

High prevalence of pyogenic spondylodiscitis cases in a third level university infectious diseases center: A case series and literature review

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Abstract. Spondylodiscitis, an infection involving the vertebrae and interposed discs, can arise from hematogenous spread or from direct virulent inoculation during spinal surgery. Symptoms are non-specific, with a subacute clinical course. Currently, the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) pandemic has led to a further delay in diagnosis, with devastating consequences and complications. The present study presents a case series with the aim of describing the etiology, clinical characteristics and complications of the cases of spondylodiscitis observed. The present study is a single-center retrospective case series of cases observed during the period from January 1 to June 30, 2022. Data were collected anonymously in an electronic spreadsheet. All patients signed a general informed consent to allow the anonymous use of their data upon admission. A total of 6 patients were admitted to hospital during the period of interest; 5 cases were primary cases (83.3%). During the same period in 2019, before the SARS-CoV-2 pandemics, only 2 cases of spondylodiscitis were diagnosed and treated, both primary infections. In 3 cases (50.0%) the infection only involved the lumbar vertebrae, in 2 cases (33.3%) it involved the dorsal and lumbar vertebrae, in 1 case it involved the localization was in the dorsal vertebrae (16.7%) and in another case, only

the cervical vertebrae were involved (16.7%). Etiology was identified in a Gram-positive germ [*Staphylococcus sciuri*, *Streptococcus agalactiae*, *Enterococcus faecalis*; methicillin-resistant *Staphylococcus aureus* (MRSA)] in 4 cases (66.6%), and in both a Gram-positive (MRSA) and a Gram-negative germ (*Pseudomonas aeruginosa*) in 1 case (16.6%). Of note, 1 case remained undetermined (16.6%). In 2 cases, an endocarditis secondary to primary spondylodiscitis was also found. On the whole, spondylodiscitis is a rare infectious disease with a subacute course, the origin of which often remains unrecognized. During the SARS-CoV-2 pandemic, the diagnostic delay led to an increase of >300% in the diagnoses at the authors' center and a worsening of the prognosis.

Introduction

Infectious spondylodiscitis (IS) is an inflammation of both the vertebrae and vertebral discs, extending towards the adjacent structures and resulting in the deterioration of the affected locations (1). Vertebral osteomyelitis is a rare occurrence, the incidence of which is ~2.4 cases per 100,000 individuals, and increasing with age (from 0.3 per 100,000 individuals aged ≤20 years to 6.5 per 100,000 individuals aged ≥70 years) (2,3).

There are two types of IS: Pyogenic and granulomatous (tuberculous, brucellar, fungal and parasitic) (4-6). Currently, tuberculosis accounts for ~24% of cases, while the majority of cases are pyogenic (5). Moreover, IS may have an acute, subacute, or chronic clinical course (7).

IS is characterized by an insidious onset and non-specific symptoms, such as back pain, fever, general malaise, weakness and weight loss. Due to the lack of specific symptoms, an early diagnosis is difficult and is often delayed by several weeks or even months (1). Diabetes, malnutrition, steroid therapy, rheumatic diseases and spinal surgery are risk factors for IS, whereas an older age worsens the prognosis (1,7,8).

Pathogens can infect the spine via three routes: By hematogenous spread, by direct external inoculation, or by

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spread from contiguous tissues (4). The most frequent route is the arterial one, which allows the seeding of infection from primary localizations to the spine (4,9). Pyogenic spondylodiscitis preferentially affects the lumbar spine (60%), followed by the thoracic (30%) and cervical spine (10%). The involvement of posterior elements of vertebrae is very rarely encountered in pyogenic spondylodiscitis, while it is more common with tuberculous and fungal spondylodiscitis (1,2,4-12).

From the literature, it is evident that there is an increased rate of primary and secondary bacterial infections during the COVID-19 pandemic (13-18). The present study is a case series study of 6 cases of pyogenic spondylodiscitis. The present study aimed to describe the prevalent etiology, together with clinical characteristics and main complications of the condition.

Patients and methods

A specific time span was selected for a retrospective evaluation. From January 1 to June 30, 2022, all case of spondylodiscitis admitted at the Infectious Disease Unit of the Garibaldi Hospital in Catania (Italy) were included. Their medical history, comorbidities, location of spondylodiscitis, time spent in hospital, age, pre-admittance treatment, possible causes of illness and clinical, laboratory and microbiology diagnosis were collected. To confirm the diagnosis of spondylodiscitis and exclude other causes, original radiographs, computed tomography images (CT), with CT-guided needle aspiration, magnetic resonance imaging (MRI) and transesophageal echocardiogram (TEE) images were evaluated. A measure of the pain intensity of the patients was performed using a numerical rating scale (NRS), which ranged from 0 (lowest pain intensity) to 10 (highest pain intensity). All the patients were >18 years of age and signed a general written informed consent for study purposes upon admission. This research was conducted according to the Declaration of Helsinki. It was approved as a retrospective minimally invasive experimental study by the Provincial Review Board of Messina on June 29, 2020, with the protocol no. 63/20 bis. During the 6-month time span, 6 consecutive cases entered the Unit of Infectious Diseases of the 'Garibaldi' Hospital in Catania, Italy for clinical management.

