

Drug Susceptibility Testing Guided Treatment for Drug-Resistant Spinal Tuberculosis: A Retrospective Analysis of 19 Patients

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Spinal tuberculosis is the most common manifestation of extrapulmonary tuberculosis. However, there have been few reports on the topic of drug-resistant spinal tuberculosis. The aim of this study was to investigate the efficacy and safety of treatment with a combination of surgery and individual chemotherapy guided by drug susceptibility testing for drug-resistant spinal tuberculosis. We retrospectively analyzed 19 patients with drug-resistant spinal tuberculosis. After surgery, individual chemotherapy was tailored for each patient according to his or her drug resistance profile and previous history of chemotherapy. The patients were followed up clinically and radiologically for an average period of 36 months. Among 19 drug-resistant spinal tuberculosis cases, 16 were multidrug-resistant tuberculosis (MDR-TB), and 3 were non-MDR-TB. The patients with MDR-TB and non-MDR-TB had undergone previous chemotherapy for an average of 12.50 \pm 2.00 months (0–55 months) and 5.50 \pm 1.20 months (0–60 months), respectively. A total of 16 patients underwent open operations, and the other 3 had percutaneous drainage and local chemotherapy. Patients received individual chemotherapy for an average of 24 months postoperatively. All patients had been cured at the final follow-up. Drug-resistant spinal tuberculosis is mainly acquired through previous irregular chemotherapy and the spread of drug-resistant strains. Treatment with a combination of surgery and individual chemotherapy is feasible in the treatment of severe complications and the prevention of acquired drug resistance.

Key words: Treatment – Spinal tuberculosis – Surgery – Chemotherapy

 $A^{\rm s}$ the most common extrapulmonary form of tuberculosis, spinal tuberculosis is a growing hazard worldwide and has an aggressive behavior

of profound vertebral destruction and severe complications. The initial optimism with tuberculosis spondylitis lessens as we see the increased number

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Surgical procedure	No. of patients	Percentage of total
Single-stage posterior focal debridement, fusion, and instrumentation	6	32
Single-stage anterior focal debridement, fusion, and instrumentation	2	10
Single-stage posterior instrumentation followed by anterior focal debridement	5	26
Single-stage posterior debridement, closing wedge osteotomy, and instrumentation	3	16
CT-guided percutaneous catheter drainage and local chemotherapy	3	16
Total	19	100

Table 1 Surgical procedures performed for drug-resistant spinal tuberculosis (n = 19)

of relapses and initial treatment failures caused by the emergence of drug-resistant tuberculosis.¹ However, drug-resistant tuberculosis of the spine has received little attention in the literature. Our study aimed to investigate the clinical characteristics and the treatment with a combination of surgery and individual chemotherapy for patients with drugresistant spinal tuberculosis.

Patients and Methods

Study population and data collection

A total of 152 patients with clinically and histologically proven spinal tuberculosis underwent surgery at the General Hospital of Lanzhou between April 2006 and January 2011. Mycobacterium tuberculosis was cultured from specimens obtained from all patients (152 of 152). A total of 50% of patients (76 of 152) produced a positive culture, which led to drug susceptibility testing (DST) later. Of these patients with a positive culture, 30.3% (23 of 76) had drugresistant patterns. The following eligibility and exclusion criteria were set for the study participants. The eligibility criteria were: DST showing resistance to at least one antituberculosis drug and a minimum follow-up period of 18 months after the initiation of individual chemotherapy. The exclusion criteria were: noncompliance with antituberculosis chemotherapy and being lost to follow-up or death. Overall, 19 patients meeting the eligibility criteria were included in the study. Medical records were reviewed for patient demographics and clinical characteristics, antituberculosis treatment history, DST profile, individual treatment modalities, and outcomes. Written informed consent was obtained from all patients.

Surgery program

Surgical procedures were performed according to the site of destruction, the complications, and the general condition of the patients. A total of 16 patients who met the absolute surgical indications underwent focal debridement, fusion, and instrumentation. The absolute surgical indications were severe deformity in 3 patients and neurologic deficit in 10 patients. In addition, percutaneous catheter drainage and local chemotherapy were selected for the other 3 patients without absolute indications (Table 1).

