Case Report

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A case of invasive Aspergillus niger spondylodiscitis with epidural abscess following COVID-19 infection in an immunocompromised host with literature review

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Introduction and Importance: Aspergillosis is defined as an opportunistic infection that may spread hematogenously. COVID-19 infection has not been reported as a direct cause or risk factor. Its treatment (e.g. corticosteroids) significantly increases the risk for invasive infections. The respiratory system remains the main target, and the Aspergillus fumigatus is the most responsible subtype. Other species like Aspergillus (A) flavus, A. niger, and A. nidulans follow in frequency. Other included sites are the skeletal muscular system and the entire spine leading to spondylodiscitis. Only a total of 118 cases of Aspergillus spondylodiscitis have been reported in the literature, and only 21 cases reporting spinal epidural abscess were identified.

Case Presentation: The authors report a new rare case of invasive A. Niger spondylodiscitis with epidural and iliopsoas abscesses in a 63-year-old North African female patient with a history of coronavirus infection (COVID-19) treated with high doses of corticosteroids. The patient had favorable medical and radiological outcomes after 6 months of antibiotic and antifungal therapy.

Clinical Discussion: Fungal spondylodiscitis is a rare pathology that may be lethal. Immunosuppression plays a determining role. Discovertebral contamination results from hematogenous dissemination, found in the majority of cases in adults. The main symptom is segmental spinal pain, with an inflammatory pattern most often predominating in the thoracolumbar spine. Clinical signs of spinal cord compression, such as paresthesias, radiculalgia, and paraplegia, can sometimes be associated. Diagnosis of such spondylodiscitis is based on cultures and/or histology, whereas in most cases, it was made by MRI. Epidural abscess remains a rare entity. The authors will explore the current literature in more detail to dissect and explain this rare entity.

Conclusion: Aspergillus spondylodiscitis remains a rare and very demanding clinical entity. Early diagnosis and well-targeted medical treatment seem the ideal solution given that this type of infection has a poor prognosis.

Keywords: abscess, aspergillus niger, itraconazole, MRI, spondylodiscitis, surgery

Introduction and importance

Aspergillus (A) is a filamentous saprophytic fungus that develops on decomposing organic matter, soil, foodstuffs, and cereals. They are also present in the human environment, notably in plants, fruits, dust, and air[1]. Aspergillosis, in itself, is defined as an opportunistic infection that most often affects the respiratory tract and may spread hematogenously[2]. Neutropenia is the main risk factor for serious, so-called invasive, infection. HIV infection, aplasia linked to chemotherapy or leukemia, for example, immunosuppressive treatment following an organ transplant, or even congenital immune deficiencies are all immunosuppressive factors that may lead to such infections[3]. COVID-19 infection has not been reported as a direct cause or risk factor[4]. However the increase in COVID-19-associated pulmonary aspergillosis may represent an indirect risk factor[5].

Aspergillosis can affect most organs. The respiratory system remains the main target, and the aspergillus fumigatus is the most responsible subtype. Other species like A. flavus, A. niger, and A. nidulans follow in frequency[6]. Other included sites are the

HIGHLIGHTS

- Fungal spondylodiscitis is a rare pathology that may even be lethal.
- The main symptom found is segmental spinal pain with an inflammatory pattern most often predominating in the thoracolumbar spine.
- Biologically, an isolated inflammatory syndrome may be present but not necessarily.
- Epidural abscess remains a rare entity.
- The standard treatment is amphotericin B.
- Surgery varies depending on the neurological damage, ranging from simple disc 'cleaning' more or less associated with bone grafting, to laminectomy and drainage of possible epidural abscess.

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skeletal muscular system in ~1.82% of cases[7] of which ~50% involve the entire spine leading to spondylodiscitis[8,9]. Only a total of 118 cases of Aspergillus spondylodiscitis have been reported in the literature[10] and only 21 cases reporting spinal epidural abscess were identified[11]. There are, at least, three dis tinct pathogenetic mechanisms proposed in the involvement of these sites, namely direct invasion by contiguous pulmonary foci, dissemination through the bloodstream, and traumatic or iatro genic inoculation[12].

The authors, through this work, report a new rare case of invasive A. Niger spondylodiscitis with epidural and iliopsoas abscesses in a 63-year-old North African female patient with a history of immunosuppression and coronavirus infection (COVID-19). The patient had favorable medical and radiological outcomes after antibiotic and antifungal therapy. The authors will explore the current literature in more detail to dissect and explain this rare entity.

This case report has been reported in line with the Surgical CAse Report (SCARE) 2023 Criteria[13].

