Neuroradiology (1991) 33: 183–185

Neuro radiology

Early invasive CNS aspergillosis

An easily missed diagnosis

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Received: 21 February 1990

Summary. A 46-year-old woman with non-Hodgkin's lymphoma presented with a new onset of seizures. A cranial CT was interpreted as normal. Eight months later, she presented with changed mental status and leg weakness, and a repeat CT scan showed multiple ring-enhancing lesions close to the left frontal sinus, with mass effect. A review of the previous CT scan showed a very small area of sinusitis as well as a small ring-enhancing lesion contiguous to it. A short course of intravenous steroids markedly relieved her symptoms, and a stereotactic biopsy confirmed *Aspergillus fumigatus* to be the cause of the infection. She was successfully treated with Amphotericin B. Central nervous system (CNS) aspergillosis is a potentially fatal disease. The therapeutic success in this case was related to a high index of suspicion at her second presentation. As the early signs of infection might be subtle and easily missed, patients at high risk for opportunistic infection should be studied carefully when new onset of CNS symptoms occur. Early initiation of therapy should improve the prognosis in such cases.

Key words: *Aspergillus fumigatus* – Stereotactic biopsy – Abscess

Although central nervous system (CNS) aspergillosis is still relatively rare, its incidence is rising, primarily because of the increased numbers of immunocompromised patients [1]. Very few individuals with CNS aspergillosis have been reported to survive; the majority of the patients succumb to the infection. In many of the patients who died, the aspergillus infection had been present within the CNS for very long periods, sometimes for years (1–4). The advent of newer imaging techniques should allow earlier diagnosis and possibly improved prognosis. Thus, a high index of suspicion is crucial.

We report a patient with non-Hodgkin's lymphoma in whom the diagnosis of multiple CNS aspergillus abscesses was made 8 months after the first manifestation of infection and who was successfully treated. Awareness of the subtle signs of early aspergillus infection may lead to early detection and therapy, and ultimately a favorable outcome.

* Recipient of a fellowship from American Physicians Fellowship

Case report

A 46-year-old woman presented to the emergency room with headaches, slurred speech, increasing sleepiness, and inability to walk of 2 weeks duration. Two years earlier, she was diagnosed as having an abdominal large cell lymphoma involving the caecum. She received chemotherapy and improved. Three months later, she presented with clinical and radiographic evidence of lower lumbar spinal compression, and CSF cytology was positive for tumor cells. A cranial CT scan was normal. She was treated with spinal irradiation followed by systemic and intrathecal chemotherapy. Her symptoms, mainly gait difficulties, improved significantly, and she was able to resume her normal activities. Three months later, she had a generalized seizure. A second cranial CT (Fig. 1) was read initially as normal. No tumor cells were detected in the CSF. She was treated with phenytoin, 300 mg daily. She remained well except for recurring seizures due to non-compliance with her medications.

On admission, she was afebrile with normal vital signs. She had marked tenderness over the left frontal sinus. The rest of the general physical examination was normal. Neurologic examination revealed a lethargic patient, who was fully oriented when aroused, with depressed mood and coherent although slow speech. The legs were weak (MRC grade 2) with decreased deep tendon reflexes and decreased vibration and position sensation. The plantar responses were flexor. The white blood count was 5700 /ml. Serum electrolytes were normal, and dilantin level was 7.8 μg/ml. A cranial CT scan revealed multiple ring-enhancing lesions surrounded by a large area of edema in the left frontal and anterior parietal lobes, with left to right midline shift. The lesions were in close contact with the posterior wall of the left frontal sinus, eroding the

