Aspergillus spondylodiscitis in a patient with liver cirrhosis and diabetes mellitus

Aspergilni spondilodiscitis pri bolnici z jetrno cirozo in sladkorno boleznijo

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Izvleček

Aspergilni osteomielitis je redka pojavna oblika invazivne aspergiloze, ki zajema 1,8 % do 5,6 % vseh oblik invazivne aspergiloze. Podobno kot velja za druge oblike invazivne aspergiloze za aspergilnim osteomielitisom najpogosteje zbolijo bolniki s hudo oslabljeno imunostjo in znanimi dejavniki tveganja za invazivno aspergilozo. V zadnjem času pa poročajo o naraščajočem številu bolnikov z invazivno aspergilozo brez tradicionalnih dejavnikov tveganja, kot so bolniki s kronično obstruktivno boleznijo pljuč, ki se zdravijo z glukokortikoidi, ali bolniki z jetrno cirozo.

V prispevku predstavljamo primer bolnice z aspergilnim spondilodiscitisom z jetrno cirozo in sladkorno boleznijo brez drugih dejavnikov tveganja za invazivno aspergilozo, ki je bila uspešno zdravljena z vorikonazolom.

Abstract

Aspergillus osteomyelitis is a rare manifestation of invasive aspergillosis, which accounts for 1.8 % to 5.6 % of all invasive aspergillosis forms. Like other forms of invasive aspergillosis, it predominantly occurs in immunosuppressed patients with well-established risk factors, but there are increasing reports of invasive aspergillosis cases in patients without traditional risk factors, such as patients with chronic obstructive pulmonary disease on corticosteroid therapy or patients with liver cirrhosis.

We present a case of *Aspergillus* spondylodiscitis in a patient without risk factors for invasive aspergillosis other than liver cirrhosis and diabetes mellitus, successfully treated with a 4-month course of voriconazole.

Introduction

Aspergillus osteomyelitis is a rare manifestation of invasive aspergillosis, which accounts for 1.8 % to 5.6 % of all invasive aspergillosis forms.[1-3] Like other forms of invasive aspergillosis, it predominantly occurs in immunosuppressed patients with well-established risk factors but there are increasing reports of *Aspergillus* osteomyelitis in moderately immunosuppressed patients, such as patients with chronic obstructive pulmonary disease (COPD) on corticosteroid therapy and even in non-immunosuppressed patients.[3-4]

We describe a case of *Aspergillus* spondylodiscitis in a patient without apparent risk factors for invasive aspergillosis other than cryptogenic liver cirrhosis and diabetes mellitus.

Case report

A 69-year-old woman with a background history of cryptogenic liver cirrhosis (Child-Pugh score C) with portal hypertension (esophageal varices, ascites, splenomegaly), idiopathic thrombocytopenic purpura and diabetes mellitus type 2 on insulin therapy was first admitted to hospital in late November 2010 with a severe lower back pain of two weeks' duration. Three weeks before admission she had undergone abscess excision on the lower left limb with the administration of ciprofloxacin and clindamycin for 10 days. A few days after the procedure she started to complain of pain in the left thigh that later moved and developed to severe lower back pain. She denied having fever or shivers. On admission, the patient was afebrile, anicteric, her vital signs were normal. Her mobility was affected due to lower back pain. The abdomen was distended with signs of ascites, the lumbosacral spine region was tender to palpation. A small postoperative wound was present on the lower left limb without any signs of inflammation. The clinical examination was otherwise normal. Laboratory results showed an elevated C–reactive protein (CRP) of 90 mg/l (normal value ≤ 5 mg/l), normal erythrocyte sedimentation rate (ESR) of 20 mm/h, normal white blood-cell count of 7.6×10^9 cells/l, with slight neutrophilia in differential. *Staphylococcus aureus* resistant to penicillin but sensitive to all other tested antibiotics, ciprofloxacin and clindamycin included, was isolated from the post-operative wound on the left lower limb. The blood cultures remained sterile. Magnetic resonance imaging (MRI) of the thoracolumbar spine showed changes consistent with spondylodiscitis at the L5–S1 level. Some preexisting degenerative changes were present at one of the thoracic levels, but without signs of inflammation.

Because of the left lower limb wound isolation, *S. aureus* spondylodiscitis was suspected. The patient was initially treated with intravenous flucloxacilin. Due to allergic skin reaction, flucloxacilin was changed after four weeks to oral ciprofloxacin and clindamycin, which she took for another 9 weeks. During the antibiotic treatment the patient's condition improved, the lower back pain partially diminished, and she was capable of walking with a three-point corset. Neurological examination at the presentation and during hospitalization did not show any neurological deficits, muscular strength was within normal range. The patient was discharged after 8 weeks of antibiotic treatment, when laboratory values showed a CRP of 51 mg/l, normal white blood-cell count of 5.2×10^9 cells/l, with normal differential and an ESR of 12 mm/h.

