Characteristics of vertebral osteomyelitis after liver transplantation

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Abstract

We performed a retrospective single-centre 1:3 case–control study to investigate the characteristics of vertebral osteomyelitis (VO) occurring in orthotopic liver transplant (OLT) recipients between 2000 and 2012. Nine cases were identified in 752 OLT recipients (1.2%), with a median time from OLT to VO of 12 weeks. In comparison with 27 VO not occurring in OLT patients (controls), VO occurring in OLT recipients was characterized by decreased levels of inflammation biomarkers (average C-reactive protein 65.1 $mg \cdot L^{-1}$ vs. 167 $mg \cdot L^{-1}$, p 0.02; average white blood cell count 4.8 × $10^9 \cdot L^{-1}$ vs. 12.9 × $10^9 \cdot L^{-1}$, p < 0.001), higher rate of fungal infections (3/9 vs. 0/27, p 0.01), lower rate of bacterial infections (3/9 vs. 25/27, p 0.001) and decreased proportion of positive blood cultures (1/9 vs. 16/27, p 0.02) despite a trend towards higher rate of multifocal infection. Microbiologic outcomes were similar between the two groups. Overall, VO in OLT patients was more difficult to diagnose as a result of altered inflammation response and specific microbial epidemiology of causal microorganisms.

Keywords: blood inflammatory markers, Fungal infection, liver transplant, microbiological diagnosis, vertebral osteomyelitis
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Introduction

Vertebral osteomyelitis (VO) is a severe infection, mostly occurring in patients with comorbidities [1]. VO are most commonly community acquired and are the result of pyogenic bacteria (ie; *Staphylococcus aureus,* streptococci and Enterobacteriaceae) according to the source of infection [1,2]. An immunocompromised status, such as immunosuppressive therapy after solid organ transplantation, could modify the epidemiology, clinical presentation and outcome of VO. In particular, orthotopic liver transplant (OLT) patients are at high risk of infection, notably bloodstream infections due to Enterobacteriaceae or fungi [3–5]. However, no specific data are available concerning VO in OLT recipients.

The aim of this study was to describe the clinical presentation, microbiologic epidemiology, therapeutic issues and outcome of VO in OLT recipients.

Methods

We performed a retrospective single-centre study of patients hospitalized in Beaujon Hospital, Clichy, France, between January 2000 and December 2012. Beaujon is a tertiary-care hospital and reference centre for liver transplantation and for vertebral surgery. We examined the hospital discharge database to identify all patients corresponding to VO (M463 1–9, M465, M86). Medical charts corresponding to these codes were critically reviewed to determine whether they met the definition of VO and the study criteria. A VO was defined by specific radiologic features (magnetic resonance imaging or computed tomographic scan) and final physician diagnosis leading to antimicrobial therapy.

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TABLE 1. Characteristics of vertebral osteomyelitis (VO) in patients with or without orthotopic liver transplant

