Aspergillus Vertebral Osteomyelitis in Immunocompetent Hosts: Role of Triazole Antifungal Therapy

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Background. A review of published cases, in addition to a recently treated patient, is presented that describes the clinical features and outcomes of triazole therapy for vertebral aspergillosis in immunocompetent patients.

Methods. Using the Medline database, cases of vertebral aspergillosis in immunocompetent patients treated with triazole were reviewed. Clinical and radiological findings, therapeutic interventions, and outcomes were analyzed.

Results. Twenty-one cases of vertebral aspergillosis treated with itraconazole or voriconazole were identified. Most cases were caused by Aspergillus fumigatus. The most common presenting symptom was back pain. The majority of cases were acquired by hematogenous infection, although one-quarter occurred after a spinal procedure. Most patients were treated successfully with a combination of antifungal therapy and surgery. Patients presenting with paraplegia had a poor outcome. The overall mortality rate was 20%.

Conclusions. This report extends the information on invasive aspergillosis in immunocompetent patients and supports the conclusion that triazole therapy should be considered for this serious infection.

Aspergillus osteomyelitis has been recognized as an emerging extrapulmonary manifestation of invasive aspergillosis [1]. In the last review of vertebral aspergillosis in this journal, published in 1999, Vinal et al. [2] reported, surprisingly, that 34% of cases were in individuals who did not have any predisposing factor or immunosuppression. Their reported mortality rate in non-immunosuppressed patients was ~30%, which is not far from the case fatality rate of 49% associated with severe diseases, such as leukemia and lymphoma [3]. Since this publication, there has been significant advancement in antifungal therapy, including the development of more triazole agents.

Since the initial report [4] (and another report of a patient regarded as immunocompetent, although he had once received 5 days of high-dose steroids and had received multiple transfusions to treat sideroblastic anemia [5]), more cases of vertebral aspergillosis occurring in immunocompetent patients and treated with triazole agents have been reported (Table 1). However, only a limited amount of information related to antifungal treatment of these complex cases has been described in these reports. To understand the management of vertebral aspergillosis in immunocompetent hosts in the era of triazole therapy more fully, a detailed case report is presented, along with a description of clinical characteristics and treatment outcomes of published cases involving immunocompetent patients treated with triazole therapy.

METHODS

Cases of vertebral aspergillosis in immunocompetent patients who were treated with triazole agents were identified through a Medline database search of the English language literature, and the reference lists were reviewed for additional cases. Cases associated with any immunosuppressive condition, such as human immunodeficiency virus (HIV) infection, hematological malignancy, or transplantation, as well as administration of any immunosuppressive medication (including
systemic or inhaled corticosteroid therapy), were excluded, as were patients with diabetes mellitus, a condition where phagocyte defense responses may be impaired. Clinical and radiological findings, therapeutic interventions, and outcomes were analyzed.

**CASE REPORT**

A 52-year-old woman was admitted to the hospital in February 2009 with severe lower back pain and 10-pound weight loss of 2 months’ duration. Her history consisted of successful treatment for pulmonary tuberculosis at 9 years of age. In addition, she had a 5-year history of intermittent cough and hemoptysis. The patient did not have any metabolic disorder, including diabetes mellitus, history of smoking, or illicit drug use. Quantitative immunoglobulins, neutrophil oxidative burst assay by flow cytometry, and T-helper lymphocyte cell count were normal. A serologic test for HIV had negative results.

A magnetic resonance image (MRI) of the lumbar spine showed bone destruction and end-plate destruction at the L4–5 level and abnormal enhancement of L2–3 and L4–5 vertebral bodies consistent with osteomyelitis and discitis (Figure 1). Computed tomography (CT) of the chest demonstrated a 7.1 × 5.6 × 4-cm lung mass in the left upper lobe medially abutting the mediastinum with multiple punctate calcifications (Figure 2). The patient’s sedimentation rate was 108 mm/h. Sputum culture grew *Aspergillus fumigatus*.

