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Fungal osteoarticular infections in patients treated at a comprehensive cancer centre: a 10-year retrospective review

P. R. Kumashi, A. Safdar, G. Chamilos, R. F. Chemaly, I. I. Raad and D. P. Kontoyiannis

Department of Infectious Diseases, Infection Control and Employee Health, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA

ABSTRACT

This study reviewed retrospectively the clinical characteristics of 28 cancer patients with fungal osteoarticular infections (FOAIs) between 1995 and 2005. Most patients (26; 93%) had haematological malignancies (19 had leukaemia); half (14) were allogeneic stem-cell transplant recipients. Twelve patients (43%) had severe neutropenia ($\leq 100/mm^3$) with a mean duration of 65 days (range 10–500 days), and ten (36%) patients had received a significant dose of corticosteroids. Most (19; 68%) FOAIs were caused by contiguous extension, while nine (32%) were associated with haematogenous spread. Pain, joint instability and local drainage were seen in 28 (100%), six (21%), and seven (25%) patients, respectively. Sixteen (57%) patients had symptoms for < 1 month. The sinuses (ten; 36%) and the vertebral spine (six; 21%) were the most common sites involved. Moulds were the predominant pathogens: *Aspergillus fumigatus* (two); non-*fumigatus Aspergillus* spp. (eight); non-specified *Aspergillus* spp. (three); *Fusarium* spp. (six); Zygomycetes (five); *Scedosporium apiospermum* (two); and *Exserohilum* sp. (one). *Candida* was the causative pathogen in four cases (including two cases of mixed FOAIs). Arthritis and post-operative FOAIs were both uncommon manifestations, occurring in two patients each. All patients received systemic antifungal therapy (combinations in 20 cases), and 19 cases underwent adjunctive surgery. The crude mortality rates (at 12 weeks) were 44% (9/20) in the patients who underwent surgery and antifungal therapy vs. 33% (2/6) in patients who received antifungal therapy alone (p not significant). FOAI is a rare, yet severe, manifestation of localised or systemic mycoses, caused predominantly by moulds, and is seen typically in patients with haematological malignancies.

Keywords Cancer patients, fungal infections, haematological malignancies, mycoses, osteoarticular infections

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INTRODUCTION

Cancer patients are at high risk for opportunistic invasive fungal infections because of predisposing factors such as chemotherapy-induced neutropenia, use of systemic corticosteroids, indwelling central venous catheters, parenteral nutrition and major surgery [1–3]. Fungal osteoarticular infections (FOAIs) are uncommon entities that often escape early detection [4,5]. Skeletal involvement results most often from the haematogenous spread of the fungus from a primary site of infection, usually the lungs or indwelling central venous catheters [6]. However, in some instances, joint infection and, to a lesser degree, bone infection may occur as a result of direct inoculation of the organism during trauma, surgery, arthrocentesis or therapeutic joint injection [7–11].

There is a scarcity of literature concerning FOAIs, particularly in patients with cancer; most studies consist of case reports or small case series [4–17]. Therefore, the present study sought to define the characteristics of patients with FOAIs who received care at a comprehensive cancer centre during the past 10 years.

Corresponding author and reprint requests: D. P. Kontoyiannis, Department of Infectious Diseases, Infection Control and Employee Health, Unit 402, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030, USA
E-mail: dkontoyi@mdanderson.org

MATERIALS AND METHODS

After obtaining institutional review board approval, the study reviewed retrospectively the medical records of all patients with FOAIs who received care at the University of Texas M. D. Anderson Cancer Center (Houston, TX, USA) between January 1995 and April 2005. Patients with FOAIs were identified by a review of clinical microbiology records, autopsy and histopathology databases, and the hospital discharge databases.

