CASE REPORT

Invasive Pulmonary Aspergillosis in the Epidural Space in a Patient with Acute Myelogenous Leukemia with Myelodysplasia-related Changes: A Case Study and Literature Review of Vertebral Aspergillosis in Japan

Ryohei Ono, Shuku Sato, Satomi Okada, Emiko Kanbe, Eri Tanaka and Yotaro Tamai

Abstract:
Vertebral aspergillosis is a rare infectious disease with a high mortality rate. We herein report a 70-year-old woman with acute myelogenous leukemia with myelodysplasia-related changes, nontuberculous mycobacteriosis, and bronchiectasis who presented with a fever and cough. Her clinical symptoms and laboratory test results suggested febrile neutropenia and pneumonia. However, her clinical course was further complicated by lower extremity weakness. Magnetic resonance imaging of the spine showed consolidation contiguously spreading toward the epidural space between the T4 and T5. Cytological testing of the pleural effusion revealed Aspergillus fumigatus. We also review and summarize previously reported cases of vertebral aspergillosis in Japan.

Key words: vertebral aspergillosis, AML/MRC, review, aspergillus fumigatus, epidural mass

Introduction

Invasive pulmonary aspergillosis generally occurs in patients with severe immunodeficiency and can be a major cause of morbidity and mortality (1). Aspergillus osteomyelitis is a debilitating and severe form of invasive aspergillosis, but it is extremely rare with a high mortality rate (2, 3). Vinas et al. (4) and Studemeister et al. (5) reviewed the literature on 41 and 21 previous aspergillus vertebral osteomyelitis cases, respectively. However, only Japanese reports of vertebral aspergillosis cases have been published, and we found none of these Japanese case reports in the English literature. We searched PubMed and Japana Centra Revuo Medicina (Igaku-Chuo-Zasshi), which is a database for Japanese medical journals, to identify case reports of vertebral aspergillosis in Japan and found 27 cases reported from 1972 to 2017 (6-31).

We herein report a rare case of invasive pulmonary aspergillosis spreading to the epidural space in a patient with acute myelogenous leukemia with myelodysplasia-related changes (AML/MRC). Previously reported cases of vertebral aspergillosis in Japan were also reviewed and summarized.

Case Report

A 70-year-old Japanese woman presented with a fever and chronic cough that had developed 1 week before admission. She had been diagnosed with nontuberculous mycobacteriosis of Mycobacterium avium and bronchiectasis with chronic cough at 30 years of age and acute myelogenous leukemia with myelodysplasia-related changes (AML/MRC) 20 months earlier. She was subsequently treated with a cycle of low-dose cytarabine, aclarubicin hydrochloride, and granulocyte colony-stimulating factor (CAG regimen) along with 15 cycles of azacitidine regimen. The azacitidine regimen had been performed seven days earlier, and a slight fever was noted. Her familial history was unremarkable.

The patient was slightly drowsy upon arrival, but her Glasgow Coma Score was 15. Her blood pressure, pulse, body temperature, and respiratory rate were 84/53 mmHg, 92 beats/min, 37.1°C, and 22 cycles/min, respectively. Her...
Table 1. Summary of Laboratory Data upon Admission.

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Blood chemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC 100 /µL</td>
<td>TP 5.1 g/dL</td>
</tr>
<tr>
<td>Neutro 14.3 %</td>
<td>Alb 2.0 g/dL</td>
</tr>
<tr>
<td>Lym 78.6 %</td>
<td>AST 12 U/L</td>
</tr>
<tr>
<td>Mono 7.1 %</td>
<td>ALT 40 U/L</td>
</tr>
<tr>
<td>RBC 255 10^6/µL</td>
<td>LDH 116 U/L</td>
</tr>
<tr>
<td>Hb 7.4 g/dL</td>
<td>ALP 621 U/L</td>
</tr>
<tr>
<td>Ht 21.5 %</td>
<td>T-Bil 1.1 mg/dL</td>
</tr>
<tr>
<td>MCV 84.3 fl</td>
<td>BUN 21.4 mg/dL</td>
</tr>
<tr>
<td>Plt 0.6 10^9/µL</td>
<td>Cre 0.66 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Na 133 mEq/L</td>
</tr>
<tr>
<td></td>
<td>K 3.4 mEq/L</td>
</tr>
<tr>
<td></td>
<td>Cl 97 mEq/L</td>
</tr>
<tr>
<td></td>
<td>Ca 8.8 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Mg 1.7 mg/dL</td>
</tr>
<tr>
<td></td>
<td>IP 4.0 mg/dL</td>
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<tr>
<td></td>
<td>Ferritin 4,371 ng/mL</td>
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<td></td>
<td>CRP 34.3 mg/dL</td>
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<tr>
<td></td>
<td>Procalcitonin 9.2 ng/mL</td>
</tr>
<tr>
<td></td>
<td>β-D-glucan 36.5 pg/mL</td>
</tr>
<tr>
<td></td>
<td>Aspergillus antigen (0.5)</td>
</tr>
</tbody>
</table>


Figure 1. Chest roentgenogram showing bilateral infiltrations.