The patient underwent decompressive laminectomy and diskectomy of L4–5. Intraoperatively, she was found to have markedly soft bone associated with purulent fluid. Histopathological examination of disk tissue demonstrated chronic inflammatory cells and septated fungal hyphae. Cultures from the vertebral tissue grew *A. fumigatus*. Susceptibility studies by macrobroth dilution (Clinical Laboratory Standards Institute methodology) showed minimum inhibitory concentration (MIC) of ≤0.5 μg/mL, and minimum fungicidal concentration

### Table 1. Clinical characteristics of immunocompetent patients with vertebral aspergillosis treated with triazole agents

<table>
<thead>
<tr>
<th>Patient</th>
<th>Reference, year</th>
<th>Age, years</th>
<th>Sex</th>
<th>Spine level</th>
<th>Presenting symptom</th>
<th>Radiological findings</th>
<th>Antifungal treatment</th>
<th>Surgery</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[4], 1989</td>
<td>72</td>
<td>M</td>
<td>T10–11</td>
<td>Back pain</td>
<td>Osteomyelitis</td>
<td>Itr</td>
<td>Debridement, bone graft</td>
<td>CR</td>
</tr>
<tr>
<td>2</td>
<td>[6], 1991</td>
<td>46</td>
<td>M</td>
<td>L4–5</td>
<td>Back pain</td>
<td>Discitis, mass</td>
<td>AmB, Itr</td>
<td>Debridement</td>
<td>CR</td>
</tr>
<tr>
<td>3</td>
<td>[7], 1992</td>
<td>34</td>
<td>M</td>
<td>L3–4</td>
<td>Back pain, weight loss, numbness</td>
<td>Discitis, osteomyelitis</td>
<td>AmB, Itr</td>
<td>Debridement</td>
<td>CR</td>
</tr>
<tr>
<td>4</td>
<td>[8], 1994</td>
<td>62</td>
<td>M</td>
<td>L2–3</td>
<td>Back pain</td>
<td>Discitis</td>
<td>Itr</td>
<td>None</td>
<td>CR</td>
</tr>
<tr>
<td>5</td>
<td>[8], 1994</td>
<td>54</td>
<td>M</td>
<td>L1–5</td>
<td>Back pain</td>
<td>Discitis</td>
<td>AmB, 5-FC, Itr</td>
<td>None</td>
<td>CR</td>
</tr>
<tr>
<td>6</td>
<td>[9], 1998</td>
<td>60</td>
<td>M</td>
<td>T11–12</td>
<td>Neural pain, spasticity</td>
<td>Discitis, osteomyelitis</td>
<td>AmB, 5-FC, Itr</td>
<td>Debridement, bone graft</td>
<td>CR</td>
</tr>
<tr>
<td>7</td>
<td>[10], 2002</td>
<td>34</td>
<td>F</td>
<td>C6–T1</td>
<td>Neck mass</td>
<td>Epidural mass</td>
<td>AmB, Itr</td>
<td>Resection</td>
<td>PR</td>
</tr>
<tr>
<td>8</td>
<td>[11], 2003</td>
<td>52</td>
<td>M</td>
<td>L2–3</td>
<td>Back pain, fusion</td>
<td>Discitis, osteomyelitis</td>
<td>L-AmB, Vor</td>
<td>Fusion, bone graft</td>
<td>CR</td>
</tr>
<tr>
<td>9</td>
<td>[12], 2004</td>
<td>68</td>
<td>M</td>
<td>T1–3</td>
<td>Paraplegia</td>
<td>Osteomyelitis, epidural abscess</td>
<td>AmB, Itr</td>
<td>Debridement</td>
<td>Death</td>
</tr>
<tr>
<td>10</td>
<td>[13], 2004</td>
<td>50</td>
<td>F</td>
<td>L4–5</td>
<td>Back pain, sciatica</td>
<td>Discitis</td>
<td>Itr</td>
<td>Debridement</td>
<td>CR</td>
</tr>
<tr>
<td>11</td>
<td>[14], 2004</td>
<td>35</td>
<td>F</td>
<td>T11</td>
<td>Paraplegia</td>
<td>Osteomyelitis, epidural abscess</td>
<td>AmB, Itr</td>
<td>Corpectomy, graft, internal fixation</td>
<td>Death</td>
</tr>
<tr>
<td>12</td>
<td>[15], 2005</td>
<td>76</td>
<td>M</td>
<td>C5–T2</td>
<td>NA</td>
<td>Discitis, osteomyelitis, epiduritis</td>
<td>AmB, Itr, Vor</td>
<td>NA</td>
<td>CR</td>
</tr>
<tr>
<td>13</td>
<td>[15], 2005</td>
<td>62</td>
<td>M</td>
<td>Spine</td>
<td>NA</td>
<td>Discitis</td>
<td>AmB, 5-FC, Vor</td>
<td>NA</td>
<td>PR</td>
</tr>
<tr>
<td>14</td>
<td>[16], 2006</td>
<td>57</td>
<td>M</td>
<td>L2–3</td>
<td>Erythema</td>
<td>Loose bone graft</td>
<td>Vor</td>
<td>Debridement</td>
<td>CR</td>
</tr>
<tr>
<td>15</td>
<td>[17], 2007</td>
<td>49</td>
<td>F</td>
<td>T8–9</td>
<td>Back pain</td>
<td>Discitis, paravertebral abscess</td>
<td>Vor</td>
<td>Debridement, bone graft</td>
<td>PR</td>
</tr>
<tr>
<td>16</td>
<td>[18], 2007</td>
<td>51</td>
<td>F</td>
<td>L4–5</td>
<td>Back pain, paraplegia</td>
<td>Discitis, paravertebral abscess</td>
<td>AmB, Caf, Vor</td>
<td>None</td>
<td>Death</td>
</tr>
<tr>
<td>17</td>
<td>[19], 2008</td>
<td>65</td>
<td>M</td>
<td>T1–6</td>
<td>Paraplegia</td>
<td>Osteomyelitis, epidural mass</td>
<td>Vor, Caf, AmB, L-AmB, Pos</td>
<td>None</td>
<td>Death</td>
</tr>
<tr>
<td>18</td>
<td>[20], 2009</td>
<td>44</td>
<td>F</td>
<td>T8–9</td>
<td>NA</td>
<td>Osteomyelitis</td>
<td>Vor</td>
<td>Surgery</td>
<td>PR</td>
</tr>
<tr>
<td>19</td>
<td>[20], 2009</td>
<td>46</td>
<td>F</td>
<td>T8–9</td>
<td>NA</td>
<td>Osteomyelitis</td>
<td>Vor</td>
<td>Surgery</td>
<td>PR</td>
</tr>
<tr>
<td>20</td>
<td>[20], 2009</td>
<td>48</td>
<td>F</td>
<td>T4</td>
<td>NA</td>
<td>Osteomyelitis</td>
<td>L-AmB, Vor</td>
<td>Surgery</td>
<td>PR</td>
</tr>
<tr>
<td>21</td>
<td>Present case</td>
<td>54</td>
<td>F</td>
<td>L2–5</td>
<td>Back pain, weight loss</td>
<td>Discitis, osteomyelitis</td>
<td>Vor</td>
<td>Debridement, internal fixation</td>
<td>CR</td>
</tr>
</tbody>
</table>

