International Journal of Infectious Diseases 14 (2010) e433–e435

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Case report

Articular aspergillosis: case report and review of the literature

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ARTICLE INFO

Article history:
Received 3 February 2009
Received in revised form 1 May 2009
Accepted 24 May 2009

Corresponding Editor: Meinolf Karthaus, Munich, Germany

Keywords:
Aspergillus
Neutropenia
Septic arthritis
Articular aspergillosis

ABSTRACT

The incidence of invasive aspergillosis is increasing due to more frequent use of immunosuppressant agents in patients with autoimmune diseases, hematological malignancies, and solid organ and hematopoietic stem cell transplants. Invasive aspergillosis most commonly affects the lungs, sinuses, and brain. Aspergillosis affecting the musculoskeletal system is rare. We describe here a case of articular aspergillosis in a febrile neutropenic patient successfully treated with voriconazole and caspofungin, and briefly review the 10 cases of articular aspergillosis that have previously been described in the literature.

1. Introduction

The genus *Aspergillus* includes more than 35 species of saprophytic molds found throughout nature. Species capable of growing at 37 °C may cause invasive disease. Aspergilli are opportunistic pathogens, with *Aspergillus fumigatus* accounting for the majority of disease, followed by *Aspergillus flavus*.[1]

Patients at risk for invasive aspergillosis include those with acute myelogenous leukemia or myelodysplastic syndrome, patients undergoing hematopoietic stem cell transplantation, patients with solid organ transplants, and patients with prolonged immunosuppression.[2] Most commonly, Aspergillus causes pulmonary, sinonasal, and brain infections. Infections of the musculoskeletal system are rare. There was a 357% increase in mortality caused by invasive aspergillosis between 1980 and 1997.[3] This observation is most likely related to the increase in the number of transplant patients and immunocompromised patients from chemotherapy and steroid use.

Articular aspergillosis is uncommon. We describe here a case of septic articular aspergillosis in a neutropenic patient and review 10 cases of articular aspergillosis previously reported in the literature.

2. Case report

An 18-year-old male with mental retardation presented to a community hospital with complaints of paleness, fatigue, and hypersomnolence of two days duration. He was found to be anemic, with a hemoglobin of 33 g/l for which he was transfused 4 units of packed red blood cells. The patient was transferred to a tertiary care center for workup of his anemia where a bone marrow biopsy revealed the diagnosis of acute lymphoblastic leukemia. A broviac catheter was inserted in the right subclavian vein and the patient was given induction chemotherapy with daunorubicin, cyclophosphamide, and vincristine. Chest radiography revealed correct positioning of the broviac catheter and normal lung fields. On day 3 post-chemotherapy, he became neutropenic.

On day 9 post-chemotherapy, while neutropenic, he developed a fever of 38.7 °C. Intravenous ticarcillin/clavulanate, gentamicin, and vancomycin were started. All blood cultures were negative and there were no sites of infection evident on clinical examination. Though he remained neutropenic, his fever resolved after two days of antibiotic treatment. Eleven days later, he again developed a fever of 39.3 °C while on ticarcillin/clavulanate, gentamicin and vancomycin, with an absolute neutrophil count of 1.0×10^9/l. Ticarcillin/clavulanate and gentamicin were replaced with meropenem. Caspofungin was added because of the concern for an invasive fungal infection. At this time, the patient started complaining of right shoulder and neck pain with movement. Physical examination revealed significant swelling of the right arm. A venous duplex of the right arm was negative for deep vein thrombosis.

A computerized tomography (CT) of the right shoulder revealed an enhancing fluid collection, suggestive of a septic joint. The shoulder joint was aspirated and sent for culture. On the following day, a magnetic resonance imaging (MRI) of the right shoulder showed right arm skin thickening, subcutaneous stranding, muscle

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1201-9712/$36.00 – see front matter
doi:10.1016/j.ijid.2009.05.012

edema, enhancing right shoulder synovitis and moderate joint effusion, suggestive of cellulitis, myositis, synovitis, and septic arthritis of the right shoulder. At the time of the MRI, the results of the culture from the right shoulder aspirate revealed *Aspergillus flavus*. Creatine kinase levels were within the normal range.

Given the positive culture, caspofungin was replaced with intravenous voriconazole for the treatment of Aspergillus septic arthritis. An arthroscopy with right shoulder joint aspiration and a muscle biopsy were performed the day after the MRI of the right shoulder. The joint fluid was positive for *Aspergillus flavus* while the muscle biopsy was negative for inflammation and for fungus. The right subclavian broviac catheter was removed given that it was on the same side as the septic joint and it was thought that the catheter may have been the source of the Aspergillus. The tip culture was negative for Aspergillus. A CT scan of the chest was done at this time to search for a pulmonary source of Aspergillus. The chest CT scan demonstrated a 1.9 cm cavitated nodule in the right middle lobe compatible with aspergillosis. There was no evidence for a contiguous infiltration of the shoulder arising from the lung infection. Most likely, the pulmonary aspergillosis was the source of the aspergillosis in the shoulder joint that spread hematogenously.

