Aspergillus fumigatus: a rare cause of vertebral osteomyelitis

Opportunistic infections including those caused by fungi have been reported with the new purine analogues. We present a case of a patient with chronic lymphocytic leukemia treated with fludarabine and cyclophosphamide that six months later developed a microbiologically documented vertebral aspergillosis.

Patients with B-cell chronic lymphocytic leukemia (CLL) have an increased risk of infection which is a common cause of morbidity and mortality. Multiple factors seem to be involved: a cellular and humoral immune dysfunction related to the disease itself and the immunosuppression related to treatments employed, particularly in advanced stages. The new purine analogues have been associated with opportunistic infections caused by uncommon agents such as Pneumocystis carinii, Listeria monocytogenes and fungi.

We present the case of a patient diagnosed of CLL who developed a vertebral osteomyelitis caused by Aspergillus fumigatus.

Clinical case

A 59-year-old woman was diagnosed in January 2002 of CLL stage C according to the Binet staging system. At the time of the diagnosis she presented a leukocyte count of 114,000 cells/mm$^3$ (7\% neutrophils, 92\% lymphocytes), 7 g/dL hemoglobin and 263,000 platelets/mm$^3$. Routine biochemical tests were normal, including the lactate dehydrogenase levels. Serum immunoglobulins levels were: IgG 1470 mg/dL, IgA 86 mg/dL and IgM 40 mg/dL. The bone marrow biopsy presented massive lymphoid infiltration with marked reduction of the other hemopoietic series. Flow cytometry immunophenotypic analysis in peripheral blood identified 94\% of B-lymphocytes with a CLL phenotype and CD38 expression. Fluorescence in situ hybridization study showed a 12q trisomy. CD4$^+$ T lymphocytes were 2,142 cells/mm$^3$.

The patient was hospitalized because of cough, dyspnea and fever. The chest x-ray showed a left basal alveolar infiltrate with ipsilateral pleural effusion. The clinical picture was classified as infectious and cefepime was empirically started.

After the resolution of the infectious episode, the patient received a first cycle of treatment with fludarabine (25 mg/m$^2$/day for 3 days) and cyclophosphamide (250 mg/m$^2$/day for 3 days). One month later, she was admitted to hospital because of reappearance of the pleural effusion. A thoracic CT scan did not reveal parenchymatous infiltrates. A mini-thoracotomy was performed and pleural and lung parenchyma biopsies were obtained. The pathological diagnosis was of reactive chronic pleuritis with neither granulomatous images nor tumor infiltration. No microbiological documentation was obtained. Subsequently, a pleuropulmonary abscess and empyema were obtained. The pathological diagnosis was of reactive chronic pleuritis with neither granulomatous images nor tumor infiltration. No microbiological documentation was obtained. Subsequently, a pleuropulmonary abscess and empyema were obtained.

Two months later the patient was readmitted to hospital complaining of a progressive mechanical lumbar pain that had developed over the previous month. She had neither fever nor other associated symptoms. Physical examination showed tenderness on the lower dorsal spinous processes without any neurological signs. The chest x-ray showed residual signs from previous surgery and increased density on the T11-T12 vertebral bodies. A nuclear magnetic resonance (NMR) revealed a destructive process and stricture of the T11-T12 discal space accompanied by bilateral erosion of the plates and a slight increase in the soft tissues that took up contrast. A CT scan-guided needle aspiration of the discal space was made, but enough material for diagnosis was not obtained. The picture was classified as osteomyelitis and empirical treatment with cloxacillin and ciprofloxacin was started.

During admission, a bone marrow biopsy showed massive lymphoid infiltration without granulomatous images or epithelioid cells; the bone marrow cultures were all negative. The clinical picture worsened with increasing lumbar pain. A second biopsy puncture was performed...
and microbiological cultures yielded Aspergillus fumigatus but the amount of tissue obtained was not enough for a pathological diagnosis. A second NMR revealed worsening of the previously described lesions and the appearance of medullary injury signs (Figure 2). Despite the lack of pathological evidence of the presence of invasive aspergillosis in the vertebral body, in view of the microbiological results, the patient was started on itraconazole (200 mg/12 hours). Finally, a third needle-biopsy was performed which confirmed the invasion of the intervertebral disk by septate hyphae. Liposomal amphotericin B was started (3 mg/kg/day), but there was no clinical improvement in the first two weeks. An arthrodese and partial resection of T11-T12, with placement of a tibial allograft was done. The resected material was sent for microbiological analysis and, in spite of the treatment with amphotericin B and itraconazole, Aspergillus fumigatus was recovered from the sample. Antifungal susceptibility tests were performed according to NCCLS recommendations prior and during antifungal treatment. The organism was susceptible to both antifungal agents. After surgery, the patient evolved satisfactorily. She was treated with liposomal amphotericin B (3 mg/kg/day) for a month, with a total cumulative dose of 5g. Treatment was completed with itraconazole during nine months. She has remained asymptomatic up to date.

Discussion

Aspergillus species is an ubiquitous saprophytic fungus and is considered an opportunistic pathogen. Vertebral osteomyelitis by Aspergillus fumigatus can be considered extremely rare. Only 39 cases have been described between 1966 and 1998. Most of them occurred in patients with immune impairment.

The main immunologic consequence of fludarabine therapy is a profound and rapid decrease in all T-cell subsets. It has been reported that CD4 cells decrease within 2 to 3 months of therapy to levels similar to those observed in AIDS patients. These levels appear to be more severe with lymphoid malignancies than with solid tumors. Purine analogue therapy has been associated with a new spectrum of pathogens typically related with T-cell dysfunctions, but the association with invasive aspergillosis has not been frequently reported. Besides, some recent communications, as our own report, may suggest the possible role of fludarabine as a predisposing factor for aspergillosis.

The differential diagnosis of vertebral osteomyelitis in the immunocompromised people should include tuberculosis, Staphylococcus sp, Salmonella sp, and less frequently Aspergillus fumigatus and other fungi. The clinical, biological and radiological characteristics are similar in all of them. Etiological diagnosis is very important in patients with acute diskitis in patients with chronic obstructive pulmonary disease. Mayo Clin Proc 2000;75:1039-54.

Itraconazole has very good activity against Aspergillus sp. Cases treated successfully treated cases with itraconazole alone have been described, but it must be verified that it is absorbed properly, achieving antifungal levels. Some in-vitro studies show that the combination of amphotericin B and itraconazole presents antagonism but conversely their association has proven to be beneficial in some cases of invasive aspergillosis. Caspofungin and voriconazole may be good options for osteomielitis caused by Aspergillus sp. Voriconazole has become a first line treatment for invasive aspergillosis and, although there is little experience with osteomielitis, the results are promising. Different antifungal combinations for the treatment of refractory invasive aspergillosis are still under investigation and their role avoiding the need of surgical treatment for osteomielitis are unknown.

Surgical treatment must be individualized, depending chiefly on the degree of bone destruction and on the risk of compression of the spinal cord, but it seems to be required in most cases of Aspergillus osteomielitis. In the present case, surgical treatment turned out to be necessary, not only because of the bad clinical evolution, but also because of the persistence of feasible fungi in the injury after two weeks of antifungal treatment.

In conclusion, although Aspergillus sp is an uncommon infectious agent in patients with CLL, we must bear it in mind in immunosuppressed patients since early diagnosis is important to avoid serious complications, particularly neurological.

References

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