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ORIGINAL ARTICLE

Treatment Outcome of Drug-Resistant Skeletal Tuberculosis: A Retrospective Analysis

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Abstract

Background Management outcomes of drug-resistant (DR) osteoarticular tuberculosis (OATB) is dismal as in pre-ATT era (1905). The studies documenting treatment outcome of DR-OATB are scarce; hence, present retrospective analysis was conducted to evaluate outcome of consecutive cases of DR-OATB.

Methods 45 consecutive patients of suspected DR-OATB were treated from 2010 onwards. Tissue samples were submitted for AFB smear, cytology/histology, liquid culture, CBNAAT/LPA besides gram's staining and aerobic/anaerobic culture. Patients were treated by individualized second-line ATT till documenting healed status by contrast MRI/PET. The changes in neurological deficit, deformities, and drug-induced adverse events were documented.

Results 37/45 patients, 15 males and 22 females, mean age 26.89 years were followed. DR was suspected observing poor clinico-radiological response/appearance of fresh lesions on ATT. All showed no growth on aerobic/anaerobic pyogenic culture. 29 (78%) had microbiologically proven drug resistance and 8 (22%) were labeled as clinical drug resistance (CDR). 18/29 had multi-drug resistance. Mean prior ATT intake was 12.03 months 15 (40%) underwent surgical decompression. Mean duration of second-line ATT was 22.5 months (9–36 months). All patients achieved healed status with 8 (21%) developed side effects, most commonly hepatotoxicity, ototoxicity, and psychiatric disturbances. Average follow-up after completion of ATT was 40.5 months.

Conclusion We report a large series where patients of DR-OATB were suspected on clinical criteria, investigated by DST, and treated. Patients with proven drug resistance were treated by individualized second-line ATT. CDR cases were treated by MDR protocol. Genotypic DST (CBNAAT/LPA) improved demonstration of DR. We demonstrated healed status on MRI/PET with no recurrence at minimum 2-year follow-up.

Keywords Spinal tuberculosis · Drug resistance · MDR-TB · Phenotypic DST · Genotypic GST · Second-line ATT

Introduction

Tuberculosis (TB) is among top 10 causes of death worldwide from single infectious agent, ranks higher than HIV. About a quarter of world's population is infected with M. Tuberculosis [1]. The emerging drug resistance has threatened the goal of elimination of TB since diagnostic accuracy and treatment outcomes are poor. Globally, there were estimated 450,000 incident cases of MDR/RR-TB in 2021, up 3.1% from 437,000 in 2020 with only 1 in 3 cases receiving treatment. An estimated 191,000 (range 119,000–264,000) deaths occurred due to MDR/RR-TB in 2021 [2].

Estimated MDR/RR-TB cases in India is 124,000 (9.1/lakh population). The first National anti-Tuberculosis Drug Resistance Survey (NDRS) revealed that 28% of TB patients were resistant to any drugs [22% among new and 36.82%

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among previously treated (PT)] and 6.19% had MDR-TB (2.84% among new and 11.62% among PT) [3]. Isoniazid (H) resistance (16% in all with 11.6% in new and 25% in PT) being driver for rifampicin-resistant TB. Factors responsible for development of drug resistance include inadequate/incomplete treatment of TB at first instance, genetic predisposition and coinfection with HIV [4].

The diagnosis of DR-TB can be made, after genotypic/phenotypic drug sensitivity testing (DST), when tissue is submitted to laboratory in a suspected case. Guidelines for DR-OATB are extrapolated from DR pulmonary tuberculosis, though both are dissimilar diseases. OATB being paucibacillary has low chances of growth on culture. Molecular methods (CBNAAT/LPA) have reduced time taken for diagnosis and improved detection of DR. When both fails to detect DR in a histologically diagnosed TB lesion, it may be treated as clinical drug resistance (CDR) on MDR protocol.

There is paucity of studies documenting suspicion, diagnosis, management, and treatment outcomes of drug-resistant OATB. We report retrospective series of consecutive cases of DR-OATB diagnosed and treated with > 2-year follow-up (FU).

Materials and Methods

45 consecutive patients, suspected, investigated, and treated for DR-OATB from 2010 onwards were listed and called for follow-up (after obtaining institutional ethics committee approval-IECHR/2020/PG/47/32). The patients were labeled presumptive drug resistance case on well-defined criteria [5]. The tissue was procured by guided biopsy/surgical debridement as indicated and was subjected for AFB smear, histology, TB culture (BACTEC/MGIT), and CBNAAT/LPA besides aerobic/anaerobic pyogenic culture.

Proven DR patients on genotypic/phenotypic culture were treated on individualized second-line ATT as guided by DR profile. Patients who did not have culture growth yet histologically ascertained TB were labeled CDR and treated as MDR OATB. The patients were surgically treated if indicated for neural deficit (decompression ± instrumented stabilization), spinal deformity (deformity correction), abscess drainage/aspiration for persistent abscesses.

Patients on subsequent visit were evaluated for improvement of well-being, weight gain, and neural deficit. Drug-induced adverse events were recorded. Complete blood picture, ESR, LFT, KFT, X-rays of the affected part were performed every two months. On completion of second-line ATT regimen, MRI/PET scan was performed to document healing. The ATT was stopped on observing complete resolution of abscess, fatty changes in T1WI or no signs of active disease on PET scan. With persistent signs of active disease, but substantially regressed lesion, ATT was continued for further three months. Normalization of ESR, CRP, X-ray signs of healing were other indices to conclude ATT (Fig. 1).