Figure 2. Computed tomography image of the chest showing the consolidation with lesions at the right upper and lower lobe, left lingular lobe, and lower lobe (red arrows).

height and weight were 156.0 cm and 36.8 kg, respectively. A physical examination revealed conjunctival pallor, furry tongue, generalized purpura, and coarse crackles at the right upper lobe. Her extremities were warm. Laboratory studies demonstrated pancytopenia and elevation of C-reactive protein (CRP) levels. In addition, serum β-D-glucan (measured by the kinetic colorimetric assay called Fungitec G-Test MK) and aspergillus antigen levels were elevated (Table 1). A sputum culture was only positive for Staphylococcus epidermidis, which is a normal flora species.

Chest roentgenogram and computed tomography (CT) of the chest showed consolidation with lesions in right S3 and S6 and left S3, S4, and S6 (Fig. 1, 2). The right S6 lesion was located at the level of the T5 vertebra. The patient was initially diagnosed with febrile neutropenia, bilateral pneumonia, and oral candida infection, which were treated with the granulocyte-colony stimulating factor ceftazidime (CFPM) 4 g/day and liposomal amphotericin B (L-AMB) 2.5 mg/kg/day. On day 2, Pseudomonas aeruginosa was detected in the patient’s blood culture, and the fever had not abated. Antibiotic therapy was escalated to meropenem (MEPM) 3 g/day based on the results of the antibiogram on day 4. However, on the same day, she complained of right lower leg weakness, although she was able to walk. On day 6, she developed right hemiplegia and left thermal hypalgesia in the T6 level, presenting as Brown-Sequard syndrome-like symptoms.

Her brain computed tomography (CT) findings were unremarkable. Magnetic resonance imaging (MRI) of the thoracic and lumbar spine showed that consolidation was contiguously spreading toward the epidural space at the level between the T4 and T5 (Fig. 3). Although radiological findings demonstrated discitis, osteomyelitis, and an epidural mass at the same levels, the patient was not given surgical treatment due to her poor condition. On day 7, the patient developed paraplegia, absent bilateral lower tendon reflexes, and bladder and rectal disturbance; thus, contrast CT of the chest and abdomen was performed (Fig. 4). The results showed bilateral hydropneumonia, intestinal gas accumulation,
and an infiltrative epidural tumor secondary to pulmonary consolidation. We immediately performed CT-guided thoracentesis from the back to examine the tumor in right S6 (Fig. 5), and cytology of the right pleural effusion and the mass detected the presence of *Aspergillus fumigatus*, which was confirmed based on the morphology and real-time polymerase chain reaction for *A. fumigatus* DNA (geniQ\textsuperscript{\textregistered}; KITASATO-OTSUKA Biomedical Assay Laboratories Company, Ltd., 1-15-1, Kitasato, Minami-ku, Sagamihara-city, Kanagawa, Japan) (5,000 copies/mL, normal range: <40 copies/mL) (Fig. 6).

A diagnosis of vertebral aspergillosis was made, so miconafungin (MCFG) 200 mg/day was added, and the dose of L-AMB was increased to 4.0 mg/kg/day on day 8. On day 9, drainage tubes were inserted under CT-guided thoracentesis, and saline perfusion was also performed using drainage tubes. Intravenous voriconazole (VRCZ) 6 mg/kg was administered every 12 hours on day 10 instead of L-AMB and MCFG and subsequently decreased to 4 mg/kg twice daily, but the patient died 14 days after hospital admission due to uncontrolled infection and multiple organ failure, including disseminated intravascular coagulation. During the hospitalization, the patient’s pancytopenia, elevated CRP, and fever never improved (Fig. 7). Catheter tip cultures of drainage tubes were also positive for *A. fumigatus*.

