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Clinical Study

Fungal spinal epidural abscess: a case series of nine patients

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Abstract

BACKGROUND CONTEXT: Fungal spinal epidural abscess (FSEA) is a rare entity with high morbidity and mortality. Reports describing the clinical features, diagnosis, treatment, and outcomes of FSEA are scarce in the literature.
PURPOSE: This study aimed to describe the clinical features, diagnosis, treatment, and outcomes of FSEA.
STUDY DESIGN: This study is designed as a retrospective clinical case series.
PATIENT SAMPLE: A continuous series of patients with the diagnosis of FSEA who presented at our institution from 1993 to 2016.
METHODS: We reviewed the electronic medical records of patients with SEA who were treated within our hospital system from 1993 to 2016. We only included SEA cases that were due to fungi. We also reviewed FSEA cases in the English language literature from 1952 to 2017 to analyze the features of FSEA.
RESULTS: From a database of 1,053 SEA patients, we identified 9 patients with FSEA. *Aspergillus fumigatus* was isolated from 2 (22%) patients, and *Candida* species were isolated from 7 (78%). Focal spine pain, neurologic deficit, and fever were demonstrated in 89%, 50%, and 44% of FSEA cases, respectively. Five of nine cases involved the thoracic spine, and eight were located anterior to the thecal sac. Three cases had fungemia, six had long symptom duration (>2 weeks) prior to presentation, seven had concurrent immunosuppression, and eight had vertebral osteomyelitis. Additionally, one case had residual motor deficit at last follow-up, one had S1 sensory radicular symptoms, two suffered recurrent FSEA, two died within hospitalization, and two died within 90 days after discharge.
CONCLUSIONS: In summary, the classic diagnostic triad (focal spine pain, neurologic deficit, and fever) is not of great clinical utility for FSEA. Biopsy, intraoperative tissue culture, and blood culture can be used to diagnose FSEA. The most common pathogens of FSEA are *Aspergillus* and *Candida* species. Therefore, empiric treatment for FSEA should cover these species while definitive identification is pending. FSEA is found in patients with poor baseline health status, which is the essential reason for its high mortality.

Keywords: Clinical features; Treatment; Outcome; Fungus; Spinal epidural abscess; *Aspergillus*; *Candida*

Introduction

Spinal epidural abscess (SEA) is a rare condition that is associated with significant morbidity. Purulent expansion within the narrow spinal canal can cause spinal cord injury through mechanical compression, vascular compromise, or spinal instability [33]. The incidence of fungal SEA (FSEA) is relatively low in the SEA population, with less than 5% of SEA attributable to fungi [11].

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FSEA is usually found in an immunocompromised host [1,4,8,12–16,22,25,26,29,30,32]. Due to its insidious onset and nonspecific presentation (eg, back pain, fever, and neurologic deficit), FSEA is often misdiagnosed on initial presentation [23]. Resulting delay in diagnosis and poor baseline health status lead to significant morbidity and mortality [27,34].

Studies on FSEA are rare; to our knowledge, only 59 cases are discussed in the literature. Thus, there is a paucity of data regarding the clinical characteristics, diagnosis, management, and outcomes of FSEA. We summarize 9 cases of FSEA identified in our institution and discuss our findings in the context of 59 FSEA cases reported in the literature.

Methods

Study design and subjects

Our institutional review board approved a waiver of consent for this retrospective study. We included all patients 18 years or older who were diagnosed with FSEA at our institution of two tertiary referral medical centers and three regional community hospitals (Fig. 1).

We identified our cohort by performing a computerized query of all patients admitted to our hospital system between 1993 and 2016 using International Classification of Diseases codes for SEA and its synonyms (ICD-9 324.1, ICD-10 G06.1). We also performed a computerized query using Current Procedural Terminology codes for "laminectomy for excision or evacuation of intraspinal lesion other than neoplasm, extradural" (CPT 63275-63278). This initial search yielded 2,756 unique patients. Screening medical records yielded 1,053 potentially eligible patients. Based on blood cultures, biopsies, or intraoperative cultures, 9 patients were diagnosed with FSEA and 870 with bacterial SEA. No organisms grew for 174 patients (Fig. 1).