Case presentation

A 63-year-old North African female patient with a history of life-threatening severe coronavirus infection (COVID-19) responsible for acute respiratory distress syndrome treated with antibiotic therapy and high doses of corticosteroids leading to tracheotomy after a prolonged stay in the ICU followed by renal aspergillosis requiring nephrostomy and managed with voriconazole for 6 weeks with simple consequences 2 years before presentation. The patient also suffered a fall from her height a few months later, causing persistent, dragging spinal pain that became resistant to usual compound painkillers, and NSAIDs, which motivated her to come to our neurosurgery department. Upon examination, the patient was afebrile and very painful walking with a standard walker. She had a significant thoracolumbar junction spinal syndrome made up of paravertebral muscular contracture and slight tenderness upon palpation of dorsal spinous processes and facet joints without any motor or sensitive palsy. Blood count showed a white blood cell count of 8940, hemoglobin count of 14 g/dl, and platelet count of 244 000 platelets per microliter of blood. Erythrocyte sedimentation rate was estimated at 30 mm/h and C-reactive protein was in normal range. Her renal function was preserved. Cytobacteriological urine examination revealed the presence of Escherichia coli. Aspergillus galactomannan antigenemia detection in serum with Enzyme-linked immunosorbent assay showed an antigen level reaching 0.95 (normal range = 0.700). Wright's serotype reaction was negative for brucellosis.

The full spine MRI (Fig. 1) showed an irregular appearance of the vertebral endplates with destruction, angulation, and anterior compression of the vertebral bodies of D10, D11, and D12 having an isosignal on both T1 and T2 sequences, with minimal heterogeneous enhancement after gadolinium injection of the vertebral bodies and discs and minimal epidural enhancement. This was associated with moderate perivertebral soft tissues infiltration without obvious collection. At the lumbar level, there was also an irregular appearance of L4-L5 endplates with hyposignal on T1-weighted-image and hypersignal on T2 sequence, and heterogeneous enhancement after gadolinium injection of the vertebral bodies and discs with moderate epidural enhancement. There was no significant peripheral soft tissues infiltration. Furthermore, the conus medullaris was of preserved thickness and normal signal with respect for both sacroiliac joints and the absence of any focal disc protrusion. All these features were in favor of a destructive D10-D11-D12 spondylodiscitis with epiduritis associated with a recent beginning L4-L5 spondylodiscitis with epiduritis and without sign of significant compression.

Faced with these suggestive radiological features, percutaneous discovertebral biopsies of both dorsal and lumbar levels were made. The bacteriological examination showed numerous altered leukocytes and a negative culture. Mycological examination, as well as the polymerase chain reaction examination for Koch's bacillus, was, in turn, negative. Histologic analysis of different specimens from both lumbar and dorsal areas showed remodeled bone tissue with images of demineralization. The bone marrow was well vascularized and infiltrated with few lymphoplasmacytic and polynuclear cells. Periodic acid Schiff staining did not show mycotic filaments or signs of malignancy. All these features suggested a pyogenic spondylodiscitis.

The patient was, therefore, put under triple antibiotic therapy made of Teicoplanin, Rifampicin, and Levofloxacin. Her spine was immobilized for analgesic purposes with a rigid and fitted lumbar brace, including additional padding for more additional support and stability. Faced with fairly significant dizziness and several episodes of vomiting linked to Levofloxacin, this latter was replaced by Cotrimoxazole. At 4 weeks of treatment, our patient improved significantly in terms of pain, and she regained her independent walking. The biological control assessment was without abnormalities as well as a second Aspergillus antigenemia. The antibiotic therapy was maintained for 3 months with significant clinical improvement. The patient was pain-free and returned to completely normal walking. Her neurological exam showed nothing special. The follow-up spinal MRI (Fig. 2) showed sequelae of infectious spondylodiscitis treated at levels D10-011 and D11-D12 without any activity signs. This was associated with a progressive L4-L5 infectious spondylodiscitis worsened compared to her previous imaging with the presence of an anterior L4 and L5 epiduritis extended to 46 mm in height and measuring 6 mm in maximum thickness. This epiduritis came into contact with both L5 roots with infiltration of the anterior and lateral paravertebral soft parts causing small collections of both iliopsoas muscles. All biological inflammatory markers were negative and the thoraco-abdominopelvic CT scan was without abnormalities. Regarding these findings, and given that our patient refused a new percutaneous discovertebral biopsy, our decision was to maintain her same antibiotic therapy for another 3 months. The control spinal MRI (Fig. 3) showed the stability of lesions at the dorsal level contrasting with progressive worsening of the L4-L5 infectious spondylodiscitis with the stability of the L4-L5 anterior epiduritis (46 mm in height and 7 mm in thickness) and both iliopsoas muscles abscessed collections.