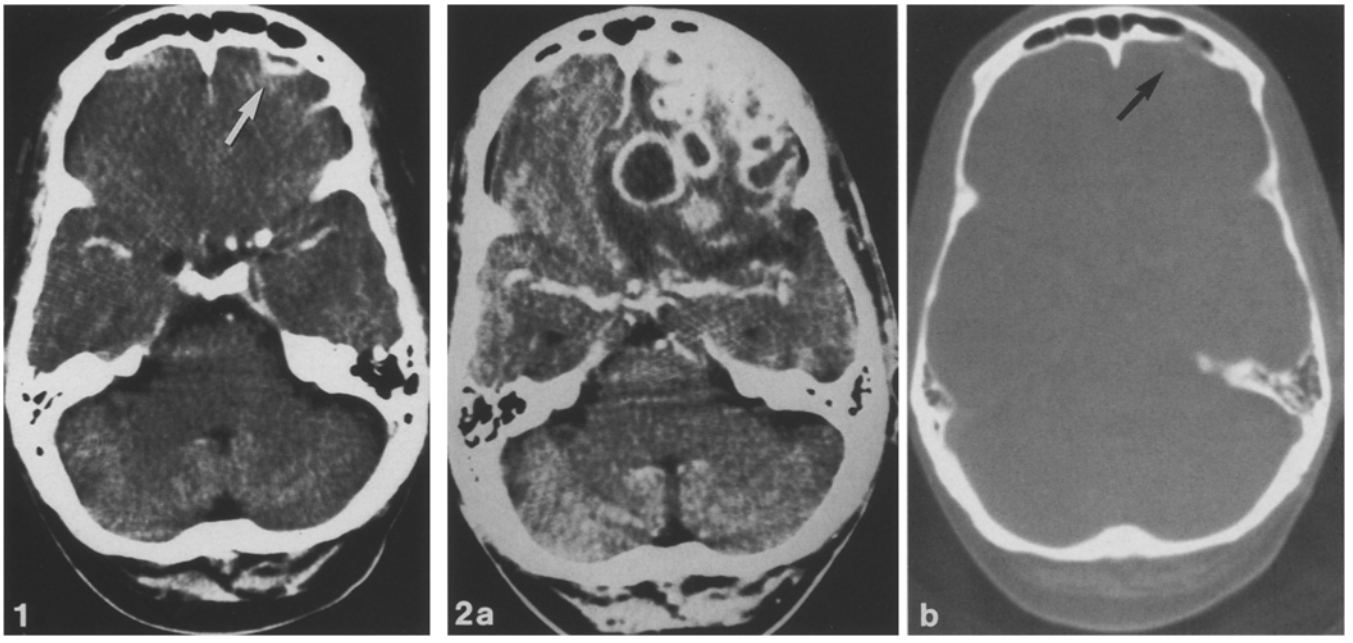

Fig. 1. Cranial CT after contrast injection. Small ring-enhancing lesion close to the left frontal sinus *(arrow)*. See text

Fig. 2. **a** Eight months later. Cranial CT with contrast showing multiple ring-enhancing lesions in left frontal lobe region, with large mass effect, before initiation of Amphotericin B. **b** Cranial CT without contrast showing the inflammatory process originating from the left frontal sinus, eroding its posterior wall *(arrow)*

wall (Fig. 2a, b). On review of her previous cranial CT, a small ring-enhancing lesion was detected adjacent to the posterior wall of the left frontal sinus, without significant mass effect, and a small region of sinusitis close to the fronto-nasal duct was also noted.

Because of her abnormal mental state, the marked mass effect seen on the cranial CT scan, and the possibility that her lesions represented a recurrence of the lymphoma, treatment with intravenous dexamethasone was initiated and led to a rapid improvement in both her mental status and leg strength. A stereotactic brain biopsy revealed characteristic branching septate hyphae of aspergillus, and a culture was positive for *Aspergillus fumigatus*. Therapy with amphotericin B was initiated, resulting in further improvement. Cranial CT done 10 months later showed only one small residual lesion without mass effect (Fig. 3).

Discussion

The fungus *Aspergillus fumigatus* is found world-wide and is a common contaminant of the upper respiratory tract. From a primary site of infection, usually the lungs, the organism may spread to the CNS, generally via the bloodstream. Alternatively, aspergillus may infect the paranasal sinuses first, causing a clinically overt sinusitis, and then extend directly to the CNS [3, 5]. Because of the close proximity of the lesion to the frontal sinus, we believe that this was the portal of entry of the fungus to the CNS in our patient. Evidence of minimal sinusitis in the region of the frontonasal duct, as seen in her earlier cranial CT scan, supports this view, even though at late stages of her disease, the CT did not show any evidence of sinusitis. Thus, it seems that even limited transient sinus disease is enough to allow aspergillus to penetrate the CNS.

