SPINAL ASPERGILLOSIS: A RARE CLINICAL CASE AND REVIEW OF THE LITERATURE

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Objective. To analyze long-term results of treatment of a patient with recurrent lumbar aspergillosis and to systematize the literature data.
Material and Methods. Long-term follow-up results of treatment of recurrent Aspergillus spondylitis in a 48-year-old patient who underwent primary surgery for reconstruction of the anterior spinal column through the anterior approach were studied. Literature data on the treatment of spinal aspergillosis from 2000 to 2022 were systematized.
Results. The key method for the etiological verification of spinal aspergillosis is percutaneous bone biopsy from the lesion, followed by histological and bacteriological examination of the material. Isolated anterior spinal column reconstruction through the anterior approach ensures the achievement of local control of the infection process, but a short course of antimycotic chemotherapy after surgery is a factor of disease recurrence. The optimal duration of antimycotic chemotherapy in the postoperative period is at least 3 months, with voriconazole being the drug of choice.
Conclusion. Spondylitis caused by *Aspergillus spp.* is a special form of inflammatory spine disease requiring obligatory percutaneous bone biopsy for etiological verification. A multidisciplinary therapeutic approach including a course of conservative antimycotic therapy for at least 3 months, surgical debridement and reconstruction of the affected spinal motion segments provide the best clinical results.
Key Words: infectious spondylitis, spinal aspergillosis, differential diagnosis, voriconazole, revision surgery.
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Spinal aspergillosis is one of the rarest infectious lesions of the vertebral column associated with certain species of mold fungi of the genus *Aspergillus spp.* [1, 2]. Meanwhile, the lung is the main target organ in the overall structure of aspergillus lesions, with a frequency of involvement with the pathological process of 85–90 [3]. Keratitis, endophthalmitis, osteoarthritis, and tumor-like lesions in the sinuses of the skull and nose are less frequent [4–6]. Annually, up to 200 thousand cases of invasive aspergillosis are recorded in the world; moreover, spinal lesions account for no more than 0.5–1.6 [7].

The risk group for the progression of the disease consists of workers on livestock and poultry farms, as well as patients with chronic obstruction lung diseases and autoimmune pathology [8]. Mycotic lesions have become more common in the past decade due to increase of number of immunocompromised people with HIV infection and the ones who use immunosuppressants for organ transplantation [9–10]. After transplantation, pulmonary aspergillosis develops in every fifth recipient, and more than half of them are fatal [11]. Mycotic lesions of the bone and joint system are extremely rare and amount to 1–2 [12–14]. Approximately half of these cases are spinal lesions [15–18].

Among the etiological forms of spinal aspergillosis, the main place is taken by fungi of the genus *Aspergillus fumigatus; A. nidulans* and *A. flavus* are less common [19–21]. The rarity and variety of clinical manifestations of spinal aspergillosis call for the systematization of existing data in terms of diagnosis and of conservative and surgical treatment.

The objective is to analyze long-term results of treatment of a patient with recurrent lumbar aspergillosis and to systematize the literature data on the issue.

Study design: case study corresponding to Class IV according to Burns et al. (2011).

Material and Methods

A male 48-year-old patient was admitted to a hospital in the unit of spinal surgery in February 2019. At the time of admission, he complained of chronic vertebrogenic pain syndrome in the lumbar spine with an intensity of up to 8 points according to VAS with irradiation to the left lower extremity and an increased level of loss of social functioning skills of up to 82 % according to ODI.

It is known from the hospital chart that the patient noted vertebrogenic pain syndrome for 1 year and 1 month and received courses of analgesic therapy (NSAIDs) without a stable therapeutic effect. According to CT findings of the lumbar spine, contact destruction of L2–L3 bodies, as well as pre- and paravertebral and epidural soft tissue components with the formation of spinal canal stenosis and compression of neural structures at the indicated level were defined (Fig. 1).

In accordance with the medical and imaging data, the diagnosis of "chronic nonspecific osteomyelitis" was established, and a course of empiric antibacterial therapy was prescribed.

At the time of admission to the hospital, the duration of the therapeutic pause was 1 year and 2 months. Considering the clinical picture and the lack of data on etiological verification, the first stage was a diagnostic percutaneous bone biopsy of L3–L4 bodies, followed by bacteriological, DNA, and histological examination of the sample. Spinal aspergillosis (*A. fumigatus*) was verified.

The reconstructive stage of the surgery was made through a lateral retroperitoneal approach for resection of the remains of the intervertebral disc and the L3–L4 vertebral bodies, anterolateral decompression of the spinal canal contents, and interbody fusion with a titanium block lattice with autograft (fragments of the iliac crest; Fig. 2).