Case 1. A 53-year-old male with a medical history of thyroidectomy, monoclonal gammopathy and cutaneous leishmaniasis presented with fever and back pain radiating to the chest, lasting for 1 month. Upon admission to the ward, the patient was in good condition, apart from intense lower back pain, mostly on the left side. His blood pressure (BP) was 150/100 mmHg, his heart rate (HR) 64 bpm, oxygen saturation (SpO₂) was 99% in ambient air (AA) and his body temperature was 36.5°C. A physical examination (PE) of the chest revealed physiological breath sounds, rhythmic heart activity and a 2/6 systolic murmur to the centrum cordis. A blood cell count analysis revealed a white blood cell (WBC) count of 6,400/ μ l, C-reactive protein (CRP) levels of 12 mg/l (normal values, \leq 5 mg/l) and an erythrocyte sedimentation rate (ESR) of 88 mm/h. During the admission, Wright's sero-diagnosis was performed to detect any contact with *Brucella spp.*, which yielded negative results, and an interferon-gamma

release assay (IGRA; QuantiFERON®, Qiagen GmbH), which yielded weak positive results. Blood and needle aspiration cultures yielded negative results. The first MRI of the spine, carried out on the 7th day since admission, revealed a spondylitis (D7-D8) and a collection of fluids inside the spinal canal (D4-D8) (Fig. 1, case 1). An antibiotic therapy with intravenous (i.v.) teicoplanin at 12 mg/kg four times a day (qid) and i.v. Fosfomycin at 4 g qid was commenced. Despite antibiotic therapy, a fever (body temperature, >37.5°C) was observed on the 17th, and 33rd day since the admission. The patient underwent another MRI on the 33rd day since the admission, which revealed a slight improvement of the vertebral inflammation and the abscess. On the 36th day since the admission, a transthoracic echocardiogram (TTE) revealed the presence of three rounded hyperechogenic formations: The first one (maximum diameter, 8x6 mm) was on the posterior flap of the mitral valve, the second one (maximum diameter, 6x3 mm) was on the front flap and the third one (maximum diameter, 7x6 mm) was on the free margin of the coronary cusp of the aortic valve. Therefore, he underwent a TEE which only confirmed the presence of two small endocarditic formations on a coronary cusp of the aortic valve, with the mitral valve free from endocarditic formations. A diagnosis of infectious endocarditis was then made. Therapy with gentamicin at 3 mg/kg qid was commenced, according to the European Society for Cardiology (ESC) guidelines (19), and teicoplanin was replaced with daptomycin at 12 mg/kg qd iv. Therapeutic drug monitoring (TDM) for gentamicin was performed. Following the appearance of a skin rash, the antibiotic treatment was terminated. Teicoplanin, gentamicin and fosfomycin were commenced again after a 48-h wash-out. The patient was treated for a total of 68 days with teicoplanin and Fosfomycin, and 15 days of gentamycin. At 3 days after gentamicin treatment was terminated, he underwent a TTE which revealed scarring on the aortic valve and a mild valvular insufficiency. After 68 days from the admission, a re-evaluation with an MRI revealed a marked regression of the spondylodiscitis images. On day 83, his blood count revealed a WBC count of 4,100/ μ l (neutrophils, 49.4%). His CRP level was 1.9 mg/l and the ESR was 17 mm/h. The patient was discharged on day 92.

Case 2. A 73-year-old female, affected by arterial hypertension, underwent a D9-L1 arthrodesis for a T11 inveterate fracture in 2020. She came to our attention as an outpatient for persisting back pain. She had also undergone an MRI of the spine which revealed inflammatory lesions at the D8-D9 level, compatible with spondylodiscitis by superinfection (Fig. 1, case 2).