During CoViD pandemic, MRI/PET could not be performed and ATT was stopped on completion of duration of regimen for 7 patients. All patients were followed every 6 months for 2 years with relevant X-rays, ESR, CRP. Neurological charting, residual spinal deformity, any other complications were recorded.

Results

37/45 patients (82%) could be reviewed, while 8 were not available at this FU. Mean age was 26 years (11–65 years) with 22 females and 15 males. 35patients had spinal tuberculosis, while one each had TB elbow and Iliac bone. The dorsal spine ($n = 12$) was most common followed by lumbar spine ($n = 11$), dorsolumbar junction ($n = 2$), lumbosacral junction ($n = 2$), cervical spine ($n = 1$), sacral spine ($n = 1$), and multifocal spinal involvement ($n = 6$). Out of 6 (16%) with multifocal involvement, one had TB elbow and lumbar spine involvement and 5 had multilevel spinal involvement (Table 1).

Spinal TB patients presented with low backache, TB elbow patient reported with local swelling, while iliac bone patient had hip pain with discharging sinus. All reported with constitutional symptoms like fever, weight loss and malaise. 9/35 (24%) of spinal TB had neurological deficits (5/9 patients with grade 4 paraplegia) 5/37 took ATT before for pulmonary TB ($n = 3$), TB lymphadenitis ($n = 1$), and Potts spine ($n = 1$).

35 spinal TB and one elbow tuberculosis patient were diagnosed on X-rays/MRI. The iliac blade involvement was suspected on X-rays/MRI and ascertained on FNAC. Mean ATT intake before being suspected and investigated for DR was 12 months (0–36 months).

7/37 patients took ATT < 2 months before their DR was established and were labeled as primary drug resistance. 4/7 had diagnostic dilemma and underwent CT-guided biopsy for tissue diagnosis, while 3/7 underwent surgical decompression for neural deficit and tissue was submitted for DST.

Rest 30/37 were suspected DR due to failure of adequate clinical response to ATT (ATT intake > 5 months), while 8 developed new TB lesions while on ATT. The microbiological confirmation of DR could be obtained in 22/30 patients and treated. 8/30 culture-negative patients with histological features consistent of TB, were labeled as clinical drug resistance (CDR) and treated as MDR cases. Among 29/37 proven drug-resistant patients, 11/29 (38%) were MDR, and 18/29 (62%) were non-MDR Patients. Isoniazid resistance was present in 21/29 (72.4%), RR in 16/29 (55.2%), FQ resistance 5/29 (17%), and second-line injectables resistance in 1/29 (3%) patients.