**NOTE.** AmB, amphotericin B; C, cervical; Caf, caspofungin; CR, complete response; Itr, itraconazole; L, lumbar; L-AmB, liposomal amphotericin B; NA, not available; Pos, posaconazole; PR, partial response; T, thoracic; Vor, voriconazole; 5-FC, 5-fluorocytosine.
(MFC) of \( \leq 0.5 \mu\text{g/mL} \) for voriconazole. Vertebral and sputum cultures for acid fast bacilli were negative.

The patient was treated with intravenous voriconazole (4 mg/kg maintenance dose) for a total of 6 weeks followed by oral administration (200 mg every 12 h). Her sedimentation rate returned to normal. A voriconazole serum trough level was 2.4 \( \mu\text{g/mL} \) while receiving intravenous voriconazole and 3.3 \( \mu\text{g/mL} \) while receiving oral voriconazole. She developed abnormal liver function test results, which normalized after decreasing voriconazole dosage to 150 mg every 12 h. A trough voriconazole blood level while receiving this dosage was 2.3 \( \mu\text{g/mL} \). The patient continued to receive this dosage for the remainder of her therapy.

The patient had persistent cough and hemoptysis and developed disabling back pain. Two months after the original surgery, she underwent left upper lobectomy with removal of her aspergilloma, followed by fusion of L4–5 and L1–2 with internal rod stabilization. Intraoperative fungal cultures remained sterile. Following the surgical procedure, the patient’s back pain resolved completely, and she completed a total of 6 months of oral voriconazole therapy. She has remained without signs or symptoms of residual disease 1 year after discontinuation of voriconazole.

**RESULTS**

A detailed summary of 21 cases of vertebral aspergillosis in immunocompetent patients, including our case (case 21), is presented in Table 1, arranged chronologically. There were 12 men (57%) and 9 women, with a mean age of 53 years (range, 34–76 years). Except for 2 cases, all infections were caused by *A. fumigatus*. *Aspergillus niger* and *Aspergillus flavus* were associated with traumatic injury (case 7) and illicit intravenous drug use (case 19), respectively.

