Spondylodiscitis in hemodialysis patients: a new emerging disease? Data from an Italian Center

Articoli Originali

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ABSTRACT

Hemodialysis (HD) patients are at high risk for infectious complications such as spondylodiscitis. The aim of this retrospective study was to evaluate the cases of infective spondylodiscitis occurred between May 2005 and October 2019 among HD patients at our center.

In 14 years, there were 9 cases (mean age 69±12 years). The main comorbidities found were diabetes mellitus (55.6% of patients), hypertension (55.6%), bone diseases (22.2%), cancer (11.1%) and rheumatoid arthritis treated with steroids (11.1%). The clinical onset included back pain (100% of cases), fever (55.6%), neurological deficits (33.4%), leukocytosis (55.6%) and elevated CRP level (88.9%).

Most cases were diagnosed by magnetic resonance imaging (66.7%) with more frequent involvement of lumbar region (77.8%). Blood cultures were positive in five patients (mostly for S. aureus); three of them used catheters as vascular access and, in two cases, their removal was necessary. The mean time interval between the onset of symptoms and the diagnosis was 34±42 days.

All patients received antibiotic treatment for a mean duration of 6 weeks; most cases were initially treated with vancomycin or teicoplanin plus ciprofloxacin. Most patients (77.8%) recovered after a mean of 3.5 months; one patient had a relapse after 2 years and one patient had long-term neurologic sequelae.

La spondilodiscite infettiva nella MH deve essere sospettata in presenza di mal di schiena, anche in assenza di febbre o fattori di rischio tradizionali. Una diagnosi precoce potrebbe migliorare il risultato. Un attento monitoraggio dell'accesso vascolare, procedure di disinfezione e tecniche asettiche sono importanti per evitare questa complicanza.

Keywords: spondylodiscitis, hemodialysis, back pain, vascular access, infectious complications, bacteremia

Introduction

Septicemia and infections contribute to 12% of deaths in uremic patients [1].

Hemodialysis (HD) patients represent a risk category for bacteremia (in particular caused by S. aureus), because of the coexistence of multiple risk factors: the immunodepression typical of uremia, the frequent venopunctures of native and prosthetic fistulas and the presence of temporary or permanent venous catheters [2–3].

One of the possible complications of bacteremia is spondylodiscitis, defined as infection of the vertebra and intervertebral disc sometimes extended to the surrounding soft tissues [4–7]. The incidence of this disease varies between 1:250,000 patients/year [8–9] and 0,4-2,4:100.000 patients/year [5] in the general population, while the major studies carried out on HD patients report an incidence of 1:80–1:215 patients/year [10–11].

Although bacterial spondylodiscitis is one of the most serious complications that can occur to dialysis patients, few cases have been reported in the literature; it is therefore not clear which is the best clinical management. Moreover, diagnosis may be often delayed due to the insidious onset of the symptoms.

Considering the cases occurred in our center, in this work we analyze the clinical features and the problems related to the diagnosis and the therapy of spondylodiscitis in HD patients; the possible risk factors related to the onset of this disease are also considered.

Methods

A retrospective study has been conducted by evaluating all cases of infective spondylodiscitis that occurred between May 2005 and October 2019 among the HD patients at our center (IRCCS Multimedica, Sesto San Giovanni, Milan, Italy).

Patients were identified according to a diagnosis of “spondylodiscitis” and “ESRD” from the hospital records. The diagnosis of infective spondylodiscitis was based on clinical data, laboratory results [5, 12] and diagnostic imaging tests [12–13]. The exclusion criteria were as follows: post-operative spinal infection, patients affected by chronic renal insufficiency not in hemodialysis, patients who received HD for less than 14 days. We finally included 9 cases.

For each patient, demographic data, personal medical history, dialytic age and type of vascular access were collected. The baseline characteristics included age, gender, primary cause of ESRD and main comorbidities (diabetes mellitus, hypertension, malignancy, bone and joint diseases). Regarding infective spondylodiscitis, initial clinical symptoms, laboratory and culture test results, diagnostic tools and location of spinal infection were collected for each patient. We focused in particular on the time interval between the onset of symptoms and the diagnosis, often delayed.

Finally, we collected data regarding the treatments performed and the patients’ outcomes.

