Spondylodiscitis complicating infective endocarditis

Andreina Carbone ,[1] Audrey Lieu,[2,3] Basile Mouhat,[1] Francesco Santelli,[4] Mary Philip,[1] Yohann Bohbot,[2,3] Laetitia Tessonnier,[5] Fanny Peugnet,[2,3] Antonello D'Andrea,[6,7] Serge Cammilleri,[5] Quentin Delpierre,[2,3] Frédérique Gouriet,[8,9] Laurence Camoin-Jau,[9,10] Mesut Gun,[2,3] Jean-Paul Casalta,[8,9] Alberto Riberi,[11] Frederic Collart,[1] Hélène Martel,[1] Florent Arregle,[1] Eric Guedj,[5] Didier Raoult,[8,9] Michel Drancourt,[8,9] Christophe Tribouilloy ,[2,3] Gilbert Habib [1,9]

ABSTRACT

Objective The primary objective was to assess the characteristics and prognosis of pyogenic spondylodiscitis (PS) in patients with infective endocarditis (IE). The secondary objectives were to assess the factors associated with occurrence of PS.

Methods Prospective case–control bi-centre study of 1755 patients with definite IE with (n=150) or without (n=1605) PS. Clinical, microbiological and prognostic variables were recorded.

Results Patients with PS were older (mean age 69.7±18 vs 66.2±14; p=0.004) and had more arterial hypertension (48% vs 34.5%; p<0.001) and autoimmune disease (5% vs 2%; p=0.03) than patients without PS. The lumbar vertebrae were the most frequently involved (84 patients, 66%), especially L4–L5. Neurological symptoms were observed in 59% of patients. Enterococci and *Streptococcus gallolyticus* were more frequent (24% vs 12% and 24% vs 11%; p<0001, respectively) in the PS group. The diagnosis of PS was based on contrast-enhanced MRI in 92 patients, bone CT in 88 patients and ^{18}F-FDG PET/CT in 56 patients. In-hospital (16% vs 13.5%, p=0.38) and 1-year (21% vs 22%, p=0.82) mortalities did not differ between patients with or without PS.

Conclusions PS is a frequent complication of IE (8.5% of IE), is observed in older hypertensive patients with enterococcal or *S. gallolyticus* IE, and has a similar prognosis than other forms of IE. Since PS is associated with specific management, multimodality imaging including MRI, CT and PET/CT should be used for early diagnosis of this complication of endocarditis.

INTRODUCTION

Infective endocarditis (IE) is a devastating infection associated with high mortality and morbidity.[1 2] Pyogenic spondylodiscitis (PS) is a rare complication of IE.[3] The incidence of PS in IE, the risk factors predisposing to this complication and its prognosis are still uncertain.[3] The presence of PS may also have therapeutic implications, such as the choice and the duration of the antibiotic therapy.

The primary objective of our study was to assess the incidence, epidemiology, clinical presentation, prognosis and therapeutic implications of PS in patients with IE. The secondary objectives were to assess factors associated with occurrence of PS.

METHODS

We studied the records of all patients prospectively diagnosed with definite IE, according to the modified Duke criteria[1] in two French centres (Amiens and Marseille) and who were registered in a dedicated database between January 1990 and July 2018.

Patient and public involvement

All patients hospitalised for suspected IE were accepted on admission to participate in this research protocol. However, they were not involved in the design, conduct, reporting or dissemination plans of our research. The study complies with the Declaration of Helsinki. Written consent was waived by La Timone Institutional Review Board, which gave its approval for this study.

Methodology of the study

We analysed demographic data, underlying illnesses, predisposing cardiac risk factors, mean delay to diagnosis, clinical features, vertebral involvement, valve involvement, laboratory tests, bacteriological diagnosis, cardiac imaging, treatment and outcome, and whether vertebral or cardiac surgery was performed. Patients were followed for at least 6 months with careful attention to detection of IE and spondylodiscitis relapses. Echocardiographic assessment was performed in all patients, and their results were analysed and reported as recommended.[1]

Imaging techniques

Various imaging techniques were performed depending or their availability and investigator preference. All patients with suspected spondylodiscitis underwent bone CT, MRI and/or ^{18}F-fluorodeoxyglucose PET/CT (^{18}F-FDG PET/CT), to confirm the diagnosis and rule out affection of further vertebral segments or complications, for example, epidural abscess.