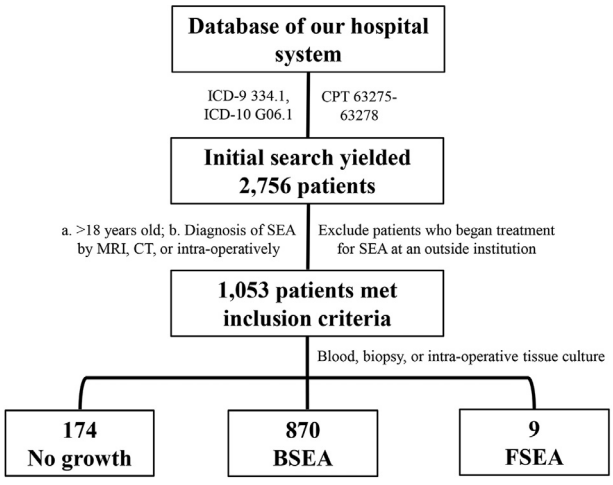

Fig. 1. Patient inclusion/exclusion flow chart. ICD, International Classification of Diseases; CPT, current procedural terminology; SEA, spinal epidural abscess; MRI, magnetic resonance imaging; CT, computed tomography; BSEA, bacterial spinal epidural abscess; FSEA, fungal spinal epidural abscess.

Outcome and other variables

We manually reviewed the electronic medical records of the nine FSEA cases. The following variables were extracted from the medical records: age at time of admission, sex, symptoms at presentation, comorbidities, concurrent infections, abscess characteristics, blood culture results, antifungal treatment, surgical details, residual neurologic deficit, recurrence, and mortality. The following laboratory values at presentation were collected: white blood cell (WBC) count (cells/mm^3), erythrocyte sedimentation rate (ESR) (mm/h), and C-reactive protein (CRP) (mg/L).

Patients were considered immunocompromised if they had an immunosuppressive condition (eg, splenectomy, ascitic hepatopathology/Hepatitis C, neoplastic process, or diabetes mellitus) or were on immunosuppressive medication. Fever was defined as a body temperature over 100.4°F (38°C) at presentation or reports of fever by health-care providers. Symptom duration was calculated from the onset of symptoms to presentation at our hospitals. Motor and nonmotor neurologic deficits were only considered present if they were novel at presentation. Pre- and posttreatment neurologic status was determined using the American Spinal Injury Association Impairment Scale for those with abscess located above L2 [17]. Abscess characteristics and presence of concurrent local spinal infections were determined by reviewing radiological reports. Age-adjusted Charlson Comorbidity Index was used to evaluate comorbidities [5,6]. Recurrence was defined as re-accumulation of the purulent material in SEA after initial clinical improvement and was assessed with follow-up radiographs. Survival was determined through Social Security Death Index and medical charts in April 2017 [21].

Statistical analysis

Categorical variables were presented as frequencies with percentages. Continuous variables were presented as a median with interquartile range (IQR). Statistical analysis was conducted using STATA 13.0 (StataCorp LP, College Station, TX, USA).

Results

From the 1,053 patients with documented SEA in our database, 879 were identified with a causative microorganism, of which 9 were attributed to fungi. Details of the nine FSEA cases are summarized in Tables 1 and 2.

