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Case Report

Intraspinal actinomycosis: a rare case report and literature review

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Abstract: To investigate the main clinical characteristics of intraspinal actinomycosis and help early diagnosis and treatment of this rare disease, we reported a case which was initially misdiagnosed as spinal cord tumor based on magnetic resonance imaging (MRI) findings. The diagnosis of intraspinal actinomycosis was eventually confirmed by histopathology. We further studied the relevant literatures to comprehensively understand this uncommon disease. We searched through PubMed database using the keywords "actinomycosis" and "spinal cord" before Mar 20, 2016. We retrieved 26 articles describing 27 actinomycosis case reports with spinal cord involvement. Then, we analyzed their clinical manifestation, diagnosis, treatment and prognosis. Together with our case, analysis of the 28 cases revealed that 71.4% (20/28) patients were diagnosed by histopathology and 32.1% (9/28) by culture. The difference between intraspinal and common actinomycosis was that most patients in our study series were immunocompetent [89.3% (25/28)]. Penicillin based treatment regimen accounted for 88.5% (23/26) intraspinal actinomycosis cases and the mean duration of antibiotic therapy was 6 months. Although rare, actinomycosis is an important pathogen for intraspinal inflammatory granulomas. Specimen biopsy or culture is essential for a correct diagnosis with biopsy highly recommended. Early initiative and long-term antibacterial therapy is crucial for improving prognosis. Direct decompressive surgical resection of spinal cord lesion is helpful for relief of symptoms.

Keywords: Actinomycosis, intraspinal, immunocompetent, early diagnosis, antibacterial therapy, surgical resection

Introduction

Actinomycosis is a chronic bacterial infection characterized by abscess formation, draining sinus tracts, fistulae, and tissue fibrosis [1]. Cervicofacial (55%), abdominopelvic (20%) and thoracic (15%) are most commonly involved in actinomycosis [2, 3], while central nervous system (CNS), especially spinal cord involvement is rare [2, 4-6]. CNS involved actinomycosis may present as brain abscess, meningitis, subdural empyema, spinal and cranial epidural abscess and actinomycetoma, which is similar to some other conditions such as malignant and granulomatous diseases. Therefore, intraspinal actinomycosis is often misdiagnosed in clinical practice [7]. In this article, we would like to present a histopathologically confirmed case of intraspinal actinomycosis and contribute to the understanding of this disease.

Materials and methods

First, we reported a rare case of intraspinal actinomycosis found in our hospital. Then, we searched through PubMed database with the keywords "actinomycosis" and "spinal cord" before Mar 20, 2016 and analysed their clinical manifestation, diagnosis, treatment and prognosis. We retrieved 26 articles describing 27 actinomycosis case reports with spinal cord involvement. Together with our case, we analyzed all the 28 patients with intraspinal Actinomycosis, then, analysed the clinical manifestation, diagnosis, treatment and prognosis, summarized the difference between intraspinal and common actinomycosis.

Case report

A 27-year-old female with insidious onset of deteriorating paresis, numbness and myoclonic