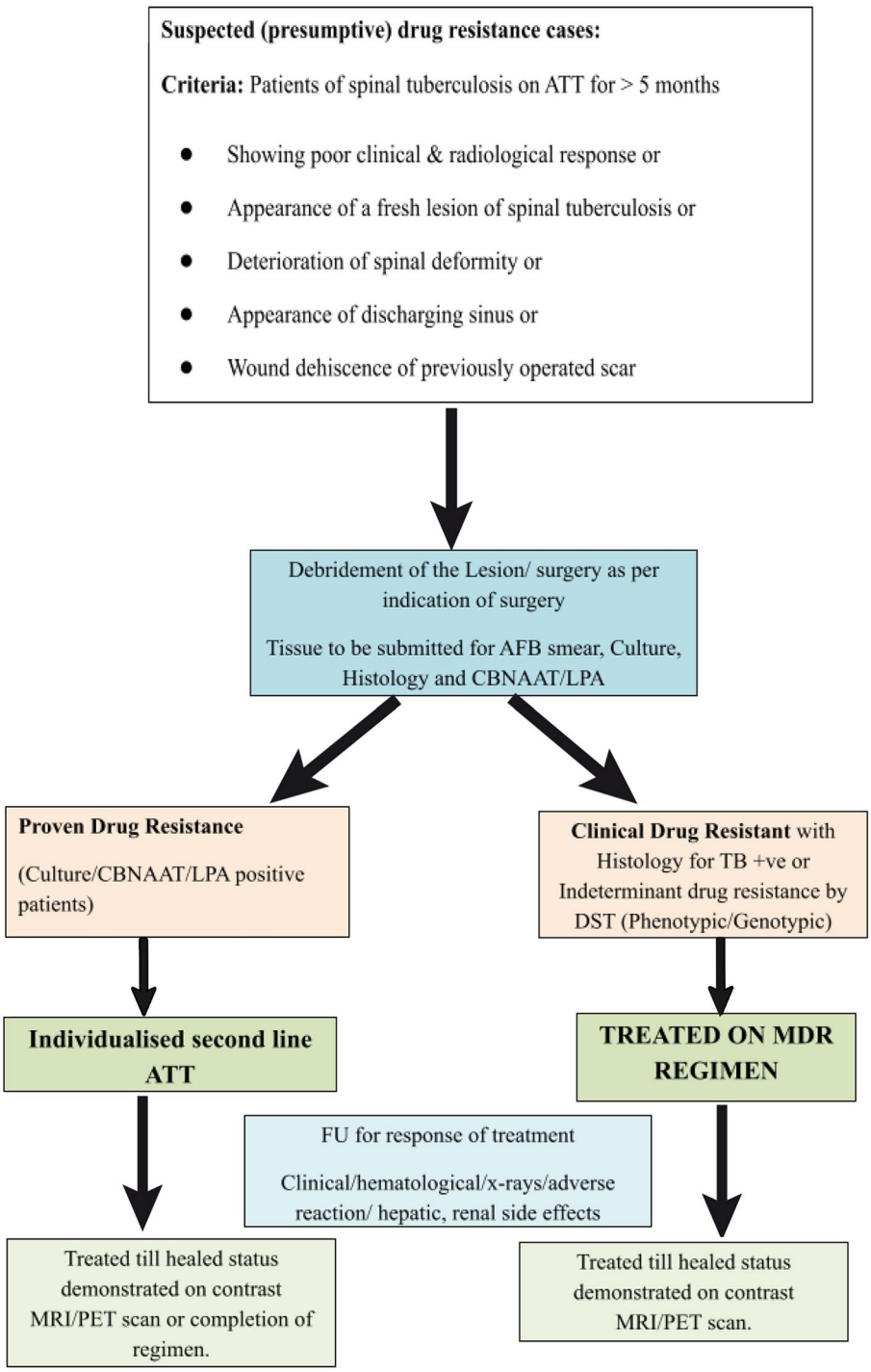

Fig. 1 Flowchart depicting methodology of the study

All patients showed no growth on aerobic/anaerobic pyogenic culture. 35/37 patients were treated by second-line ATT. One patient with isolated FQ resistance and one with low-level INH resistance were continued on Cat-I ATT. 29(82%) patients received ethambutol and pyrazinamide as part of second-line ATT. Ethionamide was used in 28(80%) and kanamycin for 6 months in 24(68%) patients. 3(9%) patients received shorter MDR regimen (high-dose moxifloxacin, isoniazid, kanamycin, ethionamide, clofazimine, pyrazinamide, ethambutol).

Second-line ATT was given for average 22.5 months (9–36 months).The ATT was stopped in 29/37 (78%) patients after observing evidence of healing on contrast MRI in 10 (27%) and PET in 19 (51%). One patient died before completion of ATT due to hepatotoxicity. One patient took ATT for 36 months with persistent activity though improved

Table 1 Demography and disease distribution of the patients included in the study

Mean age (range) in years	26 years (11–65)
Sex distribution	15 males and 22 females
Disease distribution	
A) Spinal involvement	35
Cervical spine	1
Dorsal spine	12
DL junction	2
Lumbar spine	11
Lumbosacral spine	2
Sacral spine	1
Multifocal	6
B) Extraspinal involvement	2 (elbow and ilium)
Pattern of drug resistance	
Proven drug resistant	29
Clinical drug resistant	8

clinically. On observing radiological signs of healed lesion, normal ESR/CRP, ATT was stopped. In 6 patients, second-line ATT was stopped after full course and MRI/PET could not be performed during COVID pandemic. At 2-year follow-up, relevant radiological scans showed signs of healing, with normal ESR and CRP, hence declared healed (Fig. 2).

8(21%) patients had adverse events which include hepatotoxicity ($n=2$), sensorineural hearing loss ($n=2$), ATT-induced psychiatric disorder ($n=2$), visual acuity loss ($n=1$), and alopecia ($n=1$).The average FU was 40 months (12–112 months) post conclusion of second-line ATT. No patients reported recurrence of the disease.

9/37(24%) spine TB patients with neurological deficit, underwent surgical decompression and instrumentation. All demonstrated complete neurological recovery, though 2 patients had exaggerated deep tendon reflexes without motor or sensory deficit. Kyphotic deformity was observed in 17/35 (48%) patients of spinal tuberculosis with mean pre-treatment kyphosis of 18.71 degree which progressed to final mean of 21.82 degrees, an overall increase of 4.11 degrees.

Discussion

The emergence of DR strains plagues the global fight to end TB. The often poor reported treatment outcomes, sequelae, and lack of best practice guidelines in DR spinal/osteoarticular TB poses a significant challenge [6].

Published spinal MDR-TB treatment guidelines [7] are based mainly on pulmonary DR-TB. Pulmonary tuberculosis is multibacillary and sputum sample can repeatedly be tested for AFB smear/Culture. OATB/spinal TB are paucibacillary, deep-seated lesions with difficult sample procurement [8]. The mycobacterium is fastidious, thus low detection rate on AFB smear/culture. India has the highest disease burden (26% global cases) of MDR/RR-TB in 2021 [2]. The evidence on DR-OATB includes only collection of cases. Hence, a series of consecutive cases is being reported where all cases were suspected on predefined criteria and subsequently investigated and treated with 80% > 2-year follow-up.

WHO classified cases of DR-TB as isoniazid-resistant TB, rifampicin resistant (RR-TB), MDR-TB (resistant to INH and rifampicin), pre-extensively drug-resistant TB (pre-XDR-TB) and XDR-TB. The resistance to rifampicin and fluoroquinolone is described as Pre-XDR-TB, while resistant to rifampicin, any fluoroquinolone, and bedaquiline or linezolid is as XDR-TB [9].

Besides genetic predisposition [10] and coinfection with HIV [11], most common cause of development of DR are inadequate drug therapy (suboptimal drug dosages and regimen), spurious drugs, difficulty in obtaining drugs due to limited financial resources, inadequate self-administration of drugs without direct observation in intensive phase leading to non-adherence [12] The person to person transmission of DR strains (pulmonary TB) has resulted in higher prevalence of primary drug resistance [13]. Underreporting of extrapulmonary forms of tuberculosis is highly prevalent and situation worsened during CoViD pandemic [14].