Characteristic	Liver transplant (n = 9)	No liver transplant (n = 27)	p
Patients			
Average age (y)	52.7	69.1	0.008
Average weight (kg)	66.5	76	0.25
Diabetes mellitus, *n* (%)	4 (44)	4 (15)	0.08
Average serum creatinine clearance MDRD (mL/min)	88.3	90.2	1
Charlson's comorbidity index, median (range)	0 (0–3)	1 (0–6)	0.53
Clinical presentation of VO			
Spinal pain, *n* (%)	8 (89)	18 (67)	0.39
Fever (>38°C), *n* (%)	4 (44)	20 (74)	0.13
Neurologic complication, *n* (%)	3 (33)	16 (59)	0.26
Radicular neuropathy (*n*)	2	9	
Spinal chord compression (*n*)	1	7	
Delay from clinical signs to radiologic diagnosis (wk), median (range)	5 (1–9)	3 (0.4–28)	0.58
Biologic findings at diagnosis of VO			
Average C-reactive protein (mg/L)	65.1	167	0.02
Average white blood cell count (10^9/L)	4.8	12.9	<0.001
Radiologic findings at diagnosis of VO			
Location of infection in spine			
Cervical (*n*)	0	5	
Thoracic (*n*)	3	7	
Lumbar (*n*)	4	8	
Multifocal (*n*)	2	7	
Soft tissues abscess, *n* (%)	6 (67)	15 (56)	0.7
Epidural abscess, *n* (%)	5 (56)	24 (89)	0.05
Microbiologic findings			
Bacterial infection, *n* (%)	3 (33)	25 (93)	0.001
Staphylococcus aureus (*n*)	2	8	
Coagulase-negative staphylococci (*n*)	0	1	
Streptococcus spp. (*n*)	0	7	
Escherichia coli (*n*)	1	7	
Plurimicrobial (*n*)	0	2	
Fungal infection, *n* (%)	3 (33)	0	0.01
Aspergillus fumigatus (*n*)	2		
Candida albicans (*n*)	1		
Mycobacterium tuberculosis, *n* (%)	1 (11)	2 (7)	1
No microbiologic diagnosis, *n* (%)	2 (22)	0	0.06
Positive blood culture, *n* (%)	1 (11)	16 (59)	0.02
Computed tomographic scan–guided percutaneous needle biopsy (*n*)	6	7	
Positive culture, *n* (%)	4 (66)	6 (85)	0.56
Surgical site biopsy (*n*)	1	8	
Positive culture, *n* (%)	1	6	
Microbiologic diagnosis done on another focus of infection (*n*)	1	2	
Other characteristics of infection			
Concomitant focus of infection at other site, *n* (%)	4 (44)	3 (11)	0.05
Endocarditis, *n* (%)	0	5 (18)	0.3
Antimicrobial therapy			
Total duration (wk), median (range)	12 (6–88)	12 (6–52)	0.16
Time from clinical signs to antimicrobial therapy (wk), median (range)	6 (3–10)	2 (0–30)	0.07
Time from radiologic diagnosis to antimicrobial therapy (wk), median (range)	9.5 (0–14)	2.5 (0–21)	0.17
Incorrect first-line antimicrobial therapy, *n* (%)	0	3 (11)	0.56
Surgical treatment			
Indication for surgical treatment, *n* (%)	1 (11)	11 (41)	0.22
Because of mechanical complication (*n*)	0	2	
Because of neurologic complication (*n*)	1	9	
Outcome			
Lost to follow-up, *n* (%)	0	3 (11)	0.56
Time of follow-up (mo), median (range)	48 (7–150)	4 (0.2–90)	
Microbiologic success, *n* (%)	8 (89)	19 (79)*	1
Residual back pain (*n*)	5	5†	0.23
Failure (*n*)	1	5*	
Death during antimicrobial therapy (*n*)	0	3	
VO-related death (*n*)	0	3	
VO relapse (*n*)	0	2	
Microbiologic failure on another focus of infection (*n*)	1	0	

*Among 24 evaluable outcomes.
†Among 17 cases of evaluable back pain.

All cases of defined VO occurring in OLT recipients (Z944) were included in the VO-OLT population. A control VO group (VO-C) was selected among all discharge patients with a VO diagnosis, with three control patients for one case of VO-OLT patient. Controls were selected chronologically, corresponding to the three closest dates of radiologic diagnosis of VO. An exclusion criterion for the control group was a history of solid organ transplantation.

Initial clinical, biologic and radiologic data were collected for patients in each group, as were follow-up data. Microbiologic success was defined by the absence of relapse (spine localization or other focus) of infection due to the same pathogen responsible for VO during follow-up. In case of death during antimicrobial therapy, or during follow-up and related to VO complications, clinical outcome was considered to be failure.

Univariate analysis was performed to assess differences in characteristics of VO in OLT patients. Comparison among categorical variable was performed by Fisher's exact test and among continuous variables by the Mann-Whitney *U* test.