Information was collected concerning patient demographics, type and status of the underlying malignancy at the time of FOAI diagnosis, receipt of a bone marrow or stem-cell transplant, risk-factors for invasive fungal infections, and specific risk-factors for osteoarticular infections at the time of FOAI diagnosis or within the preceding 1-month period. Specifically, the study determined the presence and duration of severe neutropenia, receipt of corticosteroids (cumulative dose and duration), presence of graft vs. host disease, diabetes mellitus or hyperglycaemia, malnutrition, underlying hepatic and renal insufficiency, surgery or trauma within the 1-month period preceding the diagnosis of FOAI, presence of an indwelling central venous catheter, and receipt of hyperalimentation. Information concerning the treatment received for the FOAI, including surgery, as well as the use of an antifungal agent within 3 months of the diagnosis of FOAI (the type of agent used, dose and duration of therapy, and whether the agent was given as prophylaxis or as empirical, preemptive or targeted antifungal therapy), was also collected. Fungal isolates were identified according to standard microbiological criteria. Outcome was assessed as crude mortality at 12 weeks from diagnosis of FOAI.

Definitions

For the purpose of this study, as there is no standardised definition, a diagnosis of FOAI was considered definite when cultures or histopathology of bone tissue were positive for fungi. A diagnosis of FOAI was considered probable when there was clinical or radiological evidence of osteoarticular infection, histologically or microbiologically confirmed invasive fungal infection in an adjacent site (e.g., sinuses), and no alternative cause of osteoarticular infection. FOAI was considered to be acute when the duration of symptoms and/or signs before diagnosis was ≤ 4 weeks, and chronic when the duration of symptoms and/or signs before diagnosis was >4 weeks. Severe neutropenia was defined as a neutrophil count $\leq 100/mm^3$ for >10 days. Significant steroid use was defined as a cumulative steroid dose of ≥ 600 mg of prednisone, or an equivalent dose of another steroid, within the 4-week period before the diagnosis of FOAI. Malnutrition was defined as a serum albumin level of ≤ 3 mg/dL at the time of diagnosis of FOAI. Renal insufficiency was defined as serum creatinine ≥ 2 mg/dL at the time of diagnosis of FOAI. Hepatic insufficiency was defined by a Child Pugh score of ≥ 7, or cirrhosis resulting from any cause, at the time of diagnosis of FOAI.

Statistical analysis

Fisher's exact test and Wilcoxon's test were used for categorical and discrete variables, respectively, as appropriate. The Mann–Whitney *U*-test was used for statistical analysis of continuous variables. A two-sided p value <0.05 was considered to be statistically significant. All analyses were performed using Prism software v.4 (GraphPad Software, San Diego, CA, USA).

RESULTS

Thirty-one patients were identified with FOAIs; of these, three had no underlying malignancy (initially referred because of FOAI mimicking bone cancer) and were excluded from further analysis. Of the 28 remaining patients, 24 had definite and four had probable FOAIs. The demographics and clinical characteristics of patients with FOAIs are shown in Table 1. Most patients had advanced haematological malignancies and typical risk-factors for invasive fungal infections, such as a history of haematopoietic stem-cell transplantation (57%), severe graft vs. host disease (46%), severe neutropenia (43%), and receipt of a signi-

Table 1. Demographics and clinical characteristics of 28 cancer patients with fungal osteoarticular infection (FOAI)

Characteristic	*n* (%)
Median age in years (range)	52 (23-89)
Male/female	15/13
Underlying malignancy	
Haematological[a]	26 (93)
Solid tumour[b]	2 (7)
Severe neutropenia[c]	12 (43)
Haematopoietic stem-cell transplant	16 (57)
Autologous	2 (13)
Allogeneic	14 (87)
Graft vs. host disease	
Acute	7 (25)
Chronic	6 (21)
Significant corticosteroid use	10 (36)
Hepatic insufficiency	15 (54)
Renal insufficiency	12 (43)
Recent surgery	2 (7)
Recent trauma	2 (7)
Intravenous hyper-alimentation	4 (14)
Indwelling central venous catheter	17 (61)
Alcohol abuse	1 (4)
Peripheral vascular disease	2 (7)
Malnutrition (serum albumin ≤ 3 mg/dL)	18 (64)
Decubitus ulcer	3 (11)
FOAI	
Acute	16 (57)
Chronic	12 (43)
Osteomyelitis	26 (93)
Arthritis	2 (7)
Foreign body	2 (7)
Source of FOAI	
Contiguous spread	19 (68)
Haematogenous spread	9 (32)
Causative fungus[d]	
Yeasts	4 (7)
Moulds	26 (93)