Upon admission to the ward, the patient was in good general condition. Her BP was 150/70 mmHg, her HR was 92 bpm and SpO₂ was 95% in AA. She complained of hyposthenia in the lower limbs, which indicated non-elicitable tendon reflexes. A blood count analysis revealed a WBC count of 7,400/ μ l, a CRP level of 310.9 mg/l, and an ESR of 65 mm/h. Wright's sero-diagnosis and IGRA tests yielded negative results. Both blood cultures and a CT-guided needle aspiration of the vertebral location revealed infection with resistant *Staphylococcus aureus*. The results of the MRI of the spine was affected by ferromagnetic artifacts of the previously positioned vertebral stabilization system. Therefore, she underwent a CT scan of the spine which revealed an alteration of the

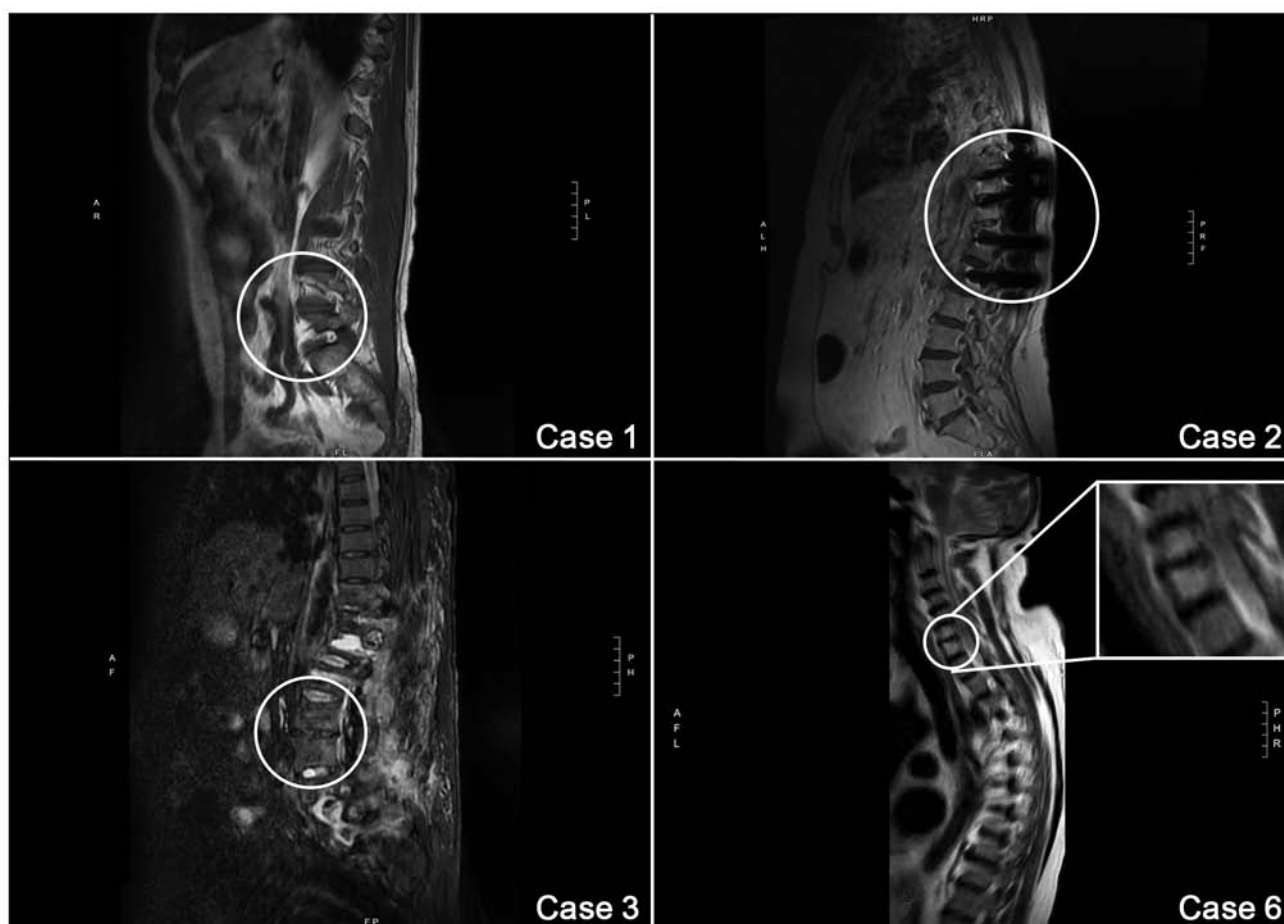


Figure 1. This four-panel figure presents the MRI results upon admission of the patients in cases 1, 2, 3 and 6. An MRI for cases 4 and 5 was performed at external facilities prior to admission to the authors' unit. Case 1: D7-D8 spondylitis with a collection of fluids inside the spinal canal (D4-D8); case 2: Inflammatory lesions at D8-D9 level, compatible with spondylodiscitis by superinfection; case 3: Subfascial and paravertebral fluid collection going from L4 to L5, also flanking the metallic bone fixators from D12 to S1; case 6: Fluid collections in the anterior epidural intra-rachides and in the left paramedian paravertebral tissues.

