *C. neoformans* var *gattii* manifests more typically with a granulomatous inflammatory response in immunocompetent people, which results in chronic disease.[3–6] A distinct clinical syndrome of infection with *C neoformans* var *gattii* leading to meningitis and optic nerve atrophy was identified in Papua, New Guinea.[7] Obviously due to the restricted distribution of *C neoformans* var *gattii* infection with both HIV and *this organism* seems to be rare.[8–10] Furthermore, research has confirmed different patterns of disease on histopathological grounds in immunocompetent and immunosuppressed people,[11] presumably due to specific virulence factors and a different interaction between host and pathogen.

The 24 year old German resident with encephalomyelitis due to *C neoformans* var *gattii* reported on here not only raises diagnostic and epidemiological questions but also illustrates the complications due to intramedullary involvement requiring a specific therapeutical approach. Despite a definite histopathological diagnosis made from a cerebral lesion and an appropriate antimycotic regimen, surgery was necessary because of spinal involvement. To our knowledge this is the first description of serologically identified *C neoformans* var *gattii* infection of the spinal cord.

Case report

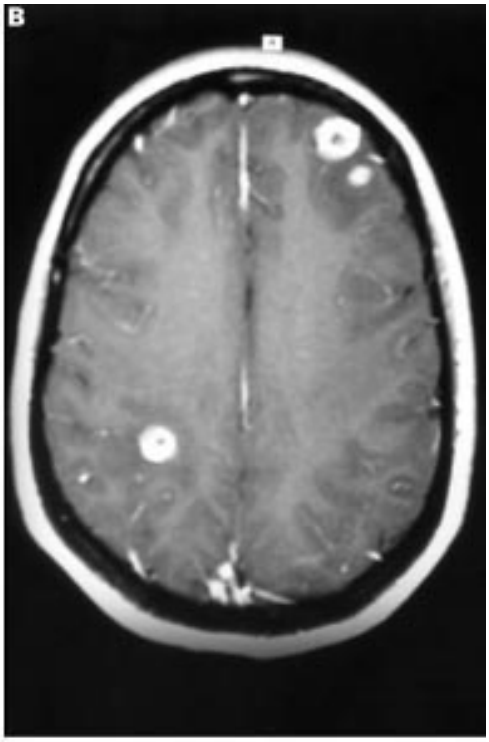
We admitted a 24 year old woman with hypaesthesia, painful dysaesthesia, gait disorder, and micturition disturbances. About 3 months before admission she developed a tingling sensention in her right foot and shin which gradually deteriorated before she felt a numbness in her left foot. Two months before admission a non-radiating lower back pain evolved which was independent of movement. Because of progressing gait disturbances and a delayed micturition the patient was transferred to our hospital. There were no headaches, nausea, fever, weight loss, night sweat, skin alterations, or icterus. Except for a history of atopic eczematous dermatitis the patient had never experienced illness. She had travelled outside Europe to the United states between 1993 and 1996 (East coast, Middle West, Florida), and to Tunesia in 1995.

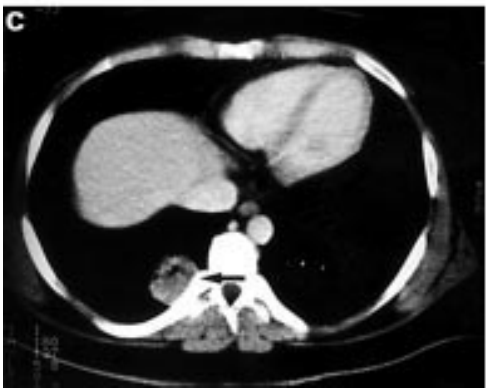
On admission in spring 1997 neurological examination suggested an incomplete transverse lesion of the spinal cord at level L3/4. Cranial nerves were normal. There was a weakness of the dorsiflexors, plantar flexors, and of the peroneal muscles on both sides graded 4/5 to 4+/5 with no signs of wasting. Strength was normal in all other muscles with no alteration in muscle tone. Whereas deep tendon reflexes in the upper limbs were symmetrically 2+ knee jerks were absent, ankle jerks were abnormally brisk. Ankle clonus could be elicited on both sides, plantar responses were flexor. There was a diffuse decrease in sensation below the knees to light

touch, pinprick, deep pain, and vibration. Joint position sense was markedly impaired in the toes and the ankles, the heel to shin test was grossly dysmetric. The Romberg test was unremarkable, gait was staggering. All cerebellar functions proved to be within normal limits as was mentation. Micturition was delayed and incomplete. The patient had no signs of meningeal irritation.