Results

In 14 years, there have been 9 cases of infective spondylodiscitis in our center, with an estimated incidence of 1:200 patients/year. The incidence was calculated by comparing the number of cases to the dialysis population over 14 years (we usually treat chronically 100 HD patients).

Table 1 shows the clinical characteristics of the patients with infective spondylodiscitis treated in our center. Sixty-seven percent of patients were male, the mean age was 69±12 years. The primary

causes of ESRD included diabetic nephropathy (3 patients, 33.4%), obstructive nephropathy (2 patients, 22.2%), autosomal dominant polycystic kidney disease (1 patient, 11.1%), arterial hypertension (1 patient, 11.1%) and unknown causes (2 patients, 22.2%). Five patients (55.6%) were affected by diabetes mellitus, 11.1% by obesity, 55.6% by arterial hypertension and 22.2% by bone diseases. One patient was known for rheumatoid arthritis and was in chronic treatment with low-dose steroids and azathioprine; none of the other patients received chronic immunosuppressive therapy. One patient was affected by prostatic cancer.

All patients had back pain as an initial symptom, 55.6% had fever, while 33.4% had neurological symptoms, such as limb weakness and paresthesia (Table 2).

Patient	Age [years]	Gender	Cause of ESRD	Comorbidities
1	62	M	Diabetes	Diabetes
2	78	M	Unknown	Myelodysplasia
3	63	M	Unknown	Obesity, arterial hypertension, hypothyroidism, diabetes
4	78	F	Unknown	Rheumatoid arthritis, osteoporosis
5	69	F	Nephrolithiasis	Diabetes, secondary hyperparathyroidism
6	73	F	ADPKD	Diabetes, arterial hypertension, Graves' disease, vasculopathy
7	88	M	Obstructive nephropathy	Arterial hypertension, prostatic cancer
8	48	M	Diabetes	Diabetes, arterial hypertension
9	61	M	Arterial hypertension	Arterial hypertension
ESRD, end stage renal disease; ADPKD, autosomal dominant polycystic kidney disease				

Table 1: Characteristics of the patients with infective spondylodiscitis in care at our center.

At hospital admission 55.6% of patients had leukocytosis, while 88.9% had elevated CRP levels (Table 2).

Six patients (66.7 %) had their diagnoses confirmed by magnetic resonance imaging (MRI) (Figure 1), while two had a CT performed prior to MRI (Table 2). One patient had his diagnosis confirmed by CT only (it was not possible to perform MRI because of the presence of a metallic foreign object in the patient's body).

Patient	Back Pain	Fever	Neurological symptoms	WBC	CRP	Diagnostic tools	Location
1	Yes	Yes	No	26700	26.7	CT, MRI	D9-D10
2	Yes	Yes	No	28000	22	MRI	L5-S1
3	Yes	No	Yes	10200	5.83	MRI	L3-L4
4	Yes	No	Yes	3800	9.9	MRI	L4-L5
5	Yes	Yes	Yes	15500	10.1	MRI	D4-D5
6	Yes	No	No	6230	8.52	CT, MRI	L4-L5
7	Yes	No	No	5290	0.3	MRI	L4-L5
8	Yes	Yes	No	22500	31.8	CT	L4-L5
9	Yes	Yes	No	7130	3.7	MRI	L1-L2
WBC, white blood cell count (cells/ml); CRP, c-reactive protein (mg/dl); MRI, magnetic resonance imaging							

Table 2: Initial clinical presentation, initial laboratory results, diagnostic tools, location of infection.

