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Case Report

Infectious spondylodiscitis: When a rare infection is associated with uncommon findings!

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ABSTRACT

Infectious spondylodiscitis (ISD) is a rare infection of the spine. ISD caused by *Acinetobacter baumannii* and *Citrobacter koseri* is even rarer. Moreover, the association between ISD and malignancy is uncommon. In these case series, we report the remarkable case of a patient diagnosed with ISD associated with bone metastatic lesions of an unknown cancer and multiple myeloma accidentally discovered due to COVID-19 infection. We also reported two cases of ISD caused by rare organisms: the first case is a man with ISD caused by a multidrug resistant *A. baumannii*, and the second is a man with *C. koseri* bacteraemia complicated by paraspinal abscess and ISD.

Espondilodiscitis infecciosa: ¡cuando una infección rara se asocia con hallazgos poco frecuentes!

Palabras clave:
COVID-19
Mieloma múltiple
Metástasis
Acinetobacter baumannii
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Bacteriemia
Espondilodiscitis infecciosa

RESUMEN

La espondilodiscitis infecciosa (EDI) es una infección rara de la columna vertebral, la enfermedad causada por *Acinetobacter baumannii* y *Citrobacter koseri* es aún más rara. Además, la asociación entre EDI y malignidad es un hecho poco común. En esta serie de casos presentamos el caso destacado de un paciente diagnosticado con EDI asociado con lesiones metastásicas óseas de un cáncer desconocido y mieloma múltiple de descubrimiento accidental con motivo de infección por COVID-19. También, reportamos dos casos de EDI causados por microorganismos inusuales: el primer caso es un hombre con EDI causada

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por *Acinetobacter baumannii* multirresistente, y el segundo es un hombre con bacteriemia por *Citrobacter koseri* complicada con absceso paraspinal y EDI.

Background

Infectious spondylodiscitis (ISD) is a rare infection of the vertebral body, the intervertebral disc and the paraspinal tissue.[1] However, its incidence has increased these last years due to a better understanding of the disease and an improvement in the health care.[2] The risk factors of ISD include an advanced age, an immunocompromised status, the presence of comorbidities and chronic debilitating diseases such as diabetes, malignancy, and renal failure.[2] Early diagnosis remains a challenge because of the nonspecific symptoms.[3] The most frequent organisms causing ISD are Gram positive organisms, in first place staphylococci.[4] Despite the rarity of this condition and the difficulty of its detection, ISD can reveal other diseases. Few cases of ISD revealing malignancy were reported in the literature.[5] There were, to our knowledge, no cases of ISD in patients with coronavirus (COVID-19) in the literature. Here, we report a case series of uncommon ISD: a case of ISD revealing multiple myeloma (MM) and bone metastases in a COVID-19 patient, and two cases of ISD caused by rare organisms: mutli-resistant *Acinetobacter baumannii* and *Citrobacter koseri*.

Case series presentation

Case 1

A sixty-seven-year-old man with a medical history of hypertension and benign prostatic hypertrophy was diagnosed with COVID-19 in December 2020. He was hospitalized in a COVID-19 ward. A computed tomography (CT) of the lungs, performed as part of the COVID-19 exploration, has unexpectedly revealed an ISD of the thoracic spine. The patient was transferred to our ward for further care of the ISD. On arrival, he was apyretic. His hemodynamic state was stable. Osteoarticular examination was impossible because of the extreme back pain. Neurological examination was normal. His lungs were clear, and his heart sounds had a regular rhythm and were normal. Laboratory values were as follow: hemoglobin (Hb) 7.2 g/dL, platelets 165,000/mm^3, white blood cells (WBC) count 13,200/mm^3, C-reactive protein (CRP) 188 mg/dL, calcium 2.69 mmol/L and creatinine 65 μmol/L. A magnetic resonance imaging (MRI) (Fig. 1) of the spine showed an ISD at the tbl6 tbl7 level associated with an anterior epiduritis tbl6 tbl7 and a posterior epiduritis T3 to T7, bilateral tbl6 tbl7 costo-vertebral arthritis, complicated by spinal cord compression. We ran further tests to label the involved microorganism: brucellosis serology, tuberculin skin test, and multiple series of haemoculture, which were all negative. Upon these findings, a bone biopsy was performed under fluoroscopy guidance. Koch bacilli PCR as well as culture on bone biopsy were negative. However, urine analysis isolated a cefotaxime and ciprofloxacin resistant staphylococcus aureus. The patient was treated intravenously with amoxicillin/clavulanic acid associated with rifampicin for a duration of 14 days. However, his condition was still deteriorating with an increasing CRP level up to 318 mg/dL. We ran another urine analysis which was negative. We switched the antibiotic therapy towards wider-spectrum antibiotics, especially since no germ has been isolated. Empirical intravenous therapy with piperacillin-tazobactam associated with ofloxacin was started. For the medullar compression, there was no indication for neurological surgery. The patient was treated with corticoids and immobilized with a rigid lumbar corset. We noted an improvement of the patient's condition with a decrease of CRP to 67 mg/dL.