Given the persistence of radiological signs of soft tissue infiltration as well as iliopsoas muscle abscesses, the patient was convinced to undergo a percutaneous biopsy of these abscesses. The cytological study revealed a very inflammatory specimen, particularly rich in polynuclear cells. It contained macrophages and lymphocytes without granuloma. The search for Mycobacterium tuberculosis, as well as anaerobic germs, was negative. Mycological culture has highlighted the incrimination of an Aspergillus Niger. The antibiotic therapy was then stopped

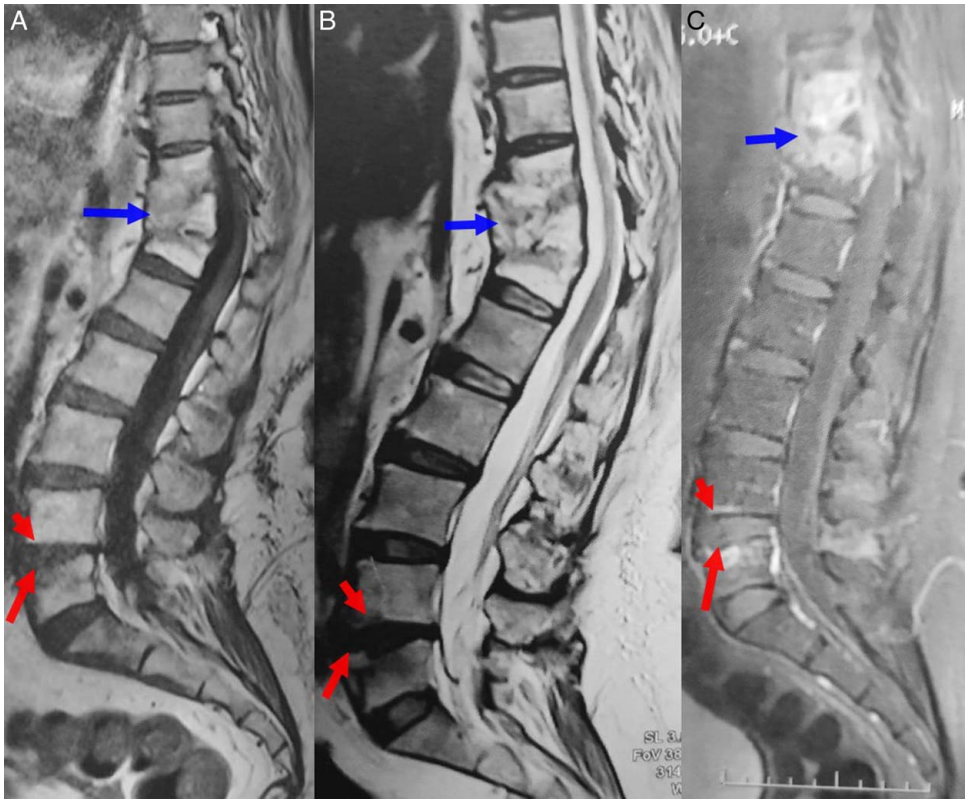

Figure 1. Spinal MRI in sagittal plane showing a destruction, angulation, and anterior compression of the vertebral bodies of D10, D11, and D12 having an isosignal on both T1 (A, blue arrow) and T2 sequences (B, blue arrow), with minimal heterogeneous enhancement after gadolinium injection (C, blue arrow) of the vertebral bodies and discs. At the lumbar level, there was an irregular appearance of L4-L5 endplates with hyposignal on T1-weighted-image (A, red arrow) and hypersignal on T2 sequence (B, red arrow), and heterogeneous enhancement after gadolinium injection (C, red arrow) of the vertebral bodies.

and the patient was put on voriconazole at a dose of 200 mg every 12 h for a period of 6 months. The control spinal MRI (Fig. 4) showed, compared to the last MRI, still absence of any activity signs at the dorsal level (D10-D11 and D11-D12) with significant improvement of L4-L5 spondylodiscitis and regression of signal abnormalities of L4 and L5 vertebral body having moderate contrast enhancement after Gadolinium injection. This was associated with the intradiscal abscess size reduction and regression of the anterior L4 and L5 epiduritis, extending to 23 mm in height and measuring 4 mm in maximum thickness. The study of the soft tissues, in turn, showed a regression of their infiltration associated with a reduction in the size of the anterior paravertebral collection extended over 6.5 cm compared to 8 in height next to L4, L5, and S1 as well as both iliopsoas muscles collections: on the right 28×10 mm versus 38×20 mm and 25×10 mm on the left versus 48×44 mm.