As the patient continued to have ongoing fever of 38.3 °C after one day of voriconazole with no clinical improvement in the right arm, caspofungin was restarted for synergistic effect with voriconazole. The galactomannan index was positive at 4.45. The patient received a total of 18 days of meropenem, vancomycin, and caspofungin, and 16 days of intravenous voriconazole. The patient was afebrile and his right arm was clinically better after 15 days of voriconazole intravenous treatment. At this time, intravenous voriconazole was switched to the oral formulation. The patient was discharged home on oral voriconazole. The patient responded very well to his treatment and continues to take the oral voriconazole while on chemotherapy for his acute lymphoblastic leukemia. At follow-up one month after treatment there were no signs of recurrent aspergillosis.

3. Discussion

Musculoskeletal aspergillosis is rare. Although Aspergillus is present ubiquitously in the environment, humans are rarely infected with Aspergillus unless they are immunocompromised, where the lungs or the skin are the usual portal of entry for invasive infections. The presence of a cavitary lung lesion in this patient would suggest that the articular infection represented secondary spread to the shoulder joint from a primary pulmonary focus. This patient had multiple sources of exposure to Aspergillus spores. He was living in an apartment undergoing renovations and he had been hospitalized in a medical ward that was undergoing reconstruction during that time.

Articular aspergillosis is uncommon. A literature search using the databases MEDLINE and EMBASE (1996–current), provided 10 reported cases of articular aspergillosis in patients who were either immunocompromised, or had had surgical interventions or joint manipulation (Table 1). The keywords 'aspergillosis', 'joint', and 'articular' were used for the literature search.

We noted that it was uncommon for caspofungin or voriconazole to be used in the treatment of articular aspergillosis. However, many of the previously described cases of articular aspergillosis occurred during the time when amphotericin B was the first-line antifungal treatment for invasive aspergillosis. Voriconazole was shown to be more effective and better tolerated compared to amphotericin B in treating invasive aspergillosis in a study involving patients with hematologic malignancies.[4]

Voriconazole has been used to treat invasive aspergillosis in the musculoskeletal system. In the case report described by Denes et al.,[5] synovial fluid analysis was performed to measure the level of voriconazole while the patient was receiving intravenous therapy. Results of their biochemical studies showed that the level of voriconazole in the synovial fluid and bone tissue was sufficient to suggest that voriconazole provides acceptable treatment for articular aspergillosis.

Caspofungin has not been well studied to determine its role as a first-line antifungal treatment for invasive aspergillosis. In a previous study, patients with hematologic malignancies with neutropenia induced by chemotherapy were diagnosed with pulmonary aspergillosis and were treated with caspofungin. The overall response rate was 56%.[6] Currently, monotherapy with echinocandins is not recommended for invasive aspergillosis.[1]

In vitro and animal studies have shown that there is synergistic activity when echinocandins are combined with triazoles.[7] This synergy is expected as echinocandins and triazoles have antifungal activities that target different sites. Combination therapy with voriconazole and caspofungin has been studied in solid transplant patients with invasive aspergillosis and bone marrow transplant recipients.[8,9] The results from these studies are mixed. In solid organ transplant patients, patients treated with combination therapy had an improved 90-day survival.[7] A similar trend to

Table 1
Cases of articular aspergillosis described in the literature.

Age/sex [Ref.]	Medical comorbidities	Joint involved	Presence of dissemination	Treatment	Outcome
59 years/male [11]	Acute lymphoblastic leukemia	Right wrist	Yes	Itraconazole	Death
18 years/male [12]	None	Both knees, ankles and metacarpal-phalangeal joints	None	Itraconazole	Complete resolution
29 years/male [13]	Renal transplant	Knee	None	Amphotericin B, rifampin	Death
51 years/male [14]	Cirrhosis	Knee	None	Itraconazole and debridement	Complete resolution
69 years/male [14]	Vascular surgery	Knee	Yes	Amphotericin B and debridement	Complete resolution
88 years/male [15]	Arthroscopic subacromial decompression with open rotator cuff repair	Right shoulder	None	Voriconazole and debridement	Complete resolution
34 years/male [16]	Renal transplant	Left ankle	None	Amphotericin B with debridement and synovectomy	Complete resolution
64 years/male [17]	Bilateral lung transplant	Right ankle	Yes	Amphotericin B with debridement (no response), was then treated with posaconazole	Complete resolution
67 years/male [18]	Right parotid epidermoid carcinoma, post-resection and irradiation therapy	Right temporo-mandibular joint	None	Debridement and amphotericin B	Complete resolution
83 years/female [5]	Osteoarthritis	Knee	Not known	Amputation/ voriconazole	Death

improved survival was seen with bone marrow transplant patients at 90 days after therapy.[7] Importantly, however, both of these trials used retrospective controls, a practice that has come under fire recently with the observation that mortality with invasive aspergillosis has progressively declined over time.[9] Nevertheless, combination antifungal therapy with a triazole and echinocandin is not unreasonable in patients with severe Aspergillus infections who do not respond to single drug therapy, in the absence of evidence-based data. Moreover, previous studies have shown that there is synergistic antifungal activity with caspofungin and voriconazole combination therapy.[10]