The MRI of the spine also showed osteolytic lesions of the spinal process of L3, the posterior arc of the 10th rib, and the right iliac bone, associated with lumboaortic and iliac ganglionic magma. The histopathological examination of the right iliac biopsy concluded to bone localizations of poorly differentiated carcinoma, whose immunohistological profile could be consistent with gastric or biliary cancer. However, the search for the primary cancer was inconclusive (tumor markers, abdominal CT and MRI all negative). A gastroduodenal endoscopy could not be performed because of the extremely altered state of the patient. Further investigations were performed: hypercalcemia of 2.73 mmol/L, plasma protein electrophoresis showing monoclonal gamma globulin increase, blood immune-electrophoresis showing hyper gamma-globulin (Immunoglobulin G and light kappa chains), and bone marrow aspirates showing 11% clonal plasma cells with dystrophic plasmocytes (Fig. 2). We concluded thus to the diagnosis of stage IIA kappa light chain and immunoglobulin G MM. In final, our patient was diagnosed with ISD of the thoracic spine associated with bone metastatic lesions of an unknown cancer and MM of accidental discovery on the occasion of COVID-19 infection. The patient's prognosis was pejorative. Only palliative treatment was indicated for the bone metastases. Regarding the MM, it was decided to start chemotherapy (thalidomide-melphalan) associated with corticoids. For the hypercalcemia, the patient was treated with intravenous Zometa associated with hyperhydration, since the electrocardiogram was normal. However, the patient has passed away a few days before the treatment began.

Case 2

A sixty-six-year-old man with hypertension and atrial fibrillation underwent cholecystectomy with choledoco-duodenal anastomosis ten years ago. He then had developed angio-

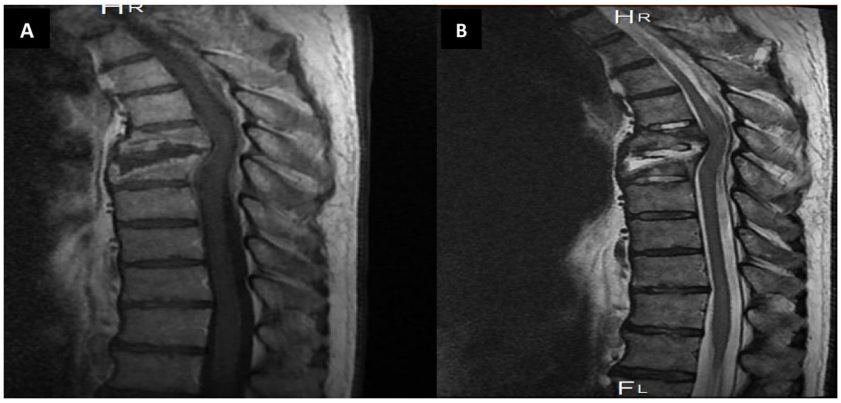

Fig. 1 – Sagittal T1-weighted after injection of Gadolinium (A), T2-weighted (B) magnetic resonance imaging (MRI) sequences of the spine show an infectious spondylodiscitis at tbl6 tbl7 level with an anterior and a posterior tbl6 tbl7 epiduritis, complicated by spinal cord compression.