Table 1
Nine fungal spinal epidural abscess cases in our hospital system

Patients	Age (y)/sex	Risk factors	Symptoms	Laboratory tests			Fungemia	Pathogen	Levels	Location	Osteomyelitis
				WBC count (10^3 cells/mm^3)	ESR (mm/h)	CRP (mg/L)					
1	54/M	Hepatitis C	Back pain, radicular pain	7.5	45	80.7	No	*Candida albicans*	T11–T12	Anterior	Yes
2	77/M	DM, renal and respiratory failure, widely used antibiotics	Back pain, left leg weakness, fever	9.5	121	177.1	Yes	*Candida glabrata*	L3–L4	Anterior and posterior	Yes
3	68/M	Prior fungal infection	Fever	18.8	82	61.4	Yes	*Candida albicans*	T11–T12	Anterior	Yes
4	21/F	Recent spinal trauma, grade 2 spleen laceration	Back pain	8.3	81	53.1	No	*Candida albicans*	L3–L4	Anterolateral	Yes
5	74/M	Prior fungal infection, anemia	Back pain, fever	10.3	Na	N/A	No	*Candida albicans*	L3–S1	Anterior	Yes
6	63/F	DM, prior fungal infection, chronic total parenteral nutrition, splenectomy	Neck pain, radicular pain, fever	22.6	90	N/A	Yes	*Candida albicans*	C6–T1	Anterior	Yes
7	40/M	Hepatitis C, intravenous drug abuse, widely used antibiotics	Back pain, radicular pain, right leg and ankle weakness, paresthesia	12.9	64	95.1	No	*Candida albicans*	L5–S1	Anterior	Yes
8	48/F	Prior surgery, Decadron	Back pain, bilateral leg weakness, urinary retention	12.6	28	N/A	No	*Aspergillus fumigatus*	T3–T5	Anterolateral	No
9	51/M	Prior fungal infection, Proventil, Azmacort	Back pain, bilateral leg weakness	13.9	110	N/A	No	*Aspergillus fumigatus*	T5–T10	Anterior	Yes

F, female; M, male; DM, diabetes mellitus; WBC, white blood cell; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

Clinical features

Focal spine pain was present in eight patients, and four patients were febrile at admission. Four patients demonstrated motor weakness (two cases with abscess above L2 with the American Spinal Injury Association grade C and two cases with abscess below L2 with moderate leg and ankle weakness). Patients reported nonmotor neurologic deficits, such as radicular pain (3 of 9), urinary retention (1 of 9), and paresthesia (1 of 9). The median time between the onset of symptoms and presentation ranged from a few hours to a few weeks: <24 hours (2 of 9), between 3 days and 2 weeks (1 of 9), and >2 weeks (6 of 9). Three patients presented with fungemia. Moreover, concurrent infections included vertebral osteomyelitis (3 of 9), spondylodiscitis adjacent to the FSEA (5 of 9), paraspinal abscess (3 of 9), and infectious endocarditis (2 of 9).

Comorbidities identified in our FSEA patients included portal hypertension (2 of 9, 1 with ascites), solid tumor within the past 5 years (2 of 9), renal failure (2 of 9), hemiplegia (1 of 9), diabetes mellitus without end organ damage (2 of 9), hepatitis C (2 of 9), gastric or peptic ulcer (4 of 9), chronic pulmonary disease (3 of 9), cerebrovascular disease (2 of 9), cerebral vessels vasculitis (1 of 9), chronic emphysema (1 of 9), myocardial infarction (3 of 9), and immunocompromised status (7 of 9, of which 2 were receiving steroids, 2 had a splenectomy or spleen laceration, 1 had Hepatitis C, 1 had Hepatitis C and ascites, and 1 had diabetes mellitus). The median age-adjusted Charlson Comorbidity Index was 5 (IQR 1–9) (Table 2).

The median WBC count was 12.6×10^3 cells/mm^3 (IQR 9.5–13.9) (Table 1). The median ESR was 81 mm/h (IQR 45–110). In all nine cases, ESR was elevated (range 28–121 mm/h). The median value of CRP was 88 mg/L (IQR 71–136).

The FSEA was located in the cervical spine in one case, the thoracic spine in five, and the lumbosacral spine in four. The median number of affected vertebral levels was 2 (IQR 2–3). With respect to the location within the spinal canal, the abscess was anterior to the thecal sac in eight cases and at multiple locations in one.

Diagnosis

Seven patients were diagnosed with *Candida* SEA, six of whom were infected with *Candida albicans* and one with *Candida glabrata*. Two patients were diagnosed with *Aspergillus* SEA. Blood cultures were done for all cases, with three positive cultures identifying the causative agent. Furthermore, three cases had biopsies and six cases had intraoperative tissue samples, all of which identified the pathogen.

