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***Case Report***

# PRIMARY EXTENSIVE DRUG RESISTANT (XDR) TUBERCULOSIS IN IMMUNOCOMPETENT FEMALE WITH STERNUM INVOLVEMENT: A CASE REPORT

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## ABSTRACT
Emerging trend of Extensively Drug Resistant Tuberculosis is difficult challenge for health care providers and always consider as consequence of previous treatment failure in patients with tuberculosis or associated with immunosuppressant conditions like AIDS. Moreover, extra pulmonary involvement in Primary drug resistant tuberculosis is rare. We report a rare case of primary extra-pulmonary XDR TB with sternum involvement in a 29-years-old, HIV-negative Asian female from Karachi, Pakistan. She was immunocompetent, married with no significant past medical history and no known exposure to pulmonary TB. She presented with insidious history of sternal swelling with constitutional symptoms. Pus culture aspirated from wound showed strain of Mycobacterium tuberculosis, resistant to R- rifampicin, H-isoniazid, E-ethambutol, Eto-ethionamide, Ofx-ofloxacin and Am-amikacin.HIV serology came out negative. Debridement of sternal wound followed by intensive second line ATT improves patient's symptoms with significant weight gain. After 5 months of treatment, patient had developed severe hypokalemia and needed hospital admission. She then refused for further antibiotic treatment. Despite counseling she was not willing to take any treatment. Her perspective for not taking medicines was because of absence of symptoms with side-effects and complex nature of regime. She is on follow-up with our team till date and reports no change in her weight. To the best of our knowledge, this is the first case of its kind. While Primary XDR TB is a rare event in immunocompetent person, our case is even rarer with extra-pulmonary bone involvement. This case report demonstrates the possibility of silent epidemic of drug resistant tuberculosis in South Asian region. Notification of such cases will bring awareness among physicians and enable them for early detection and prompt treatment of such cases. No define line of treatment for such cases present till date. There is also a strong urgent need to address treatment options for in World Health Organization Tuberculosis guidelines to prevent morbidity and mortality.

***Keywords:*** *Sternum, XDR TB, MDR TB, Extra-Pulmonary Involvement, Acquired Immunodeficiency Syndrome*

## INTRODUCTION
Tuberculosis is one of the leading causes of death globally and now emergence of Extensive Drug Resistant Tuberculosis (XDR TB) stain creates threat for health care system as well as general population. Correct diagnosis and management of XDR TB is very important because treatment options are limited, complicated, expensive and have many side effects. It has also been observed that the treatment outcome is even poorer then of Multi Drug Resistant Tuberculosis (MDR TB) (Kim *et al.*, 2007). According to WHO Global TB Report 2013, globally, on an average 9.6% cases of MDR – TB have XDR and in Pakistan 4% of patients enrolled with Drug Resistance TB have XDR.
Raising Emergence of drug resistance tuberculosis is always thought to be acquired, either due to inadequate and interrupted treatment in patients with previous tuberculosis (Jeon *et al.*, 2008; Zhao *et al.*, 2009) or associated with low immune-competency in patients especially with HIV (Gandhi *et al.*, 2006; Suchindran *et al.*, 2009). Primary XDR TB considered being rare in HIV negative individuals even if they

belong to endemic areas. Through several search engines we find small data on primary XDR TB. Figures from South Korea and China (Zhao *et al.*, 2009) suggest presence of Primary XDR in HIV-uninfected patients but transmission from positive contact with XDR was suspected in most of the cases and it is also important to keep in mind that China (Tanh *et al.*, 2011) and South Korea fall in list of countries with highest MDR and XDR TB prevalence, whereas estimated burden of drug-susceptible TB is quite high in South Asia but drug resistant tuberculosis rates are comparatively low. We were unable to find data regarding primary XDR in immunocompetent individuals from South Asia as well as Africa.

Moreover the involvement of extra-pulmonary sites in primary extensive drug resistant TB has never been reported before and a little data is available regarding primary MDR tuberculosis with extra-pulmonary involvement (Goyal *et al.*, 2014).