Results

During the study period, 752 OLT were performed, and VO occurred in 9 OLT recipients (1.2%). Characteristics of the nine VO-OLT patients are summarized in Table 1. Median age was 56 (range 28–61) years. Four had diabetes mellitus. Underlying liver disease leading to OLT were chronic hepatitis C (n = 4), chronic hepatitis B (n = 2), autoimmune hepatitis (n = 2) and alcoholic cirrhosis (n = 1), with associated fatty liver disease in three patients. Two had hepatocellular carcinoma at the time of OLT. In two cases, OLT was a second procedure. Median Model for End Stage Liver Disease score at OLT was 24 (range 19–40). Immunosuppressive therapy combined tacrolimus (n = 9) with mycophenolate mofetil in eight patients and azathioprine in one patient. Six patients were still receiving prednisone at the time of VO. Median time from OLT to VO diagnosis was 12 (range 4–41) weeks. During the time from OLT to VO, eight patients had at least one infection leading to antimicrobial therapy (bloodstream infections in six patients, ventilator-associated pneumonia in three and *Clostridium difficile* colitis in five). Two patients had four courses of antibiotic therapy, one had three, three had two and two had one course between OLT and VO.

At the time of diagnosis of VO, eight patients had back pain, four had fever and none had severe sepsis. Three patients had neurologic symptoms (radicular neuropathy in two, spinal cord compression in one). Median time from clinical symptoms of VO to radiologic diagnosis was 5 (range 1–9) weeks.

At diagnosis, median C-reactive protein (CRP) in VO-OLT patients was 33 (range 8–187) mg/L, with only two VO-OLT patients with CRP >50 mg/L; median white blood cells count was 4.7 (range 3.1–6.8) × 10^9/L. White blood cell count was normal (<10 × 10^9/L, with neutrophils <7.5 × 10^9/L) in all nine VO-OLT patients, whereas white blood cell counts were <10 × 10^9/L in eight VO-C patients (30%). No data were available for CD8 and CD4 T cell counts in OLT-VO patients at the time of diagnosis.

Radiologic findings on magnetic resonance imaging (n = 8) or computed tomographic scan (n = 1) included, in addition to features of VO, epidural abscess in five patients and paravertebral soft tissues abscess in six. Location of VO was lumbar (n = 4), thoracic (n = 3) or multifocal (n = 2). Microbiologic diagnosis of VO was definite for 7 patients. Three patients had bacterial VO (*Staphylococcus aureus* in two, *Escherichia coli* in one), three had fungal VO (*Aspergillus fumigatus* in two, *Candida albicans* in one) and one had VO due to *Mycobacterium tuberculosis*. Identification was done by blood culture in only one case (*S. aureus*). The eight other VO-OLT patients had negative blood culture results at the time of diagnosis. Percutaneous needle biopsy was performed for six of them and was positive in four (*A. fumigatus, C. albicans, E. coli, M. tuberculosis*). In one case, diagnosis was made on surgical samples taken during laminectomy (*S. aureus*). The last patient had multifocal infection caused by *A. fumigatus,* and microbiologic diagnosis was made by assessment of a cutaneous biopsy sample. For the two patients with negative percutaneous needle biopsy findings, there was no microbiologic diagnosis. In four patients, infection was disseminated in multiple foci: brain and disseminated skin lesions for one patient with *A. fumigatus* VO, lung and liver transplant for one patient with *M. tuberculosis* VO, infection of a soft tissue hematoma in one patient with *S. aureus* VO and knee arthritis for one patient with *C. albicans* VO; none had endocarditis.

Median time from clinical symptoms to antimicrobial therapy was 6 (range 3–10) weeks. Total duration of treatment was 12 (range 6–88) weeks. Duration of antimicrobial therapy was 12 (range 12–17) weeks for bacterial infections and 60 (range 11–88) weeks for fungal infection. Tuberculosis VO was treated for 52 weeks. For undocumented VO, an empirical antimicrobial therapy was based on previous bloodstream infections: daptomycin associated with cefotaxime in one patient and vancomycin in one, during 6 and 10 weeks, respectively. With the occurrence of VO in OLT patients, immunosuppression tended to be reduced as much as possible. Corticosteroids were stopped in 2 patients, and tacrolimus posology was reduced in 4 other patients, mostly because of drug–drug interactions (antifungal therapy), including one patient for whom corticosteroids were stopped and tacrolimus posology was reduced.

One patient had spinal cord compression leading to surgery, with laminectomy and spinal osteosynthesis.

Outcome was favourable in eight patients, with microbiologic success. One patient experienced relapse of infection at another focus (*Aspergillus fumigatus* and brain abscess). Five had residual back pain, with three requiring morphine. The patient with osteosynthesis also had neurologic sequelae. One patient died during follow-up as a result of hepatic failure (18 months after the end of antimicrobial therapy).