Most patients (52%) acquired their infection by a presumed hematogenous route (Table 2). Vertebral aspergillosis following spondylodesis with internal fixation (case 6), discectomy (cases 2 and 10), fusion and internal fixation (case 14), and epidural corticosteroid injection (case 16) were reported. In only 1 case, believed to be acquired hematogenously (case 20), was there a known underlying spinal disease (chondrosarcoma). The most common presenting symptom was back pain. Most patients presented with discitis or osteomyelitis at 1 or more levels of the cervical, thoracic, or lumbar spine. Paraspinal or epidural abscess, or mass, were reported in 7 cases (33%). Eighty-one percent of patients, most of whom underwent surgical procedures, had a favorable response to triazole therapy. Death occurred in 4 cases and was associated with multiorgan failure. All patients who died had developed paraplegia. Reported residual effects following antifungal therapy included back pain (cases 8 and 15), kyphosis (cases 6 and 15), and limb weakness (cases 10 and 17).

Thirteen patients also received therapy with amphotericin B, ranging from 1 week to 2 months in duration. Amphotericin was discontinued in one-third of these cases (cases 2, 8, 9, and 11) because of toxicity. Triazole therapy was tolerated by all patients,
except for 1 patient who developed photosensitivity rash due to voriconazole at the end of his course of treatment (case 8). Seven patients received exclusively itraconazole or voriconazole, and all of these patients had favorable responses. The duration of triazole therapy in successful cases ranged from 1 month to ≥12 months. One patient experienced relapse of infection after a 10-week course of itraconazole (case 2).

**DISCUSSION**

Vertebral aspergillosis can be classified into 3 major categories, depending on the mode of acquisition. Direct inoculation related to trauma, spinal surgery, or epidural injection occurs rarely and manifests generally within months after the procedure [6, 11, 19]. Contiguous spread from pleuropulmonary disease generally affects the thoracic spine [13]. Hematogenous infection arising from a pulmonary focus occurs mainly in immunosuppressed patients and is caused almost exclusively by *A. fumigatus* [2]. Hematogenously acquired *A. flavus* and *Aspergillus terreus* vertebral osteomyelitis has been associated with illicit intravenous drug use [20, 21]. Reported cases of vertebral aspergillosis in immunocompetent hosts were caused almost exclusively by *A. fumigatus*. Most were acquired hematogenously, although one-quarter occurred following a spinal procedure. Three of the cases (9, 17 and 21) illustrate that, although rare, vertebral osteomyelitis can be a serious complication of pulmonary aspergillosis, either by direct extension or hematogenous spread from a pulmonary focus. Interestingly, our patient had a distant history of pulmonary tuberculosis, which may have led to the development of an aspergilloma in an area of cavitary pulmonary disease. In the appropriate setting, vertebral osteomyelitis secondary to aspergillosis needs to be considered in the immunocompetent patient with chronic back pain.

Although none of the reported cases of vertebral aspergillosis were in individuals who had conditions known to predispose to invasive aspergillosis, the morbidity associated with this infection was substantial. Back pain was the most common presenting symptom. Most patients developed discitis and osteomyelitis at 1 or multiple vertebral levels. More than one-half of the patients had complete responses, and nearly another one-third had partial response to the treatment rendered. Several patients developed persistent back pain, kyphosis, or neurological deficit. The mortality rate was 19% in this group of immunocompetent patients, all of whom had triazole therapy as part of their course. The mortality rate of the immunocompetent patients reviewed by Vinas et al [2] was ~30%, and none of the patients who died received triazole therapy. In both series, the prognosis of patients who developed paraplegia was poor, and deaths were often associated with multiple organ failure, sepsis, and other medical complications.

The innate immune system protects immunocompetent hosts from invasive aspergillosis [22]. Nevertheless, several reviews describe invasive aspergillosis in immunocompetent hosts causing invasive sinus disease in atopic individuals, invasive pulmonary disease following heavy inoculum exposure or influenza infection, and cerebral aspergillosis from sinonasal extension of disease [23–25]. Invasive aspergillosis in critically ill patients has been described and has been attributed to sepsis-related immunoparalysis or phagocytic dysfunction [26]. Although genetic polymorphisms may account for host susceptibility to invasive aspergillosis, the immunopathogenesis of invasive aspergillosis in some immunocompetent hosts remains unexplained [27].

Complications related to amphotericin therapy occurred in one-third of cases treated with this antifungal agent. On the other hand, triazole therapy was tolerated in all cases, except for 1 patient who developed photosensitivity due to voriconazole. Itraconazole and voriconazole blood levels were monitored in 3 successful cases. Because of the uncertain bioavailability of oral itraconazole, monitoring of itraconazole blood levels is recommended [28]. Pascual et al [29] demonstrated the usefulness of pharmacotherapeutic drug monitoring for safe and effective administration of voriconazole. Our patient developed hepatotoxicity that resolved after the dosage of voriconazole was decreased (while safe therapeutic serum levels were maintained).