The patient underwent thorough radiological evaluation. Spinal cord MRI was performed initially. In sagittal slice orientation (figure A) an irregularly shaped intramedullar lesion with a smooth border at the L1 vertebral level (18×18×12 mm) was detected which caused distension and a partial displacement of the caudal spinal cord. On T2 weighted MRI a lesion with a moderately increased signal intensity was seen. On non-enhanced T1 weighted MRI the isointense signal intensity of the lesion was shown in comparison with the healthy spinal cord. After administration of gadolinium a circular enhancement of the lesion was detected. In axial T1 weighted images six small spheral lesions seemed to be joined to a conglomerate tumour with narrowing of the subarachnoidal space. Corresponding myelography showed a distension of the dural space between T12 and L2 vertebral level as well as a spreading of the cauda equina. On T2 weighted MRI the cranial and caudal parts of the spinal cord adjacent to the lesion had an increased signal intensity due to pathological involvement. On cerebral MRI (figure B) six lesions with a diameter up to 10 mm were detected with a signal behaviour similar to the intramedullar lesion. Thoracic CT (figure C) showed a dorsomedially located soft tissue lesion (35×30×45 mm) of the right lung adjacent to the pleura. This lesion had an irregular inner structure with a moderate rim enhancement and multiple gas inclusions.

A CSF examination showed no pleocytosis, morphologically normal cells, but a markedly raised protein concentration (4668 mg/l) with intrathecal IgG-synthesis and a few oligoclonal IgG bands. Glucose and lactate concentrations were normal. No pathogenic organisms could be identified in the CSF with gram stain, Indian ink stain, or Ziehl-Neelsen stain.





(A) T1 weighted sagittal MRI of the spine with cryptococcal lesion and perifocal gadolinium enhancement at level L1. (B) Cerebral MRI with multifocal contrast enhancing cryptococcal lesions. (C) Thoracic CT; dorsomedially located soft tissue lesion in the right lung with slight contrast enhancement and multiple gas inclusions (arrow).

Serological testing in serum and CSF for bacteria, parasites, protozoa, and fungi was negative with the exception of *C neoformans* capsular antigen in serum with a titre of 1:256. *C neoformans* antigen in CSF was negative. No condition related to immunosuppression such as HIV, leukaemia, lymphoma, pregnancy, gammopathy, or diabetes mellitus could be detected.

Diagnostic stereotactic biopsy of a brain lesion was performed. Histopathology showed chronic mixed granulomatous inflammation (lymphocytes, plasma cells, neutrophil granulocytes, macrophages) with reactive astrogliosis. Yeast cells corresponding to *C neoformans* could be seen with Grocott stain and alcian blue stain confirming the diagnosis of *C neoformans* encephalomyelitis with multiple cryptococcomas. *C neoformans* was proved culturally from biopsy. The isolate could be identified as *C neoformans* var *gattii* serotype B (Crypto Check®, Iatron Laboratories Inc, Tokyo/Japan). We started intravenous antifungal therapy with amphotericin B (0.5 mg/kg body weight), 5-fluorocytosin (200 mg/kg body weight), and fluconazole (800 mg/day) for 6 weeks followed by a 3 week course with AmBisome (4 g/kg body weight) and fluconazole (800 mg/day) after an interval of 4 weeks. With this therapy no significant change in size of the cryptococcal lesions either in the brain or the spinal cord could be identified on MRI.

Therapeutic strategy was complicated due to the myelitis. Because of the possible risk of irreversible spinal cord damage we administered steroids, which led to a significant remission of symptoms due to a reduction of the inflammatory response and the perifocal oedema. Twice, however, tapering off steroids led to severe relapses. Thus, we decided to perform decompressing laminectomy with local expansion of the dura. At surgery the exclusive intramedullary nature of the lesion was confirmed showing a hard, greyish, and fusiform tumour of the conus medullaris.