The interpretation of radiological and nuclear data was made by experienced radiologists and nuclear medicine physicians, respectively. Diagnostic criteria included oedema of the vertebrae and disc, paravertebral/epidural inflammation or abscess, bone erosion, and enhancement of vertebrae and disc after injection of gadolinium for MRI.[4] CT criteria included erosion/destruction of the endplates and vertebral bodies as well as

paravertebral/epidural inflammation or abscess formation.[5] ^{18}F-FDG PET/CT criterion for infection was visual, considered positive when FDG uptake was higher than bone marrow uptake in adjacent vertebrae and/or soft-tissue uptake was present.[6] PS diagnosis was further confirmed either by positive blood cultures and clinical follow-up or positive histopathological or microbiological samples gathered by open surgery or core needle biopsy.

Definitions

The diagnosis of IE was based on the modified Duke criteria.[1] The diagnosis of PS was established in the absence of prior surgery or spinal instrumentation, by the presence of compatible clinical picture (spinal pain and/or localised tenderness) and consistent imaging findings on plain x-ray films, CT, MRI and/or the isolation of the microbiological specimen in blood specimens or percutaneous bone biopsy.[7] In doubtful cases, the gold standard for the diagnosis of PS was an expert consensus of the Endocarditis Team, established 3 months after admission, and based on data obtained during follow-up, including results of clinical, microbiological and repeat imaging new information.

Statistical analysis

Patients with and without PS were compared using R software (V.3.5.1). Analysis results were presented as mean and SD for continuous variables and as frequency and percentage for

Table 1 Patients' characteristics

	All (n=1755)	IE+spondylodiscitis (n=150)	IE without spondylodiscitis (n=1605)	P value
Demographic and clinical data				
Age, years (range)	67 (51–87)	69 (51–87)	66 (52–80)	0.0266
Male sex, n (%)	1248 (71)	115 (76)	1133 (70)	0.065
Aortic prosthesis, n (%)	292 (17)	24 (16)	268 (17)	0.82
Mitral prosthesis, n (%)	176 (10)	15 (10)	161 (10)	0.27
Diabetes mellitus, n (%)	272 (15)	28 (19)	244 (15)	0.26
Hypertension, n (%)	626 (36)	72 (48)	554 (34)	<0.001
Coronary artery disease, n (%)	147 (8)	17 (11)	130 (8)	0.17
Renal insufficiency, n (%)	210 (12)	9 (6)	201 (12)	0.18
Cancer, n (%)	272 (15)	28 (19)	244 (15)	0.26
Autoimmune disease	47 (3)	8 (5)	39 (2)	0.35
Positive blood cultures, n (%)	1454 (83)	140 (93)	1314 (82)	<0.001
Causative pathogens				
Staphylococcus species, n (%)	537 (30)	44 (29)	493 (30)	0.27
– *aureus*, n (%)	390 (22)	29 (19)	361 (22)	0.27
– coagulase negative, n (%)	147 (8)	15 (10)	132 (8)	0.13
Streptococcus gallolyticus, n (%)	223 (13)	36 (24)	187 (11)	<0.001
Enterococcus species, n (%)	225 (13	36 (24)	189 (12)	<0.001
Echocardiographic data				
Location of IE:				
Aortic valve, n (%)	659 (38)	66 (44)	593 (37)	0.09
Mitral valve, n (%)	618 (35)	55 (37)	563 (35)	0.7
Tricuspid valve, n (%)	107 (6)	8 (5)	99 (6)	0.12
CDRIE, n (%)	204 (12)	7 (5)	197 (12)	0.005
Size of vegetation, mm	12 (2–22)	12 (2–22)	12.5 (3–21)	0.48
Cardiac surgery, n (%)	949 (54)	82 (55)	867 (54)	0.88
IE complications				
Total systemic embolism, n (%)	801 (46)	78 (52)	723 (45)	0.1
Heart failure, n (%)	391 (22)	41 (27)	350 (21)	0.12
Septic shock, n (%)	159 (9)	14 (9)	145 (9)	0.9
Mycotic aneurysm, n (%)	56 (3)	8 (5)	48 (3)	0.12
In-hospital mortality, n (%)	240 (14)	24 (16)	216 (13)	0.39
1-year mortality, n (%)	387 (22)	32 (21)	355 (22)	0.82
Site of pyogenic spondylitis				
Cervical		15 (10.9%)		
Thoracic		28 (20.4%)		
Lumbar		89 (66.9%)		
Others		5 (3.6%)		
Multifocal		22 (16.1%)		
Epiduritis		21 (15.3%)		
Psoas abscess		11 (8%)		
Vertebral abscess		9 (6.6%)		
Duration of antibiotic treatment (days (IQR))		70 (42–336)	44 (28–200)	0.0001