Compared to VO-C, age of VO-OLT patients was lower (p 0.008). CRP level and white blood cell count were lower in VO-OLT patients (p 0.02, and p < 0.001, respectively). Blood cultures were less frequently positive in VO-OLT patients compared to controls (p 0.02). Rate of fungal VO was higher (p 0.01) and rate of bacterial VO lower (p 0.001) among VO-OLT

patients. No patient had undocumented VO in the control group, versus two in the VO-OLT group, without statistical significance. There was also a trend towards higher rate of multifocal infection in VO-OLT patients (p 0.05) (= 1).

Duration of time from clinical signs to diagnosis and rate of microbiologic success did not significantly differ between the two groups.

Discussion

Nine cases of VO occurring in OLT patients are reported herein. To our knowledge, it is the first study describing the characteristics of VO in this specific population.

Although clinical presentation was comparable to the control group, and despite the occurrence of VO during hospitalization and close follow-up as a result of liver transplantation, duration of time from clinical symptoms to diagnosis was not different between the two groups. CRP level and white blood cell count were lower than in the control group. In a study reporting pyogenic VO in immunocompetent patients, no patient had normal white blood cell count [2]. The lower level of these blood inflammatory markers may be explained by the immunosuppressive status of the OLT patients and have probably played a role in the time for imaging and diagnosis of VO. Lower blood cell count could also be related to residual hypersplenism during the early posttransplant course and to mycophenolate mofetil treatment. However, elevation of CRP level in a liver transplant recipient is strongly suggestive of an infectious complication, and diagnosis of VO must be considered.

The trend towards a higher rate of epidural abscess (defined by dural thickening with fixation of gadolinium or iodine) in the VO-C group (89% vs. 56%) could be explained by the presence of a spine surgical unit in our centre with a specific recruitment of patients with neurologic signs associated with VO. Indeed, among the 24 patients with epidural abscess in the VO-C group, 16 had neurologic signs. This recruitment bias does not apply to patients who are already followed in our centre for OLT.

Concerning microbiologic diagnosis, the rate of positive blood culture was lower in the VO-OLT group despite a trend towards higher frequency of multifocal infections, leading to a biopsy procedure (percutaneous or surgical) being performed to optimize diagnosis. Multiple previous antibiotic therapies could have played a role in these difficulties to obtain microbiologic diagnosis [6]. Trend to longer duration of time between clinical signs and start of antimicrobial therapy in the VO-OLT patients may thus be partially explained by this delayed microbiologic diagnosis.

Differences in microbiologic epidemiology of causal pathogens for VO-OLT patients, notably with the higher rate of fungal infection, may be explained by patients' immunocompromised status, reflected by number of previous infections before VO. High antibiotic selective pressure related to previous antibiotic exposure certainly may had an impact [4]. The high incidence of *Clostridium difficile* colitis during the time between OLT and VO also reflects this high antibiotic exposure. Because of the particular epidemiology of VO in this population, our results emphasize the need for multiplication of samples, including bacterial, mycobacterial and fungal cultures and histologic study to optimize microbiologic diagnosis.

Despite their immunocompromised status, the rate of favourable outcome in VO-OLT patients was comparable to the control group. Few data are available concerning the duration of antimicrobial therapy for immunocompromised patients. For bacterial VO, no data suggest longer therapy duration for these patients [1]. Our results support the decision not to lengthen the duration of antibiotic therapy in this population. For fungal VO, no guideline is available for duration of therapy [7,8]. Considering the Infectious Diseases Society of America guidelines for *Candida* spp. and *Aspergillus fumigatus*–related osteomyelitis, antifungal therapy must be prolonged more than 6 to 8 weeks, and up to 12 months, for candidiasis [9,10]. These guidelines are mostly supported by case series or reports. In the three fungal VO cases reported herein, discontinuation of antimicrobial therapy was decided in regard to clinical and imaging evolution after a median of 60 weeks without relapse. Because of drug interactions, plasma levels of calcineurin inhibitors (e.g. tacrolimus and ciclosporin) should be closely monitored when associated with antifungal treatment.

Transparency declaration

All authors report no conflicts of interest relevant to this article.

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