The method for DST

Clinical specimens were obtained from patients during open operations or percutaneous drainage. The quality-assured culture and DST were carried out using the BACTEC MGIT 960 system (Becton-Dickinson, Sparks, Maryland) and the proportion method on Lowenstein-Jensen medium. For all drugs except pyrazinamide, the following critical concentrations were used: 1 and 10 µg/mL isoniazid, 50 and 250 µg/mL rifampicin, 5 and 50 µg/mL ethambutol, 10 and 100 μ g/mL streptomycin, 5 and 50 µg/mL levofloxacin, 1 and 10 µg/mL paraaminosalicylic acid (PAS), 25 and 100 µg/mL protionamide, 0.1 and 1 µg/mL pasiniazide, 50 and 250 µg/mL rifapentine, 10 and 100 µg/mL capreomycin, and 10 and 100 µg/mL amikacin. The result of DST is often reported within 2 months after primary cultures.

DST-guided individual chemotherapy

Depending on the previous treatment and contact history of the patient, it was sometimes necessary to institute empiric chemotherapy while the results of DST were still pending. The regimens were adjusted as necessary once the test results were available. Patients with DST results showing susceptibility to any first-line drug were treated with standard chemotherapy. If the results of DST showed resistance to any first-line drug, individual chemotherapy was tailored for these patients based on their previous chemotherapy history and strain susceptibility profile. There were several principles for individual chemotherapy^{2,3}: (1) any first-line drug to which the isolate had proven to be sensitive; (2)

Preoperative				Postoperative		
	No. of patients	А	В	С	D	Е
A	0	0	0	0	0	0
В	3	0	0	0	3	0
С	4	0	0	0	1	3
D	3	0	0	0	0	3
E	9	0	0	0	0	9

Table 2 Preoperative and postoperative neurologic status by the ASIA score system

an injectable drug for a minimum period of 6 months; (3) a quinolone; (4) the addition of any appropriate second-line drugs, such as ethionamide and cycloserine, to achieve a combination of 4 to 5 effective regimens; and (5) other drugs, such as amoxicillin or clavulanate and clofazimine. Among the 19 patients, 2 patients with monoresistance to levofloxacin or PAS acid were treated with standard regimens, whereas the other patients were adjusted to individual regimens.

Follow-up index

The following indices were recorded preoperatively, and at 1, 3, 6, 9, and 12 months of follow-up and every 6 months thereafter: (1) clinical presentation; (2) X-ray, computed tomography (CT) and magnetic resonance imaging (MRI) scans; and (3) erythrocyte sedimentation rate, hepatic function, and renal function. Fusion assessment was determined by X-ray according to the criteria defined by Bridwell *et al.*⁴ Additionally, the American Spinal Injury Association (ASIA) score system was used to evaluate neurologic deficits.

Results

Demographic and clinical characteristics

Of the 19 patients, 13 were female and 6 were male. The median age was 41 years (32–65 years). Five patients had involvement of 6 levels, 3 had involvement of 4 levels, 5 had involvement of 3 levels, and 6 had involvement of 2 levels. All patients had received previous irregular chemotherapy for a mean period of 10 months (5–60 months). Ten patients (53%) had neurologic deficits, and the ASIA classifications were: grade B, 3 patients; grade C, 4 patients; and grade D, 3 patients. Kyphotic deformity was present in 5 patients, and the average kyphosis angle was 47° (35° –92°).