The patient kept on her clinical improvement. She persisted pain-free and completed normal walking. At discharge, she was referred to the infectious disease department for further management.

Clinical discussion

Fungal spondylodiscitis is a rare pathology that may even be lethal. This entity requires long-term medical treatment and, often, surgical treatment[14]. Aspergillosis represents a fairly rare disease given that its own incidence does not exceed 12 cases per year/1 000 000 people[15]. Despite its rarity, the prevalence of Aspergillus spondylodiscitis has exceeded that of Candida[16]. Reduction in immune defense factors plays a determining role in the occurrence of Aspergillus spondylodiscitis. Recent adminis tration of corticosteroid therapy is found in ~30% of cases of aspergillus spondylodiscitis reported in the literature[17]. Corticosteroid therapy, at high and prolonged doses, is recog nized as a factor favoring aspergillosis: the generally accepted threshold for increasing the aspergillus risk is 1 mg kg–1 d–1 of methylprednisolone or prednisone for 1–3 weeks[18]. Our patient received corticosteroid therapy during her previous coronavirus infection at doses higher than the threshold in the literature. Neutropenia appears to be another major risk factor whether or not it is associated with corticosteroid therapy[18,19]. Its severity and duration are taken into account: the risk of aspergillus increases if the level of polynuclear neutrophils is less than 500/mm^3 for a period greater than or equal to 2 weeks or in case of neutropenia less than 100/mm^3 whatever or the duration. This entity was not seen in our case. Patients with neoplasia under going polychemotherapy[17,20,21], kidney, and heart transplant recipients under immunosuppressive treatment combined with corticosteroids[17,20,21] are particularly exposed to aspergillus infection. Finally, intravenous drug injection, HIV infection, alcoholism, and splenectomy are also risk factors[22]. COVID-19 infection has not been reported as a direct cause or risk factor for spinal aspergillosis[4]. However, in 2022, Makhdoomi *et al.*[4] reported a case of spinal aspergillosis in an