CDRIE, cardiac device–related infective endocarditis; IE, infective endocarditis; IQR, interquartile range.

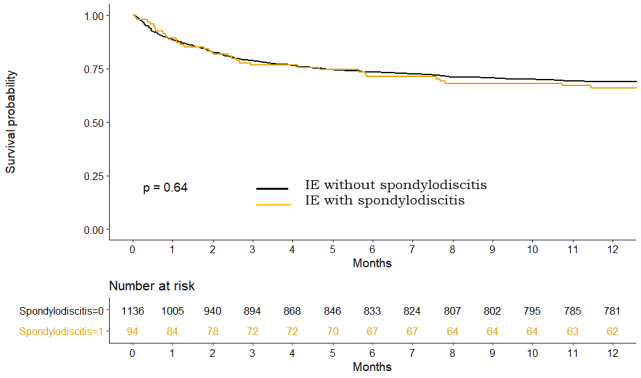

Figure 1 Kaplan-Meier survival curves for 1-year mortality in infective endocarditis (IE) according to the presence or not of spondylodiscitis.

categorical variables. Mantel-Haenszel test and linear random-effects models were performed to compare the two groups for categorical and continuous variables, respectively, taking also into account the potential cluster effect given that patients come from two different centres, Amiens and Marseille (online supplementary table 1). The value of $p<0.05$ was considered as significant. The Kaplan-Meier survival curves were presented to compare the survival curves between IE and spondylodiscitis–IE group by using the log-rank test, after a case-matching procedure to compare patients with similar characteristics in terms of sex and age. Further, a multivariable Cox regression model was performed to test if potential confounders have an impact on the mortality of patients with or without ES (online supplementary table 2).

RESULTS

During this study, 1755 patients with IE were analysed, such as in our preliminary analysis.[8] Baseline characteristics and main results are shown in table 1. Patients with PS were older, had more arterial hypertension and autoimmune disease than others. Among the 150 patients with PS, the diagnosis of PS was done within a delay ranging between 0 and 35 days (median 4, IQR 8.25). PS was clinically suspected in most patients, but 41% of them were asymptomatic and diagnosed by imaging alone.

Blood cultures were more frequently positive in the PS group (93% vs 82%, $p<0.001$). Enterococci and *S. gallolyticus* were more frequent in the PS group. Echocardiographic findings and biochemical data were similar between patients with and without PS.

The localisation of PS was lumbar in most cases and L4–L5 was the most frequently involved. PS was complicated in 30% (15.3% epiduritis; 8% psoas and 6.6% vertebral abscess).

The diagnosis of PS was based on contrast-enhanced MRI in 92 patients and bone CT in 88 patients. ^{18}F-FDG PET/CT was positive in 56 patients. Imaging tests performed included bone CT only in 10.3% of patients, vertebral MRI only in 24.6%, both vertebral CT and ^{18}F-FDG PET/CT in 13.5%, both vertebral MRI and ^{18}F-FDG PET/CT in 2.4%, both vertebral CT and MRI in 19.8%, all three imaging techniques in 26.2% and ^{18}F-FDG PET/CT only in 3.2% of patients. Vertebral biopsy was performed in eight patients and was diagnostic of PS in five cases.

