A Case of Poly Drug Resistant –Tuberculous sternal osteomyelitis in an immunocompetent male.

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Abstract
Primary Sternal Tuberculosis is rare and accounts for < 1% cases of skeletal TB. Most cases are reported from TB endemic countries. Drug resistant sternal tuberculosis has been sporadically reported in literature. We present here a case of polydrug resistant Tuberculosis of sternum in an immunocompetent male. AFB culture showed resistance to Streptomycin(S) and Isoniazid (H). Patient was started on modified ATT with HREZ + Levofloxacin + Amikacin. Total duration of treatment was 10 months. Poly drug resistant TB can lead to amplification of resistance and MDR - TB on treatment with the standardized 1st line drugs. DST results at baseline and previous treatment history should be considered to design the appropriate regimen. At least 3 or 4, likely effective drugs should be selected for duration of 9-18 months.

Keywords
Amplification of resistance, Drug sensitivity testing, Treatment failure

Background
Tuberculosis still accounts for the most prevalent of all infectious diseases with more than 10 million people getting affected annually and approximately 1.7 million deaths.[1] Osteoarticular involvement is seen in up to 10% of cases of extra pulmonary TB.[2] Primary Sternal Tuberculosis is even rarer and accounts for < 1% cases of skeletal TB. Most cases are reported from TB endemic countries like India, Pakistan and Brazil, but also reported from Switzerland, UK, USA and Saudi Arabia.[3-5]

The emergence of drug resistant (DR) strains in TB is becoming a global health concern. Patterns of resistance include *Monoresistant, Polyresistant, Multidrug resistant (MDR)* and *Extensively drug resistant* (XDR).[6]

We present here a case of a poly drug resistant TB involving the sternum. So far only few cases of Drug Resistant TB involving the sternum have been reported in literature[5, 7-10] and we were unable to find a similar case with poly drug resistant sternal TB.

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Case history
66–years –old male, previously well, presented with c/o fever and significant weight loss for 1 month. He was unwell for 2 years with on and off fever, productive cough and bilateral chest pain. He was prescribed ATT, took for 10 days but discontinued by himself. There was no past history of TB or TB contact, previous hospital admission or any surgical intervention. Physical examination was completely normal except for moderate pallor.

Investigations revealed normocytic normochromic anemia with hemoglobin = 6.4g/dl, WBC=11.6, ESR=134, CRP=164, Ferritin=850, Albumin = 2.6 and ALP=427. Chest X-ray revealed mediastinal widening. (Fig 1)

CT Chest with contrast showed erosions and destruction of body of sternum with adjacent fluid collection suggestive of abscess and osteomyelitis. Multiple enlarged mediastinal, axillary and para aortic necrotic lymph nodes were noted. Erosions and soft tissue density were also seen at D8-9 vertebral body (Fig 2).

Patient remained febrile despite IV antibiotics, so open thoracatomy was done with drainage of abscess and resection of ribs and cartilage. Histopathology revealed chronic granulomatous inflammation with necrosis and Genexpert

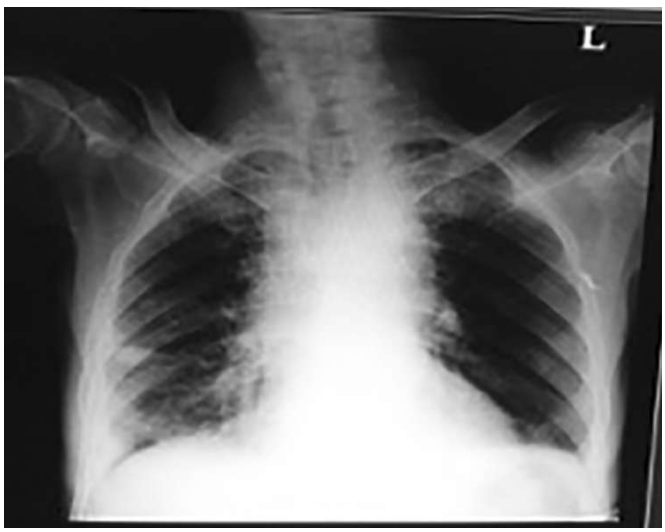

Fig 1. Chest Xray showing mediastinal widening

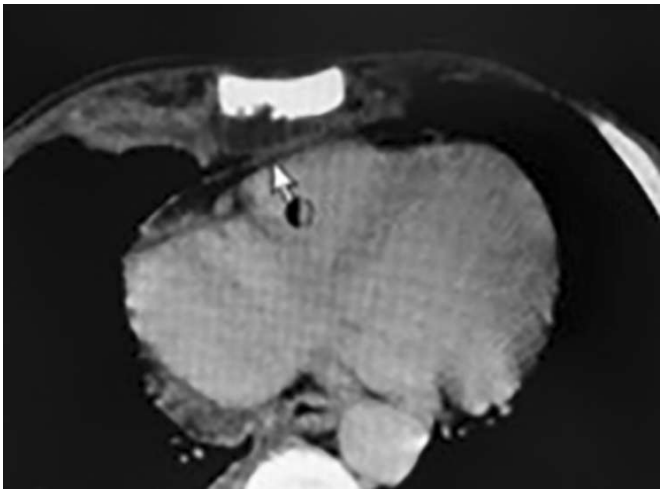

Fig 2. CT scan Chest with arrow pointing at fluid collection

(PCR) was positive for *Mycobacterium Tuberculosis* with no Rifampicin resistance detected.