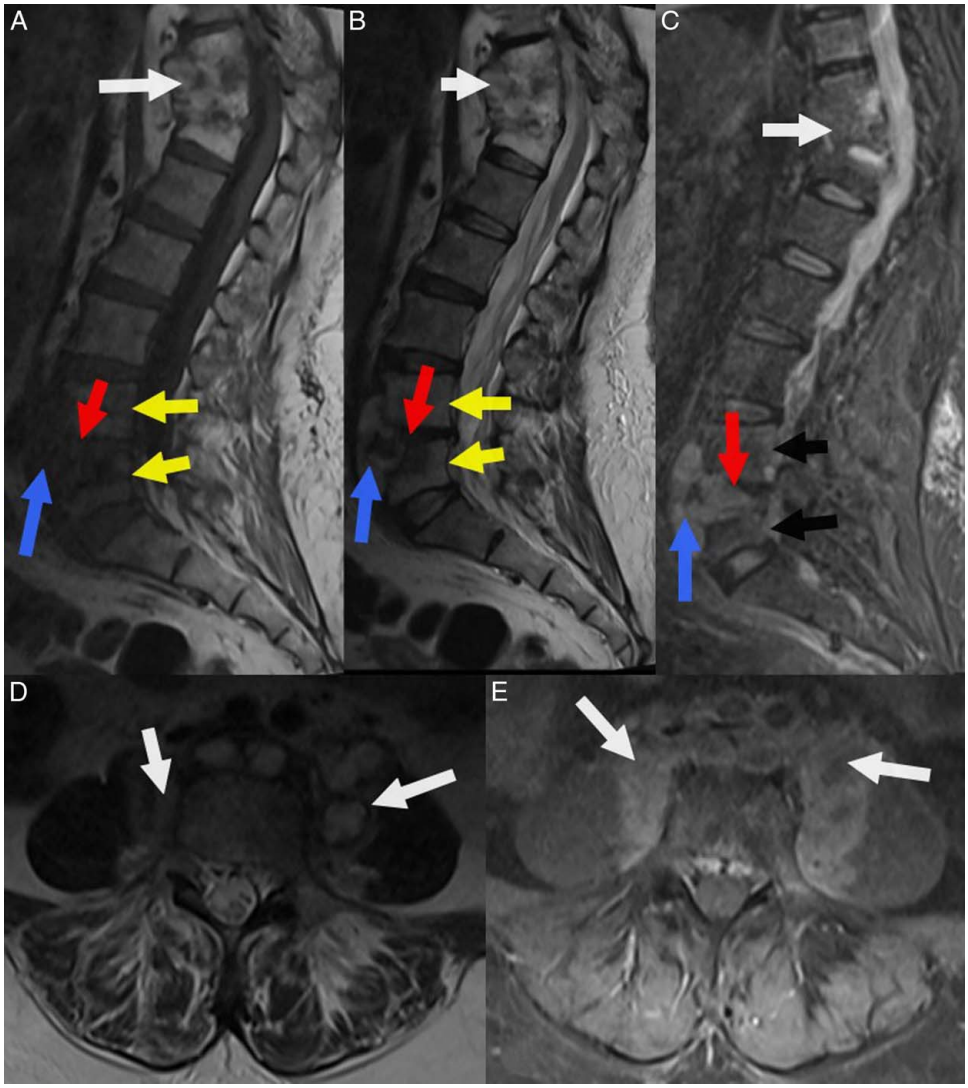

Figure 2. Follow-up spinal MRI in sagittal (A, B, C) and axial (D, E) plane performed 3 months after antibiotic therapy showing: – Sequelae of infectious treated thoracic spondylodiscitis with almost total fusion of D10, D11, and D12 responsible for thoracolumbar hinge angulation (A, B, C; white arrows). – Irregularities and subchondral erosions of the lower vertebral endplate of L4 and upper L5 with signal abnormalities of L4 and L5 vertebral body in hyposignal on T1-weighted image (A; yellow arrows) and hypersignal on T2-weighted image (B; yellow arrows) and moderate enhancement after Gadolinium injection (C, black arrow). – Intradiscal abscess (A, B, C; red arrows). – Anterior L4 and L5 epiduritis (A, B, C; blue arrows) coming into contact with both L5 roots and infiltration of the anterior and lateral paravertebral soft parts causing small collections of both iliopsoas muscles (D, E; white arrows).

85-year-old man 7 months after COVID-19 infection. More recently, Prayag *et al*.[23] reported a series of four patients with vertebral osteomyelitis caused by Aspergillus species secondary to COVID-19 infection. Our patient is, therefore, another rare case of vertebral aspergillosis secondary to prior COVID-19 infection.

Discovertebral contamination results from hematogenous dissemination, found in the majority of cases in adults; while contamination by contiguity from a pulmonary focus has been described in children[21]. Dai *et al*.[24] published in 2020 a series of six cases in which the hematogenous route was the most frequent way. They also mentioned, through a review of the literature, that among the 66 cases of aspergillus spondylodiscitis reported, all were transmitted by blood. In our patient, corticosteroid therapy, received during her COVID-19 infection, was probably able to induce immunosuppression sufficient to allow the development of aspergillus spores in transit in the pulmonary alveoli and their hematogenous dissemination towards the thoracolumbar spine. Another infection route is lumbar disc surgery suggesting the possibility of direct inoculation of the fungus[25].

Clinically, aspergillus spondylodiscitis lacks specific features. The average time between the clinical symptoms onset and diagnosis can reach 5.7 months. This type of fungal infection most often has an insidious onset with nonspecific symptoms. As a result, their diagnosis may be delayed[14]. The main symptom found is segmental spinal pain with an inflammatory pattern most often predominating in the thoracolumbar spine, as it was described in our case. Clinical signs of spinal cord compression such as paresthesias, radiculalgia, and paraplegia can sometimes be associated with it, the infection being able to extend to the epidural space in 20% of cases[26,27] as it was seen in our patient.