The spectrum of the pathology of aspergillus infection is broad. Aspergillus may cause cerebral mycotic aneurysms, meningitis, and intracerebral mass lesions [1]. The fungi may invade blood vessels, causing inflammation of their walls, mycotic aneurysms and thrombosis of large arteries, leading to stroke syndromes or subarachnoid hemorrhage [3, 6]. In the CNS, the pathology consists of hemorrhagic necrosis surrounded by granulomatous inflammation. Multiple small abscesses often occur near the area of infarction, sometimes coalescing to a large cavity with active infection in its wall.

CNS aspergillosis can manifest with generalized seizures, focal neurologic deficits, changes in the level of consciousness, or brainstem syndromes, such as dysarthria, dysphagia, facial weakness, and abnormalities of eye movements [3, 4]. EEG may show a localizing voltage depression, corresponding with the brain disease [3]. Cranial CT and MRI scans are generally abnormal, showing lucencies with variable degrees of enhancement, either homogeneous or in ring form. These lesions may be associated with large areas of edema [3, 6, 7]. Nevertheless, the CT scan findings may be neither sensitive nor specific for the diagnosis. The extent of brain disease may be underestimated by CT, and indeed a patient with established CNS aspergillosis was reported to have a normal cranial CT scan [3]. Early lesions may be missed, even when electroencephalography and neurological examination show localizing signs [3].

Our patient's neurologic presentation was new onset of seizures. An enhanced cranial CT scan showed a tiny

Fig. 3. A follow-up cranial CT with contrast, 10 months after the initiation of therapy. There is a residual lesion in frontal lobe *(arrow)*

ring-enhancing lesion in contact with the posterior left frontal sinus, without mass effect. This CT scan was interpreted initially as normal. An EEG was not obtained, and it was decided to follow her clinical response to anticonvulsant therapy.

She later presented with drowsiness and leg weakness. The brain CT showed multiple abscesses with a large mass effect. With intravenous steroid treatment, her symptoms resolved rapidly, providing suggestive evidence that the marked brain swelling was an even more important cause of her neurologic presentation than the abscesses per se.

Definitive diagnosis of the aspergillus infection requires biopsy of the lesion, with histopathologic examination and culture [1]. The morphologic appearance of hyphal forms is characteristic, and growth of the organism supports the diagnosis [1]. Stereotactic biopsy was used in our patient, and in one described in a previous report [9]. This technique provided both biopsy and drainage [9], and obviated the need for craniotomy.

Some authors advocate the removal of the infected tissue as critical to the successful treatment of patients with focal CNS aspergillosis [1]. Our patient, however, showed a dramatic response to intravenous treatment with amphothericin, without craniotomy or extensive debridement.

In many patients with CNS aspergillosis, the interval between onset of symptoms and diagnosis is long, often more than 6 months. In spite of the chronicity of the process, the survival rate is low [2]. Our patient, who had the intracranial infection for at least 8 months before diagnosis, had a relatively benign course and an excellent response to therapy. This suggests that this particular patient had a competent immunologic defense system, in spite of the lymphoproliferative disease and its treatment. Moreover, although steroids have a significant immunosuppressive effect, a limited course of steroid treatment may provide symptomatic improvement in the acute phase of the disease, in patients with significant brain edema.

This case emphasizes that the cranial CT findings in the early stage of aspergillus infection of the CNS may be very subtle. In patients who are at high risk for developing ring-enhancing brain lesions from other causes such as specific tumors, hematomas, or hemorrhagic infarcts, special care should be taken, as the differential diagnosis is difficult [10, 11]. Attention should be paid also to the sinuses and even tiny sinus abnormalities should be investigated. Nevertheless, it is encouraging that even in patients who have evidence of a long-standing invasive aspergillus infection the disease may be successfully treated.

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