During the postoperative period, the patient was given a two-month course of antimycotic chemotherapy (voriconazole 200 mg twice a day). According to the control examination (6 months after surgery), there was a relief of vertebrogenic and radicular pain syndrome and a decrease in loss of social functioning skills to 26 % according to the ODI.

In 2 years and 6 months after the primary surgery, there was a progression of vertebral destruction at the L2–L4 level with the establishment of a fistulous tract and an elevation in vertebrogenic pain syndrome up to 6 points according to the VAS. The control radiation examination (CT) findings are illustrated in Fig. 3.

A two-stage revision surgery was performed: posterior out-of-focus instrumental fixation with a hybrid structure, removal of an interbody implant, resection of L2–L4 bodies, installation of negative pressure wound therapy (NPWT) system for lumbotomic wound healing. An anterior fusion was performed on the 14th day after the first revision surgery. The wound healed by primary intention, and the patient was discharged from the hospital on the 10th day.

The duration of the course of antimycotic chemotherapy was extended to six months. The prospective follow-up was for 12 months; a recurrence-free course of spinal aspergillosis and persistent relief of vertebrogenic pain syndrome were observed (Fig. 4).

To systematize data on the treatment of spinal aspergillosis, literature sources were searched and reviewed using the following databases: eLibrary, PubMed, Clinical Key.

Search depth: from 2000 to 2022 inclusive. Keywords: "aspergillosis of the spine", "aspergillus spondylitis", "mycotic spondylitis" in Russian, and "aspergillus spondylodiscitis", "aspergillus spondylitis" in English.

Criteria for including articles in the analysis: 1) a design that corresponds to Burns et al. (2011) types IIB–IV; 2) a prospective follow-up of at least 2 months; 3) a clear indication of the type of diagnostic and therapeutic treatments; and 4) a description of the concurrent pathology.

At the initial stage, 47 papers were selected, 21 of which fully complied with the inclusion criteria. The description of the publications is given in the Table.

The final analysis included 32 case studies. Distribution of cases by localization: C (2/6 %), T (8/25 %), T/L (7/22 %), L (14/44 %), L/S (1/3 %). *A. fumigatus* (62.5 %) holds the leading position in the etiological structure of pathogens of aspergillus spondylitis; *A. flavus* (12.5 %), *A. nidulans* and *A. niger* (6.2 %) are less common.

Results and Discussion

At the outset of the disease, vertebrogenic pain syndrome is the most common and nonspecific clinical manifestation of spinal aspergillosis [16, 19, 32]. The primary granulomatous nature of the inflammatory process promotes the development of pronounced soft tissue components (pre- and paravertebral, and epidural abscesses), which in 10–20 % of cases is followed by neurological impairment due to compression of intracanal neural structures [12, 20]. There are no specific medical or imaging markers of the disease. Meanwhile, percutaneous bone biopsy with a puncture needle from the lesion remains the priority technique for etiological verification. The enzyme-linked immunosorbent assay (ELISA), recommended as an additional technique for serological diagnostics, does not have high sensitivity and, as an isolated diagnostic technique, does not enhance the frequency of verification of the process [3, 5].

An important clinical challenge associated with the difficulties of the differ-

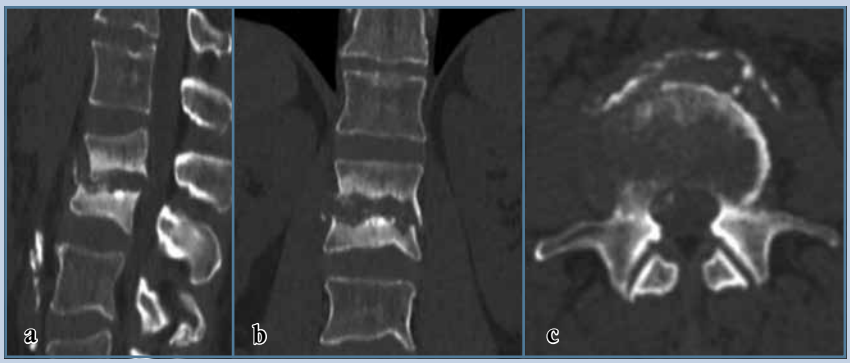

Fig. 1
CT scan of a male 48-year-old patient before surgery: contact destruction of L2–L3 bodies, paravertebral soft tissue component, local kyphotic deformity of type IIA according to Rajasekaran (2017): **a** – sagittal view; **b** – frontal view; **c** – axial view

ential diagnosis of spinal aspergillosis is the mimicing of tuberculous spondylitis [21, 35–37]. For example, according to X-ray diagnostics, extensive soft tissue components (abscesses) in aspergillosis of the spine (that mainly spread paravertebrally) can be treated as manifestations of granulomatous inflammation, including tuberculous spondylitis [9, 15, 16, 34].