Treatment

Depending on the anatomy of the abscess, cocurrent infections, and spinal stability, different surgical

Table 2
Treatment and outcome of our nine fungal spinal epidural abscess cases in our hospital system

Patients	Surgery (approach)	Antifungal treatment	Follow-up period (d)	ACCI	Outcome
1	No	LAmB (IV, 3 mg/kg, qd, 4 w), nafcillin (IV, 2 g, q4h, 6 w), fluconazole (PO, 400 mg, qd, 10 m)	327	4	Back pain
2	Laminectomy (posterior)	Micafungin (IV, 100 mg, qd, 6 d)	0	10	Died during hospitalization
3	No	Fluconazole (IV, 400 mg, qd, 3 d), LAmB (IV, 450 mg, qd, 4 w), flucytosine (PNGT, 1500 mg, q6h, 4 w), micafungin (IV, 150 mg, qd, 4 w), fluconazole (PO, 400 mg, qd, 6 w)	79	9	Died within 90 days
4	Debridement and drainage (lateral)	Fluconazole (IV, 400 mg, qd, 3 d), fluconazole (PO, 400 mg, qd, 6 m)	222	1	Without residual symptoms
5	No	Caspofungin (IV 50 mg, qd, 8 w), flucytosine (4 w), Fluconazole (PO, 600 mg, qd, 3 m)	15	6	Died within 90 days
6	Laminectomy and corpectomy and iliac crest bone fusion (posterior+anterior)	AmB (IV, 35 mg, qd, 12 w)	768	5	Recurrence within 60 days
7	Microdiscectomy (anterior)	Fluconazole (PO, 400 mg, qd, 12 m)	583	1	S1 sensory radicular symptoms
8	Laminectomy and corpectomy and instrumentation (posterior+lateral+anterior)	LAmB (IV, 2 w), voriconazole (PO, 6 m)	66	1	Bilateral leg weakness
9	Laminectomy (posterior)	AmB (IV, 60 mg, qd, 6 w)	0	11	Recurrence, died during hospitalization

LAmB, liposomal amphotericin B; IV, intravenous; qd, every day; q4h, every 4 h; q6h, every 6 h; d, days; w, weeks; m, months; PO, orally; PNGT, by nasogastric tube; ACCI, age-adjusted Charlson Comorbidity Index.

approaches were employed, such as laminectomy, discectomy, corpectomy, and wound incision and drainage (Table 2). Six patients received surgery, of which five used an external orthosis postoperatively. After the diagnosis of FSEA was confirmed, all nine patients were treated with antifungal agents. These included micafungin, flucytosine, amphotericin B, fluconazole, caspofungin, and voriconazole. Further details of antifungal treatment are listed in Table 2.

Outcomes

The median follow-up time was 11 weeks (IQR 2–47). Eight patients had no motor deficit at last follow-up, and one patient had weakness in the bilateral lower extremities (American Spinal Injury Association grade C). One case had S1 sensory radicular symptoms. There were two recurrences at the same level due to the same fungi. Two patients died during initial hospitalization and two others died within 90 days after discharge. The median time to death was 64 days.

FSEA in the literature

Of the 59 cases in the literature (Table 3), 61% were men, and the median age was 49 years (IQR: 35–62). Of these, five cases had an age less than 18 years. The most common symptom was local pain, and three quarters of the cases had neurologic deficit. In total, 41% had an elevated WBC count. Most cases had elevated levels of inflammatory markers ESR (93%) and CRP (67%). *Aspergillus* species (60%) were the most common, followed by *Candida* species (29%) (Fig. 2). Nearly half of the published cases involved the thoracic spine. A total of 45 (81%) cases received surgery. Four (8.0%) cases had recurrent FSEA and 14 (28%) died during hospitalization or within 90 days after discharge.