IE complications, such as systemic embolism, heart failure and septic shock, were similar in the two groups (table 1), as were in-hospital and 1-year mortality (figure 1). No difference was observed in the survival curves between patients with or without PS, even considering significant confounders (age, presence of hypertension and presence of autoimmune disease) by Cox analysis (online supplementary table 2).

There was no difference in the incidence of IE relapses between patients with and without PS ($p=0.79$).

The median duration of total antibiotic therapy was 70 days (IQR 42–336, mean 65.17 days, ±48.7SD), with initial intravenous antibiotic therapy and subsequent oral therapy. Amoxicillin monotherapy was the most frequently used intravenous antibiotic. Amoxicillin with rifampicin was the most commonly intravenous association regimen (9%). An oral monotherapy was used in 59% of cases, including amoxicillin (58%), ceftriaxone (12%) or sulfamethoxazole (11%). The most commonly oral association was quinolone plus rifampin (7.8 %).

Complete recovery without disability at 12 months from diagnosis was achieved in 128 patients (85.3%) with PS. At 6 months of follow-up, 10 patients (6.6%) presented with IE relapse, and 3 patients had a spondylodiscitis relapse. Surgical treatment of spondylitis was required in five cases (3.9%).

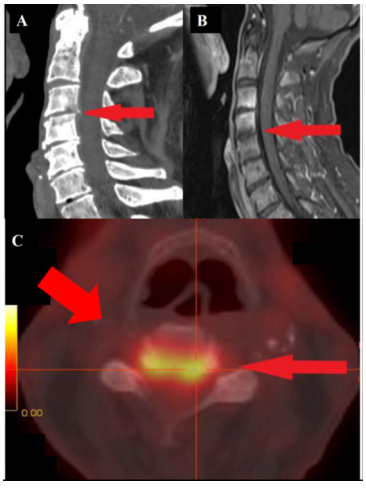

Figure 2 Streptococcal endocarditis complicated by a C3–C4 spondylodiscitis. (A) Sagittal CT showing loss of intervertebral space (lysis) between C3 and C4 (arrow). (B) Bone MRI in the same patient showing pathological low signal intensity (T1 sequence) between C3 and C4 (arrow). (C) Severe ^{18}F-FDG PET/CT uptake between C3 and C4 (arrow).

Key questions

What is already known on this subject?

- Pyogenic spondylodiscitis (PS) is a rare complication of infective endocarditis (IE). The incidence of PS in IE, the risk factors predisposing to this complication and its prognosis are still uncertain.

What might this study add?

- PS is observed in 8.5% of IE, in older hypertensive patients with enterococcal or *S. gallolyticus* IE, and has a similar prognosis than other forms of IE.

How might this impact on clinical practice?

- The relatively high frequency of PS in IE implies a careful research of vertebral infection in patients with IE for early detection of this severe complication, particularly in Enterococci and *S. gallolyticus* IE.

DISCUSSION

This study reports the largest series of PS complicating IE. The main results are

1. The frequency of PS is 8.5% of IE cases.
2. Patients with IE and PS are older than patients without PS and more frequently had Enterococci and *S. gallolyticus* infections.
3. MRI, CT scan and ^{18}F-FDG PET/CT are useful for the diagnosis of this complication of IE
4. The presence of PS is not associated with a worse long-term prognosis when the diagnosis is made early and an appropriate and prolonged antibiotic therapy is performed.