In early May 2011 (3 months after discharge) the patient again complained of lower back pain. She did not experience any neurological deficits and denied fever. On admission, the laboratory values showed a normal leukocyte count of 5.16×10^9 cells/l, an elevated CRP of 127 mg/l and ESR of 82. MRI of the thoracolumbar spine was performed, which revealed signs of spondylodiscitis at the L5–S1 level, together with spondylodiscitis signs at the Th5–L1 levels with abnormal enhancement of disc spaces as well as associated end-plate destruction of vertebral bodies. Small epidural anterior abscess collection with a diameter of 2–3 mm was observed, extending from Th5 to L1 without spinal channel stenosis. Transpedicular biopsy of the discus at the L5–S1 and Th12–L1 levels was performed, and samples taken for microbiological and histopathological investigations. Histopathological findings at the L5–S1 level did not show any signs of inflammation, and the disc culture for bacteria including acid-fast bacilli and fungi was negative. At the Th12–L1 level histopathological examination of the disc tissue revealed a chronic to acute fibropurulent inflammation with hyphae seen on Grocott's methenamine silver stain. The disc culture was negative for bacteria, including acid-fast bacilli, but grew *Aspergillus fumigatus*. Susceptibility studies showed a minimum inhibitory concentration (MIC) of 0.125 µg/ml for voriconazole and an MIC of 0.094 µg/ml for amphotericin B. Serum galactomannan (2.06 ELISA index; negative value ≤ 0.5 ELISA index) as well as the serum beta D glucan test (> 500 pg/ml; negative value ≤ 59pg/ml) were positive. The blood cultures were sterile. Although at the time of admission

the chest radiograph revealed no infiltrates, a thorax computed tomography (CT) scan was performed, which, apart from mild interstitial oedema, revealed consolidations in the posterior part of the right upper pulmonary lobe and in the apical segments of the right lower pulmonary lobe with a small cavitation of approximately 7 ml in the latter, which could be interpreted as imaging findings of semi-invasive pulmonary aspergillosis. Because the patient did not have any respiratory symptoms, we did not perform any further diagnostic tests to confirm semi-invasive pulmonary aspergillosis such as bronchoscopy or biopsy of the affected area. The sinus cavity CT scan and heart echography were normal.

The therapy with voriconazole was started, initially with a loading dose of voriconazole 6 mg/kg intravenously every 12 hours for two doses. Due to liver failure, the maintenance dose was reduced to 150 mg (2 mg/kg) intravenously twice daily. Because of the absence of neurological deficits and/or spinal instability, surgical intervention was not indicated. After two weeks of voriconazole treatment, an important clinical and laboratory improvement was noted and after three weeks of intravenous voriconazole administration, the patient was discharged on oral voriconazole 150 mg twice daily. After 8 weeks of therapy the voriconazole dosage was lowered to 100 mg twice daily because of worsened liver function (increased liver function test values, episode of hepatic encephalopathy) and a slightly higher voriconazole serum trough level (performed by high performance liquid chromatography–5.5 mcg/ml). The control voriconazole serum trough level was within normal range (4.2 mcg/ml). We continued with voriconazole therapy for a total period of four months. At the end of this period, the patient was capable of independent walking with a three-point corset, with minimal back pain. At the last follow-up examination sixteen months after the discontinuation of voriconazole therapy in January 2013, she was feeling well and the laboratory results of CRP and ESR were within the normal range.

Discussion

Aspergillus osteomyelitis is an unusual presentation of invasive aspergillosis.[5] The most commonly reported site of *Aspergillus* bone infection is the spine, followed by long-bone infection. Similar to other forms of invasive aspergillosis, most cases of *Aspergillus* osteomyelitis occur in immunosuppressed patients, with the most common underlying condition being chronic granulomatous disease in children and the condition of immunosuppressive drug therapy for cancer, organ transplant, intravenous drug abuse and steroid use in adults. However, Vinas et al. found that 34.1 % (14/41) of *Aspergillus* spondylodiscitis cases reported in the literature until 1998 did not have any known predisposing factor or immunosuppression.[4] Another review of 43 cases of *Aspergillus* spondylodiscitis in immunocompetent patients was published recently.[6]