**Discussion**

*Aspergillus* spp. have emerged as major causes of morbidity and mortality in immunocompromised hosts. Patients with osteomyelitis caused by *Aspergillus* spp. had an overall mortality rate of 25% (2). However, patients with vertebral osteomyelitis had lower mortality rates (4). The major clinical features of the 27 previously reported cases of vertebral aspergillosis in Japan and our case are summarized in Table 2 (6-31).

The mean age of the population ± standard deviation was 58.1 ± 16.4 years (range, 8-77 years), of which 19 were men and 9 women. Young patients with chronic granulomatous disease were described in two cases out of the 28 cases of vertebral aspergillosis. *A. fumigatus* was detected in 11 cases (39%), but the *Aspergillus* spp. detected in the other cases were not described in detail. The most common presenting symptom of vertebral aspergillosis was extremity weakness (68%), followed by back pain (61%), chest pain (18%), urinary problems such as incontinence or dysuria.
Causes of vertebral aspergillosis can be divided into three main categories. Direct inoculation related to trauma, spinal surgery, or epidural injection occurs rarely and manifests generally within months after the procedure, while contiguous spread from pulmonary disease mainly affects the thoracic spine. Hematogenous infection occurs generally in immunosuppressed patients. A previous study reported that about half of patients acquired the infection by a presumed hematogenous route (5). However, in Japan, 16 cases (57%) acquired the infection by a presumed contiguous spread. This is due to the high prevalence of tuberculosis and lung cancer in Japan, which is a tuberculosis middle-burden country (6). Our study reported 10 cases of tuberculosis (36%) and 5 cases of lung cancer with surgical and radiation treatment (18%) as predisposing factors, respectively. Usually, patients with chronic lung disease are prone to *Aspergillus* colonization and infection. Patients infected with nontuberculous mycobacteriosis may have coexisting lung disease, such as bronchiectasis or chronic obstructive pulmonary disease. Although our case had a history of nontuberculous mycobacteriosis and bronchiectasis, a recent study showed that patients with bronchiectasis and nontuberculous mycobacterial disease have a higher prevalence of coexisting *Aspergillus*-related lung disease than those with bronchiectasis and without nontuberculous mycobacteria (7). Therefore, nontuberculous mycobacterial disease or bronchiectasis should be considered risk factors for vertebral aspergillosis. The hematogenous spread was observed in 8 cases (29%), but only 1 (4%) of these cases was due to wound infection by direct inoculation.

The thoracic vertebrae were the most frequent sites of infection (82.1%), while the lumbar vertebrae and cervical

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**Figure 4.** Contrast CT of the chest and abdomen showing bilateral hydronephrosis (a, c), intestinal gas accumulation (b), and the epidural mass (d).

**Figure 5.** CT-guided thoracentesis from the back into the mass in right S6.
spine were involved in 25.0% and 10.7% of the cases, respectively. The thoracic vertebrae are easily affected by contiguous spread arising from pulmonary diseases. Most patients presented with discitis or osteomyelitis at one or more levels of the cervical, thoracic, or lumbar spine. Epidural mass was reported in 21 cases (75%). Since the radiological findings are nonspecific, the definitive diagnosis of vertebral aspergillosis requires the isolation of the organism from bone specimens obtained by a needle biopsy or open biopsy or from aspirate of adjacent fluid collection (4). Our study suggested that CT-guided thoracentesis may be an effective way of obtaining specimens.

A total of 17 patients (61%) were treated with antifungal agents, while 20 patients (71%) received surgical treatments. The overall mortality rate was 61%, and the recovery rate was 39%. About 7 of the 11 patients who survived from vertebral aspergillosis were given both surgical and antifungal treatments. The penetration of antifungal agents in bone tissues is controversial. Denes et al. reported VRCZ may have a role in managing infection at the bone since the concentration of the VRCZ was high in the bone (34). However, the amphotericin concentrations were found to be high in

**Figure 6.** The results of cytology of patient’s pleural effusion showing *Aspergillus fumigatus* (left: Papanicolaou stain, right: Grocott’s methenamine silver stain; ×1,000).