"Primary drug resistance" is said to be existing naturally, as it occurs when the patient has not been exposed to particular drug. Such an innate resistance is thought to be rare in spinal TB, but its incidence is steadily increasing. The average frequency of de novo isoniazid resistance is 1 in 10^6, for rifampicin 1 in 10^8; hence, multiple drugs are administered during ATT [15]. Our 7 patients in this series were of primary drug resistance since these patient did not take ATT long enough for present disease, and drug resistance was demonstrated when tissue was submitted after CT-guided biopsy (n-4) and surgical decompression in three.

"Acquired drug resistance" develops due to exposure of the strain to ATT with consequent selecting out of resistant mutant bacilli [16]. DR is suspected in pulmonary TB when sputum remains AFB positive despite 4-month ATT. However, in spinal/osteoarticular TB, with paucibacillary/deep-seated lesions, repeated tissue sampling is not possible. Treatment response is evaluated on imaging, which has a lag period. Hence DR spinal TB is suspected (presumptive) when patient on ATT for 5 months or more showing poor clinico-radiological response to healing, appearance of fresh OATB lesion, deterioration of spinal deformity, appearance of discharging sinus, wound dehiscence of previously operated scar [5]. We suspected DR on observing therapeutic failure on ATT in 30/37 patients. The DR was proven by DST in 22/30 (73.33%) patients to validate these criteria.

The patient with negative DST but with histological features of tuberculosis labeled as clinical drug-resistant cases

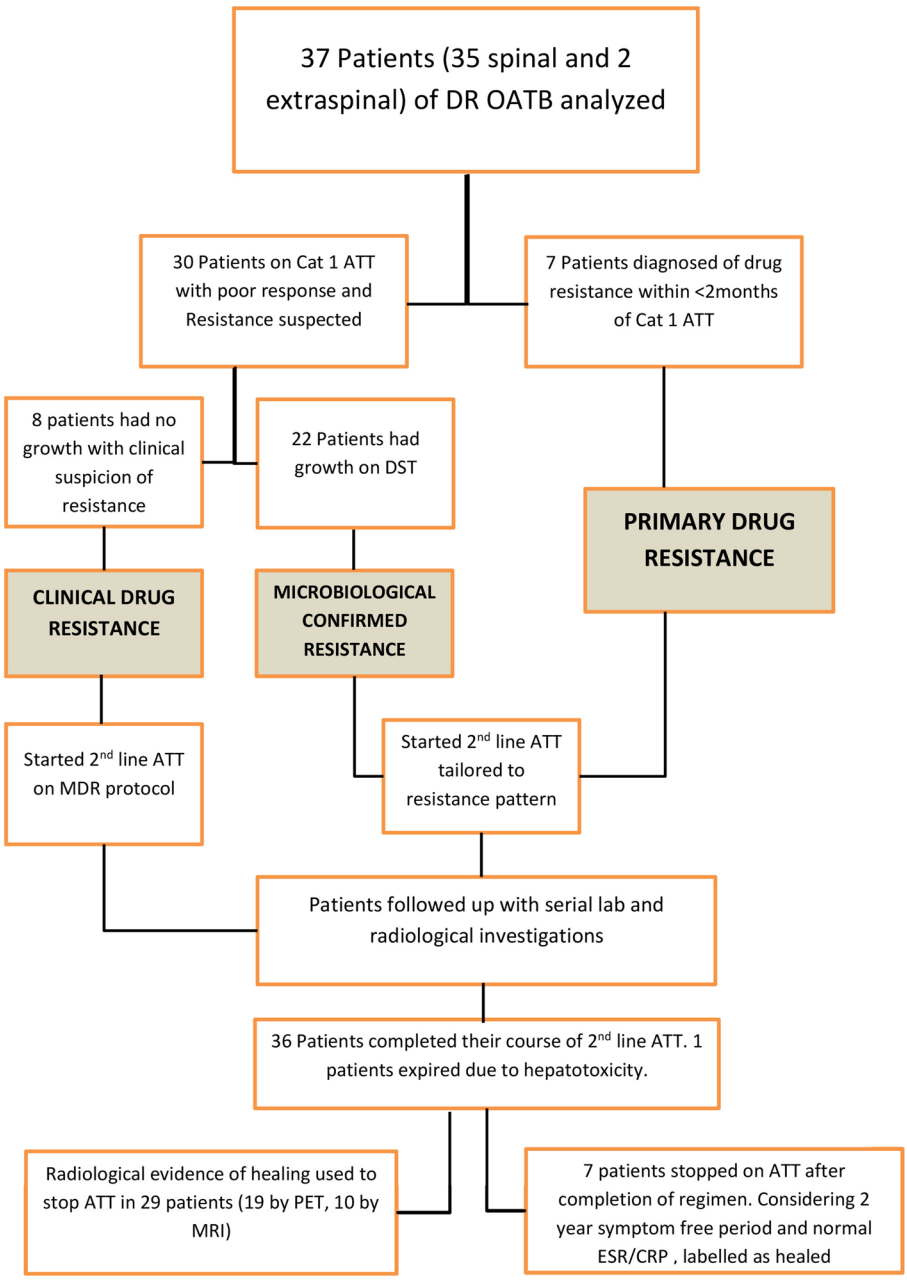

Fig. 2 Flowchart summarizing the results of the study

(Fig. 3). We had 8/30 (26.6%) cases of CDR; however, with availability of genotypic DST, more and more cases will be proven DR. No study is available in literature where drug resistance was suspected and reported the observations only of patients with proven resistance [17–19].