The patient has been free of steroids since then and she recovered gradually from her neurological deficits over the course of 1 year. Antigen titres decreased to 1:8 under continuous oral fluconazole therapy with 200 mg/day. But only after 2 years of antimycotic therapy did MRI demonstrate a reduction in the size of the cerebral and spinal lesions, which still showed an intensive contrast enhancement. The pulmonal cryptococcoma had disappeared.

Discussion

To date, infections with *C neoformans* var *gattii* in humans have almost exclusively been acquired in tropical and subtropical areas. Different to *C neoformans* var *neoformans*, which has its ecological niche in pigeon droppings *C neoformans* var *gattii* has its natural habitat associated with *Eucalyptus* trees.[12–14] Therefore infection with *C neoformans* var *gattii* is mainly reported from Australia and the South Pacific, the United States, Latin America, and Sub-Saharian Africa.[1–10 12 15] Although de novo infections with *C neoformans* var *gattii* in Europe have been suggested,[16–18] most infections in Europeans were probably acquired outside Europe. As a result of an increasing exportion of *Eucalyptus* trees from Mediterranean countries (for example, Morocco, Tunesia, Italy, Spain, Portugal, Greece) and India an expanding distribution of *C neoformans* var *gattii* is seen.[13 14 18] Cryptococci seem to be exported on contaminated seeds and seedlings of some *Eucalyptus* trees. Recent reports on outbreaks of cryptococcosis in goats due to *C neoformans* var *gattii* in Spain[19] will give new epidemiological insights. Although we cannot trace back the mode of infection in our patient we assume that she could have inhaled the aetiological agent of her mycosis in Tunisia or in California,[20] where she remembers that she was directly exposed to *Eucalyptus* trees.

However, the above mentioned reports and our case show that cryptococcosis should be included in the differential diagnosis of single or multifocal mass lesions of the CNS in patients residing in Europe. Because in Europe clinical suspicion of cryptococcosis is mainly confined to immunocompromised patients the diagnosis can easily be overlooked in immunocompetent patients. The mycoserological results in our patient demonstrate the necessity of *C neoformans* antigen screening in serum—even in the absence of pleocytosis or a positive antigen test in the CSF, which might be explained by the lack of meningeal involvement. If possible, biopsy should be obtained, even when serum or CFS already tested positive, because cultural examination is important to make the fungal isolate available for serotyping as a predictor of the clinical course. It is known that infection with *C neoformans* var *gattii* tends to follow a more chronic course in immunocompetent people[4–5] than infection with *C neoformans* var *neoformans*. In this setting specific therapeutic strategies may be required.

Spinal cord disease, as in our patient, is a rare presentation of cryptococcosis never reported on in Europe. As opposed to brain lesions myelitis almost inevitably leads to clinical manifestations reminiscent of a spinal tumour. According to our review of the world literature lesions unequivocally confined to the medulla have only been reported in four patients.[21–24] Other case reports were not precise in their discription of the exact anatomical site.[25 26] As in other mycotic infections of the spinal canal the typical spinal cryptococcal granulomas are located intradurally-extramedullarly, extradurally, or in the cauda equina.[19 22–26]The incidence of combined cerebral and spinal disease has not yet been delineated but imaging of the brain should be performed in any case of spinal cryptococcosis.

Whether therapy for intramedullary disease can be limited to antifungal medication is doubtful because of the risks of secondary ischaemia and irreversible damage to the spinal cord. As in parasitic infections with a predilection for the spinal cord such as schistosomiasis, corticosteroids can be of benefit to protect the spinal cord and eventually lead to a marked clinical improvement.[27 28] However, cortico-

steroids are likely to maintain the underlying cryptococcal infection despite neurological improvement because of their immunosuppressive mode of action. In our patient *C neoformans* capsular antigen titre in serum only fell after discontinuing steroid therapy. Thus, to avoid irreversible spinal cord damage, we decided to perform decompressive laminectomy with a local extension of the dura as a palliative treatment instead of administering corticosteroids. Nevertheless, we would not recommend decompressive laminectomy as first line treatment because of the individuality of our case. Correspondingly, resection of an intramedullary located cryptoccocic granuloma is no alternative, dispite the fact that successful surgery has been reported once.[22] However, in exclusively extramedullary cryptoccocosis resection can have a curative effect as stated before.[29–31] In conclusion, surgical options in spinal cryptococcosis highly depend on the precise anatomical site of the disease and the response to medical treatment.

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