D8-D9 soma. The patient underwent a TTE and TEE on the 19 and 25th day of hospitalization, respectively. These imaging tests did not reveal any endocardial vegetation. Antibiotic therapy with daptomycin at 8 mg/kg qid (i.v.) and rifampicin at 10 mg/kg twice a day (bid; i.v.) was commenced. Treatment with meropenem at 1 g three times a day (tid; i.v.) was added based on the antibiogram due to a mild increase in CRP levels, for a total of 40 days. A consulting neurosurgeon gave no indication of surgery and suggested to mobilize the patient with a back brace. She also underwent kinesiotherapy daily for neuromuscular reinforcement. The patient was discharged on day 58 in good general condition. She continued the antibiotic treatment with rifampicin at 450 mg bid, doxycycline at 100 mg bid and cefixime 400 mg at qid for an additional 28 days.

Case 3. A 73-year-old female, presented to the Infectious Diseases Unit of the 'Garibaldi' Hospital in Catania, affected by diabetes mellitus type 2, arterial hypertension, dyslipidemia, depressive syndrome, post-thyroidectomy hypothyroidism. She had undergone an arthrodesis of thoracic and lumbar vertebrae in 2015 and 2017. Following a surgical wound dehiscence, the prosthetic material used for the arthrodesis was removed and cultured, revealing infection

with methicillin-resistant *Staphylococcus aureus* (MRSA) and *Enterococcus faecalis*. Therefore, she was admitted to the infectious disease ward to undergo antibiotic treatment. Upon admission, she was feverish, but in a good overall condition; her BP was 110/60 mmHg, her HR was 75 bpm, her SpO₂ was 96% in AA and her body temperature was 38.0°C. A PE highlighted a fistula formation on the surgical scar. Blood tests revealed a WBC count of 9,000/ μ l, CRP levels of 45.2 mg/l and an ESR of 89 mm/h. Serial blood testing and imaging were performed during the admission. An MRI of the spine revealed the presence of a subfascial and paravertebral fluid collection going from L4 to L5, also flanking the metallic bone fixators from D12 to S1 (Fig. 1, case 3). A CT of the spine revealed a continuity solution of ~13 cm in the skin and subcutaneous tissue of the lumbar region with hyper dense material inside. Moreover, this area was surrounded by partially colliquated tissue up to the fascial plane. Based on the sensitivity test performed on a culture, a targeted antibiotic therapy with teicoplanin at 10 mg/kg qid and doxycycline at 100 mg bid for 28 days, and gentamicin at 3 mg/kg qid for 14 days was commenced. Following a neurosurgical consultation, the need for debridement surgery of the fistula and surrounding tissue was highlighted; however, succumbed due to sepsis following surgical debridement.

Case 4. A 55-year-old male, whose clinical history revealed recurrent dental abscesses, complained of lower back pain for ~1 month following a fall. He had undergone antalgic therapy with no benefit. Therefore, he referred to the emergency department of another hospital, where he was diagnosed with lumbar sciatica. For the persistence of the symptomatology, he underwent an MRI of the spine at an external outpatient clinic, which highlighted spondylodiscitis in L1-L2 with lysis of the anterior cortical profile, and an abscess in front of the vertebral soma from T10 to L2. Upon admission to the Infectious Diseases Unit of the 'Garibaldi' Hospital in Catania he was in a fair general condition, complaining of lower back pain (visual analogue scale, 7) with functional limitation. His BP was 120/90 mmHg, his HR was 85 bpm, his SpO₂ was 97% in AA and his temperature was 37.2°C. Blood tests revealed a WBC count of 11,800/ μ l (neutrophils, 81.9%), CRP levels of 139.7 mg/l and an ESR of 89 mm/h. Wright's sero-diagnosis yielded negative results. The patient underwent a CT-guided aspiration of a vertebral abscess. Pus culture revealed the presence of MRSA, while a blood culture revealed the presence of mixed flora, with methicillin-susceptible *Staphylococcus aureus* and *Pseudomonas aeruginosa*. On the 8 and 25th day he underwent a TTE and TEE, respectively to exclude endocarditic formations of the valve systems. He had several sudden high fever peaks (maximum body temperature, 38.5°C). The fever disappeared soon after the commencement of empirical antibiotic therapy with teicoplanin at 12 mg/kg qd, levofloxacin at 750 mg qd and fosfomycin at 4 g qid. The empirical antibiotic therapy regimen was selected according to the patient's medical history and imaging tests. Since the antimicrobial sensitivity tests revealed that the etiological agent was sensitive to all the antimicrobials used for the empirical treatment, the therapy was not changed. The patient underwent this treatment for a total of 42 days. At the time of discharge, blood tests revealed a WBC count of 4,300/ μ l CRP levels of 9.7 mg/l and an ESR of 14 mm/h. The patient was then discharged in a good general condition with a lumbar back brace, according to the suggestion of the neurosurgeon. He continued antibiotic treatment with doxycycline at 100 mg bid and levofloxacin at 750 mg qid for a further 28 days. The second spine CT, performed at the end of the treatment, revealed the disappearance of the abscess and residual spondylosis in L1-L2.