Patient was started on anti tuberculous therapy with Isoniazid (H), Rifamipicin (R), Ethambutol (E) and Pyrazinamide (Z) with Pyridoxine. Patient became afebrile after 1 month but complained of generalized weakness with no significant weight gain at 2 months.

AFB CS reported resistance to Streptomycin(S) and H and sensitivity to R, E and Z, which meant that the isolate was *Polydrug resistant*. Therapy was modified to HREZ + Levofloxacin + Amikacin (for 3 months). HREZ and Levofloxacin were continued for another 7 months. ATT was stopped after 10 months of treatment and patient remained clinically stable. ESR came down to 22 and CRP to 3.5.

Discussion

Most cases of drug resistant TB involving sternum are reported from India and one from Pakistan.[5,7-11] A brief review of drug resistant Tuberculosis involving the sternum is presented in Table1. Most cases are of Multi-drug resistant (MDR) Tuberculosis from India[5,7, 9-10] and one case of Extensively drug resistant (XDR) TB of sternum was reported from Pakistan[(11)]. So far to our knowledge no case of PDR Tuberculous Sternal osteomyelitis has been reported.

Resistance to two or more first-line drugs but not to both isoniazid and rifampicin is called polydrug resistant TB. It has a global prevalence of 17% along with mono resistant TB.[1,6] Mostly remains undiagnosed as drug sensitivity testing (DST) is not routinely performed in resource limited settings, where it is seen more commonly.[1,6] It can lead to amplification of resistance (i.e. acquisition of resistance to other drugs) and MDR - TB on treatment with the standardized 1st line drugs, if remains undetected.[1-6] Therefore, performing DST using rapid tests is imperative before starting treatment.[6] Genexpet/Line Probe Assay (LPA) are rapid, sensitive and cost effective than conventional phenotypic testing.[1,6] Resistance testing to both isoniazid and rifampicin using LPA gives results within a day or two, while Xpert MTB/RIF only tests for rifampicin resistance.[1,6]

The standardized 1st line regimen of WHO has resulted in treatment failure and amplification of resistance in many studies (failure rates of 18-44%).[1, 6] Very few randomized clinical trials have been done to determine best treatment options.[(1)] At least 3 or 4, likely effective drugs should be selected.[6] DST results at baseline and previous treatment history should be considered to design the appropriate regimen.[6] Choice of drugs include combination of first and second line ATT including injectables depending on the DST results, given for duration of 9-18 months.[6] Appropriate treatment of PDR TB can prevent development of MDR – TB.[1-10]

Conclusion

Tuberculous sternal osteomyelitis, a rare entity, has to be suspected to be diagnosed. Drug resistance is emerging as a menace even in less common EPTB scenarios. Rapid tests and DST are imperative for managing drug resistant cases. As literature suggests, most cases are still responsive to second line drugs (SLDs).

Table 1: Literature review of cases with Drug Resistant Sternal TB

	No of patients	Age of patients	Gender	Symptoms	Pattern of Resistance (AFB cuture)	Duration of treatment	Surgical Debride-ment	Outcome	Treatment given
Yadav *et al* (2016)	1	21 years	F	Painful swelling on anterior chest wall	Resistant to Isoniazid, Rifampicin --- Multidrug resistant	24 months	No	Treated	Kanamycin, Levoflox, Cycloserine, Ehionamide, PAS powder and Ethambutol, Pyrazimide

Khan *et al* (2007)	2	Not specified	Not specified	Not specified	Resistant to Isoniazid, Rifampicin --- Multidrug resistant	24 months	No	Treated	Streptomycin, Ethionamide, Ofloxacin, Pyrizinamide and Ethambutol
Haseeb *et al* (2015)	1	29 years	F	Painful swelling on anterior chest wall plus fever and weight loss	Resistant to (R)- rifampicin, (H)isoniazid, (E)-ethambutol, (Eto)-ethionamide, (Ofx)-ofloxacin and (Am)-amikacin - Extensively drug resistant	5 months Stopped by patient because of adverse effects	Yes	Remained symptom free	Capreomycin, Moxifloxacin, Ethionamide, Cycloserine, PAS, Linezolid, Clarithromycin, Amoxicllin/ Clavunate, Pyrizinamide,
Mohan K *et al* (2013)	1	25 years	M	Anterior chest wall swelling with fever and weight loss	Resistant to isoniazid (INH) and rifampicin (R)	24 months	No	Treated	Kanamycin, Levofloxacin, Ethionamide, para aminosalicylic acid (PAS) and Ethambutol
Goyal S *et al* (2014) [11]	1	12years	F	Pain and swelling chest wall plus fever and weight loss	Resistant to isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E), and streptomycin (S)	18 months	Yes	Treated	Kanamycin, Pyrizinamide, Ethoinamide Ofloxacillin, PAS

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