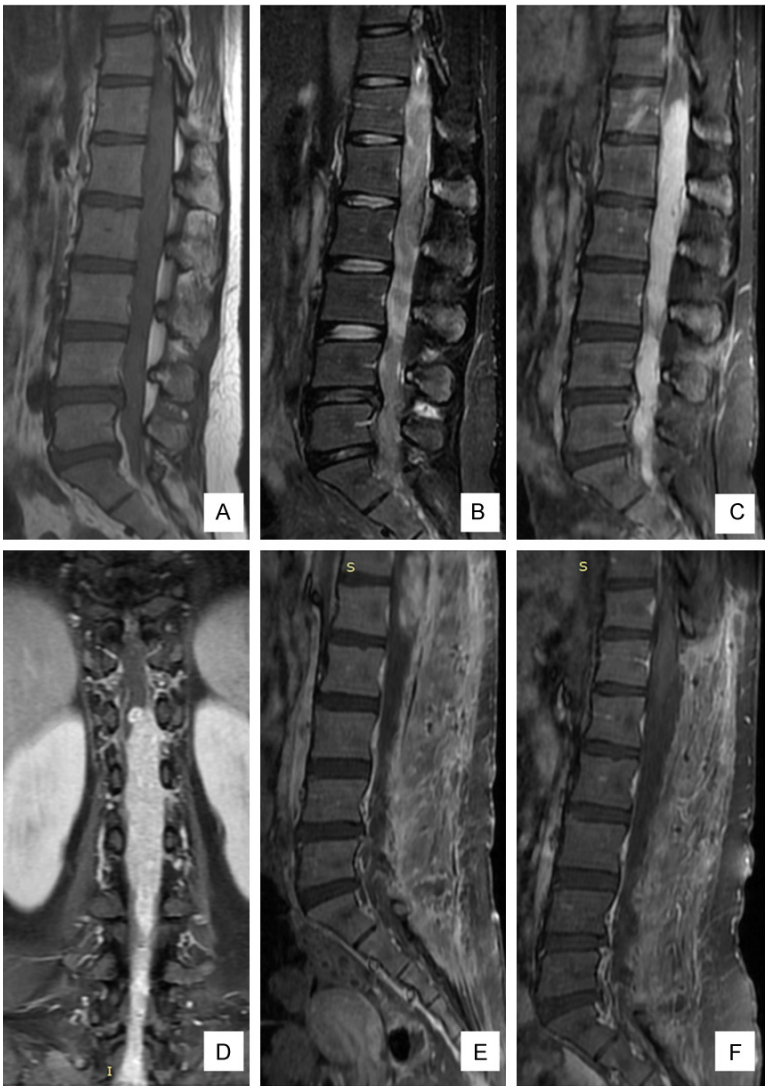

Figure 1. Magnetic resonance imaging show wing lesion involving spinal cord from T12 to S1. A. T1-weighted sagittal imaging shows a mass-shaped and slightly hypointense lesion from T12 to S1. B. T2-weighted sagittal imaging shows the previous isointense lesion. C. The sagittal contrast-enhanced T1-weighted imaging shows the obviously enhancing and well-defined lesion. D. The coronary contrast-enhanced T1-weighted imaging shows the lesion. E. After surgery, the sagittal contrast-enhanced T1-weighted imaging reveals that most of the lesion were removed while a residual small patchy of enhancing foci. F. On 6-month follow-up MR imaging, the enhancing lesion completely disappeared.

twitches of left lower limb was admitted to neurosurgery department, Shanghai Jing'an District Center Hospital.

The patient complained with a fever and backache in 34th week of her pregnancy. Because of the excruciating back pain, she subsequently had elective caesarean section for early delivery in 36th week of pregnancy. After delivery, her fever and back pain had resolved but similar symptoms recurred one month later. Progressively, she developed numbness, weakness and cramp in her left lower limb, as well as nausea, vomiting and fluctuating impairment of consciousness. Then she was found to have hydrocephalus and subsequently underwent ventriculo-peritoneal (V-P) shunt. Cerebrospinal fluid (CSF) examination during the surgery showed WBC 9×10^6/L ($0\text{-}8\times10^6$/L), protein 1923 mg/L (120-600 mg/L), glucose 2.94 mmol/L (2.5-4.5 mmol/L) and chloride 125 mmol/L (120-132 mmol/L). After V-P shunt, her consciousness recovered but back pain persisted. Her neurological deficits deteriorated with weakness of both lower limbs and gradually progresses. Eventually, she was unable to walk or stand. Besides, spinal magnetic resonance imaging (MRI) showed a suspected intra-spinal tumor involving T12 to L5. As a result, she was admitted to Jing'an Hospital for spinal decompressive resection surgery.

Neurological examination revealed proximal dominant muscle weakness in the left leg. Hypoesthesia with a multi focal distribution was also found in the left lower extremity. Laboratory results revealed a normal total leucocyte count of 7.53×10^9/L, with the proportion of neutrophils 72.6%, hemoglobin (Hb) level 13.7 g/dl, and platelet count 285×10^9/L. Liver function, renal function and coagulation tests were within the normal range. No abnormality was found in thoracolumbar computer tomography (CT) scan, while spinal cord occupying lesion was found at level T12 to S5 in MRI scan. Therefore, ependymoma was considered as the primary diagnosis (**Figure 1A-D**).