The shift in emphasis towards oral administration of voriconazole as antimycotic chemotherapy has been noted since 2007, while the optimal treatment duration remains a crucial issue. In this regard, according to the results of the literature review, the treatment duration ranges from 2 weeks to 12 months, mean 3 months, while the recurrence-free course of the process has been achieved in all cases. The highest incidence rate of fatal outcomes was observed in patients receiving antimicrobial therapy within 4-6 weeks after surgery.

In the structure of concomitant pathology recorded in patients with spinal aspergillosis, immunodeficiency conditions predominate, associated both with immunosuppressive therapy after organ transplantation (3 cases) and primary oncohematological diseases (5 cases) [10, 15, 19, 26, 27, 29, 30, 32].

Since 2022, cases of spinal aspergillosis on the background of systemic glucocorticoid therapy in patients with associated pneumonia, COVID-19 are described in the literature [20, 33].

There are four main approaches to surgical treatment: 1) debridement and reconstruction of the anterior column through the anterior approach (13 cases); 2) three-column reconstruction through the combined approach (8 cases); 3) debridement of the epidural space and anterior column through the posterior approach without posterior instrumental fixation (5 cases); and 4) debridement of the epidural space and anterior column through the posterior approach with posterior instrumental fixation (4 cases).

Considering the predominant involvement of the anterior column of the spine, debridement and reconstruction of the vertebrae in the vast majority of cases was performed through an isolated anterior approach that in the long-term period ensured a recurrence-free course of the mycotic process in 84.6 % of cases.

We consider that the chosen surgical approach in the presented case study corresponded to the accepted approaches. Nevertheless, the antimycotic therapy with the duration of 2 months was insufficient. It was a factor in the recurrence of spinal aspergillosis. The involvement of adjacent spinal motion segments

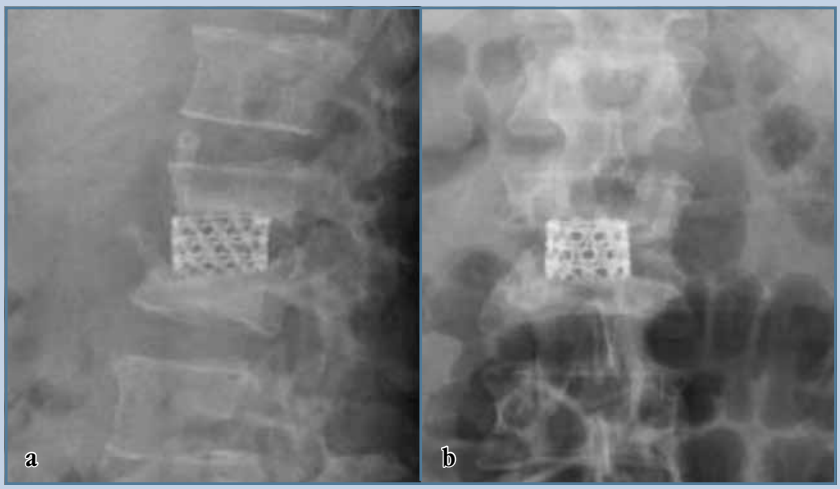

Fig. 2
Radiographs of the spine of a male 48-year-old patient after abscessotomy, marginal resection of L2–L3 bodies, anterior decompression of the dura mater, anterior fusion with a titanium block lattice with autologous bone: **a** – sagittal view; **b** – frontal view