Case 5. An 83-year-old male, affected by bradycardia treated in 2020 with a bicameral pacemaker (PM), prostate cancer diagnosed in 2019 for which he underwent radiotherapy, and carrier of a left knee prosthesis, underwent an orthopedic evaluation at a private practice, and an X-ray of the spine, pelvis and hip with evidence of advanced spondylarthrosis in L3-L4, L5-S1, due to the appearance of sudden sacroiliac pain ~4 months prior to hospitalization. For his history of prostate cancer, upon the advice of the orthopedist, he underwent a total body scintigraphy. The examination revealed hyperaccumulation of radiopharmaceuticals in the lumbar vertebrae, due to dystrophic-degenerative pathology. His oncologist then suggested therapy with cortisone and non-steroidal anti-inflammatory drugs. Pain reappeared upon the end of the treatment. Therefore, he referred to the emergency department of another hospital in Catania and was admitted to the neurosurgery ward.

During this admission, he was diagnosed with lumbar sciatica and left lumbosacral spondylar disco-arthritis and was then discharged with an antalgic therapy based on morphine-like drugs. He had to terminate the antalgic treatment due to the appearance of drowsiness. As the lower back pain persisted, he underwent an MRI of the lumbosacral spine at a private practice, which revealed spondylar-discopathy L3-L4, L4-L5 and L5-S1 with bilateral abscesses in the context of the psoas muscles. Upon admission to the Infectious Diseases Unit of the 'Garibaldi' Hospital in Catania, he was in good general clinical conditions. Vital parameters were good: His BP was 120/50 mmHg, his HR was 80 bpm, his SpO₂ was 98% in AA and his temperature was 36.5°C. An empirical antibiotic therapy with teicoplanin at 12 mg/kg/die and rifampicin at 12 mg/kg/die was commenced after obtaining samples for blood cultures. Due to the accessory diagnostic hypothesis of endocarditis, he underwent a TTE on the 3rd day of admission. The examination revealed the presence of a formation on the left aortic cusp and a thickening of the other cusps attributable to endocarditic vegetations projecting in the left ventricle and determining moderate aortic insufficiency. After 2 days, a TEE was performed, which confirmed the presence of three mobile vegetations, one in each aortic cusp, and two vegetations on the anterior mitral flap, while the electro-catheter of the PM was free from vegetations. Therefore, gentamicin at 3 mg/Kg qid was added to the treatment regimen and was administered for 17 days on TDM. On the 11th day since the admission, a CT of the spine revealed lumbo-arthritis with osteophytes bridge and at the level of L3-L4 and L4-L5 bone lysis and structural alteration of the lithic type. From the blood cultures a methicillin-resistant *Staphylococcus sciuri* was isolated. The bacteria tested sensitive for empirical antibiotic treatment, which did not require any adjustments.

On the 30th day of hospitalization, the patient exhibited dyspnea and a sensation of thoracic constriction. An ECG was performed, and the troponin curve was raised. After performing a coronary angiography, which revealed an occlusion of ~90% of the right coronary artery, he underwent a percutaneous transluminal coronary angioplasty with the placement of two stents. After 7 days in a cardiological environment for post-treatment observation, the patient returned to the authors' ward to continue treatment for IS. He underwent 56 days of treatment with rifampicin 12 mg/kg/die and teicoplanin 12 mg/kg/die. However, on the 60th day since the admission, the patient discharged himself against medical advice.

Case 6. A 73-year-old male, affected by diabetes mellitus, obesity, previous cancer of the anal-rectal joint for which he underwent chemo- and radiotherapy with resulting actinic phimosis, dyslipidemia and arterial hypertension, referred to the Emergency Department of the 'Garibaldi' Hospital in Catania for the appearance of cervicalgia, hypotonia and mild functional impotence of the upper limb, reporting a recent infection of the inner ear. He was bedridden following a left femur fracture which occurred 7 months prior to admission. He was first admitted at the Internal Medicine Ward of the 'Garibaldi' Hospital, where he underwent a CT scan of the cervical spine. The examination revealed a protrusion of the intervertebral discs between C4-C5 and C5-C6, and the

Table I. Demographic data of the patients in the present case series.