cholitis, and a bilioduodenal anastomosis was performed. The abdominal CT scan revealed a poorly limited multilocular hepatic abscess (Fig. 3). The patient improved on cefotaxime and metronidazole conducted intravenously for 14 days associated with gentamicin for 3 days. A follow-up abdominal CT-scan showed the persistence of the hepatic abscess. Moreover, a spinal MRI, performed one month after the diagnosis of the angiocholitis to explore mechanic low-back pain, revealed abnormalities of the facet joint surfaces of L2 and L3, hypointense signal at T1-weighted images, and hyperintense at T2-weighted images, associated with peri-vertebral and peri-discal thickening, enhanced after injection of gadolinium, predominantly on the left anterior epidural space, consistent with lumbar ISD at the L2 L3 level (Fig. 4). On arrival, his vital signs were normal, his heart sounds were normal and his lungs were clear. Bowel sounds were clear. His abdomen was soft and tender on palpation. The neurological examination was normal. The left iliac crest was tender on palpation. No fever was noted along the hospitalization. Urine analysis performed on admission and results were within the normal range. Laboratory values were as follow: Hb 11.2 g/dL, platelets 287,000/mm^3, WBC count 8500/mm^3, and CRP 28 mg/dL. Renal and hepatic functions were within the normal ranges. After negative exhaustive infectious investigations, including brucellosis serology, tuberculin skin test, and multiple series of haemoculture, a liver biopsy of the abscess was performed isolating a multi-resistant *A. baumannii*. The patient improved on tigercycline and colistin. He had no adverse reactions and tolerated the treatment, apart from slight pruritus, which was managed with antihistaminic drugs. A follow-up abdominal CT scan showed a decrease in abscess size from 5 to 3 cm after 21 days of intravenous antibiotic therapy. The patient was discharged from the hospital after completed two months of antibiotics. Taking into consideration the multiresistant nature of the germ and the persistence of the hepatic abscess, and after consulting with infectious diseases doctors, we decided to follow-up the antibiotic therapy with trimethoprim sulfamethoxazole for a period of six weeks with regular monitoring of blood count and renal function. The patient concluded six weeks of oral antibiotic and no infection relapse after four months of follow-up to this day was observed. A follow-up MRI performed two months after the resolution of oral antibiotics showed a reduction in soft tissue infiltration.

Case 3

A sixty-three-year-old man, with a past medical history hepatitis C, was admitted to our hospital with two months history of recurrent fever and inflammatory lombosciatica. On examination, he was not clinically septic. The examination of the spine was difficult due to the extreme pain. His neurological examination was normal. The cardio-respiratory and the abdominal examinations were normal. His WBC was normal, and his CRP was 164 mg/dL. MRI of the spine revealed an ISD at the level of L3 L4 with paravertebral abscess and epiduritis (Fig. 5). Brucellosis serology, tuberculin skin and urine analysis were negative. Histopathological examination of the spinal biopsy revealed the presence of inflamed granulation, and culture of the pus identified growth of *C. koseri*. The blood culture was also positive for *C. koseri*. He was started on cefotaxime associated with gentamicin for three days, then associated with ofloxacin for 12 days intravenously. Oral antibiotics, including ofloxacin and trimethoprim sulfamethoxazole, were carried on. On the second day of oral antibiotics, the patient developed allergic lesions of toxidermia as well as leucopenia of 3300 e/mm^3. Fortunately, the patient's toxidermia settled after 48 h of antihistaminic drugs and topical steroids. The patient was kept on oral ofloxacin monotherapy. Blood count normalized within a week. The antibiotic was continued for another two months. He was reviewed at the outpatient clinic at two weeks and one month after discharge. He reported the return to his normal life style. A follow-up MRI, performed three months after treatment interruption, showed a reduction of the epiduritis as well as the paravertebral abscess.