Amongst our 29 microbiologically confirmed cases (Figs. 4, 5), most common resistance was against INH (21/29, 72.4%) followed by rifampicin in 16/29 (55.2%), FQ in 5/29 (17%) and second-line injectables resistance in 1/29 (3%). The literature supports our observation of isoniazid resistance being most common followed by rifampicin resistance although individual percentage prevalence showed variation [18–22] (Table 2). Mohan et al. ($n = 111$) documented resistance where patients were recruited after DST results and had high INH resistance (92%) and rifampicin in 81% in their cohort [21]. The first national anti-tuberculosis drug resistance survey revealed MDR-TB prevalence as 6.19% among all TB patients. The survey considered all sputum positive patients (with/without DR), while we expressed our percentages among the drug resistance cases only hence cannot be compared [3].

35/37 patients received second-line ATT, while 2 with isolated fluoroquinolones resistance were treated with standard ATT. 25 patients including CDR patients received conventional longer MDR regimen (6mLfx/Mfx-Cyc-Km-E-Z-Eto and 12–18m Lfx/Mfx-Cyc-E-Eto) in accordance to

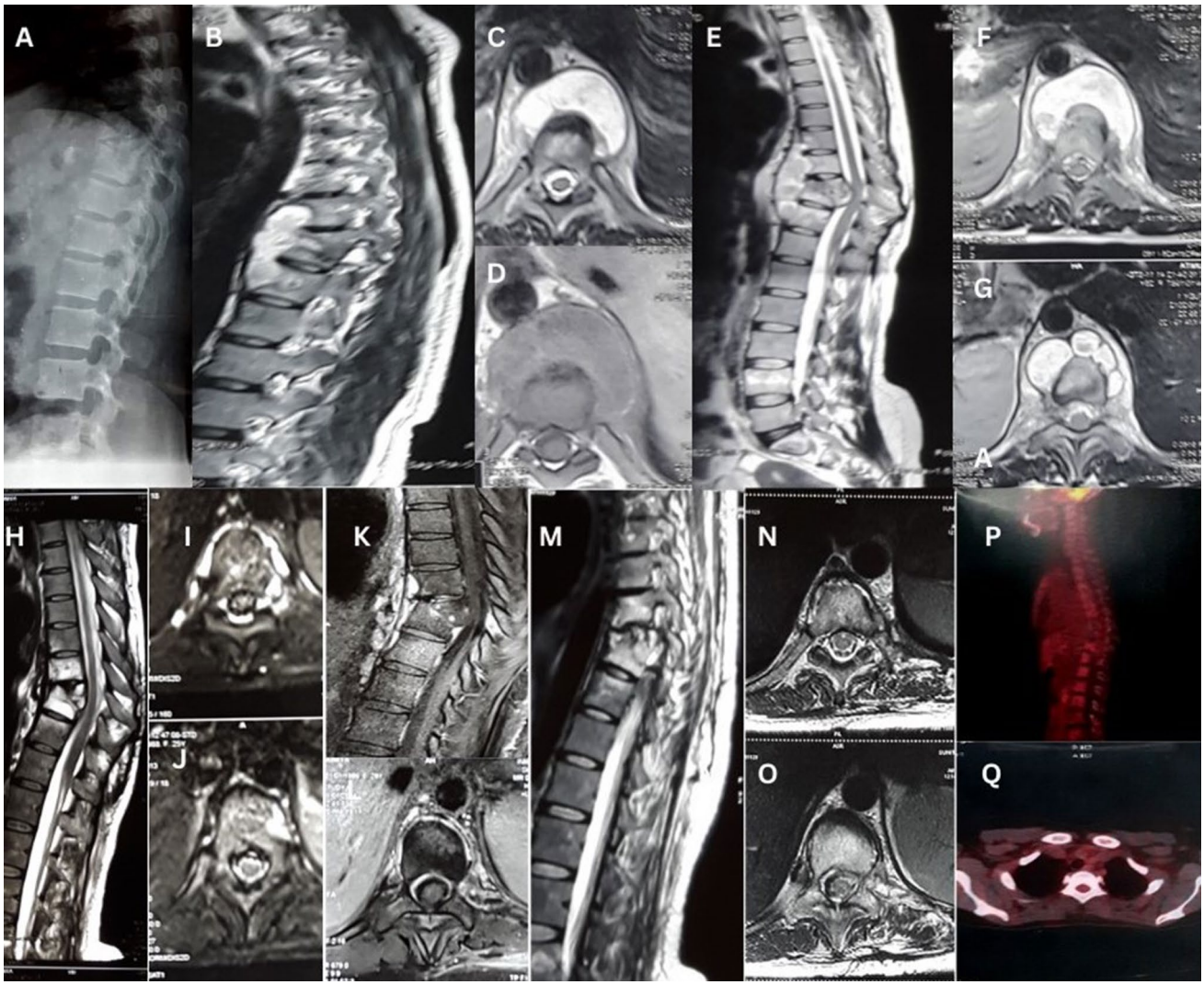

Fig. 3 28/F presented with pain and deformity with lower back. X-ray (**A**) shows decreased intervertebral space at D9–D10 and MRI (**B**–**D**) with destruction of vertebral bodies and pre and paravertebral collections suggestive of TB spine. Patient started on Cat 1 ATT. Another MRI at 6 months of ATT shows persistent collection (**E**–**G**). Patient was taken up for Anterolateral decompression and tissue sample revealed negative TB culture but positive for TB PCR and HPE. Patient was labeled as clinical drug resistant and started on second-line ATT. 6 months (**H**–**J**) and 12 months (**K**, **L**) MRI on second-line ATT patient showed improvement with minimal active disease. MRI at 18 months showed near complete collapse of D9 vertebral body with fatty marrow changes (**M**–**O**). The ATT was stopped. PET scan at 1-year follow-up showed no metabolically active disease (**P**, **Q**), thus a healed lesion

then prevalent WHO guidelines [23]. Three patients received shorter MDR regimen(4–6 Bdq(6m)-Lfx/Mfx-Cfz-Z-E-Hh-Eto /5Lfx/Mfx-Cfz-Z-E) [9], while 7/35 received tailored second-line regimen according to their drug resistance profile.