PS is a neurological and life-threatening condition which may progress to abscess formation with spread to adjacent structures and destruction of the intervertebral disc and vertebral bodies, resulting in spinal instability and neural compression.[9] A 11.5% incidence of PS has been reported by Murillo *et al*[10] in their series of 607 patients with IE. They reported *Staphylococcus aureus* and *S. viridans* as the most frequent pathogens, but found no difference of frequency of Enteroccoci and *S. gallolyticus* between patients with IE with or without PS. More recently, Anis *et al* found *S. aureus* to be the most common IE pathogen (63%) in patients with both IE and osteoarticular infection.[11] Conversely, we observed that Enterococci and *S. gallolyticus* were much more frequently observed in patients with PS in our series. This observation may be related to the older age of the patients with PS and the likely more frequent underlying vertebral lesions in this population.[12 13]

Several imaging techniques can be used to diagnose PS (figure 2). MRI is the most used due to its high sensitivity in the diagnosis of infection and evaluating the extent of disease. However, it may be sometimes difficult to perform, particularly in patients with pacemaker or defibrillator. In addition, it may be difficult to differentiate degenerative process from compression fractures and non-infective inflammatory disease.[14] Fuster *et al*,[15] in a series of 26 patients, showed that ^{18}F-FDG PET/CT was useful in the diagnosis of PS, with a sensitivity of 83% and a specificity of 88%. A recent meta-analysis reported that ^{18}F-FDG PET/CT had a better diagnostic accuracy than MRI[16] for the diagnosis of PS, presenting the advantage to diagnose PS and also to detect other peripheral infective foci and cardiac involvement.[17]

The duration of the antibiotic treatment in patients with IE with PS is not evidence based and still a matter of debate. Antibiotic therapy from 6 to 12 weeks[18] to a minimum of 3 months[19] has been recommended in isolated PS. In our series, prolonged antibiotic therapy in patients with IE and PS was associated with good outcome, few PS relapses and need for surgery. Conversely, although antibiotic duration is usually prolonged in IE associated with PS, this duration might tend to be shortened, according to the publication of Bernard *et al*, who showed that 6 weeks of antibiotic treatment, in isolated PS, was not inferior to 12 weeks of antibiotic treatment with respect to the proportion of patients with pyogenic vertebral osteomyelitis cured at 1 year.[18]

LIMITATIONS

The main limitation is inherent to long-term observational studies, including the changing availability over time of imaging techniques. It was also not possible to calculate the specificity and the sensibility of imaging technique in the absence of a control group and because the tests had not been performed in the whole cohort. In addition, since no consecutive screening was performed in patients with IE, there could have been additional cases of PS not recognised due to lack of perceived signs/symptoms of PS. Finally, although patients were prospectively included, the analyses were performed retrospectively. The retrospective nature of the study might have had an impact in the diagnostic tools used for the diagnosis of PS, as well as in the treatment for endocarditis and PS, since patients were included between 1990 and 2018.

CONCLUSIONS

The high frequency of PS in IE implies a careful research of vertebral infection in patients with IE for early detection of this severe complication, particularly in Enterococci and *S. gallolyticus* IE. Integrated multimodality imaging plays a pivotal role in the diagnosis of PS complicating IE. An appropriate oral therapy after the discharge is associated with good outcome and a low incidence of PS relapse.

Author affiliations
[1]Cardiology Department, APHM, La Timone Hospital, Marseille, France
[2]Pôle Coeur-Thorax-Vaisseaux, Department of Cardiology, University Hospital Amiens, Amiens, France
[3]Research Unity 2 EA 7517, MP3CV, Jules Verne University of Picardie, Amiens, France
[4]Department of Social Sciences, University Federico II, Naples, Italy
[5]Department of Nuclear Medicine, La Timone Hospital, Marseille, France
[6]Luigi Vanvitelli University—Naples, Monaldi Hospital, Naples, Italy
[7]Dipartimento di Scienze Cardio-Toraciche e Respiratorie, Università degli Studi della Campania "Luigi Vanvitelli, Naples, Italy
[8]URMITE, Aix Marseille Université, UM63, CNRS 7278, IRD 198, INSERM 1095—IHU, Marseille, France
[9]Aix Marseille University, IRD, APHM, MEPHI, IHU—Méditerranée Infection, Marseille, France
[10]Department of Hematology, La Timone Hospital, Marseille, France
[11]Department of Cardiac surgery, La timone Hospital, Marseille, France

Twitter Audrey Lieu @Lieu and Gilbert Habib @Gilbert HABIB

Contributors All authors have participated in the work and have reviewed and agreed with the content of the article. AC, BM and GH were mainly responsible for the conduct and writing of the study. All other authors contributed to the planning and reviewing of the study.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