Discussion

The findings of this case series highlight several significant uncommon aspects of ISD. The first case of ISD was associated

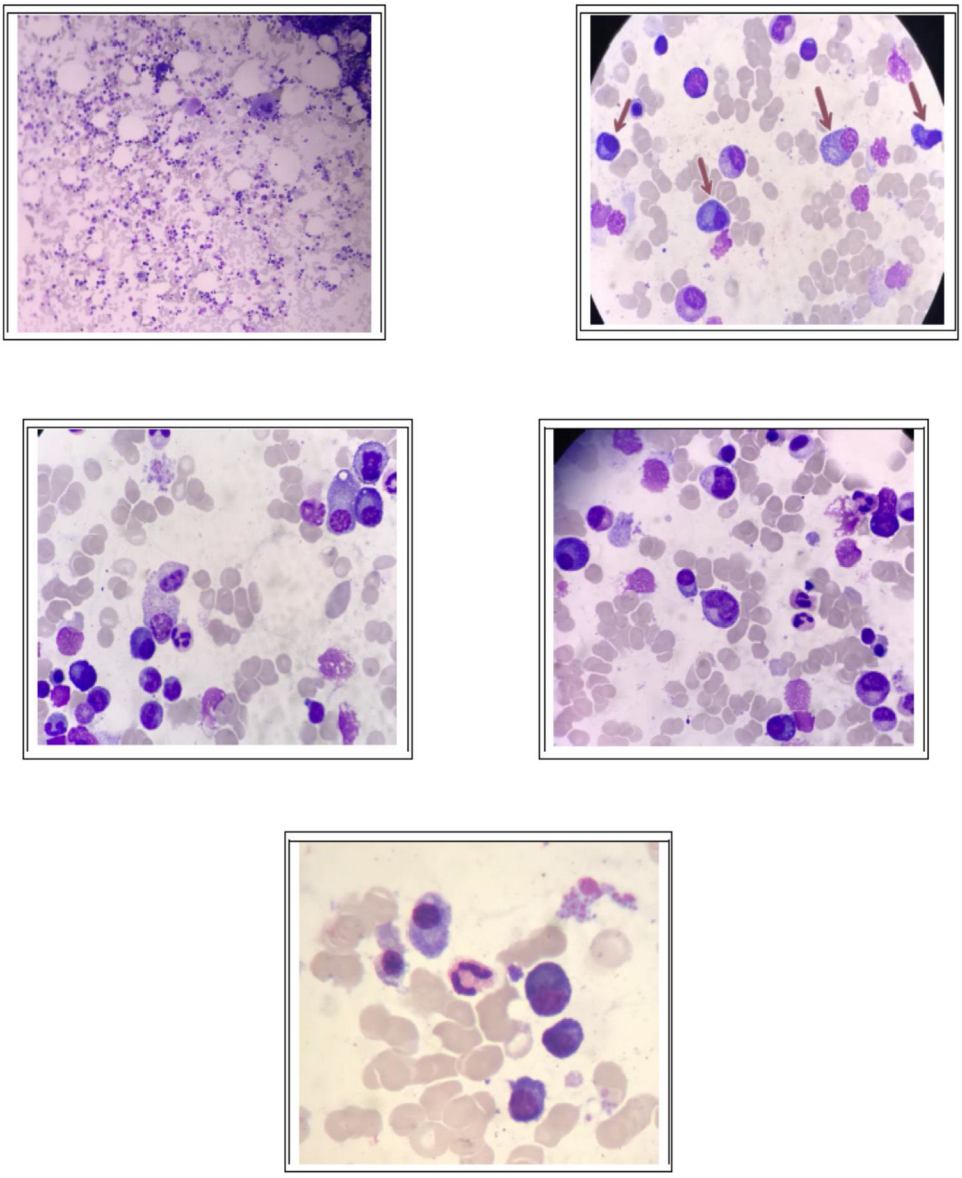

Fig. 2 – Bone marrow aspirates showing 11% clonal plasma cells made of dystrophic plasmocytes with loss of nucleus eccentricity and intracytoplasmic vacuoles.

with MM and bone metastases in a COVID-19 patient, and the two other cases were caused by rare organisms.