Case no.	Sex	Age, years	Predisposing factors
1	Male	53	Thyroidectomy, gammopathy, cutaneous leishmaniosis
2	Female	73	Spine surgery D9-L1
3	Female	73	Spine surgery D12-L5, diabetes mellitus, hypothyroidism
4	Male	55	Recurrent dental abscesses
5	Male	83	Carrier of pacemaker, radiotherapy for prostate cancer
6	Male	73	Diabetes mellitus, obesity, rectal cancer chemo- and radiotherapy

presence of posterior marginal-somatic osteophytes in C3-C4, C5-C6 and C6-C7. He also underwent an MRI of the column, which revealed the presence of fluid collections in the anterior epidural intra-rachides and in the left paramedian paravertebral tissues (Fig. 1, case 6). Blood culture analysis yielded positive results for *Streptococcus agalactiae*. A specific antibiotic therapy was commenced with levofloxacin at 750 mg qid, and he was transferred to the Infectious Diseases Unit of the 'Garibaldi' Hospital in Catania. Upon admission, he was in a good general condition with a BP of 125/70 mmHg, a HR of 60 bpm, a SpO₂ of 96% in AA, a body temperature of 36.6°C, hemo glucose test resulted 230 mg/dl. Blood test analyses revealed a WBC count of 8,730/ μ L a CRP level of 226.8 mg/l and an ESR of 55 mm/h. Wright's sero-diagnosis yielded negative results, as IGRA did. A TTE was performed, excluding infectious endocarditis. Treatment with rifampicin at 600 mg bid (i.v.) and teicoplanin at 600 mg bid was commenced, in addition to levofloxacin 750 mg/die for a total of 28 days. A contrast cervical MRI revealed that the anterior epidural intra-rachides collection extended from C4 to D1 and highlighted the presence of a second collection in front of the C6-C7 cervical vertebral bodies. A consulting neurosurgeon ruled out the chance of a surgical approach and recommended the use of a cervical collar.

Results

The median age of the included patients in the present study was 63 years [interquartile range (IQR), 59.5-75], with a male to female ratio of 2:1. The median interval between the onset of symptoms and admission was 6 months (IQR, 1.9-10.5).

The risk factors predisposing to spondylodiscitis are presented in Table I. The most frequent localization of spondylodiscitis observed in the patients in the present case series was the lumbar spine (in 3 cases, 50%), the thoracic spine in 2 cases (33.3%) and the cervical spine in 1 case (16.7%). In the 5 cases in which it was possible to isolate the pathogenic microorganism, a targeted and specific therapy was carried out, while in the remaining case, a broad-spectrum empirical therapy was set up.

CT scan was used as the selected radiological analysis tool for all patients for monitoring epidural and paraspinal abscesses, and at diagnosis, in patients who could not undergo an MRI. All patients had radiographic findings of intervertebral disc space narrowing with the erosion of the vertebral endplate and the collapse of the vertebral bodies at the infectious level. Moreover, 1 patient (16.7%) had epidural abscess, 2 patients

(33%) had paraspinal abscess accumulation, 1 patient had both paraspinal and epidural abscesses (16%) and 1 patient had no abscesses (16%).

A TTE was performed in all patients with non-post-surgical spondylodiscitis. In 2 cases, the suspicion of infectious endocarditis was raised, and the diagnostic procedure continued with the TEE, confirming the infectious endocarditis. In one of the 2 cases, methicillin-resistant *Staphylococcus sciuri* was isolated in the blood, while in the other case, it was not possible to detect the pathogen.

The median length of the hospital duration was 41.5 days (IQR, 32.8-54.0). All patients received parenteral antibiotics, and the median duration of antimicrobial therapy was 55.0 days (IQR, 30.0-64.3). In addition, 1 patient underwent surgical treatment.

Positivity in the IGRA test required a rifampicin-sparing antibiotic treatment. All patients received a combination therapy of at least two antibiotics for spondylodiscitis, and in cases of associated infectious endocarditis, gentamicin was added for a duration of 14 days. In total, 5 out of the 6 patients received teicoplanin in combination with rifampicin (2/5 patients) or fosfomycin (2/5 patients) or doxycycline (1/5). In 2 cases, and particularly those with a microbiological isolate, levofloxacin was used. Along with antimicrobial therapy, pain management was carried out. The drug dosages were progressively decreased, with the reduction of the pain. In 1 case, surgical treatment was necessary to remove infected fixation materials.

A total of 3 patients, following clinical improvement and the results of laboratory data, were discharged with oral therapy and 2 patients were transferred to other departments for further treatment; 1 patient succumbed due to sepsis following surgical debridement.

Discussion

In the present case-series, the most frequent cause of spondylodiscitis was haematogenic dissemination, as reported in the literature. The majority of patients with spondylodiscitis have at least one of the risk factors, such as old age, diabetes, an immunocompromised state, steroid therapy, infection in other foci, history of spinal surgery (20-22). No association was observed with urinary tract infections, although some studies have reported such an association (3,4,21,23).