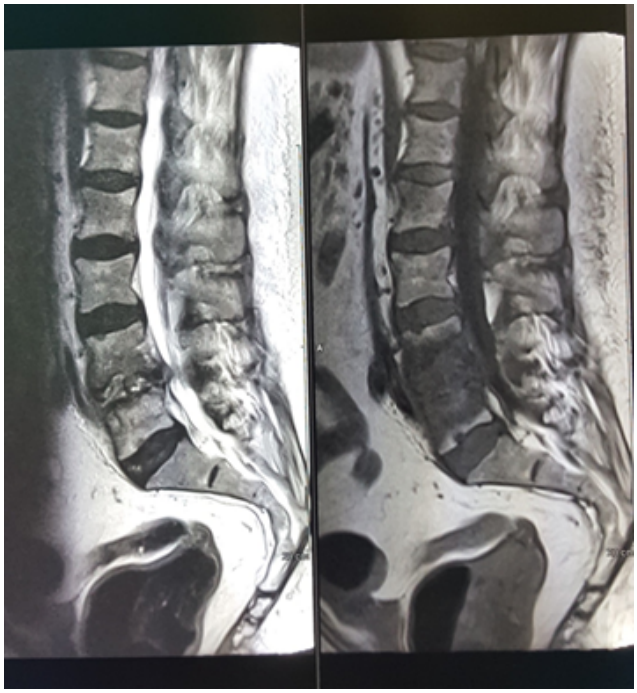

Figure 1: MRI of the lumbosacral spine without gadolinium contrast showing discitis at the L4–L5 level (patient n. 6)

All patients had performed a spine radiograph that turned out not to be diagnostic. In no case it was necessary to perform a FDG-PET for the diagnosis of spondylodiscitis. Echocardiography was performed in 2 cases, both negative for valvular vegetation, to exclude infective endocarditis.

The lumbar level was the most common site of infection (7 patients, 77.8 %); in 2 patients (22.2 %), the thoracic spine was also involved, while in no case the cervical spine was involved (Table 2).

The mean dialytic age was 33±38 months, as reported in Table 3. Four patients (44.4 %) used an arteriovenous fistula (AVF) as vascular access for hemodialysis, 1 patient (11.1 %) used an arteriovenous graft (AVG), 3 patients (33.4 %) used a tunneled cuffed catheter (TCC), and 1 patient (11.1 %) used a non-tunneled catheter (NTC) (Table 3). Two patients had experienced thrombosis of the arteriovenous fistula for hemodialysis and underwent endovascular surgery. The surgical interventions had not been successful; for this reason, central venous catheters for hemodialysis had been positioned (a tunneled cuffed catheter in one case, a non-tunneled catheter, then removed and replaced, in the other). Blood cultures were positive in five cases, four for S. aureus (Table 3) and one for S. agalactiae. In the first of our 9 cases, the non-tunneled catheter, which was the source of the infection, was removed and replaced. In the second case the infection was successfully treated without the need of removing the tunneled cuffed catheter. In the third and fourth cases, the patients had AVFs and no sign of local infection. In the fifth case, the removal of the TCC was necessary due to the persistence of a septic status related to the catheter. A NTC was subsequently placed and an AVF was created.

A bone biopsy was performed in three instances (Table 3). In the first case, the patient developed a paraplegia with level D4 during hospitalization; she was therefore subjected to a neurosurgical operation of bone marrow decompression. The bone culture test confirmed the diagnosis of S. aureus spondylodiscitis. Despite surgical intervention and the use of targeted systemic antibiotic therapy, the recovery of lower limb function was not achieved. In the second case, a bone biopsy was performed because of the persistence of painful symptoms after months of antibiotic therapy;

the cultural exam of the disc and the vertebral body was negative; the patient was then discharged with a diagnosis of chronic spondylodiscitis. In the third case, the bone biopsy was also performed due to the persistence of painful symptoms and the exam resulted negative. The mean time interval between the onset of symptoms and the diagnosis was 34±42 days (Table 3). All patients received antibiotic treatment and the mean treatment duration was 6 weeks (Table 4). In most cases, vancomycin or teicoplanin plus ciprofloxacin were used as initial antibiotics (Table 4). The aim of the initial empiric treatment was to cover Staphylococci and Gram-negative bacilli. One patient underwent surgical intervention due to progressive neurologic deficits, as reported above. In four cases, the use of an orthopedic corset was prescribed (Table 4).
One patient had another infective spondylodiscitis within 2 years, caused by a different organism to in his first event. One patient had long-term neurologic sequelae despite surgical treatment. The others 7 patients recovered after a mean of 3.5 months (Table 4).