Discussion

Fungal infections of the spinal epidural space are generally considered to be opportunistic, occurring in immunosuppressed populations. The incidence of FSEA in our SEA database is 1.02%, lower than the 3.45% incidence previously reported by Del et al. [11]. Due to the low incidence, there is not much data available for FSEA. With our nine FSEA cases, we hope to provide further insight into the clinical features, diagnosis, treatment, and outcomes of SEA.

In our cases as well as in the literature, the most common clinical manifestations of FSEA are focal spine pain, neurologic deficit, and fever (Table 3). Together, these symptoms constitute the classic diagnostic triad for SEA [10]. Of the 38 cases in the literature with presentation data, 11 (30%) had all three symptoms of the triad, 20 (53%) had two symptoms, and 7 (18%) had

Table 3
Characteristics of fungal spinal epidural abscess: 9 cases in our hospital system and 59 cases in the literature

Variables	59 cases in the literature	9 cases in our hospital system
Age	49 (35–62)	54 (48–68)
Men	33 of 54 (61%)	6 of 9 (67%)
Symptoms		
Local spine pain	39 of 41 (95%)	8 of 9 (89%)
Motor/sensory deficit	40 of 53 (75%)	4 of 8 (50%)
Fever*	26 of 38 (68%)	4 of 9 (44%)
Radicular pain	13 of 36 (36%)	2 of 9 (22%)
Laboratory tests		
White blood cell count $>10\times1{,}000/mm^3$	14 of 34 (41%)	6 of 9 (67%)
Erythrocyte sedimentation rate >20 mm/h	26 of 28 (93%)	8 of 8 (100%)
C-reactive protein level >6 mg/L	8 of 12 (67%)	5 of 5 (100%)
Pathogen		
Aspergillus	33 of 55 (60%)	2 of 9 (22%)
Candida	16 of 55 (29%)	7 of 9 (78%)
Region of spine		
Cervical	9 of 53 (17%)	1 of 9 (11%)
Thoracic	26 of 53 (49%)	5 of 9 (56%)
Lumbar	23 of 54 (43%)	4 of 9 (44%)
Sacral	9 of 53 (17%)	2 of 9 (22%)
Location of abscess relative to thecal sac		
Anterior	24 of 31 (77%)	8 of 9 (89%)
Posterior	6 of 31 (19%)	1 of 9 (11%)
Osteomyelitis	33 of 35 (94%)	8 of 9 (89%)
Immunocompromised	21 of 58 (36%)	4 of 9 (44%)
Surgery	45 of 53 (81%)	6 of 9 (67%)
Recurrence	4 of 50 (8%)	2 of 9 (22%)
Mortality (within 90 days)	14 of 50 (28%)	4 of 9 (44%)

Nonparametric continuous variables are presented with median and interquartile range. Categorical variables are presented with frequencies and numbers.
* More than 100.4˚F (38˚C).

one symptom only. In our nine cases, only one (11%) patient had all components of the triad. Our findings demonstrate that the classic diagnostic triad is not of great clinical utility for FSEA, just as the classic diagnostic triad is not particularly useful in the prompt diagnosis of bacterial SEA [9, 10]. Many FSEA patients have long symptom duration (>2 weeks) prior to presentation. FSEA ought to be high on the differential diagnosis for patients who present with long symptom duration combined with the appropriate risk factors.

Abscess characteristics of FSEA cases described in the literature are similar to those of our nine cases (Table 3). Most FSEA are located in the thoracic spine, which represents the largest region of the spine. Furthermore, *Aspergillus* most commonly infects the lungs, allowing for dissemination into the thoracic epidural space. [16]. All FSEAs that involved the sacral spine also involved the lumbar spine. Only one patient in the literature involved the thoracic, lumbar, and sacral vertebrae. In 77% (24 of 31) of the cases, the abscess was anterior to the thecal sac. This may be due to the ease of hematogenous dissemination through the more abundant blood vessels of the anterior spinal column [16, 24].