The clinical symptoms of spondylodiscitis are associated with the affected region, with back pain being the first symptom to appear, as observed in the cases described herein

and in literature, and this may be followed by neurological deficits, such as muscle weakness, numbness and paralysis, which are often misdiagnosed as overload disorders of the spine, delaying the correct diagnosis. In the majority of cases, the disease affects the lumbar region, followed by the thoracic and cervical region. In all the cases in the present case series, pain radiated from the spine to the upper or lower limbs, depending on the localization of damage (3,7,24). Usually, post-operative spondylodiscitis has a more acute onset, with symptoms appearing from days to few weeks after the procedure and being led by pain. This delay is related to the development of inflammatory tissue in the intervertebral space, and pain increases over time (7). It is important to always consider vertebral osteomyelitis in patients complaining of back pain, whose ESR is increased. As vertebral osteomyelitis is a localized infection, fever may be absent, particularly in elderly patients, and when there is no sign of a concurrent bloodstream infection (22).

Microbiological isolates are of utmost importance to pass from an empiric treatment to a targeted one. Moreover, if there is no sign of any concurrent life-threatening infection, it has been suggested to begin an antimicrobial treatment with i.v. antibiotics on the basis of microbial identification and sensitivity tests (2,12). As reported in the literature, the most frequently isolated bacterium in spondylodiscitis is *Staphylococcus aureus* followed by *Enterobacteriaceae* (4,7,12,22,24). The present case series confirms the data reported in the literature. In fact, following the exclusion of tuberculosis and brucellosis infections, the authors were able to isolate at least a microorganism in 5 cases, and the most common was *Staphylococcus* spp. When there are no positive blood cultures, a bone biopsy must be performed to identify the agent responsible for vertebral osteomyelitis and to select an appropriate therapy (11,22). Although in the present case series it was not possible to perform the bone biopsy, the abscess was drained, where possible, following evaluation by the interventional radiologist, and the collected liquid was placed in culture. The most frequent reasons for a negative culture on a bone biopsy or on material of aspiration, or on blood culture, are sampling errors and prior antibiotic therapy (22).

As reported in other studies, an MRI has the highest definition of paravertebral and epidural spaces, and it allows for the early detection of vertebral osteomyelitis and the assessment of any compression of neural elements, with high sensitivity and specificity (3,8,25-27). The use of a CT scan with contrast may be an alternative when searching for bone destruction, in order to plan a spinal biopsy and surgery (6). However, a CT scan has a lower sensitivity and specificity than an MRI, and it should only be preferred when an MRI is contraindicated (7). In the present study, all patients underwent an MRI upon admission to the ward and were followed-up with an MRI or CT scan at the end of the treatment period. Nuclear medicine is becoming increasingly used for the diagnosis of infectious diseases (28,29). Abnormal metabolic activity can be highlighted with high sensitivity using gallium-67 citrate and technetium-99m radioisotopes. These techniques have a ~94% sensitivity in the diagnosis of discitis and are particularly useful in detecting early disease. However, false negative results have been observed, particularly in elderly patients. It is suggested that the most probable cause may be regional

ischemia; therefore, a negative result does not offer a definitive exclusion. 18F-Fluorodeoxyglucose PET has been increasingly used to localize vertebral abnormalities and monitor response to treatment (25,30).

The treatment of spondylodiscitis is highly variable, depending on the team of physicians and local preferences, although some therapeutic guidelines are available. This results in high outcome variability (5,30). It has been established that bone is a difficult-to-treat tissue, since a number of antibiotics are not able to reach adequate concentrations in it. Fluoroquinolones, clindamycin and rifampicin achieve excellent levels in bone; β -lactam antibiotics and glycopeptides achieve moderate levels, whereas aminoglycosides concentrate poorly in bone (25). When treatment cannot be delayed, particularly in febrile patients with suspected dissemination of the infection, empiric antimicrobial therapy should be selected among those drugs active against *Staphylococci*, including MRSA, *Streptococci* and Gram-negative bacilli. Usually, these regimens include vancomycin plus a cephalosporin active on Gram-negative bacilli. In the case of allergy or intolerance, daptomycin and a quinolone may be included (11). In Italy, teicoplanin, a glycopeptide with a higher tolerance and easier handling than vancomycin is also available and has been approved for use in acute bacterial skin and skin structure infections, bone and joint infections, community-acquired and healthcare-acquired pneumonia, complicated urinary tract infections and infectious endocarditis (31). The availability of this drug allowed for the use of vancomycin for the patients described herein. In the present case series, teicoplanin was often combined with rifampicin, an anti-staphylococcal antibiotic with an excellent penetration into the bone. In addition, fosfomycin (i.v.) was also used in complicated cases. Fosfomycin exhibits good activity against Gram-positive and Gram-negative microorganisms, even on multidrug-resistant strains, and it also reaches a good concentration in bone (32-34). However, only a limited number of studies on the use of this drug for osteomyelitis are available (35-37). Conservative treatment for non-specific spondylodiscitis consists of 6 to 12 weeks of antibiotic treatment (i.v.), which may be combined with bed rest and/or an orthosis. Conservative treatment is the treatment of choice in the majority of the cases. Antibiotics are administered (i.v.) for at least 2-4 weeks and then orally (2,5,10,21,25). A high risk of treatment failure is associated with a shorter antibiotic (i.v.) course. The decision to discontinue the treatment should be dependent on patient improvement, CRP and ESR normalization (7).