[a]There were nine patients with acute myelogenous leukaemia, three with chronic myelogenous leukaemia, five each with chronic lymphocytic leukaemia and non-Hodgkin's lymphoma, two with myelodysplastic syndrome, and one each with multiple myeloma and Hodgkin's lymphoma.
[b]One each with melanoma and osteosarcoma.
[c]Neutropenia at the time of FOAI diagnosis.
[d]Three patients had a mixed fungal infection: one with *Aspergillus flavus* and *Candida albicans*, one with *Rhizopus* and *Candida tropicalis*, and one with *A. flavus* and *Fusarium*).

ficant dose of corticosteroids (36%) (Table 1); additional predisposing factors included the presence of indwelling central venous catheters (61%) and hyper-alimentation (14%). Co-morbidities were also present in most (91%) of the patients; none had a history of intra-articular steroid injection or drug abuse.

Clinical presentation of FOAIs

FOAIs were acquired more frequently from a contiguous site (19/28; 68%) than from haematogenous spread. Multifocal bone involvement was seen in only one patient. Most (86%) patients had been receiving systemic antifungal agents at the time of diagnosis of FOAI (fluconazole in 11 patients, amphotericin B-based regimens in three, voriconazole in eight, and itraconazole in two). FOAIs were considered to be acute in most (57%) patients, manifesting predominantly with pain at the involved site (100%); fever (32%), joint symptoms (25%) and drainage from the affected site (25%) were encountered less commonly. The presence of hardware was seen in only two patients with FOAIs (one with an intra-medullary nail in the tibia, and one with a femoral modular prosthesis).

More than half of the 19 patients with FOAIs resulting from contiguous spread had sinusitis (56%), with involvement of the ethmoid (five patients), maxillary (four) and sphenoid (one) bones. Other sites involved were the vertebrae (two patients), tibia (two), fibula (one), distal phalanx of toe (two), fifth metatarsal (one) and mandible (one). Among the nine patients with FOAIs resulting from haematogenous spread, four had vertebral involvement, one had involvement of the second toe, one had an FOAI of the radius, one had an FOAI of the triquetral bone in the wrist, and one had multifocal involvement of the left wrist and left ulna, as well as septic arthritis with an FOAI of the knee. There were no significant differences in risk-factors and clinical characteristics between the patients with FOAIs with sinusitis and those with FOAIs without sinusitis (Table 2).

The most common fungi isolated were moulds (24; 86%), comprising *Aspergillus* spp. (n = 10), namely *Aspergillus flavus*, *Aspergillus terreus*, *Aspergillus fumigatus* and *Aspergillus nidulans* in four, three, two and one patient(s), respectively, and non-*Aspergillus* moulds (n = 14), comprising *Fusarium* spp. (six), Zygomycetes (five), *Scedosporium apiospermum* (two) and *Exserohilum* (one); there were four culture-negative cases in which the diagnosis—*Aspergillus* spp. (three) and Zygomycetes (one)—was based on histopathology. There were four FOAIs caused by yeasts (*Candida albicans* and *Candida tropicalis*, two each), including two cases of mixed FOAIs. There was no case of FOAI caused by endemic fungi. Three patients had a mixed FOAI caused by more than one fungus; all mixed FOAIs were associated with contiguous spread, including two cases of sinusitis and one case of mandible bone involvement.

Aspergillus spp. accounted for most (7/9; 78%) FOAIs associated with haematogenous spread, but were encountered less frequently in FOAIs associated with contiguous spread (6/19; 32%), with Zygomycetes (5/19; 26%) being the next most common pathogens. In the vast majority of cases of FOAIs, diagnosis was established by histopathology (22/28; 79%) and/or bone culture (24/28; 86%).