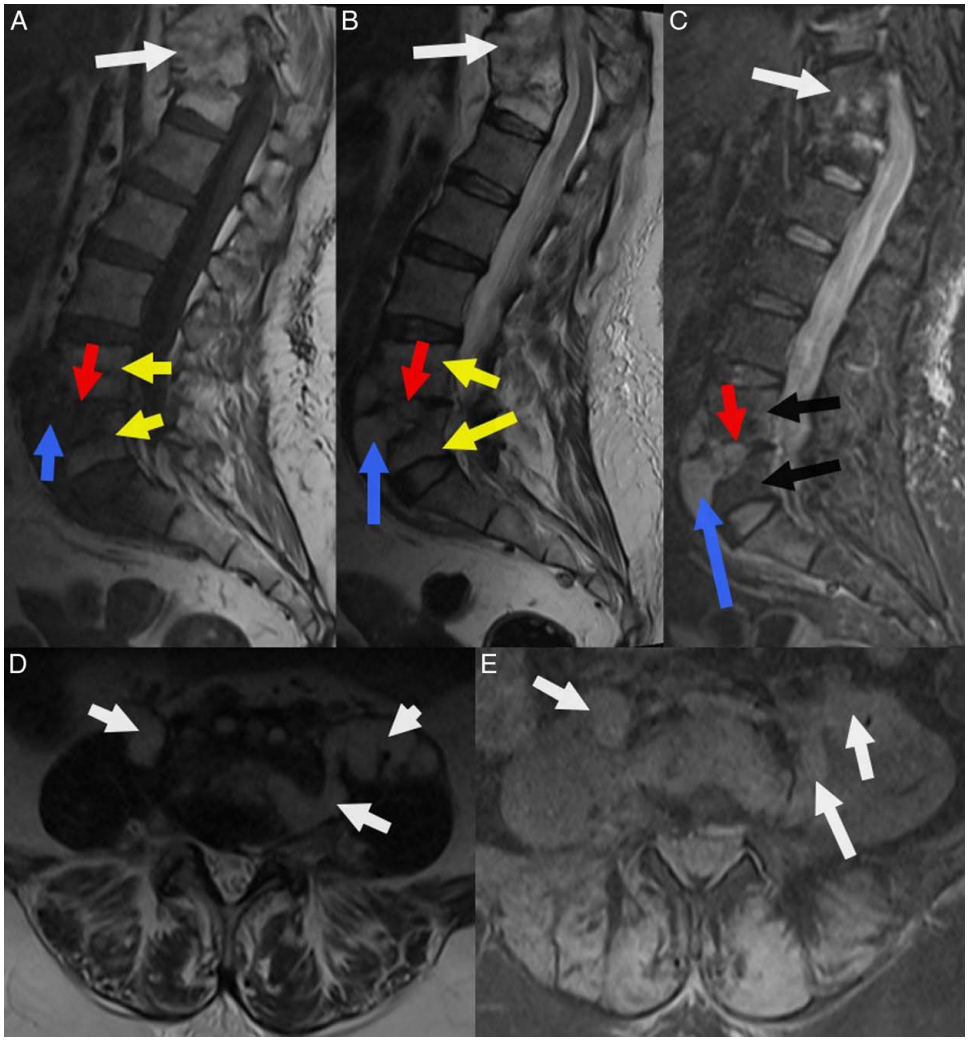

Figure 3. Follow-up spinal MRI in sagittal (A, B, C) and axial (D, E) plane performed 6 months after antibiotic therapy showing: – Sequelae of infectious treated thoracic spondylodiscitis with an almost total fusion of D10, D11, and D12 responsible for thoracolumbar hinge angulation (A, B, C; white arrows) and without any infectious activity signs. – Irregularities and subchondral erosions of the lower vertebral endplate of L4 and upper L5 with signal abnormalities of L4 and L5 vertebral body in hyposignal on T1-weighted image (A; yellow arrows) and hypersignal on T2-weighted image (B; yellow arrows) and moderate enhancement after Gadolinium injection (C, black arrow). – Intradiscal abscess (A, B, C; red arrows). – Increase in anterior L4 and L5 epiduritis (A, B, C; blue arrows) coming into contact with both L5 roots and infiltration of the anterior and lateral paravertebral soft parts causing both iliopsoas muscles abscesses (D, E; white arrows).

Among the 66 cases reported in the literature, 56 had low back pain, 27 had neurological damage, and the remaining 25 had fever. Among the 66 cases reported in the literature, 56 had low back pain, 27 had neurological damage, and the remaining 25 had fever[28]. Our patient had painful walking with significant afebrile thoracolumbar junction spinal syndrome without any motor or sensitive palsy.

The diagnosis of such spondylodiscitis is based on cultures and/or histology, whereas in 1994 after 1994, the diagnosis was made by MRI. Recently, diagnosis has been based in some cases on serology and molecular techniques[10]. Biologically, an isolated inflammatory syndrome may be present but not necessarily[22]. Normal levels of inflammatory markers such as C-reactive pro tein or erythrocyte sedimentation rate do not exclude aspergillo sis since immunocompromised subjects are incapable of devel oping a significant inflammatory reaction[29]. Hyperthermia and leukocytosis are also inconstant with poor sensitivity and specificity[24]. In our patient, the blood count showed a white blood cell count of 8940. Erythrocyte sedimentation rate was estimated at 30 mm/h and C-reactive protein was in normal range.