The most reliable method of diagnosis for FSEA is tissue biopsy with histologic examination and culture. Once SEA is suspected radiographically, direct sampling of the infected fluid or tissue via image-guided biopsy should be performed to confirm the diagnosis and to guide antimicrobial therapy [27]. Due to the risk of seeding into the subarachnoid space, lumbar puncture should be avoided [27]. In our series, all SEAs were diagnosed using magnetic resonance imaging, and all pathogens were identified through computed tomography (CT)-guided biopsy, intraoperative tissue culture, or blood culture. Compared with intraoperative biopsy, it is somewhat more difficult to obtain enough of truly infectious tissue with CT-guided biopsy. However, all three cases that used CT-guided biopsy cultured out fungal pathogens. Blood cultures are rarely positive in FSEA, and laboratory contamination is a well-recognized problem [7]. We also found that FSEA was rarely associated with fungemia. Nonetheless, blood cultures should be routinely obtained as they may guide antifungal agent selection when tissue cultures are not helpful or available. Furthermore, based on the 59 cases in the literature, ESR and CRP are much more sensitive than WBC counts for FSEA, and the laboratory test values of our cases are consistent with this finding. Although ESR and CRP are elevated in most FSEA cases [3, 31], normal inflammatory marker levels do not rule out FSEA because immunocompromised patients may not be able to muster an inflammatory response. Moreover, monitoring

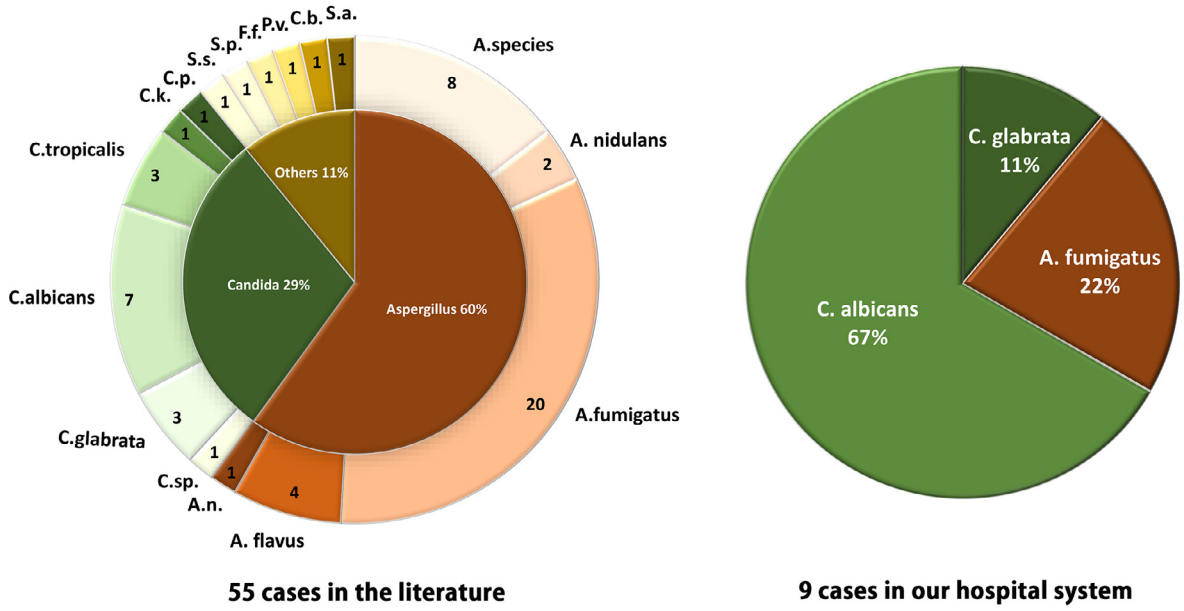

Fig. 2. Pathogens of fungal spinal epidural abscesses. A, *Aspergillus*; C, *Candida*; A.n., *Aspergillus niger*; C.p., *Candida parapsilosis*; C.k., *Candida kefyr*; C.sp., other *Candida* species; S.s., *Sporotrichum sckenkii*; S.p., *Scedosporium prolificans*; F.f., *Fusarium falciforme*; P.v., *Phaeoacremonium venezuelense*; C.b., *Cunninghamella bertholletiae*; S.a., *Scedosporium apiospermum*.

inflammatory marker levels may be useful in assessing response to treatment [16, 18].