Table 2. Univariate analysis of clinical characteristics of patients with fungal osteoarticular infections (FOAIs) with sinus involvement compared with those of patients with FOAIs without sinus involvement

Characteristic	FOAIs with sinusitis (n = 10)[a]	FOAIs without sinusitis (n = 18)	OR (95% CI)	p
Median age in years (range)	51 (29–63)	53 (26–89)		0.8
Male	5/10 (50%)	10/18 (56%)		0.9
Haematological malignancy	10/10 (100%)	16/18 (89%)		0.5
Haematopoietic stem-cell transplant	7/10 (70%)	9/18 (50%)		0.4
Severe neutropenia	6/10 (60%)	6/18 (33%)		0.2
Significant corticosteroid use	4/10 (40%)	6/18 (33%)		0.9
Diabetes mellitus	6/10 (60%)	8/18 (44%)		0.7
Renal insufficiency	4/10 (40%)	8/18 (44%)		0.7
Hepatic insufficiency	6/10 (60%)	9/18 (50%)		0.7
Malnutrition (serum albumin ≤3 mg/dL)	6/10 (60%)	12/18 (67%)		0.6
Indwelling catheter	7/10 (70%)	10/18 (56%)		0.6
Haematogenous spread	0/10 (0%)	10/18 (56%)	25.9 (1.3–510)	0.004
GCSF use	5/10 (50%)	7/18 (39%)		0.9
Surgery	9/10 (90%)	10/18 (56%)		0.09
Overall mortality at 12 weeks	4/10 (40%)	7/16 (43%)		0.9

[a]FOAIs with sinus involvement were caused by Zygomycetes (four), *Fusarium* spp. (two), *Aspergillus* spp. (two), *Candida tropicalis* (one), and *Exserohilum* sp. (one). There were two mixed FOAIs with sinus involvement, one with *Rhizopus* and *C. tropicalis*, and one with *A. flavus* and *Fusarium*.
GCSF, granulocyte colony-stimulating factor.

Treatment

Most (20/28; 71%) patients received combination antifungal therapy. The mean duration of treatment was 5 months (median 3 months; range 11 days to 18 months). Nineteen of the 28 patients underwent surgery for the FOAI. Of these, 15

patients had surgery within 1 week of diagnosis of the FOAI. Seven patients underwent irrigation and debridement, including one patient who also had hardware removed. Three patients underwent more extensive and radical surgery that included thoracolumbar fixation and arthrodesis, and one patient had an infected toe amputated. Most patients with sinusitis and contiguous bone involvement underwent extensive sinus debridement and excision of the sinuses, with turbinectomy, septectomy, or both. One of the two patients who had FOAI associated with the presence of hardware had the hardware removed following diagnosis of FOAI.

Adjunctive antifungal treatment with granulocyte colony-stimulating factor was administered to 12 patients with FOAIs; one patient with FOAI caused by *Fusarium* received adjunctive antifungal treatment with hyperbaric oxygen; three patients with FOAIs caused by *Fusarium*, *Rhizopus* and *A. flavus*, respectively, received white blood cell transfusions.

Outcome

The mean duration of follow-up after the diagnosis of FOAI was 9 months (range 11 days to 36 months). Information concerning outcome was available for 26 patients. The overall mortality rate at 12 weeks was 42% (11/26); the crude mortality rate was 44% (9/20) in patients who underwent surgery and received antifungal therapy, compared with 33% (2/6) in patients who received antifungal therapy alone (p not significant).

DISCUSSION

To the best of our knowledge, this is the largest study of FOAIs among cancer patients. Moulds were the most common cause of FOAIs among patients with cancer, especially those with haematological malignancies. Half of the patients had a relatively acute presentation, albeit with clinical symptoms and signs that were non-specific. Thus, focal pain, the most common symptom, was present in all patients, but fever, drainage and joint instability were variably present. Most patients had bone involvement by contiguous extension, with the sinuses being the most common sites of bone involvement by contiguous extension of infection. Despite the significant proportion of FOAIs associated with sinus involvement, which have a distinct pathophysiology compared with other types of FOAIs, there were no differences in the clinical characteristics and outcomes of patients with FOAIs with or without sinus involvement. These findings are in contrast to the view that FOAIs usually occur as a result of haematogenous spread [3,6].