The Infectious Diseases Society of America (IDSA) guidelines recommend either amphotericin or voriconazole for the treatment of *Aspergillus* osteomyelitis, whereas the British Infection Society recommends amphotericin in combination with

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**Table 2. Reported modes of acquisition of vertebral aspergillosis in immunocompetent patients**

<table>
<thead>
<tr>
<th>Mode of acquisition</th>
<th>No. (%) of cases (n = 21)</th>
<th>Case number(s)</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma</td>
<td>1 (5)</td>
<td>7</td>
<td><em>Aspergillus fumigatus</em>, <em>Aspergillus niger</em></td>
</tr>
<tr>
<td>Spinal surgery/procedure</td>
<td>5 (24)</td>
<td>2, 6, 10, 14, 16</td>
<td><em>A. fumigatus</em></td>
</tr>
<tr>
<td>Contiguous spread</td>
<td>2 (10)</td>
<td>9, 17</td>
<td><em>A. fumigatus</em></td>
</tr>
<tr>
<td>Hematogenous</td>
<td>11 (52)</td>
<td>1, 3, 4, 5, 8, 11, 15, 18, 19, 20, 21</td>
<td><em>A. fumigatus</em>, <em>Aspergillus flavus</em></td>
</tr>
</tbody>
</table>

**NOTE.** Modes of acquisition were not recorded for 2 (10%) of cases (cases 12 and 13). Hematogenous spread was implied when no obvious primary site of infection was identified (cases 1, 3, 4, 8, 11, 18, and 20) or when the case was associated with endocarditis (case 5), intravenous drug use (cases 15 and 19), or mycetoma (21).
flucytosine for treatment of serious *Aspergillus* osteomyelitis and recommends itraconazole for the treatment of stable patients [30, 31]. Amphotericin alone has been used successfully for treatment of immunocompetent patients with vertebral aspergillosis [32]. However, the superiority of voriconazole over amphotericin B deoxycholate for primary therapy of invasive aspergillosis has been demonstrated [33]. Both itraconazole and voriconazole are less toxic than amphotericin B, can be administered orally, and achieve bone concentrations above the usual *Aspergillus* MIC [4, 34, 35]. In addition, triazole serum drug levels can be monitored to allow for safe and efficacious administration. Few reports describe the use of posaconazole for *Aspergillus* osteomyelitis [36, 37]. Direct comparison of amphotericin versus azoles is not possible because of possible publication bias, variable use of adjunctive surgery, use of multiple chemotherapy agents in the majority of cases, and uncertainty as to whether some agents may have been preferentially used in cases of different acuity. However, 8 patients received only azoles as their chemotherapy, and their tally of 5 patients with complete response and 3 patients with partial response compares favorably with the outcomes for the remaining patients, which included 4 deaths.

The length of antifungal therapy for vertebral aspergillosis has not been established. The IDSA guidelines recommend a minimum of 6–8 weeks of antifungal therapy in non-immunocompromised patients with *Aspergillus* osteomyelitis [30]. The recommended length of therapy in the IDSA guidelines for *Candida* osteomyelitis is 6–12 months [38]. Published case reports of immunocompetent patients with vertebral aspergillosis describe long-term administration of triazole agents (Table 1). One patient’s osteomyelitis relapsed after 10 weeks of primary therapy with itraconazole (case 2). Our patient was treated successfully with a 6-month course of voriconazole. Voriconazole was initially administered intravenously because of the severity and extent of the infection, lack of comparative efficacy studies, and initial concerns regarding variability of serum drug levels. Once the patient’s vertebral infection was stabilized and her mycetoma was resected, she safely completed her treatment with oral voriconazole. In light of the favorable response to oral voriconazole in the latter part of her treatment, a shorter course of intravenous voriconazole may have been reasonable.

Most patients in our series underwent surgical debridement and decompression of the spine. Only 2 evaluable patients received antifungal therapy alone that resulted in complete response. Most authors favor surgical treatment if there is advanced disease or neurological impairment [39]. Vertebral aspergillosis can result in severe destruction of the spine and lead to kyphosis and spinal instability. Some patients, including ours, required spine stabilization with fusion or fixation. Although separating the individual roles of surgery and antifungal therapy was not possible, most patients who received combined surgical and medical therapy had favorable outcome. In summary, our review of reported cases of vertebral aspergillosis in immunocompetent patients supports the use of triazole antifungal therapy in treating this serious and life-threatening infection.

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### References