Drug resistance patterns and antituberculosis treatment history

Of all of the patients, 16 were multidrug-resistant tuberculosis (MDR-TB), and 3 were non-MDR-TB. The rates of resistance to all drugs were 51.2% to isoniazid, 47.3% to rifampicin, 32.1% to streptomycin, 22.6% to pasiniazide, 18.0% to rifapentine, 12.2% to ethambutol, 3.80% to levofloxacin, 2.1% to PAS, 2.1% to protionamide, 0% to capreomycin, and 0% to amikacin. Monodrug resistance was found in 16 patients, and resistance to 2 drugs was found in 3 patients, to 3 drugs in 5 patients, to 4 drugs in 2 patients, to 5 drugs in 3 patients, and to 6 drugs in 3 patients. The mean turnaround time of DST was 42 days (32-60 days). The mean delay in diagnosis for spinal tuberculosis (the time interval between the onset of symptoms and establishment of spinal tuberculosis clinically) was 8.52 \pm 6.15 months (1– 30 months), and the mean delay in diagnosis for drug-resistant spinal TB (the time interval between making the diagnosis of spinal tuberculosis and DST demonstrating drug-resistant patterns) was 8.25 \pm 2.76 months (1.2-72 months). The patients with MDR-TB and non-MDR-TB had undergone previous chemotherapy for mean periods of 12.50 ± 2.00 months (0–55 months) and 5.50 \pm 1.20 months (0–60 months), respectively.

Treatment outcomes

The 19 patients received individual chemotherapy for an average of 24 months (range, 16–28 months). The mean follow-up duration was 36 months (18–76 months). All patients had been cured at the final follow-up. Follow-up radiography proved that definitive fusion was achieved in 17 patients and probable fusion in 2 patients. The average fusion period was 8 months (6–16 months). The average kyphosis angle was 18° (6°–32°) postoperatively, and 5 patients had no significant loss of correction at the final follow-up. The ASIA scores of the 10 patients with neurologic deficits preoperatively and postop-

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eratively are shown in Table 2. The mean erythrocyte sedimentation rate was 6 mm/h (0-26 mm/h) at the final follow-up. A total of 2 patients had gastrointestinal side effects from chemotherapy, 1 patient had mild urticaria, and 2 patients had drug hepatitis. Among these 5 patients, 3 required a modification of regimen, and the other 2 tolerated the 18 to 24 months of chemotherapy well, after symptomatic management. Local recurrence was observed in 3 patients (15.8%) postoperatively, when the results of DST had not yet been revealed (Fig. 1). Of these 3 patients, 2 presented with sinus formation at the incision, and 1 presented with progressive neurologic deficit. After focal redebridement, excision of the sinus and individual chemotherapy, all of the 3 patients achieved complete cure without recurrence.

Discussion

Tuberculosis of the spine is an ancient disease, and its dismal outcomes in the preantibiotic era have improved significantly because of potent antitubercular drugs and advances in surgical treatment.⁵ However, spinal tuberculosis is still a life-threatening disease because of the emergence of drugresistant strains. Despite this, there have been few studies on the topic of the clinical characteristics and drug resistance profiles of, or the treatment outcomes for, drug-resistant spinal tuberculosis.

The development of drug-resistant spinal tuberculosis is mainly acquired through previous improper antituberculosis regimens, poor patient compliance, a prolonged diagnosis of drug resistance (a mean period of 8.25 ± 2.76 months in this study), and the spread of drug-resistant strains. Because DST for tuberculosis spondylitis is not routinely undertaken in resource-limited countries, most settings in China use a standardized or empiric regimen, without the assessment of drug susceptibility. In our study, the proportion of resistance to first-line drugs and some second-line drugs (pasiniazide, rifapentine, and levofloxacin) was much greater than that of other drugs, which indirectly demonstrated that standardized or empiric regimens consisting of these drugs have been widely used in this area. In our experience, improper antituberculosis chemotherapy has been proven to be the main cause of acquired drug resistance. Thus, the DST should be carried out for all initial treatment and retreatment for spinal tuberculosis. Optimal treatment of drug-resistant tuberculosis of the spine relies first on the early detection of such patients. Because of the difficulty in obtaining repeated focal samples, such as pus or granulomas, to isolate the organism, the signs of the emergence of drug-resistant spinal tuberculosis should be considered clinically before the result of DST is demonstrated by a lack of clinical or radiologic improvement, by the appearance of a new lesion or a sinus formation, or by rapid and profound vertebral destruction after chemotherapy for 3 to 5 months.⁶ Delayed individual treatment may result in acquired drug resistance. Therefore, there is an urgent need to include cultures and DST in the clinical pathway for the treatment of spinal tuberculosis. The methods of DST using the BACTEC MGIT 960 system can provide definitive results, but they usually require at least 36 days to produce the strain susceptibility profile, leading to inadequate treatment and further acquired resistance. In our study, all of the 3 local recurrences occurred before culture results and DST were available; the reason for this outcome may have been improper chemotherapy during this period. Therefore, developing new, rapid, and accurate molecular DST methods, such as commercial INNO-LiPA, Genotype MDR-