The increasing frequency of this type of infection reflects the expanded rate of elderly and immunocompromised populations.[6] Certain risk factors associated to ISD are important to keep in mind in the clinical setting of the disease. The predisposing factors include male gender, age, diabetes mellitus, other immunosuppressed conditions, cancer, chronic steroid use, anti-rheumatic medications, intravenous drug abusers, a history of recent injury or trauma, and a history of recent invasive procedure.[7,8] The clinical presentation of ISD is heterogenous. The most frequent symptoms are the following: unremitting inflammatory back or neck pain (up to 90% of patients), fever (60–70% of pyogenic ISD), weight loss and anorexia, and neurological deficit (10–50% of cases).[6,9,10] In fact, ISD should be suspected in case of new or worsening back pain or any of the following manifestations: fever, endocarditis, hemodialysis, intravenous access, recent bacteremia, intravenous drug abuse, and/or new neurological deficit.[11] Diagnostic delay is usually two to six months after the initial symptoms, especially since radiographs are of little help in the early stages of the infection.[11] An exhaustive neurological examination is obligatory in order to detect neurological complications. One should look for “red flags” which include signs of radicular or cord compression suggesting abscess formation, severe sepsis or septic shock, and endocarditis. Inflammatory markers (CRP and VS) are helpful in screening for ISD with sensitivity more than 95%.[11] Blood cultures are positive in 60% of bacterial ISD.[12] Every effort should be made in order to a microbiological diagnosis.[12]

Secondary imaging is of extreme importance in diagnosing ISD because of the radiological delay that could take up

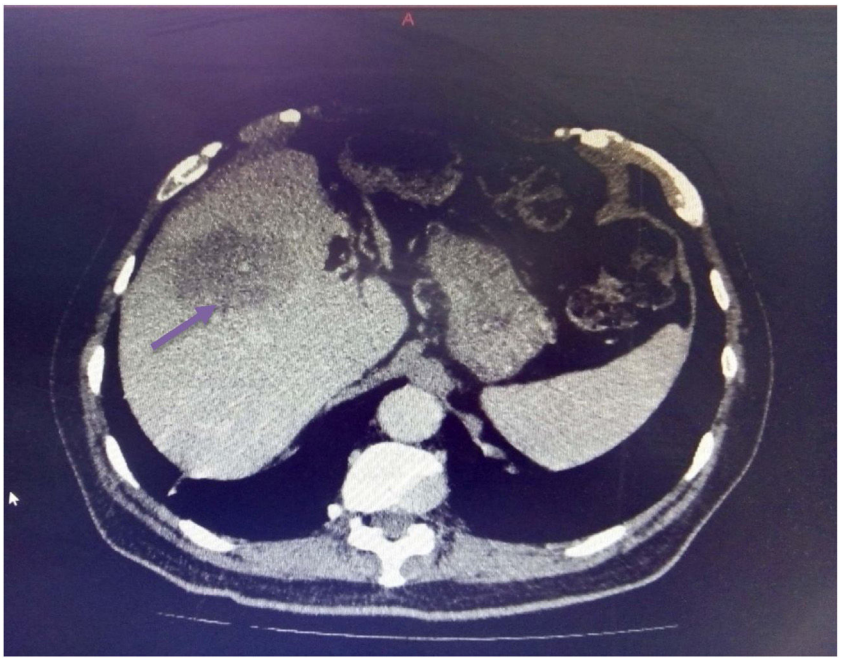

Fig. 3 – Abdominal CT scan shows a centrolobular hypodense multilocular lesion (arrow).