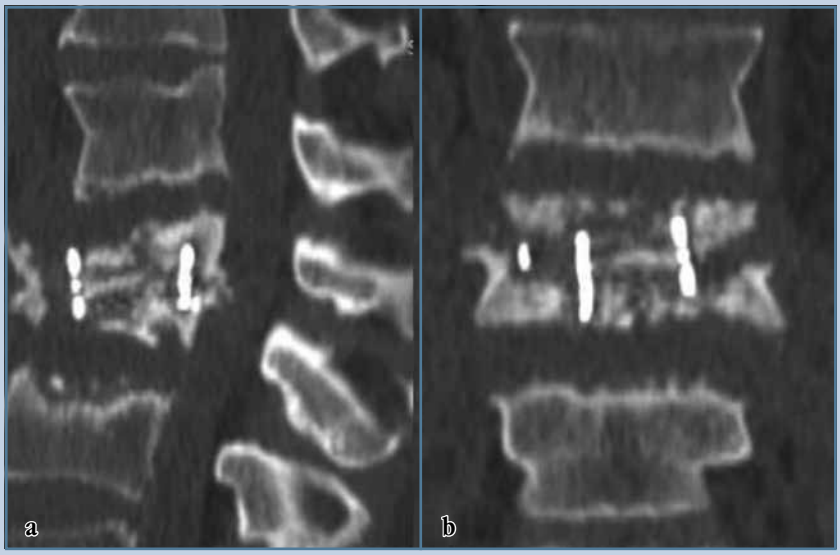

Fig. 3
CT scan of a male 48-year-old patient after surgery: progression of destruction in the contact segments, destabilization of the titanium block lattice with autologous bone, **a** – sagittal view; **b** – frontal view

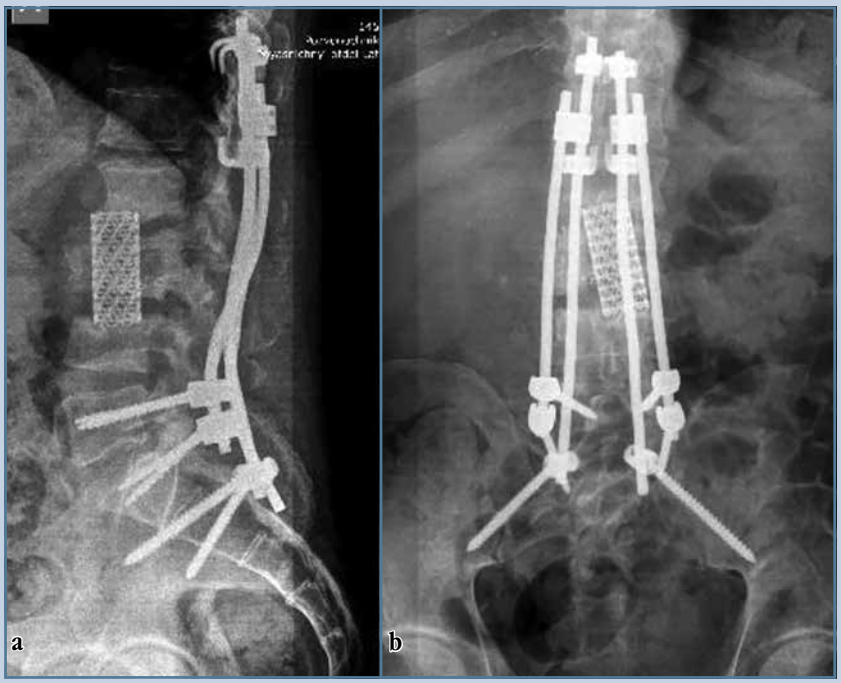

Fig. 4
Radiographs of a male 48-year-old patient 10 months after the revision surgery: stable position of the anchor elements of the metal instrumentation, no signs of recurrence of the mycotic process: **a** – sagittal view; **b** – frontal view

requires the necessity of extension of the anterior column resection length to three segments that, in turn, requires an additional spinopelvic fixation and posterior fusion using autografts.

Conclusion

Aspergillus spp. associated spondylitis is a special form of inflammatory spinal disease requiring mandatory diagnostic percutaneous bone biopsy for etiological verification. A multidisciplinary therapeutic approach, including a course of conservative antimycotic therapy for at least 3 months, debridement, and reconstruction of the affected spinal motion segments, ensures the best clinical outcomes.

The study had no sponsors.
The authors declare that they have no conflict of interest.
The study was approved by the local ethical committees of institutions.
The processing of the medical history materials was done with the patient's written consent.
All authors contributed significantly to the research and preparation of the article, read and approved the final version before publication.