REFERENCES

1 Habib G, Lancellotti P, Antunes MJ, *et al*. 2015 ESC Guidelines for the management of infective endocarditis: the Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J* 2015;36:3075–128.
2 Le Moal G, Roblot F, Paccalin M, *et al*. Clinical and laboratory characteristics of infective endocarditis when associated with spondylodiscitis. *Eur J Clin Microbiol Infect Dis* 2002;21:671–5.
3 González-Juanatey C, González-Gay MA, Llorca J, *et al*. Rheumatic manifestations of infective endocarditis in non-addicts. A 12-year study. *Medicine* 2001;80:9–19.
4 Arbelaez A, Restrepo F, Castillo M. Spinal infections: clinical and imaging features. *Top Magn Reson Imaging* 2014;23:303–14.

5 Abbey DM, Hosea SW. Diagnosis of vertebral osteomyelitis in a community hospital by using computed tomography. *Arch Intern Med* 1989;149:2029–35.
6 Bassetti M, Merelli M, Di Gregorio F, *et al*. Higher fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) uptake in tuberculous compared to bacterial spondylodiscitis. *Skeletal Radiol* 2017;46:777–83.
7 Pigrau C, Almirante B, Flores X, *et al*. Spontaneous pyogenic vertebral osteomyelitis and endocarditis: incidence, risk factors, and outcome. *Am J Med* 2005;118:1287.
8 Carbone A, Mouhat B, Lieu A, *et al*. P3666 Spondylitis: a frequent and severe complication of infective endocarditis. *Eur Heart J* 2019;40:ehz745.0521.
9 Cheung WY, Luk KDK. Pyogenic spondylitis. *Int Orthop* 2012;36:397–404.
10 Murillo O, Roset A, Sobrino B, *et al*. Streptococcal vertebral osteomyelitis: multiple faces of the same disease. *Clin Microbiol Infect* 2014;20:O33–8.
11 Anis HK, Miller EM, George J, *et al*. Incidence and characteristics of osteoarticular infections in patients with infective endocarditis. *Orthopedics* 2020;43:24–9.
12 Giordan E, Marton E, Scotton G, *et al*. Outcomes and risk factors for spontaneous spondylodiscitis: case series and meta-analysis of the literature. *J Clin Neurosci* 2019;68:179–87.
13 Berbari EF, Kanj SS, Kowalski TJ, *et al*. 2015 Infectious Diseases Society of America (IDSA) clinical practice guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults. *Clin Infect Dis* 2015;61:e26–46.
14 Hong SH, Choi J-Y, Lee JW, *et al*. MR imaging assessment of the spine: infection or an imitation? *Radiographics* 2009;29:599–612.
15 Fuster D, Tomás X, Granados U, *et al*. Prospective comparison of whole-body (18)F-FDG PET/CT and MRI of the spine in the diagnosis of haematogenous spondylodiscitis: response to comments by Soussan. *Eur J Nucl Med Mol Imaging* 2015;42:356–7.
16 Kim SJ, Pak K, Kim K, *et al*. Comparing the diagnostic accuracies of F-18 FDG PET and MRI for the detection of spondylodiscitis: a meta-analysis. *Spine* 2018.
17 Roque A, Pizzi MN, Cuéllar-Calàbria H, *et al*. ^{18}F-FDG-PET/CT angiography for the diagnosis of infective endocarditis. *Curr Cardiol Rep* 2017;19:15.
18 Bernard L, Dinh A, Ghout I, *et al*. Antibiotic treatment for 6 weeks versus 12 weeks in patients with pyogenic vertebral osteomyelitis: an open-label, non-inferiority, randomised, controlled trial. *Lancet* 2015;385:875–82.
19 Park K-H, Cho O-H, Lee JH, *et al*. Optimal duration of antibiotic therapy in patients with hematogenous vertebral osteomyelitis at low risk and high risk of recurrence. *Clin Infect Dis* 2016;62:1262–9.