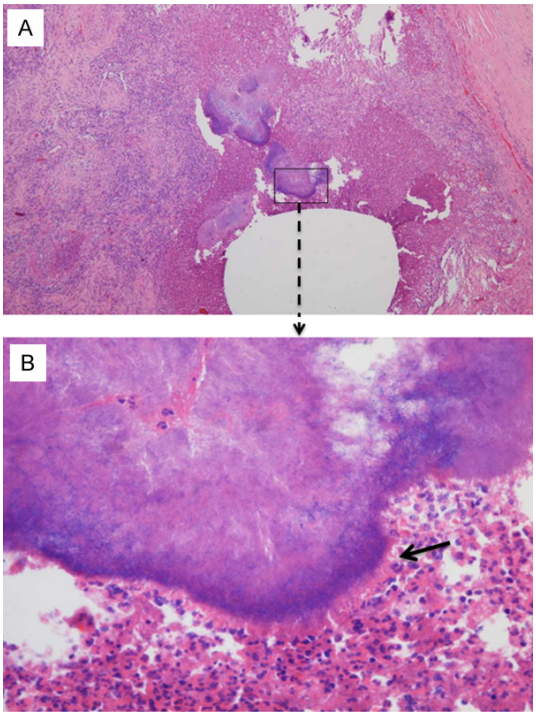

Figure 2. Histopathological changes showed actinomycotic colonies with radical bacterial colony and filamentous bacteria. A. Three sulfur granules embedded within an abscess (HE×40). B. Star-like eosinophilic Splendore-Hoeppli material with clubbed ends between the bacterial and abscess is a characteristic phenomenon of actinomycosis (HE×400).

After admission, the muscle weakness in her legs rapidly worsened. An intraspinal tumor resection was performed on August 14, 2014. Gelatinous dark mass with tough texture and rich blood supply, surrounding spinal cord and cauda equine was found in the spinal canal in the operation. Confirmed by post-operative MR scan, most of the mass had been removed (**Figure 1E**). Microscopic examination of the specimen revealed diffused distribution of focal periodic acid-Schiff (PAS) positive abscess, with plenty of lymphocytes, plasma cells and histocytes infiltration, which suggested infection.

After the operation, the patient had a fever fluctuating between 38~39°C Amikacin, clindamycin, metronidazole and vancomycin were given sequentially. She was subsequently transferred to the department of infectious diseases. Her surgical wound was poorly healed with continuous drainage. Laboratory results showed mild anemia with Hb 10.2 g/dl, elevated erythrocyte sedimentation rate (ESR) 41 mm/hr and serum albumin 27 g/L. T-SPOT test was weakly positive, serum latex agglutination test for Cryptococcus was negative, and HIV, HBV and HCV were all tested negative. Immune cell subsets analysis for the percent of T cell (CD3, CD4 and CD8), B cell (CD19) and NK cell provided no evidence of immune suppression. After 2 weeks of treatment, her body temperature returned to normal.

Although no definite pathogenic microorganism was identified through tissue culture, some low virulent organisms, especially rare fungi were clinically suspected. Itraconazole was chosen for empirical antifungal therapy. Meanwhile, the histopathological result suggested sulfur granules embedded within abscess and star-like eosinophilic Splendore-Hoeppli material with clubbed ends between the bacterial and abscess (**Figure 2**), which was a characteristic of actinomycosis. Therefore, the patient was diagnosed with intraspinal actinomycosis on the basis of pathological evidences.

The patient was then treated with a high dose of penicillin (6.4 million IU, Q8h) combined with doxycycline (0.1 g, Q12h) intravenously for 8 weeks, followed by oral amoxicillin/clavulanate and doxycycline for 2 months. After that, MRI scan showed that the intraspinal enhancing lesions had shrunk significantly (**Figure 1F**).

Discussion and literature review

Actinomycosis can take place in various anatomical sites including face, bone and joint, respiratory tract, genitourinary tract, gastrointestinal tract, central nervous system, skin, and soft tissues [8]. Most intraspinal actinomycosis cases are attributed to local or hematogenous spread [9]. However, only a few cases of intraspinal actinomycosis have been reported so far [2, 10-12]. We searched Pubmed database using keywords “actinomycosis” and “spinal cord”. Until March 20, 2016, 26 published articles with English abstract were found with 27 cases of intraspinal actinomycosis reported. Therefore, including our case, a total of 28 intraspinal actinomycosis cases were summarized in our report (**Table 1**).

In general, the male-to-female ratio is discrepant in different reports. The ratio was 20:6 in an earlier retrospective study in 1996 [13], while the proportion of male was up to 84.2% in

Table 1. Summary of 28 intraspinal actinomycosis cases from previous literatures and our report