**Figure 7.** The clinical course of the patient. CFPM: Cefpime, CRP: C-reactive protein, L-AMB: Liposomal amphotericin B, MCFG: Micafungin, MEPM: Meropenem, VRCZ: Voriconazole.
<table>
<thead>
<tr>
<th>Case Reference/ Year</th>
<th>Author</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Predispensing factors</th>
<th>Predispensing factors</th>
<th>Presentation</th>
<th>Radiological finding</th>
<th>Artificial treatment</th>
<th>Surgical treatment</th>
<th>Antitubercular agents</th>
<th>Antibiotics</th>
<th>Outcomes</th>
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<td>1</td>
<td>[13][1996] Kawai</td>
<td>38</td>
<td>M</td>
<td>ND</td>
<td>Neck pain, back pain</td>
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<td>ND</td>
<td>CS-12</td>
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<td>Lamictinomycin, single user</td>
<td>Death</td>
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<td>2</td>
<td>[21][1987] Kon</td>
<td>53</td>
<td>M</td>
<td>ND</td>
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<td>ND</td>
<td>CS-4</td>
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<td>Alive</td>
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<td>[10][1993] Maki</td>
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<td>M</td>
<td>ND</td>
<td>Chest pain, back pain</td>
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<td>ND</td>
<td>CS-6</td>
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<td>M</td>
<td>ND</td>
<td>Back pain</td>
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<td>ND</td>
<td>CS-14</td>
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<td>ND</td>
<td>Long-term ophthalmic disease</td>
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<td>ND</td>
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<td>[13][1992] Hongra</td>
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<td>ND</td>
<td>Lower extremity weakness</td>
<td>Tuberculosis, chronic osteomyelitis</td>
<td>ND</td>
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<tr>
<td>8</td>
<td>[10][1994] Kurojima</td>
<td>56</td>
<td>M</td>
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<td>CS-4</td>
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<td>Death</td>
<td></td>
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<tr>
<td>9</td>
<td>[13][1992] Hitomi</td>
<td>44</td>
<td>M</td>
<td>ND</td>
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<td>Death</td>
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<td>[13][1993] Yama</td>
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<td>M</td>
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<td>Death</td>
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<td>[13][1998] Okawa</td>
<td>41</td>
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<tr>
<td>14</td>
<td>[13][1998] Okawa</td>
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<td>F</td>
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<td>ND</td>
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<td>15</td>
<td>[13][1999] Hanra</td>
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<td>Right lower extremity weakness</td>
<td>Tuberculosis, chronic osteomyelitis</td>
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<td>16</td>
<td>[13][2000] Gotama</td>
<td>68</td>
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<td>Left lower extremity weakness</td>
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<td>Death</td>
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<td>17</td>
<td>[23][2000] Ukkuro</td>
<td>61</td>
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<td>18</td>
<td>[23][2000] Ukkuro</td>
<td>62</td>
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<td>ND</td>
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<td>ND</td>
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<td>19</td>
<td>[23][2003] Itohate</td>
<td>75</td>
<td>F</td>
<td>ND</td>
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<td>20</td>
<td>[23][2003] Sagana</td>
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<td>ND</td>
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<td>21</td>
<td>[23][2003] Suzuki</td>
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<td>22</td>
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<td>64</td>
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<td>Discontinued osteomyelitis, epidural mass</td>
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<td>Death</td>
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</table>

**Table 2. Literature Review of Vertebral Aspergillosis Reported in Japan**

**Notes:**
- **ND:** No data
- **ITCZ:** Itraconazole, FLCZ, Itraconazole, single user
- **AMC:** Amoxicillin, single user
- **VFZ:** Voriconazole, single user
- **MPC:** Meropenem, single user
- **FRZ:** Fluconazole, single user
- **TFLZ:** Tionemone, single user
- **AMR-B:** Amoxicillin-ampicillin, single user
- **APAM-R:** Ampicillin-ampicillin, single user
- **APAZ:** Amoxicillin-ampicillin, single user
- **apy:** Amoxicillin, single user
the bone marrow of dogs and rabbits following the administra-
tion of any of the currently available formulations, in-
cluding L-AMB. No data are available for MCFG, although
this has been used to treat a few patients with bone/joint in-
festions, in combination with amphotericin (35).

In summary, our review of reported cases of vertebral as-
pergillosis in Japan suggested that patients with a history of
pulmonary diseases such as tuberculosis, including non-tuber-
culous mycobacteriosis, bronchiectasis, or lung cancer
treated with surgery or radiology, should be screened for as-
pergillosis. If such patients develop extremity weakness or
back pain, MRI of the spine should be performed to diag-
ose vertebral aspergillosis. CT-guided thoracentesis should be
considered in order to identify the cytology. Antifungal
therapy in combination with surgical treatment should be
given to treat serious and life-threatening infections as the
condition allows.

The authors state that they have no Conflict of Interest (COI).

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