Blood cultures are rarely positive in aspergillus infections[30]. On the other hand, aspergillus serology confirms the etiological diagnosis even though they prove to be of little contribution in most literature reports[30]. Other more recent studies indicate that the 'sōna Aspergillus Galactomannan Lateral Flow Assay' (AGM LFA) is also diagnostically significant[31]. It is an immunochro matographic test, which makes it possible to detect Aspergillus galactomannans in serum and bronchoalveolar lavage samples in cases of pulmonary involvement. In our case, we performed the enzyme-linked immunosorbent assay (ELISA) technique in patient's serum to detect the Aspergillus antigenemia.

MRI, more than CT, is the reference examination to make the diagnosis. The association of T1 hypersignal enhanced by

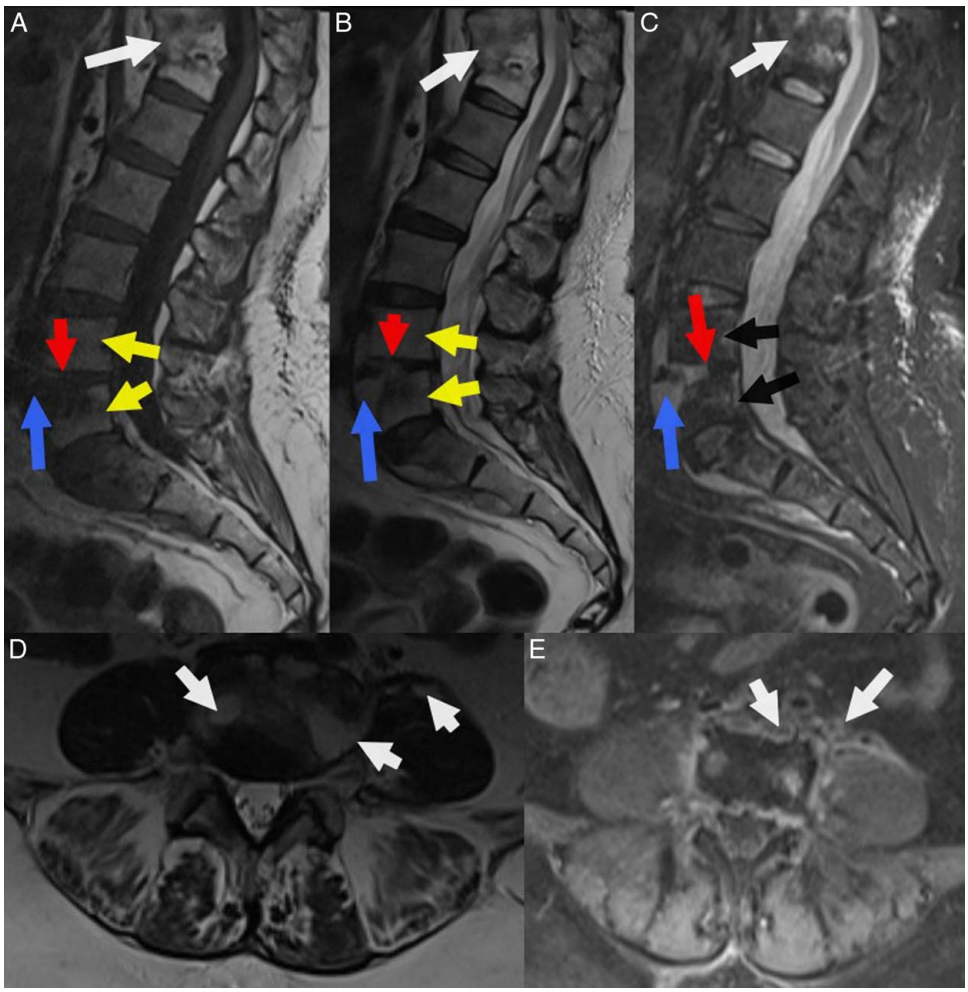

Figure 4. Follow-up spinal MRI in sagittal (A, B, C) and axial (D, E) plane performed 6 months after voriconazole therapy (400 mg daily) and antibiotics withdrawal showing: – Sequelae of infectious treated thoracic spondylodiscitis with an almost total fusion of D10, D11, and D12 responsible for thoracolumbar hinge angulation (A, B, C; white arrows) and without any infectious activity signs. – Regression of signal abnormalities of L4 and L5 vertebral body in hyposignal on T1 weighted image (A; yellow arrows) and hypersignal on T2-weighted image (B; yellow arrows) with persistant moderate enhancement after Gadolinium injection (C, black arrow). – Reduction in size of the intradiscal abscess (A, B, C; red arrows). – Regression of the anterior L4 and L5 epiduritis (A, B, C; blue arrows), extending to 23 mm in height and measuring 4 mm in maximum thickness. – Reduction in size of the anterior paravertebral collection extended over 6.5 cm compared to 8 in height next to L4, L5, and S1 as well as both iliopsoas muscles collections: on the right 28×10 mm versus 38×20 mm and 25×10 mm on the left versus 48×44 mm (D, E; white arrows).