	Authors	Publication year	Sex	Age (years)	Spinal segment (s) involved	Diagnostic basis	Course of treatment	Outcome	Ref
1	Wang T, et al	Our case	Female	27	T, L, S	Histopathology	>6 months	Partial improved	-
2	Thango NS, et al	2015	Male	40	T	Histopathology	>6 months	Asymptomatic	[30]
3	Patil VR, et al	2014	Male	30	T, S	Histopathology	NA	NA	[3]
4	Hung PC, et al.	2014	Female	7	C	Histopathology	NA	Recovered completely	[16]
5	Kapmaz M, et al.	2014	Male	82	T, L	Culture	>12 months	Partial improved	[15]
6	Duvignaud A, et al	2013	Male	52	C	Molecular biology	>9 months	Recovered completely	[7]
7	Fichte S, et al	2013	Male	55	C, T	Microbiology and histology	11 months	Recovered completely	[24]
8	Ramos MI, et al	2012	Male	29	C, T	Histopathology	>2 months	NA	[2]
9	Dewan A, et al	2012	Male	22	L, S	Histopathology	12 months	Improved dramatically	[31]
10	Dua RK , et al	2010	Male	26	T	Histopathology	3 months	Partial improved	[20]
11	Dua RK , et al	2010	Female	30	C	Histopathology	3 months	Partial improved	[20]
12	Xu GP, et al	2008	Female	55	C	Histopathology	6 months	Recovered completely	[10]
13	Honda H, et al	2008	Male	43	T	Microbiology	>12 months	Partial improved	[22]
14	Jeannin S, et al	2008	Female	57	NA	Histopathology	Long term	Recovered completely	[25]
15	Vernon V, et al	2007	Male	30	C	Histopathology	NA	Partial improved	[4]
16	Gaïni S, et al	2006	Male	38	T	Culture	16 months	Improved slowly	[6]
17	Fenichel I, et al	2006	Male	51	T	Histopathology	NA	Partial improved	[26]
18	El Murr T, et al	2001	Male	32	NA	Histopathology	Long term	Partial improved	[23]
19	Eftekhar B, et al	2001	Male	26	C, T	NA	7 months	Partial improved	[32]
20	Houman MH, et al	2001	Male	31	C	NA	NA	Asymptomatic	[11]
21	Yung BC, et al.	2000	Man	32	T	Microbiology	NA	Improved dramatically	[9]
22	Oruçkaptan HH, et al	1998	Female	31	C, T	Histopathology	6 months	Improved dramatically	[5]
23	Ushikoshi S, et al	1998	Male	33	T, L	Histopathology	8 weeks	Partial improved	[12]
24	David C, et al	1997	Male	27	C	Culture	NA	Improved dramatically	[14]
25	Bellingan GJ	1990	Female	58	C3-C4	Histopathology and culture	>3 months	Improved dramatically	[21]
26	Müller PG	1989	Male	40	T	Histopathology and microbiology	>12 months	Partial improved	[27]
27	Alday R, et al	1989	Female	60	T, L	Microbiology	>5 months	Partial improved	[33]
28	Dikshteĭn EA, et al	1984	Male	7	T, L	Necropsy	NA	Die	[34]

T indicates thoracic segment; L, lumbar segment; S, sacral segment; C, cervical segment; NA, not mentioned.

another study [2, 4]. Based on the cases we reviewed, male was much more susceptible to intraspinal actinomycosis, with the proportion of male being 71.4% (20/28) (**Table 2**).

Manifestations of intraspinal actinomycosis are usually nonspecific with insidious onset. As shown in **Table 2**, local neurological symptoms, including limbs weakness (69.2%, 18/26), paresis or restricted movement (53.8%, 14/26), hypoesthesia or paresthesia (26.9%, 7/26), were most common and associated with the lesion-involved spinal cord segments. Neurological symptoms usually indicate the range of involved spinal cord segments. Persistent back pain is usually the initial complaint that alarms doctors. Fever is common but not always accompanied as only 65% (13/20) patients had a fever. Among the cases with spinal cord involvement, thoracic lesions are most frequently involved, with a proportion of 74.1% (20/27), followed by cervical (48.1%, 13/27), lumbar (29.6%, 8/27) and sacral (11.1%, 3/27) lesions (**Table 2**).

Most cases are considered as hematogenous spread from lung to spine, while isolated focal actinomycosis is also common. Based on the reported intraspinal cases, 46.2% (12/26) of them with other organs involved and 67.7% (8/12) of them showed the initial infected sites were the lungs.

Actinomycosis tends to occur in immunocompromised people, but sometimes it may also appear in immunocompetent people with transient host defense decline [1, 14-16]. Based on the cases we've reviewed, 89.3% (25/28) patients with intraspinal actinomycosis were immunocompetent (**Table 2**). As for the case we report, no congenital or acquired immunodeficient factors were found in the patient other than pregnancy. During pregnancy, sex hormone levels and immune system function ch-