Patient	Dialytic age [months]	Vascular access	Blood culture	Bone biopsy	Diagnostic delay
1	45	NTC	S. aureus	Not executed	1 month
2	24	AVF	Negative	Not executed	3 months
3	3	TCC	S. aureus	Not executed	5 days
4	57	AVF	Negative	Not executed	10 days
5	12	AVF	S. aureus	S. aureus	3 weeks
6	120	AVG	Negative	Negative	4 months
7	16	TCC	Negative	Not executed	3 weeks
8	1	TCC	S. aureus	Negative	3 days
9	15	AVF	Streptococcus agalactiae	Not executed	5 days
AVF, arteriovenous fistula; AVG, arteriovenous graft; NTC, non-tunneled catheter; TCC, tunneled cuffed catheter					

Table 3: Dialytic age, vascular access for hemodialysis, culture results, time interval between onset of symptoms and diagnosis

Patient	Antibiotics	Duration of antibiotic therapy	Surgical treatment	Orthopedic corset	Outcome
1	Vancomycin plus gentamicin	4 weeks	No	Yes	Recurrent after 2 years
2	Vancomycin plus ciprofloxacin; then teicoplanin plus ceftazidime	8 weeks	No	No	Resolution after 2 months
3	Vancomycin plus ciprofloxacin plus ceftazidime	8 weeks	No	No	Resolution after 3 months
4	Teicoplanin plus ciprofloxacin	4 weeks	No	Yes	Resolution after 3 months
5	Vancomycin plus ciprofloxacin	8 weeks	Yes, bone marrow decompressio n	/	Paraplegia D4
6	Levofloxacin plus rifampicin	4 weeks	No	Yes	Resolution after 8 months
7	Ciprofloxacin	8 weeks	No	No	Resolution after 3 months
8	Teicoplanin; then Linezolid	8 weeks	No	Yes	Resolution after 4 months
9	Vancomycin plus levofloxacin	4 weeks	No	No	Resolution after 1 month

Table 4: Treatments and outcome of patients

Discussion

In our center there have been 9 cases of infective spondylodiscitis over 14 years, with an estimated incidence of 1:200 patients/year, which is in line to what has been previously reported in the literature regarding HD patients [10–11].

The mean age of the patients considered in our study was 69±12 years, suggesting, as is also reported in the literature, that in recent years spondylodiscitis has evolved from an acute pathology with a high mortality mostly affecting young patients to a more indolent disorder affecting elderly patients, with a reduced mortality but more frequent relapses and debilitating sequelae [14].

The most frequent comorbidities found in our patients were diabetes mellitus (55.6%), arterial hypertension (55.6%) and bone diseases (22.2%). Several risk factors for spondylodiscitis are reported in the literature: diabetes mellitus, intravenous drug abuse, liver disease, immunodeficiency, alcoholism, rheumatoid arthritis, steroid therapy, immunosuppressive therapy, tumors [15–16]. The prevalence of arterial hypertension among our cases of spondylodiscitis appears lower than that of the hemodialysis population (55.6% vs 80%); however, the relationship reported in previous studies between arterial hypertension and spondylodiscitis in HD patients is an association, not a cause and effect relationship. The prevalence of diabetes mellitus in our sample appears to be higher than that reported in the literature among hemodialysis patients (55.6% vs 30%). This could indicate that diabetes can favor infectious processes, including spondylodiscitis, and confirms that diabetes mellitus could be a risk factor for vertebral infections, as reported in previous studies. It is interesting to note that in our case series one patient was treated for rheumatoid arthritis with low-dose steroids and azathioprine at the time of the spondylodiscitis episode; another patient was affected by prostatic cancer.

Our small sample of patients seems therefore representative of the main risk factors for spondylodiscitis, except for alcoholism and liver disease; in it we found diabetes mellitus, rheumatoid arthritis, steroid therapy and cancer. Moreover, other risk factors, related to the state of uremia and to dialysis treatment, may play a decisive role in the onset of spondylodiscitis: they are the immunodepression typical of uremia, the frequent use of central venous catheterization as vascular access for hemodialysis, the frequent venopuncture of the fistulas, both native and prosthetic, and the endovascular surgery procedures for thrombosis of the vascular access, with the consequent greater risk of bacteremia and infectious complications [2–3]. In our case series, 44.4% of patients used an AVF as vascular access for hemodialysis, 11.1% used an AVG, 33.4% used a TCC, and 11.1% used a NTC. Two patients had experienced thrombosis of the arteriovenous fistula, requiring endovascular surgery. Moreover, the blood cultures resulted positive for S. aureus in three of the four patients with central venous catheter and the catheter removal was necessary in two cases. A previous article reports that 91% of their spondylodiscitis cases used a central venous catheter instead of an arteriovenous fistula as vascular access for hemodialysis [17]. For this reason, possible preventive strategies in hemodialysis patients are the choice of AVF as vascular access, as it is associated with a lower incidence of spondylodiscitis compared to the TCC [11], and the close monitoring of the vascular access, paying particular attention to disinfection procedures and aseptic techniques [18].