Hepatic failure was generally not recognized as a risk factor for invasive aspergillosis. But recently, several authors have reported the occurrence of invasive aspergillosis in patients with more subtle immune dysfunction, such as patients with COPD on corticosteroid therapy or liver cirrhosis.[7-10] Significant defects in neutrophil function and declines in peripheral CD4 lymphocyte counts, which both play an important role in host defence against *Aspergillus* in patients with Child-Pugh class B and C liver cirrhosis were described.[11,12] Our patient also had diabetes mellitus, a condition where phagocyte response can be impaired.[13]

Most *Aspergillus* spondylodiscitis cases follow hematogenous dissemination from the sinopulmonary tract. The disease rarely develops via contiguous spread from the lung or aortic focus, or occurs as a result of direct inoculation related to trauma, spinal surgery or epidural injection.[14] Although in immunocompetent patients direct inoculation or contiguous spread of infection is more common than in immunosuppressed patients, in the group of immunocompetent patients reviewed by Studemeister more than one half of the infections were acquired hematogenously,[14] which was probably the case in our patient.

Lumbar vertebrae are the most common site of *Aspergillus* vertebral infection (53.7 %), followed by the thoracic (46.3 %) and cervical spine (2.4 %). The involvement of multiple bones and joints is described in 21.9 % of the cases.[4] As in pyogenic vertebral osteomyelitis, back pain is the most common initial complaint of the *Aspergillus* vertebral osteomyelitis.[4,14] 29.3 % of the patients reviewed by Vinas had a neurological deficit at the presentation, and a paraspinal or epidural abscess was reported in 33 % (7/21) of immunocompetent patients.[14]

MRI is the most sensitive and specific imaging tool for diagnosing spondylodiscitis but is not specific for vertebral aspergillosis.[4] Positive histological or culture results from a tissue biopsy of a normally sterile and clinically or radiologically abnormal site consistent with an infectious disease process are currently the standard for diagnosing proven invasive aspergillosis.[15] Thus the diagnosis of *Aspergillus* spondylodiscitis depends on the isolation of *Aspergillus* from bone biopsy and histological documentation of typical hyphae.[4]

In our patient, not only was there extensive involvement of Th5 to L1 present, which was confirmed by the disc histopathology and culture as *Aspergillus* infection, but she had also had an episode of spondylodiscitis at a different (L5–S1) level some months before. Unfortunately, the etiological agent was not confirmed in the first episode, when empiric antibiotic therapy, which proved to be successful, was started without bone or disc biopsy. But in the second episode the histopathology result of the disc biopsy of the L5–S1 level did not show any signs of inflammation and the bacterial and fungal culture was negative. We concluded that in this previous episode pyogenic spondylodiscitis unrelated to the later episode of *Aspergillus* spondylodiscitis at the different level was successfully treated.

The drug of choice for invasive aspergillosis including osteomyelitis is voriconazole. Case reports and case series describe a successful use of voriconazole in bone infections[2,3] and the available data regarding voriconazole concentration in bone are encouraging.[16] However, voriconazole should be used cautiously in patients with severe liver failure[17] since it is potentially hepatotoxic and hepatically metabolized with only 5 % of the drug appearing unchanged in the urine. The standard loading dosing regimens followed by maintenance doses that are 50 % of the normal are therefore recommended for individuals with mild to moderate hepatic cirrhosis (Child-Pugh A and B). No data are available on the rate of clearance in individuals with severe liver cirrhosis, as was the case in our patient.[18]

The optimal duration of treatment for *Aspergillus* osteomyelitis has not been determined.[3] The published case reports of immunocompetent patients with *Aspergillus* spondylodiscitis describe long-term treatment with triazole agents[14] and some recommend treatment with voriconazole for at least 3–6 months with individualization in different cases.[2] The Infectious Diseases Society of America guidelines recommend a minimum treatment of 6–8 weeks in immunocompetent patients, which is considerably shorter than the treatment recommended for *Candida* bone infection, for which 6–12 months of antifungal treatment with fluconazole is indicated. For immunocompromised patients the consideration of long-term suppressive therapy or treatment throughout the duration of immunosuppression is recommended.[17]

Most authors recommend surgical treatment in the cases of advanced disease, spinal instability or if there are symptoms of spinal cord compression, and most patients in case series underwent surgical debridement and decompression of the spine.[14] The type and extent of surgery should be individualized. Some patients require percutaneous needle aspiration while others require laminectomy with abscess drainage and debridement with the possibility of autologous bone grafting.[4]

In conclusion, our case report adds to the knowledge about invasive aspergillosis in patients without the traditional risk factors and calls attention to the fact that liver cirrhosis could be one of the possible risk factors for *Aspergillus* spondylodiscitis. Our patient responded well to the treatment with voriconazole for a total period of four months. Because of the absence of neurolo-

gical deficits and advanced localized disease, surgical treatment was not employed. Sixteen months after the discontinuation of the antifungal therapy she was feeling well.

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