Table 2. Clinical manifestations of 28 intraspinal actinomycosis cases

Symptoms and signs		Percentage (N/N)
Sex	Male	71.4% (20/28)
	Female	28.6% (8/28)
Age (year)		Average 37.54 (range 7-82)
Immuno-compromised	Yes	10.7% (3/28)
	No	89.3% (25/28)
Spinal involved	Cervical	48.1% (13/27)
	Thoracic	74.1% (20/27)
	Lumbar	29.6% (8/27)
	Sacral	11.1% (3/27)
Organ involved except spinal cord		46.2% (12/26)
Weakness in limbs		69.2% (18/26)
Paresis or restricted movement		53.8% (14/26)
Numbness or paresthesia		26.9% (7/26)
Fever		65.0% (13/20)*
Diagnostic basis	Histopathology	71.4% (20/28)
	Microbiology	32.1% (9/28)
	Molecular biology	3.6% (1/28)
Surgery		67.9% (19/28)
Treatment with penicillin		88.5% (23/26)
Total duration of treatment	<3 months	15.4% (4/26)
	≥3, <6 months	15.4% (4/26)
	≥6, <12 months	23.1% (6/26)
	≥12 months	46.2% (12/26)
Prognosis	Partial improved	72% (18/25)
	Recovered completely	24% (6/25)
	Die	4% (1/25)

Some of the statistical data do not cover all cases because not all of the clinical manifestations are mentioned in their literatures. *Almost one-third of the cases do not mention fever or not, so only 19 cases can provide the data about fever.

ange to protect the fetus from attack of maternal immune system, which also influences maternal immune response to pathogens. Pregnancy-related "Th2 bias", which is a shift from T helper cell type 1 (Th1)-dominated to T helper cell type 2 (Th2)-dominated immune responses, can increase the severity of certain infections, including plasmodium falciparum malaria, leprosy, influenza, varicella, viral hemorrhagic fevers, and measles [17]. The sudden exacerbation of the patient's condition may be a result of "Th2 basis" during pregnancy.

The final diagnosis of actinomycosis should be confirmed by culture of the pathogen or biopsy (histopathological evidence) [3]. Due to the difficulty of actinomycetes cultivation, most actinomycosis can only be diagnosed based on histopathological evidence. In a retrospective study of 68 cervico-facial actinomycosis cases [18], twenty-two of them (32%) were confirmed by histopathological examination. However, of all the 28 intraspinal actinomycosis cases we've reviewed, 20 patients (71.4%) were diagnosed by histopathology, 9 patients (32.1%) by culture and only 1 patient (3.6%) by a new molecular biological method (**Table 2**). Two of them were diagnosed by histopathology and culture simultaneously. Therefore, diagnosis of intraspinal actinomycosis still primarily relies on pathology/biopsy for now. Despite the risk of invasive examination and surgery, biopsy is still recommended when intraspinal actinomycosis is highly suspected. Early diagnosis and treatment might greatly improve the prognosis of this disease, otherwise severe neurological sequelae would probably happen.

The recommended treatment for intraspinal actinomycosis was prolonged durations (6~12

months) and high doses of penicillin G or amoxicillin [15, 19]. Penicillin based regimen was applied and took effect in 88.5% (23/26) of the intraspinal cases we've reviewed (**Table 2**), and the mean duration of antibiotic therapeutics was 6 months (range, 2~16 months) (**Table 1**). However, the duration could probably be shortened to 3 months if the patient had surgical resection [2, 12, 20]. Acceptable alternatives or adjuvant antibiotics include tetracycline, erythromycin and clindamycin [6, 12, 14, 20-23]. Adequate duration of treatment could reduce the risk of recurrence and local complications [11, 16, 24, 25].

Surgery is recommended when epidural abscesses exist, spinal compressive symptoms exacerbate, response to antibiotic therapeutics is poor, and spinal malformation happens [26]. With proper indications, surgical decompressive resection of the spinal canal may help relieve symptoms or shorten the duration of antibiotics therapeutics [5, 27]. Since delayed or inappropriate treatment could lead to severe neurological sequelae, timely and well-targeted surgical intervention could greatly improve the outcome in this condition.

The most common way of Actinomyces invading human body is taking advantages of breakages in the gastrointestinal mucosa [28, 29]. However, previous reports indicated that focal actinomycosis could disseminate to other distant organs [30]. The patient we report suffered a recurrent toothache during pregnancy, suggesting a probable odontogenic invasion. Given the possibility of ondontogenic actinomycetes infection, personal oral hygiene and appropriate removal of dental plaques would be of great significance for preventing actinomycosis.

Conclusion

Intraspinal actinomycosis is a rare, pathogen-caused, granulomatous inflammatory disease. Biopsy and pathogen culture remain the main approaches of diagnosis, and biopsy is highly recommended for its high detectable rate. Prompt treatment with high dose of penicillin and prolonged antimicrobial therapy would improve prognosis. Surgical decompressive resection of spinal canal may relieve neurological symptoms and prevent severe neurological sequelae to some extent.

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Disclosure of conflict of interest

None.

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