In our case series, all patients had back pain at the onset of symptoms, while fever and neurological symptoms were present only in some. The literature also describes back pain as the main clinical manifestation of the disease; it is present in 90% of all cases, at the level of the affected bone metamer [15]. Fever is not a constant finding and is present only in half of the cases, while neurological symptoms are found in 30% of patients with spondylodiscitis [15–16]. At

hospital admission 55.6% of our patients had leukocytosis, 88.9% had elevated CRP levels. In the literature, leukocytosis is reported in 40% of cases and an increase in inflammatory indices in 80% of them [19].

Magnetic resonance imaging of the spine is the most sensitive and specific radiological method to diagnose vertebral osteomyelitis; it is also the procedure of choice to assess the extent of the disease, the involvement of soft tissues and neurological structures and the possible presence of abscesses [13]. Spine radiography is often performed first and shows alterations in 89% of cases [13]; however, it has a reduced sensitivity and specificity, especially in the early stages [20]. CT is less sensitive than MRI and is generally used when the latter is contraindicated, as well as to perform CT guided percutaneous biopsy [20]. A final exam that can help locate abnormalities and monitor the response to treatment is FDG-PET, which is especially indicated in cases where the patient cannot undergo MRI [12, 21]. In our case series, 66.7% of patients had their diagnoses confirmed by MRI, one patient had his diagnosis confirmed by CT, while two patients had a CT performed prior to MRI. In no case we performed FDG-PET.

In our sample of patients, the lumbar spine was the most common site of infection, followed by the thoracic spine. Generally, the lumbar vertebrae are the most frequently affected (60-70% of cases in the literature) given their wide vascularization [22]. As reported in previous studies, in 10% of cases the infection localizes at the cervical level (the site that can most frequently lead to neurological complications); in 20-30% of cases it is localized at the thoracic level, while the sacral localization is found in less than 10% of cases [5, 23].

In our study, blood cultures were positive in five instances, four for S. aureus and one for S. agalactiae. Spondylodiscitis are generally due to a hematogenous infection by S. aureus (50% of cases in the literature), but episodes caused by Gram-negative, P. aeruginosa, S. epidermidis, Streptococci of group C and G have been described (especially in diabetic patients) [4]. Generally, blood cultures are positive in 50-70% of patients with vertebral osteomyelitis [15–16].

We performed a bone biopsy in three cases. CT-guided percutaneous vertebral disc biopsy may be considered in patients with negative blood cultures who do not respond to antibiotic therapy; it identifies the pathogen in 60-70% of cases. The possibility of identifying the causative pathogen is reduced if the patient has previously taken antibiotics. The histological examination of the biopsy may show disc necrosis and neutrophil infiltration, too [5]. In patients with suspected spondylodiscitis, with persistent symptoms despite antibiotic therapy and negative microbiological tests (blood culture and disc biopsy) it is indicated to repeat a second percutaneous biopsy and eventually proceed with an open biopsy, that is positive in 75% of cases [5, 12].

All our patients received antibiotic treatment, in most of the cases vancomycin or teicoplanin plus ciprofloxacin as initial therapy. Randomized controlled trials on empirical antibiotic therapy have not yet been conducted and therefore no antibiotic, alone or in an association, is currently considered superior to the others in treating this infection. Usually, an empirical antibiotic therapy is set up with broad-spectrum antibiotics with anti-staphylococcal activity (for example vancomycin or teicoplanin), also associating an agent with anti-negative bacilli activity [24–25]. Antibiotic therapy should continue for at least 4-8 weeks (up to 6-12 weeks) [24–25]. In our case series, the mean treatment duration was 6 weeks.