## CASES

We report a case of 29 years old female Asian patient from Karachi, Pakistan, who presented to pulmonology clinic with 3 months history of chest pain accompanied by progressively increasing tender sternal mass. In addition she reported low grade fever and weight loss. She had no prior significant medical or surgical history and there was no known exposure to TB. She was house wife and belongs to good socio-economic class. Symptomatic treatment with anti inflammatory drugs and antibiotics given prior to presentation did not provide any relief. On clinical examination of anterior chest she had 8 * 10 cm tender and firm mass, with no discharging sinus or erythematous skin. On clinical examination lymphadenopathy was not appreciated and chest was clear to auscultation.

Plain Chest X-Ray (posteroanterior view) showed mediastinal widening. CT scan chest showed osteomyelitis of anteromedial portion of manubrum sterni near its upper end with infiltration into soft tissues. No abnormality found in lung parenchyma or pleura but single aorto-pulmonary lymph node enlargement was noted. Three phase bone schintigraphy showed only local pathology in sternum and there was no involvement in any other part of body.

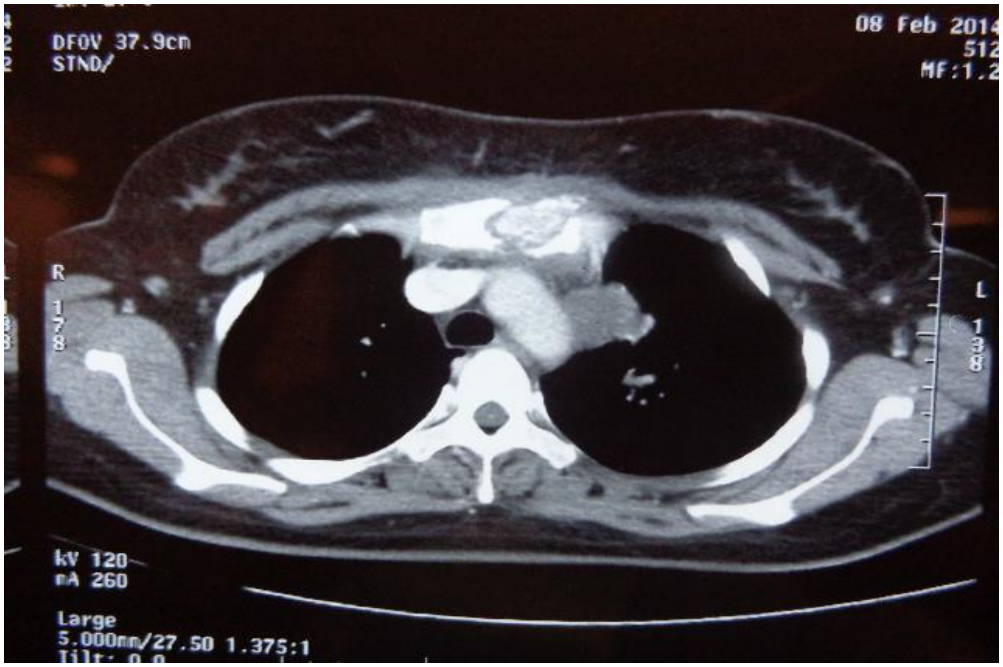


**Figure 1: CT Scan of Chest of Patient**

**Figure 2: Pre-Operative Picture of Patient's Wound**

She was referred to Thoracic surgery for excisional biopsy. Sample of pus was sent for diagnostic test to WHO approved BSL 3 lab. Since she belongs to high risk area, pus was also sent for AFB smear, AFB culture sensitivity and line probe assay prior starting treatment. AFB smear was positive (5 bacilli/100 field) and line probe assay showed Rifampicin and INH resistance. Results of other investigations revealed raised ESR and mild anemia. Histopathology report was consistent with granulomatous inflammation.