Fig. 1 Male patient, age 41 years. The patient presented with a persistent backache for 1 year and was admitted to our clinic in 2009. (a, b) Preoperative radiograph and CT showed destruction of T8-T9 vertebrae. (c) MRI additionally showed paravertebral abscess formation and compression of the spinal cord. The patient underwent single-stage posterior focal debridement, autograft fusion, and instrumentation after admission. However, the patient refused to undergo DST for economic reasons. He received a combination of rifampicin and isoniazid, provided for free by the local Centre for Disease Control, after discharge from the hospital. (d, e) At a 3-month follow-up, radiography and MRI revealed the postoperative recurrence of spinal tuberculosis, and severe incision dehiscence was also observed. The patient received CT-guided percutaneous catheter drainage and local chemotherapy. Thirty-eight days postoperatively, the result of DST demonstrated that the *M tuberculosis* strain was resistant to isoniazid. Then, the patient received a modified regimen, including pyrazinamide, ethambutol, rifapentine, levofloxacin, and streptomycin, for 24 months. Streptomycin was discontinued after 6 months of treatment. (f) Two-year follow-up radiographs and MRI showed the recurrence site had healed, and satisfactory bony fusion was achieved. The sinus tract achieved complete cure, and the erythrocyte sedimentation rate was decreased to 2 mm/h.

TBplus, and Xpert MTB/RIF, is essential for the early diagnosis of drug-resistant tuberculosis, and some of these methods are also suitable for resource-poor countries.⁷ However, most of the current rapid diagnosis systems were designed for rifampicin and isoniazid, and there is still no molecular DST method to detect simultaneously all of the first-and second-line drugs.

Although there is little evidence to guide surgeons in treating drug-resistant tuberculosis of the spine effectively, this investigation demonstrated that it could be cured with a combination of the available drugs and surgery. There are several principles for the chemotherapy of patients with drug-resistant spinal tuberculosis, and the chemotherapy program for drug-resistant spinal tuberculosis should be administered by specialized physicians. Because of the complexity of the disease, side effect monitoring and directly observed therapy should be guaranteed for good treatment compliance. All of the patients in our series achieved a cure after 18 to 24 months of individual chemotherapy, which suggested that a satisfactory clinical outcome could be achieved with DST-guided chemotherapy in patients with drug-resistant spinal tuberculosis. In our experience, spinal instability, severe deformity, and progressive paraplegia are absolute surgical indications for spinal tuberculosis.8 Patients with absolute indications often require surgical treatment to eradicate the foci thoroughly, to prevent the development of neurologic deficits and deformity, and, if it exists, to manage drug resistance. Furthermore, CT-guided percutaneous biopsy, catheter drainage, and local chemotherapy are alternative methods for patients with relative indications (massive cold abscesses and nonresponse to conservative treatment), and these processes can obtain the focal tissue needed to perform cultures and DST, as well as decrease the patient's burden of M tuberculosis strains.^{9,10} In the investigation, 3 patients without severe complications accepted percutaneous catheter drainage and local chemotherapy, whereas the other patients who met the absolute indications underwent 1-stage focal debridement, fusion, and instrumentation, according to the particular condition of each patient. At the final follow-up, all of the patients achieved a good outcome in the following parameters: healing of disease, deformity correction and maintenance, improvement in neurology, and bony fusion of affected segments.

To summarize, drug resistant tuberculosis spondylitis is an aggressive disease. As we battle it, DST with antituberculosis drugs, in combination with surgery and individual chemotherapy, and regular monitoring of adverse effects are important, not only for therapeutic success, but also for the prevention of acquired drug resistance. The limitations of this study are its retrospective nature and the small number of patients. Long-term follow-up of a prospective cohort study is needed in the future.

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