Table

Description of publications included in the systematic literature review

Author	Number of cases	Localization/ etiology	Treatment strategy	Outcome
Van Ooij et al. [17]	4	T1, T/L2, L1/ *A. fumigatus* (4)	Amphotericin B 2 g per day for 2 months, reconstruction of the anterior column through the anterior approach	Improvement — 2, progression of neurological deficit — 1, fatal outcome due to the primary disease — 2
Ur-Rahman et al. [21]	1	T/*A. flavus*	Amphotericin B 2 g per day for 6 weeks, debridement of the anterior column through the posterolateral approach + posterior instrumental fixation	Fatal outcome due to the disease progression
Gupta et al. [22]	1	T/*A. niger*	Amphotericin B 700 mg per day + itraconazole 200 mg per day for 3 months, debridement of the anterior column through the anterior approach	Fatal outcome due to the disease progression
Auletta et al.[23]	1	T/*A. flavus*	Amphotericin B 2 g per day + rifampicin 300 mg per day for 6 weeks, debridement of the anterior column through the anterior approach	Recurrence-free course
Chi et al. [24]	1	C/*A. flavus*	Amphotericin B 2 g per day, debridement of the anterior column through the posterior approach	Fatal outcome due to intraventricular hemorrhage complicated by mycotic meningoencephalitis
Saigal et al. [25]	1	T/L/ *A. fumigatus*	Percutaneous bone biopsy, amphotericin B 2 g per day, debridement of the anterior column through the posterior approach	Recurrence-free course
Vaishya et al. [18]	1	T/ *A. fumigatus*	Amphotericin B 2 g per day, reconstruction of the anterior column through the anterior approach + posterior instrumental fixation	Fatal outcome 2 months after surgery due to generalization of the process
Son et al. [26]	1	L/*A. fumigatus*	Reconstruction of the anterior column in the cervical spine through the anterior approach	Recurrence 1 month after surgery, antimicrobial therapy regimen is not presented
Weclawiak et al. [27]	1	T12–L1/ *A. fumigatus*	Percutaneous bone biopsy, voriconazole 200 mg per day for 6 months	Recurrence-free course
Tew et al. [28]	1	T/ *A. fumigatus*	Voriconazole 200 mg per day for 2 weeks, debridement of the anterior column through the posterior approach	Fatal outcome 2 weeks after surgery due to generalization of the process
Nicolle et al. [10]	1	C/*A. flavus*	Percutaneous bone biopsy, voriconazole 200 mg per day for 12 months	Recurrence-free course
Raj et al. [29]	1	L/S/ *A. fumigatus*	Percutaneous bone biopsy, laminectomy, debridement of L5–S1 without posterior instrumental fixation, voriconazole 200 mg per day for 3 months	Recurrence-free course
Shashidhar et al. [30]	1	L/*A. fumigatus*	Percutaneous bone biopsy, decompression + posterior instrumental fixation, voriconazole 200 mg per day for 3 months	Recurrence-free course
Yoon et al. [15]	1	L/*A. fumigatus*	Empiric anti-tuberculosis chemotherapy for 1 month, percutaneous bone biopsy + laminectomy of L2, reconstruction of the anterior column through the anterior approach	Preservation of lower paraparesis type D according to Frankel, recurrence-free course
McCaslin et al. [31]	1	T/L/ *A. fumigatus*	Percutaneous bone biopsy, voriconazole 6 mg per kg daily for 4 weeks, laminectomy, debridement without posterior instrumental fixation	Fatal outcome 2 weeks after surgery due to generalization of the process

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Description of publications included in the systematic literature review

Author	Number of cases	Localization/ etiology	Treatment strategy	Outcome
Lyons et al. [19]	1	L3– L4/ *A. nidulans*	Percutaneous bone biopsy, voriconazole 200 mg per day for 6 weeks, 360° reconstruction through combined approach	Prolongation of voriconazole 300 mg per day for 7 months, recurrence-free course for 3 years
Sohn et al. [32]	1	L/*A. terreus*	Percutaneous bone biopsy, voriconazole 200 mg per day for 4 weeks	Recurrence 4 months after the moment of completion of the first course of chemotherapy, the resumption of chemotherapy for 9 months; recurrence-free course
Dai et al. [13]	6	T_1, T/L1, L4/ *A. fumigatus* (2), *A. niger* (1) *Aspergillus spp.* (3)	Voriconazole 200 mg per day for 4 months, debridement of the anterior column through the posterior approach + posterior instrumental fixation (5), without surgery (1)	Recurrence-free course
Prayag et al. [33]	4	T/L1, L3/ *Fumigatus* (3), *A. nidulans* (1)	Percutaneous bone biopsy, reconstruction of the anterior column from the anterior approach (L), decompression + posterior instrumental fixation (T/L), voriconazole 200 mg per day for 3 weeks	Recurrence-free course
Rashid et al. [34]	1	T/ *A. fumigatus*	Empiric anti-tuberculosis chemotherapy for 1 month, percutaneous bone biopsy, decompression + posterior instrumental fixation, voriconazole 200 mg per day for 3 months.	No clinical effect of empiric anti-tuberculosis chemotherapy, recurrence-free course after surgery and a course of antimicrobial therapy
Keerthi et al. [20]	1	L/*A. fumigatus*	Percutaneous bone biopsy, voriconazole 200 mg per day for 3 months	Recurrence-free course

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