The recommended therapy also consists in immobilization, with bed rest with analgesia for at least 2-4 weeks, followed by the gradual mobilization with orthopedic corset; this was prescribed to four of our patients. Surgery can be indicated if there are neurological deficits, radicular compression, a need to prevent and correct instability and deformity, severe persistent pain, or when it is necessary to perform drainage of abscesses or open biopsy [6, 23]. In our case series, only one

patient underwent surgical intervention due to progressive neurologic deficits.

The mortality rate for spondylodiscitis among HD patients is reported at 16.7%. In our case series, no patient died due to infection, although one had a second infective spondylodiscitis within 2 years and another suffered from long-term neurologic sequelae, despite surgical treatment. The others seven patients recovered after an average of 3.5 months.

An early diagnosis that identifies, where possible, the responsible microorganism, could prevent the development of such complications and could improve the outcome for patients, allowing for a prompt resolution of the infective episode [14]. An algorithm on the possible diagnostic/therapeutic workup for the management of suspected cases of spondylodiscitis among hemodialysis patients is shown in Figure 2.

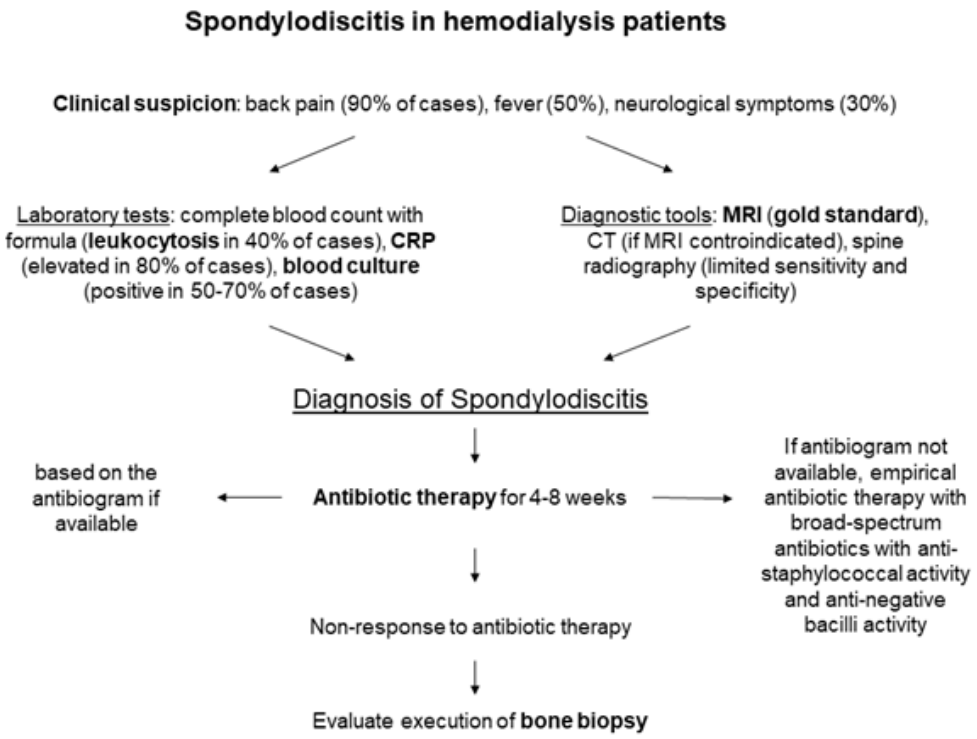

Figure 2: Algorithm on the possible diagnostic/therapeutic workup for the management of suspected cases of spondylodiscitis among hemodialysis patients.

Our study certainly presents some limits due to the reduced number of cases and its descriptive and retrospective nature. However, it is the first Italian study that focuses on this rare disease, characterized by important mortality and complications, especially among hemodialysis patients, and on the diagnostic delay that often occurs.

Conclusions

Infective spondylodiscitis must be suspected in the presence of back pain in HD patients, even in the absence of fever and traditional risk factors. In order to improve the outcome for patients and obtain a prompt resolution, it is important to get an early diagnosis by identifying, if possible, the responsible microorganism, and to avoid any delays in the diagnosis. Finally, the close monitoring of vascular access, and a great attention to disinfection procedures and aseptic techniques are all important to avoid these serious infectious complications.

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