Regarding treatment of DR-OATB, Jain et al. reiterated [24] that drugs prescribed should be based on DST of the community which may not be available in most of the low-resource countries, particularly for spinal TB. One should use drugs which have never been used. Preferably five (at least four) new drugs should be added that include a fluoroquinolone and one injectable drug as advocated by WHO at that time [23]. Bactericidal drugs should be preferred. One should never add a single drug to a failing regimen. The drugs should be given in a single dose in a daily dosage regimen. No intermittent therapy be used. The patient should be counseled not to stop treatment even if discomfort/side effects persists/appears.

Shifting from the earlier regimen which had injectables, WHO now recommends all-oral regimens [9, 25]. These now followed regimens consider:

a. Regimen for isoniazid-resistant TB: 6(H)REZ-Lfx (6-month treatment regimen composed of rifampicin,

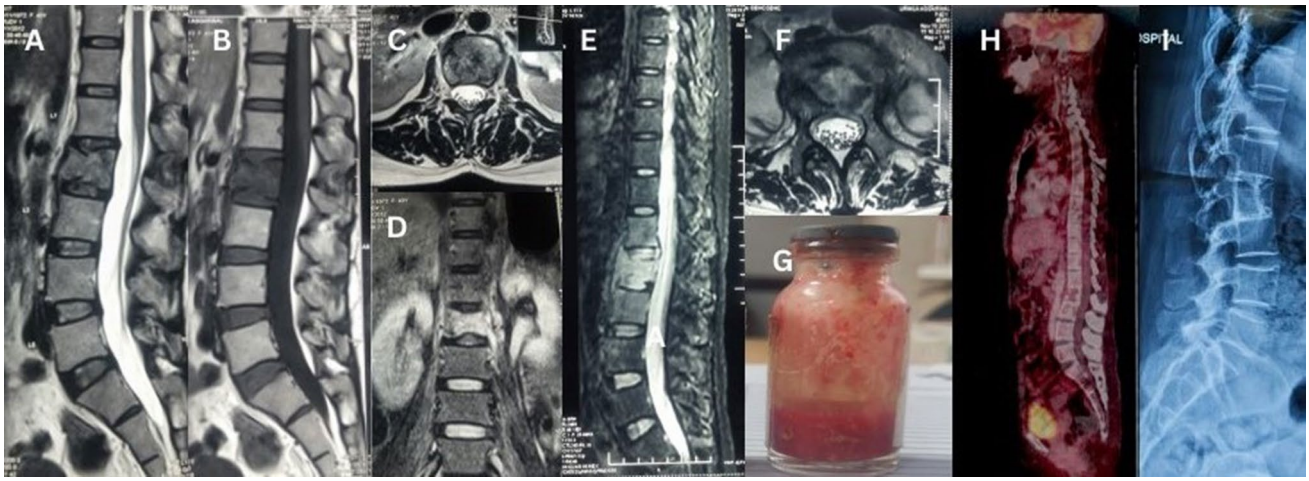

Fig. 4 45/F presented with persistent low back ache following which an MRI was done that demonstrated destruction of L2 vertebrae (**A**–**D**). Patient was started with Cat 1 ATT. 6 months on ATT patient had deterioration of symptoms and follow-up MRI showed progression of disease and bilateral psoas abscess (**E**, **F**). Pus was aspirated from the right Petit's triangle (**G**) and sent for DST which revealed resistance to INH, Rif, E and S. Patient was started on second-line ATT. On 24 months completion of ATT, patient underwent PET–CT that had no evidence of metabolically active disease (**H**) and hence second-line ATT stopped. 7-year follow-up X-ray show sound ankylosis (**I**) with normal ESR and CRP

ethambutol, pyrazinamide, and levofloxacin. Isoniazid can be added if 4-drug FDC (HREZ) will be used.

b. Shorter regimen for MDR/RR-TB: 4–6 Bdq(6 m)-Lfx/Mfx-Cfz-Z-E-Hh-Eto/5 Lfx/Mfx-Cfz-Z-E (shorter all-oral bedaquiline-containing regimen).
c. Shorter regimen for MDR/RR-TB with quinolone resistance: 6–9 Bdq-Pa-Lzd (6–9-month treatment regimen composed of bedaquiline, pretomanid, and linezolid—BPaL regimen).
d. Longer regimen for MDR/RR-TB: 18 Bdq(6 m)-Lfx/Mfx-Lzd-Cfz (18-month treatment regimen composed of bedaquiline for the first 6 months and levofloxacin or moxifloxacin, linezolid, clofazimine for 18 months).