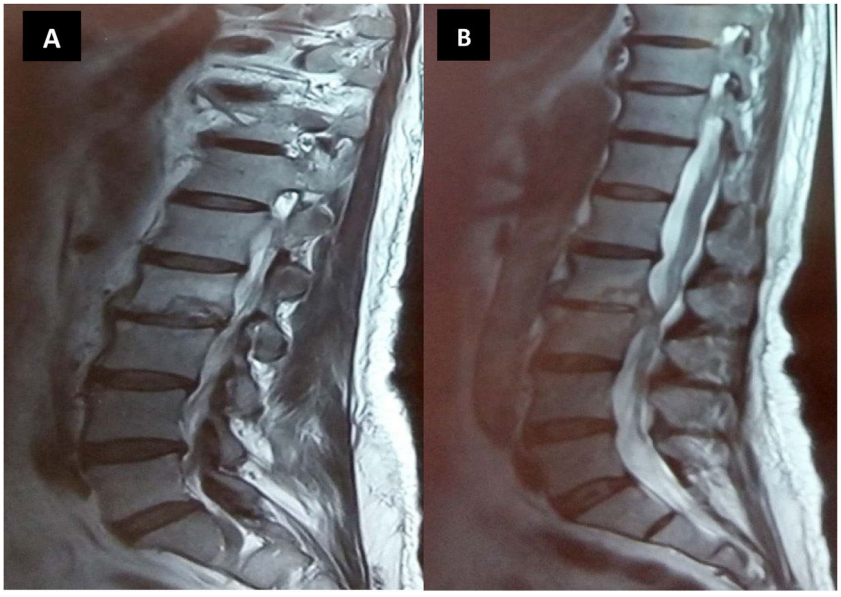

Fig. 4 – (A) Sagittal T1-weighted after injection of Gadolinium MRI sequence of the lumbar spine shows an irregular inferior plateau of L2 associated with erosions, (B) sagittal T2-weighted MRI sequence shows a heterogeneous hyperintense signal of the inferior plateau of L2 surrounded by a hypointense border.

to 6 weeks.[11] The abnormalities found in radiographs of the spine may include a disc space narrowing, blurring of the end-plates, loss of height of the affected vertebral bodies, bony erosive changes, and soft tissue extension.[13] Spinal contrast-enhanced MRI with use of Gadolinium remains the imaging modality of choice.[14] The inflammatory response consists of oedematous change within the bone marrow. T1-weighted sequence shows a reduced signal intensity of the vertebral body, endplate and disc, while T2-weighted sequence shows an increased signal intensity. Peripheral enhancement with Gadolinium and a central hypo-intense area is detected in epidural abscesses.[15]

In case of contraindication of MRI, contrast-enhanced CT-scan can help establish diagnosis. Abnormalities, which can be visible in the first two weeks in 50% of cases, include hypo-density and flattening of the involved disc, erosions of the vertebral endplates, and soft tissue swelling.[15] CT can also be used to guide percutaneous disc biopsy.[6]

Back to our cases, we reported an original case of a patient with ISD associated with bone metastatic lesions of

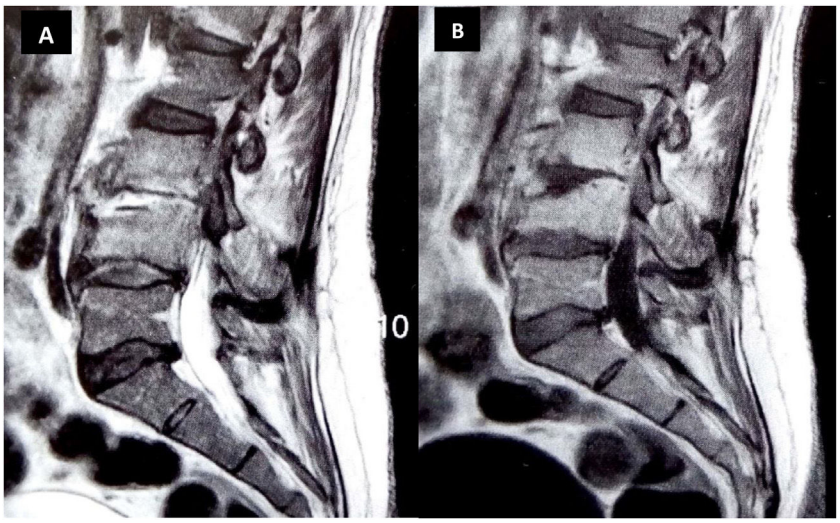

Fig. 5 – (A) Sagittal T1-weighted after injection of Gadolinium MRI sequence of the lumbar spine shows a heterogeneous hyperintense signal of L3, L4, and the prevertebral soft tissue, associated with an epiduritis, (B) sagittal T2-weighted MRI sequence shows a heterogeneous hyperintense signal of L3, L4, and the intervertebral disc.