There have not been many studies that provide guidelines for antifungal treatment in articular aspergillosis. Amphotericin B has commonly been used to treat Aspergillus infections, but has not been shown to have good penetration in bone and joint tissue. Therefore, it is recommended that amphotericin B be combined with a second antifungal agent for treating aspergillosis in the musculoskeletal system.[10] Triazoles have been shown to have sufficient anti-Aspergillus activity in bone and joint tissue, allowing this group of antifungal drugs to be used as monotherapy for treating articular aspergillosis. Echinocandins have not been shown to be effective as a single treating agent and their penetration into bone and joint tissue is not known. It is recommended that it be used in combination therapy with another antifungal agent that has good bone penetration.[10]

Aspergillosis should be suspected in patients who are neutropenic or immunocompromised and not responding to broad-spectrum antibiotics. This report emphasizes the importance of fluid cultures in immunocompromised patients with suspected septic arthritis and the need to consider initiating empirical antifungals in patients who are immunocompromised with a suspected fungal infection. Voriconazole has been shown to have sufficient penetration into synovial fluid and bone for the treatment of articular aspergillosis.

Conflict of interest: No conflict of interest to declare.

Acknowledgements

We would like to thank Dr Timothy Brewer and Dr Donald Sheppard for their support and for reviewing the manuscript.

References

1. Krishnan-Natesan S, Chandrasekar PH. Current and future therapeutic options in the management of invasive aspergillosis. *Drugs* 2008;**68**:265–82.
2. Rüping MJ, Vehreschild JJ, Cornely OA. Patients at high risk of invasive fungal infections: when and how to treat. *Drugs* 2008;**68**:1941–62.
3. McNeil MM, Nash SL, Hajjeh RA, Phelan MA, Conn LA, Plikaytis BD, et al. Trends in mortality due to invasive mycotic diseases in the United States, 1980-1997. *Clin Infect Dis* 2001;**33**:641–7.
4. Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW, et al. Invasive Fungal Infections Group of the European Organization for Research and Treatment of Cancer and Global Aspergillus Study Group. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 2002;**347**:408–15.
5. Denes E, Bournediene A, Durox H, Oksman A, Saint-Marcoux F, Darde ML, et al. Voriconazole concentration in synovial fluid and bone tissues. *J Antimicrob Chemother* 2007;**59**:818.
6. Candoni A, Mestroni R, Damiani D, Tiribelli M, Michelutti A, Silvestri F, et al. Caspofungin as first-line therapy of pulmonary invasive fungal infections in 32 immunocompromised patients with hematologic malignancies. *Eur J Haematol* 2005;**75**:227–33.
7. Marr KA, Boeckh M, Carter RA, Kim HW, Corey L. Combination antifungal therapy for invasive aspergillosis. *Clin Infect Dis* 2004;**39**:797–802.
8. Singh N, Limaye AP, Forrest G, Safdar N, Muñoz P, Pursell K, et al. Combination of voriconazole and caspofungin as primary therapy for invasive aspergillosis in solid organ transplant recipients: a prospective, multicenter, observational study. *Transplantation* 2006;**81**:320–6.
9. Upton A, Kirby KA, Carpenter P, Boeckh M, Marr KA. Invasive aspergillosis following hematopoietic cell transplantation: outcomes and prognostic factors associated with mortality. *Clin Infect Dis* 2007;**44**:531–40.
10. Kirby A, Hassan I, Burnie J. Recommendations for managing Aspergillus osteomyelitis and joint infections based on a review of the literature. *J Infect* 2006;**52**:405–14.
11. Gunsilius E, Lass-Flörl C, Mur E, Gabl C, Gastl G, Petzer AL. Aspergillus osteoarthritis in acute lymphoblastic leukemia. *Ann Hematol* 1999;**78**:529–30.
12. Mekan SF, Saeed O, Khan JA. Invasive aspergillosis with polyarthritis. *Mycoses* 2004;**47**:518–20.
13. Alvarez L, Calvo E, Abril C. Articular aspergillosis: case report. *Clin Infect Dis* 1995;**20**:457–60.
14. Steinfeld S, Durez P, Hauzeur JP, Motte S, Appelboom T. Articular aspergillosis: two case reports and review of the literature. *Br J Rheumatol* 2007;**36**:1331–4.
15. Sohail MR. *Aspergillus fumigatus* septic arthritis complicating intra-articular corticosteroid injection. *Mayo Clin Proc* 2004;**79**:578–9.
16. Ersoy A, Akdag I, Akalin H, Sarisozen B, Ener B. Aspergillosis osteomyelitis and joint infection in a renal transplant recipient. *Transplant Proc* 2007;**39**:1662–3.
17. Lodge BA, Ashley ED, Steele MP, Perfect JR. *Aspergillus fumigatus* empyema, arthritis, and calcaneal osteomyelitis in a lung transplant patient successfully treated with posaconazole. *J Clin Microbiol* 2004;**42**:1376–8.
18. Lo WL, Chang CS, Yang AH, Kao SY. Apergillosis of the temporomandibular joint following irradiation of the parotid region: a case report. *Int J Oral Maxillofac Surg* 2003;**32**:560–2.