gadolinium injection and T2 hypersignal in the vertebral endplates and disc is very suggestive[32]. Epidural abscess remains a rare entity. In a bibliographic review of the literature carried out on PubMed, only 21 cases reporting Aspergillus spinal epidural abscess were identified[11]. Our patient is, therefore, a new con tribution to the literature

When biological examinations are in favor of aspergillus infection, a CT-guided biopsy is indicated to establish the diagnosis[33]. A blood culture must also be systematically performed in parallel with the biopsy. Although its positive rates are a little low, this blood culture may guide the choice of antifungals if tissue culture is not possible. In our patient, we did not perform blood culture and diagnosis was directly made by the Mycological culture of the specimen.

The standard treatment is amphotericin B (1 mg kg–1 d–1), possibly associated with 5-flucytosine (100 mg kg–1 d–1) in severe forms with relay to itraconazole[34]. Although some advocate the surgical approach in principle whether or not there are neurological complications associated with spondylodiscitis[35]. In 1994, Cortet *et al*.[34] published a study of nine cases of aspergillaus spondylodiscitis for which medical treatment alone resulted in a cure. Since then, the use of itraconazole in the case of aspergillus spondylodiscitis has become widespread due to its oral intake, its good tolerance and its excellent effectiveness. The recommended dose for the treatment of fungal disc infections is 3–5 mg kg–1 d–1[21,35,36]. Recently, and according to the latest 2016 American Society of Infectious Diseases guidelines on the treatment of aspergillosis[37], voriconazole is recommended as the primary treatment for invasive aspergillosis, including bone involvement as we adopted for our patient. In cases of resistance or poor tolerance to conventional antifungal treatment, itraconazole is indicated as an alternative way[38].

Surgery is reported in 40% of cases in the literature, due to insufficient medical treatment and/or neurological complications.

The surgical procedure varies depending on the neurological damage, ranging from simple disc 'cleaning' more or less associated with bone grafting[22,25,36], to laminectomy[27,39,40], and drainage of possible epidural abscess[41]. Posterior osteosynthesis is sometimes necessary if multiple vertebrae and discs are destroyed or if posterior stability is compromised in order to avoid serious after-effects[17,20,42]. Our patient did not undergo any surgery as she had no neurological palsy and she improved well radiologically on her last follow-up MRI.

The prognosis will take into account the host's immunity as well as its general state of health. The response to different treatments will largely depend on individual factors, including neuropathies, underlying defects, and early diagnosis and treatment[43].

Given the rarity of Aspergillus spondylodiscitis with its Niger subtype and the invasive nature of this entity complicated by epidural abscess, our case appears a contributing addition to the current literature emphasizing the importance of keeping in mind this type of fungal infection, especially in immunocompromised subjects in order to start treatment and avoid complications.

Conclusion

Aspergillus spondylodiscitis remains a rare and very demanding clinical entity. Its clinical signs are not specific and its diagnosis depends on both imaging and histology. Appropriate antifungal treatment based ideally on susceptibility testing combined with surgery, if necessary, represents the current standard of care. Early diagnosis and well-targeted medical treatment seem the ideal solution given that this type of infection has a poor prognosis. In the future, additional studies seem obligatory, given that this very particular infectious entity remains rare, and requires very appropriate treatment.

Ethical approval

Not applicable.

Consent

Written informed consent was obtained from the patient for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Not applicable.

Author contribution

M.B. and B.K.: study concept, data interpretation, and writing the paper; M.B. and E.E.K.: writing the paper; M.B.: study concept; M.B., M.Z.B.: study concept and validation.

Conflicts of interest disclosure

The authors declare no conflict of interest.

Research registration unique identifying number (UIN)

Not applicable.

Guarantor

Mehdi Borni.

Data availability statement

Not applicable.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Patient perspective

During hospitalization and at the discharge, the patient has given the opportunity to share their perspectives on the intervention the boy received and she was satisfied with the care.

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