The 6-month BPaLM regimen, comprising bedaquiline, pretomanid, linezolid (600 mg), and moxifloxacin, may be used programmatically in place of 9-month or longer (> 18 months) regimens, in patients (aged ≥ 15 years) with MDR/RR- TB who have not had previous exposure to bedaquiline, pretomanid, and linezolid (defined as > 1-month exposure). This regimen may be used without moxifloxacin (BPaL) in the case of documented resistance to fluoroquinolones (in patients with pre-XDR-TB). Drug susceptibility testing (DST) to fluoroquinolones is strongly encouraged, but DST should not delay treatment initiation.

The 9-month, all-oral, bedaquiline-containing regimens are preferred over the longer (> 18 months) regimen in adults and children with MDR/RR-TB, without previous exposure to second-line treatment (including bedaquiline), without fluoroquinolone resistance and with no extensive pulmonary TB disease/severe extrapulmonary TB. In these regimens, 2 months of linezolid (600 mg) can be used as an alternative to 4 months of ethionamide. Access to rapid DST for ruling out fluoroquinolone resistance is required before starting a patient on these regimens. Decisions on appropriate regimens should be made according to clinical judgement and patient preference, considering DST results, patient treatment history, risk of adverse events, and severity and site of the disease.

15/37 (40%) spinal TB patients underwent surgery which include 7/15 (46%) decompression + instrumentation and 8/15 (56%) decompression alone. The indications of surgery for DR cases are generally same as for sensitive disease, which include instability, deformity correction for severe/progressive deformity, gross/increasing neurological deficits, spinal TB in children with positive spine at risk signs, incapacitating pain not allowing ambulation [26].

When to stop ATT has always been a debatable issue. Should we stop at conclusion of prescribed regimen or after demonstrating healed status on imaging. No study with DR-OATB has used clear end point to conclude the second-line ATT. We stopped ATT after once imaging finding on contrast MRI/PET in 29 patients suggested complete healing of the lesion. We performed imaging at the prescribed MDR regimen (20–24 months). In the presence of signs of persisting active disease, the ATT was extended with 3 monthly follow-up in 10/37 patients until they showed imaging evidence of healing. One patient died due to comorbidities. The complete loss of marrow edema, resolution of paravertebral collections, and replacement of vertebral body marrow by fat (observed as hyperintense signal on both T1WI, and T2WI) [27] were considered as MRI observations of healed

