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Invasive cerebral aspergillosis in a patient with aplastic anemia. Response to liposomal amphotericin and surgery

Sir,

Invasive aspergillosis (IA) of central nervous system is a rare but well described disease with a mortality of over 95% in spite of antifungal and surgical therapy. We present a case of cerebral abscess due to *Aspergillus fumigatus*, cured with liposomal amphotericin and surgery.

A 16-year old male with severe medullary aplasia began receiving immunosuppressive treatment according to the protocol of the *German Aplastic Anaemia Study Group.*[1] On day 6 of the treatment he developed a crisis comicial. He was afebrile and physical examination did not reveal any abnormality. NMR scans (Figure 1) showed a mass in the left parietal lobe with zones of subacute bleeding and peripheral edema causing partial collapse of the left ventricle with heterogeneous contrast capture. Chest radiography and lumbar puncture were normal.

As the patient remained asymptomatic and the radiologic image was unspecific, it was decided to await new developments. On day 36, a chest radiograph showed consolidation in the lower left lobe. Physical examination showed right-sided loss of sensation and minimal paresis of the left arm. CT showed growth of the parenchymatous lesion with encapsulation. Bronchoalveolar lavage and cerebral biopsy yielded *A. fumigatus.*

Conventional amphotericin was initiated at a dose of 1 mg/kg/day. Two weeks later, the patient began to develop respiratory symptoms so itraconazole was added at a dose of 600 mg/day. The absence of clinical or radiologic response after 32 days of treatment, together with the development of nephrotoxicity made it necessary to change to a liposomal amphotericin (Ambisome®) at a dosage of 1.5 mg/kg/day.

On day 123, no hematologic response had been produced, so the same immunosuppressive cycle was begun again.

After 20 days of treatment with liposomal amphotericin, the pulmonary infiltration disappeared while the cerebral lesion was unchanged, so surgical excision was carried out. After surgery, liposomal amphotericin was suspended and itraconazole treatment maintained at 800 mg/day.

Two weeks after the operation, bradypsychia was observed and another CT scan (Figure 2) showed relapse of the lesion. At that moment, hematologic response began. After 40 days of treatment, no improvement in the lesion was seen, so another therapeutic change to liposomal amphotericin was made and another excision of the aspergilloma and the infiltrated parietal bone carried out. Liposomal amphotericin was maintained for 350 days (total dose: 35 g) with good tolerance and follow-up maintenance for 12 months with itraconazole at 200 mg/day. Control CT scans show no relapse of the aspergilloma to date. Physical examination is normal, with no neurological deficit.

IA is a common infection in immune-compromised patients. Diagnosis is difficult in the absence of histologic confirmation. The mortality associated with Aspergillus infection in this type of patient is high. In a review by Stevens,[2] only 8 of 33 patients responded to treatment. The most common clinical manifestations are persistent fever in spite of broad-spectrum antibiotic treatment, the appearance of pulmonary infiltration and, at the CNS level, focal neurologic deficits.[3] Recent publications[4] consider the appearance of cerebral infarcts in IA-risk patients, even without lung disease, to be an indication for the start of aggressive antifungal treatment.

The treatment of cerebral aspergillosis has been

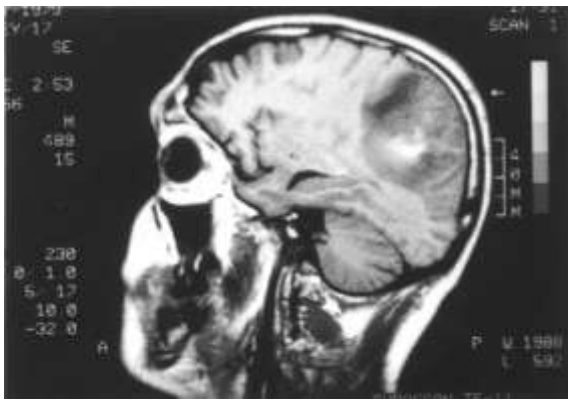

Figure 1.

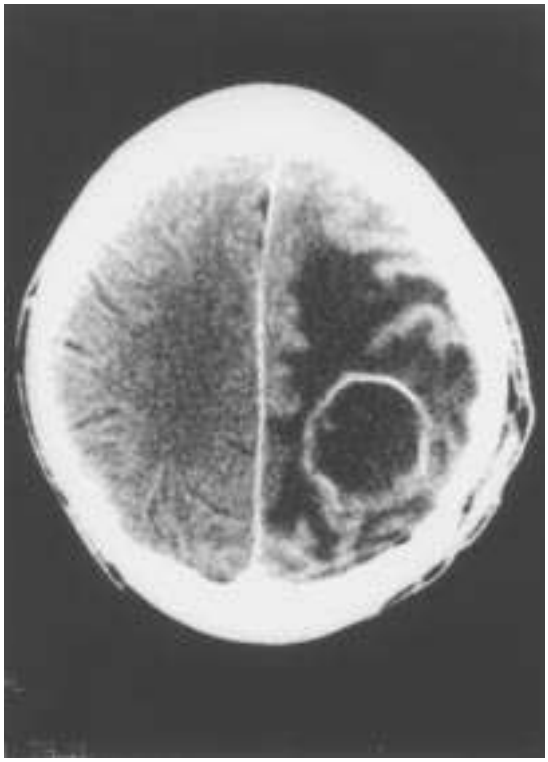

Figure 2.

reviewed by various authors.[2,5-7] The treatment of survivors included a combination of antimycotics and/or neurosurgery. We began therapy with conventional amphotericin without response and it was not possible to increase the dose because of the nephrotoxicity which developed. Liposomal amphotericin at a low dosage led to resolution of the clinical picture, and was well tolerated in spite of the high cumulative dose.

The action of itraconazole against Aspergillus is good both *in vitro* and *in vivo*[8] and some publications have compared its effectiveness with that of amphotericin in patients with cerebral aspergillosis.[9,10] In our patient, a high dose was not effective. As plasma concentrations were not measured we do not know if a suitable therapeutic level was reached.

The duration of treatment of IA in neutropenic patients is not well established. There is a consensus that treatment should be maintained until disappearance of lesions and/or recovery from the neutropenia.

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Key words

Aspergillus, cerebral abscess, liposomal amphotericin, neurosurgery, immunosuppression

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Transient response of myeloma clone to pamidronate therapy

Sir,

Several studies have previously reported that IL-6 mediates the growth of multiple myeloma cells in either an autocrine or paracrine fashion. More recent studies indicate the paracrine mechanism as that being mainly responsible for the growth of myeloma cells. Tumor cells trigger IL-6 secretion by interacting through adhesion molecules with the bone marrow stromal cells which are the major source of IL-6 production in MM.[1] The efficacy of pamidronate, a second-generation bisphosphonate, in inhibiting osteoclastic activity and reversing cancer-associated hypercalcemia has been widely demonstrated.[2] Berenson *et al*.[3] also showed in a randomized study that pamidronate was effective in reducing skeletal events.