Although FOAI is rare, even in severely immunocompromised individuals, it is a relatively frequent infection in patients with chronic granulomatous disease [18]. It is of interest that *A. nidulans*, an uncommon fungal pathogen with low pathogenic potential, is the predominant *Aspergillus* sp. isolated from these patients, and has been associated with involvement of small bones and a less favourable outcome compared with FOAIs caused by *A. fumigatus* [18]. In the present study, moulds were the fungal pathogens isolated most frequently from patients with either haematogenous spread or contiguous involvement of bone. In addition, non-*fumigatus Aspergillus* spp., mainly *A. flavus* and *A. terreus*, comprised the majority of *Aspergillus* isolates. *Aspergillus* and Zygomycetes were the most common fungal pathogens found in patients who had sinusitis with contiguous bone involvement. The presence of mixed FOAIs caused by *Candida* spp. and moulds might reflect the fact that the study population comprised heavily immunocompromised patients. Although it is difficult to account for the pathogenicity of *Candida* spp. in mixed FOAIs with sinus involvement, it is tempting to speculate that tissue damage caused by *Candida* could facilitate the subsequent development of angioinvasive mould infection.

The published literature concerning FOAIs includes a heterogeneous spectrum of diseases with different prognoses [4–6,8,9,12,13,15–17,19–24], and there is no standard treatment for patients with FOAIs. More specifically, there is no consensus on the optimum dose and duration of antifungal therapy, the value of combination antifungal therapy, or the timing and extent of adjunctive surgery [3,24]. Most authorities believe that incomplete debridement of a bone infection will result in treatment failure, and that radical debridement of infected or necrotic bone is particularly important in a compromised host [19,23]. Historically, the most common therapy for FOAIs has consisted of amphotericin B combined with surgical debridement [4,9,11,13,15,21].

Stratov *et al*. [12] showed that cure rates were 14% when amphotericin B was used alone, compared with 75% when it was combined with surgery. Similar outcomes have been noted in case reports of FOAIs caused by other moulds, including *Fusarium*, *S. apiospermum* and Zygomycetes [10,11,14,15].

Most of the patients in the present study underwent aggressive surgery within 1 week of diagnosis of an FOAI. However, early and aggressive surgical intervention had no apparent influence on outcome. Other factors might have contributed to the overall outcome, such as the relatively late diagnosis in many patients, and the fact that almost half of the patients had an advanced or treatment-refractory malignancy.

The recent availability of potent oral azoles might revolutionise the treatment of FOAIs. A recent study of voriconazole for the treatment of bone aspergillosis [22] showed a response rate of 83% in patients without underlying immunosuppression, compared with 43% among immunocompromised patients. In addition, there was no apparent difference in outcome between patients who underwent surgery and received antifungal therapy, and those who received antifungal therapy alone. The ability to switch the route of voriconazole administration from intravenous to oral is an additional benefit of this drug in the management of FOAIs caused by moulds such as *Aspergillus* spp. Overall, voriconazole, an agent with fungicidal activity against *Aspergillus*, might become the treatment of choice, and might also obviate the need for surgical debridement in selected cases of FOAIs when combined with timely diagnosis.

Limitations of the present study include its retrospective nature, the relatively small study population, and the lack of controlled groups with antifungal monotherapy, combined antifungal therapy, or antifungal therapy with surgery. Another limitation of the study, as in other studies on osteoarticular infections, is the definition of outcome. Most studies have offered various definitions, e.g., cure, improvement, eradication, failure and recurrence, with each definition having a different meaning that makes comparisons among studies difficult. In addition, it is difficult to separate the effects of the infection and its treatment from the effects of co-morbidities that can affect mortality.

In conclusion, FOAIs are rare, yet severe, manifestations of localised or systemic mycoses in cancer patients, seen typically in patients with haematological malignancies, with moulds being the predominant causes.

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