Although *Aspergillus* species were responsible for most FSEAs in the literature, most of our cases were due to *Candida* species. This discrepancy may be due to publication bias, in which more rare pathogens are preferred to be published. However, in both the literature and our cases, the vast majority of FSEAs were due to these two types of species (Fig. 2). Therefore, for patients with suspected fungal infection, it is crucial that broad-spectrum antifungal agents cover *Aspergillus* and *Candida* species.

Historically, amphotericin B (AmB) has been used owing to its long-standing availability, but its effectiveness has been questioned when not combined with surgery [2]. This could be explained by the low concentration of AmB that reaches the bone [2, 20]. Moreover, 94% of the FSEA cases in the literature were found to have osteomyelitis (Table 3). On the other hand, numerous studies, including a large randomized, controlled trial, demonstrated the superiority of voriconazole over AmB in the treatment of invasive aspergillosis (most cases due to pulmonary infection), resulting in improved survival and lower toxicity [19]. Therefore, according to the treatment guidelines of aspergillosis proposed by the Infectious Disease Society of America, voriconazole is recommended as the primary treatment for invasive aspergillosis, including *Aspergillus* osteomyelitis [35]. Itraconazole is recommended as an alternative therapy of invasive aspergillosis for refractory cases intolerant to routine antifungal therapy [2].

For initial treatment of *Candida* SEA, there is no specific recommendation. The Infectious Diseases Society of America recommends fluconazole as initial treatment for *Candida* vertebral osteomyelitis and *Candida* septic arthritis [28]. Another treatment option, which is strongly recommended, would be an echinocandin (caspofungin, micafungin, or anidulafungin) followed by fluconazole [28].

C. glabrata poses a unique challenge owing to its inherent resistance to many antifungal drugs. The resistance of *C. glabrata* to fluconazole particularly limits its usefulness. Therefore, liposomal amphotericin B remains the treatment of choice [8]. The antifungal treatment of FSEA should be guided by consultation of Infectious Diseases specialists.

In our nine cases of FSEA, more than half resulted in recurrence or death either during hospitalization or within 90 days after discharge. This is likely due to the immunocompromised status and overall poor health status of patientswith FSEA. High age-adjusted Charlson Comorbidity Index suggests that FSEA patients have many comorbidities. Reviewing the literature from 1952 to 2017, the mortality of FSEA is 28% and the percentage of residual neurologic deficit is 20%. The response and outcome of these patients to therapy are largely dependent on host factors, including neurologic condition at presentation, underlying medical disease, and early diagnosis and treatment. There is a current shift in emphasis from waiting for definitive diagnosis to screening high-risk patients using nonculture methods to facilitate early initiation of antifungal therapy in the hope of improving outcomes.

This study has several limitations. Foremost, this is a retrospective case series limited by the inherent flaws that accompany this study design such as using search algorithms for patient selection and miscoding of diagnoses. Second, due to the small sample size, we were not able to

perform more than descriptive analysis.Third, some variables we collected suffer from interobserver variability (eg, motor and nonmotor neurologic deficits) or are unreliable (eg, duration of symptoms). We attempted to account for this by categorizing these variables to represent meaningful differences. Last, the limited follow-up limited us in evaluating final outcomes, such as neurologic deficit and recurrence, for some patients.

Conclusions

In summary, the classic diagnostic triad (focal spine pain, neurologic deficit, and fever) is not of great clinical utility for FSEA. Biopsy, intraoperative tissue culture, and blood culture can be used to diagnose FSEA. The most common pathogens of FSEA are *Aspergillus* and *Candida* species. Therefore, empiric treatment for FSEA should cover these species while definitive identification is pending. FSEA is found in patients with poor baseline health status, which is the essential reason for its high mortality.

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