However, as previously observed, there are no updated guidelines for the duration and selection of antibiotic therapy (4,7,25,38). In the present case series, the i.v. therapy had to be terminated before the lower limit of 6 weeks only in 1 case due to the patient leaving the hospital. The other cases were treated intravenously for >4-6 weeks, and even continued with oral therapy as their clinical conditions dramatically improved, allowing discharge.

Patients should use a brace, corset, or lumbar support belt. The immobilization of the affected segment is of utmost importance in conservative therapy, since adequate immobilization replace prolonged bed rest, improving the quality of life of the patients from the first days of treatment. For the

cervical spine, immobilization can be achieved using a collar or halo-fixator. For the mid-thoracic spine, a reclining brace is sufficient (2).

In some cases, targeted antimicrobial treatment is not sufficient and surgical debridement and stabilization is required. The decision to use a surgical approach should be made on the basis of clinical signs, such as the presence or signs of roots in the MRI, spinal cord or dura mater compression, mechanical instability or spinal deformity due to bone destruction or severe deformity, and intractable pain (5,6). Clinically unsuccessful medical treatment, for example in a patient with persisting pain, may also be an indication for surgery (6,39). Finally, surgical treatment is necessary if the antimicrobial treatment does not stop the progression of the disease. Surgery consists of removing the mechanical cause of pain; therefore, decompression of neural structures or drainage of abscesses are the most frequent procedures (3,4,7). Surgery is associated with a high operative risk, particularly in elderly patients; therefore, a conservative approach should be preferred, particularly if clinical symptoms and destruction of the spine are mild, or when the operative risk appears too high (21).

The present study had some limitations. Due to the retrospective design, some important clinical characteristics may not have been recorded. Moreover, the duration of i.v. antibiotic treatment was selected on a case-by-case basis according to clinical, microbiological and laboratory resolution. Moreover, it was not possible to perform a bone biopsy for microbiological diagnosis. The strength of the present study is the through the description of diverse cases, which are all included in the 'spondylodiscitis' category, but present a detailed overview of different aspects of the same disease.

In conclusion, the present study describes six different cases of spondylodiscitis. This infectious disease is difficult to diagnose, due to its confusing clinical characteristics; the cases described herein demonstrate that it must be always considered as a differential diagnosis in a patient with back pain and increased levels of inflammatory markers. It is also important to investigate the simultaneous presence of abscesses, as well as endocarditis, as both can be either the result or the cause of an infectious spondylodiscitis. Antibiotic therapy should be i.v., and it should be carried out for at least 6 weeks, starting from an empirical therapy. A take-home message of this article is related to the short time during which an otherwise rare occurrence was observed in such a high prevalence. The diagnostic delays and lack of specialized cures, due to the COVID-19 pandemic, have led to the misdiagnosis of primary infections causing the occurrence of secondary spondylodiscitis. Possibly, due to the persistent status of emergency, even more rare diseases presenting with a high prevalence may be observed in the future.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

MC, AM, BSC and GN conceptualized the study. BSC and GN supervised the study. MC and BB were involved in project administration and in formal analysis. BB, AEC, EP, LT, CM, EVR, LL, RR, AZ and RB were involved in clinical and laboratory investigations. MC, BB, AEC, EP, LT, CM, EVR, LL, RR, AZ and RB were involved in data curation. BB, MC and AM were involved in the writing and preparation of the original draft. MC, AM, BSC and GN were involved in the writing, reviewing and editing of the manuscript. All authors have read and approved the final manuscript. MC, AM, and BSC confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present study was conducted according to the Declaration of Helsinki. It was approved as a retrospective minimally invasive experimental study by the Provincial Review Board of Messina on June 29th, 2020, with the protocol no. 63/20 bis. Patients signed a written informed consent to the use of their data for research.

Patient consent for publication

Patients signed a written informed consent to the use of their data for research and publication purposes upon admission.

Competing interests

The authors declare that they have no competing interests.

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