an unknown cancer and MM discovered on the occasion of COVID-19 infection. In fact, older people with hematological malignancy or neoplasia are at higher risk of COVID-19 because of the debilitated immunocompetent status. COVID-19 leads to an important acute systemic inflammatory reaction known as a "cytokine storm".[16] The COVID-19 infection was an opportunity to detect the ISD and thus the silently evolving malignancies in our patient. To our knowledge, this is the first case of ISD associated with MM. In the literature, there was only one case of renal cancer with vertebral metastase revealed by Eikenella corrodens ISD.[5] Patients with MM and neoplasia are not only at higher risk for COVID-19, but also for treatment difficulties. Our patient's prognosis was pejorative making thus palliative treatment our only option. However, it has been reported that molecule inhibitors targeting interleukin-6 signaling are highly effective in the treatment of MM as well as COVID-19.[17] In fact, it has been showed that interleukin-6 signaling plays an important role in the pathogenesis of MM.[17] The rate of mortality reported in series of cancer patients with cancer associated to infections is higher than that of patients without neoplasia.[18,19] However, the rate of mortality may be overestimated by the advanced malignancies and the non-curative status, as was the case in our patient. A large case series exploring the impacts of COVID-19 infection in cancer patients conducted by the Brazilian National Cancer Institute showed that the rates of complications and COVID-19 specific death were significantly high.[20] Clinical fragility was associated with an advanced age, an advanced disease-stage, the presence and number of metastases, the non-curative treatment.[20,21] Our patient had several mortality risk factors. Moreover, treatment received by the patients of the Brazilian National Cancer Institute cohort within the previous two-months did not seem to decrease the rate of mortality.[20]

We also reported two cases of ISD caused by rare organisms. ISD caused by Acinetobacter species is rare, and is usually multidrug resistant.[2,22] To our knowledge, there are only two studies in which ISD occurring in postoperative procedures and caused by *A. baumannii*.[2,23] In our case, the patient underwent cholecystectomy with choledoco-duodenal anastomosis that was complicated by angiocholitis and ISD. Management of *A. baumannii* bone infections has not been well established. Only two case series studies have reported the success of therapy with prolonged tigercycline treatment.[2,23] Studies have confirmed the penetration of tigercycline in bones,[24,25] with a mean bone concentration of 898 ng/g.[24] In Sipahi and al's study,[23] tigercycline was started as a salvage therapy in eight patients with post-neurosurgical Acinetobacter ISD after failure of several different antibiotics including vancomycin or teicoplanin. Tigercycline was combined with another antibiotic in case of susceptibility pattern. Our patient had received tigercycline associated with colistin. Data related to tigercycline in the treatment of ISD is rare.[2,24,25] These data, suggest that tigercycline may be the best therapeutic option for the management of refractory ISD induced by multiresistant Acinetobacter. The mean treatment duration in Sipahi's case series was 37 days.[23] The treatment was conducted for 102 days in a patient with postoperative ISD caused by multidrug resistant *A. baumannii*.[2] This was the longest time that any patient was treated with tigercycline in the literature. Our patient had received 60 days of intravenous tigercycline.

C. koseri, which belongs to the family of Enterobacteriaceae, is also a rare organism causing ISD.[26] Citrobacter was mostly isolated from the urinary tract in adults.[4] Risk factors for *C. koseri* are not well known, but studies have shown that it was more frequent in immunocompromised patients or with a history of invasive procedures.[1,26] In our patient's case, the source of the bacteremia that had led to the ISD with the paraspinal abscess had not been identified. Our case did not concord with most reports on Citrobacter infection, where the urinary tract infection has been identified as the most frequent site of involvement.[4] *C. koseri* is rarely resistant to ampicillin and first-generation cephalosporins.[27] No recommendations about the duration of antibiotic therapy have

been determined. For this reason, we have continued the oral treatment in our patient for two months.

Conclusion

Taking our cases together, we conclude that the diagnosis of ISD should not limit the detection of other associated diseases. In fact, infection can be associated with malignancy, especially since malignancy is a risk factor for such conditions. It can also be combined with other infections such as COVID-19. Besides, the treatment of ISD should only be started after the isolation of the causal organism, since rare organisms are getting more frequent.

Availability of data and material

The authors can confirm that all relevant data are included in the study.

Ethics and dissemination

The Regional Committee of Medical Research Ethics has approved the trial protocol.

* Patients were asked for informed consent to receive treatment and participate in the research described.

* The research complies with the current regulations on the bioethical research. We obtained the authorization of the ethics committee of the institution.

* The authors state that the article does not contain any personal information to identify patients.

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Conflicts of interest

None.

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