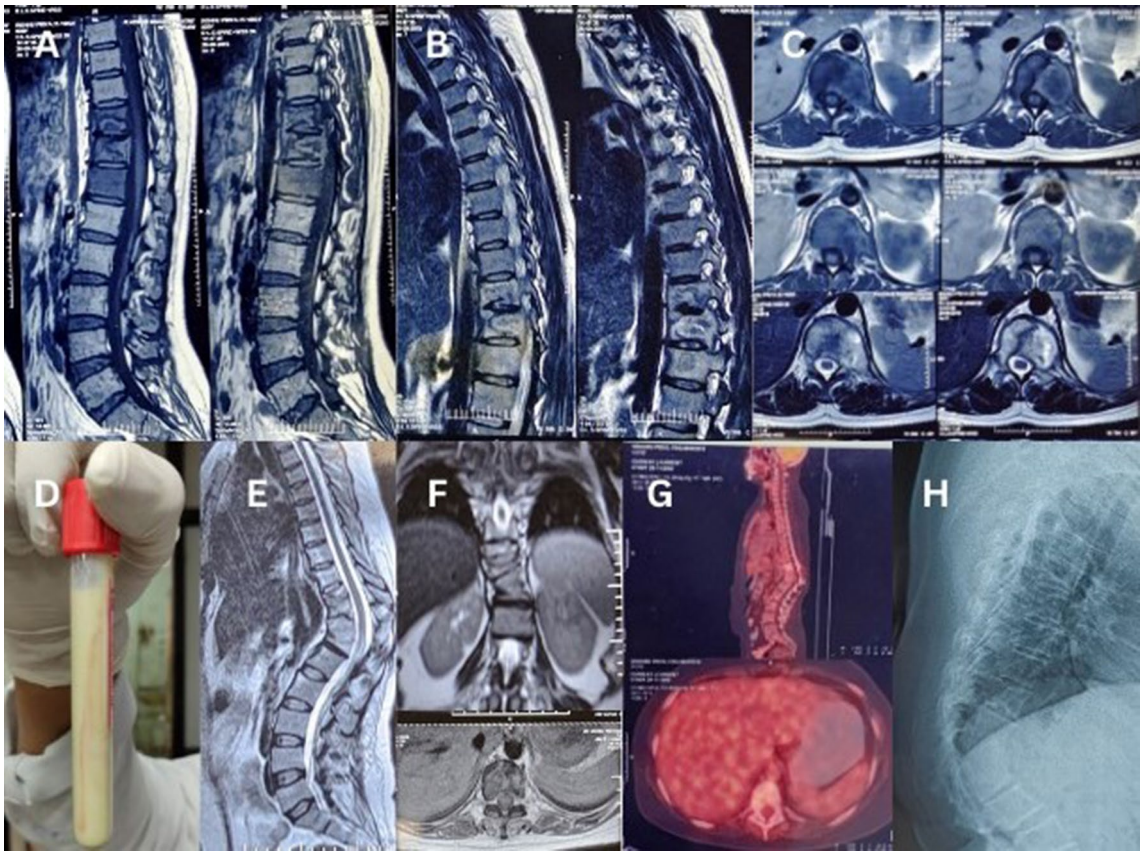

Fig. 5 28/F presented with abdominal and low back ache along with constitutional symptoms. CECT abdomen done that showed spondylodiscitis at D10–D11 (**A**). Subsequently a MRI also was performed that was suggestive of Potts spine D10–D11 with associated pre and paravertebral collections (**B**, **C**). Patient was started on Cat 1 ATT. 12 months on Cat 1 ATT patient developed psoas abscess that was aspirated and sent for DST (**D**). The report came to be INH and Rif resistant and patient was started on second-line ATT. 18 months post initiation of second line, MRI performed showed collapse of D9–D12 vertebra with patchy enhancement suggestive of residual disease (**E**, **F**). On 24 months of second-line ATT, PET–CT done showing minimal FDG uptake and non-FDG avid collapse of lower dorsal vertebrae. Patient was stopped on second-line ATT 3 months post PET scan (**G**). 3-year follow-up X-ray shows kyphosis but sound ankylosis (**H**) with normal ESR and CRP

Table 2 Resistance pattern documented in various studies

Literature	Total patients	Drug resistant	MDR patients	Isoniazid resistance	Rifampicin resistance
Xu et al. [18]	152	19	16	51.2%	47.3%
Litao et al. [19]	35	35	12	54.3%	48.6%
Bhosale et al. [20]	150	43	7	74%	46%
Mohan et al. [21]	686	111	87	92.7%	81.9%
Sinha et al. [22]	235	167	124	61.7%	57%
Current study	37	29	11	72%	55%

lesion. Jain et al. reported that with presence of ambiguous MRI findings (enhancing lesion) after full clinical resolution of symptoms and completion of ATT, increased uptake on FDG-PET corroborates the presence of active infection. FDG-PET provides a quantitative measurement of the absolute fraction of the injected dose reaching a tissue called the standard uptake value (SUV). SUV values are raised in cases of active tuberculosis [24]. In a similar study, Mittal et al. [28] reported on 37 spinal TB patients and concluded and found FDG-PET/CT to be more useful to ascertain the healed status than MRI. They found PET scan to be only imaging modality to demonstrate healed status, when MRI is not available in view of presence of metallic (stainless steel) implant for instrumented stabilization. We in the

present study concluded ATT using PET scan ($n=19$) and MRI ($n=10$). We did not encounter any other study where patients were treated till healed status was demonstrated. Hence, in our study, 35 patients took second-line ATT for a variable length with mean 22.5 months (9–36 months).

The second-line ATT was stopped in 7 patients at completion of regimen without contrast MRI/PET in view of covid pandemic. At 2-year FU, these patients had no relapse with normal ESR/CRP and healed lesion on plain X-rays. This may be a case that we may conclude ATT on a fixed regimen schedule, while treating DR-OATB since cases are being treated after DST.

One of the most important independent factors underlying treatment failure is side effects of medications. We observed 8 (21%) patients developing one or more side effects after initiation of second-line ATT. Most frequent side effects were hepatotoxicity ($n=2$), sensorineural hearing loss ($n=2$), and ATT-induced psychiatric disorder ($n=2$). One patient died during the course of management because of ATT-induced hepatitis while other patient required multiple inpatient admissions due to severe anemia. Yang et al. reported 256 pulmonary MDR-TB patients documented one or more side effects in 95 (37.1%) patients. The frequently encountered side effects included gastrointestinal disturbance (18.4%), psychiatric disorder (5.5%), arthralgia (4.7%), hepatitis (3.9%), peripheral neuropathy (3.1%), hypothyroidism (2.3%), epileptic seizures (2%), dermatological effects (2%), ototoxicity (1.6%), and nephrotoxicity (1.2%) [29].

We reported average follow-up of 40 (12–112) months post conclusion of second-line ATT. Patients were subjected to radiographs of the involved part and ESR and CRP monitoring at the present FU. No patient reported with recurrence.

Conclusions

The emergence of DR-OATB has threatened the goal of control and elimination from world. The patient on ATT for 4–5 months showing with an adequate clinico-imaging response, appearance of new lesion/abscess, worsening of kyphotic deformity/neural deficit, wound dehiscence in a postoperative case is the pointer to suspect drug resistance. The tissue from these patients should be subjected to histopathology and phenotypic/genotypic DST to prove drug resistance. The patients should be started on individualized second-line ATT. In cases with histopathological evidence of TB and inconclusive DST, we should treat them as CDR by MDR regimen, although considering high diagnostic accuracy of genotypic DST, these would be a rare possibility. Patients should be followed up in their entire course of chemotherapy and once the regimen gets completed, the healed status must be validated by contrast MRI/PET scan.

Declarations

Conflict of Interests On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical Approval This retrospective analysis was conducted after taking institutional ethics committee approval and informed consent of all patients was also obtained.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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