Diagnosis of tuberculosis was made but patient had low pre-test probability and prevalence of primary MDR in Pakistan is less than 2 % (Javaid *et al.*, 2008) so MDR was considered unlikely. This case was also discussed in review panel meeting of pulmonologists and international data for reference was searched through Google scholar. Decision for complete wound debridement was made with subsequent 1st line anti-tuberculosis therapy including Rifampacin, Isoniazid, Pyrazinamide and Ethambutol.

In meanwhile bronchoscopy was done and BAL sample was sent for Gene-xpert, AFB smear and AFB Culture to 2 different laboratories. Her fever got settled with the prescribed regime but she failed to gain weight.

## RESULTS AND DISCUSSION

### *Results*

Surprisingly her drug sensitivity reports of pus showed Extensive drug resistant tuberculosis. The strain of Mycobacterium tuberculosis was resistant to R- rifampicin, H-isoniazid, E-ethambutol, Eto-ethionamide, Ofx-ofloxacin, and Am-amikacin. BAL samples were negative for AFB smear, AFB C/S and Gene Xpert and result of Human immunodeficiency virus was also negative.

Complete wound debridement was already done by thoracic surgeon. Initially patient was reluctant to take complicated regime but after discussion she agreed and was started on XDR standard regime as per WHO protocol since 20/03/2014.

***Case Report***

Patient reported symptom free period with gain in weight and improvement in appetite and general health after initiation of regime with Cm, Mfx, Eto, Cs, PAS, Lzd, Clr, Amx/Cluv, Z, B6.

After 5 months of initiation of therapy she started having tingling sensation in her both lower limbs and progressive weakness in both lower limbs. She subsequently needed hospital admission for life threatening hypokalemia. Appropriate treatment was given to her for condition. After discharge from hospital she refused to continue any treatment and despite of long counseling sessions she decided not to take any further anti-tuberculosis treatment. Till date she is symptom free and her weight remains stable.

***Discussion***

To our best knowledge, this is the first case with primary extensively drug resistant Tuberculosis involving bone, reported from South Asia.

Exact data regarding prevalence of primary extensive drug resistant TB, from our part of World, is lacking. Available consensus, however, shows that Drug resistant TB in certain high risk groups is on increasing trend in Pakistan ( Hasan *et al.,* 2010; Saleem *et al.,* 2012; Ejaz *et al.,* 2010) but these were cases with acquired form of disease but not primary. Renewed vigilance in form of early diagnosis with quality assured laboratories and treatment according to WHO recommendations is required to prevent the spread of this form of TB (Sotgiu *et al.,* 2009). The objective of this report is to high light the fact that drug resistant tuberculosis can not only be seen at unusual parts of body and but high index of suspicion for this form of TB is also needed, even in HIV-negative population for prompt diagnosis and successful treatment.

This patient report no known exposure to tuberculosis nor did she received any medical help in past. She was a house wife. On contact tracing no positive cases were found in her surrounding so transmission from a positive contact was questionable.

Reactivation of latent foci and hematogenous or lymphogenous spread of pulmonary infection to other body parts especially bones are well known phenomena but primary bone involvement without lung involvement is uncommon and poorly understood. In reviewing the literature TB Osteoarthritis accounts only 10% of total cases and sternum involvement is even rare (Eyer *et al.,* 2014). A very few number of cases regarding primary sternal involvement with MDR tuberculosis are reported (Goyal *et al.,* 2014) but no data regarding sternal involvement in patients with XDR tuberculosis exist till date so there is no clear line of management in such cases.

Previously experts use different pathways of treatment in patients with drug susceptible tuberculosis sternal osteomyelitis, few believe in effectiveness of medical treatment alone (Eyer *et al.,* 2014; Khan *et al.,* 2007) and others suggested aggressive debridement adjunct with chemotherapy (Goyal *et al.,* 2014), but adequate consensus are lacking regarding treatment of primary extra-pulmonary XDR TB. Successful treatment will not only reduce the mortality but also help to reduce the spread of tuberculosis.

In this case physician decided to treat the patient aggressively with debridement surgery followed by standard 2$^{nd}$ line chemotherapy but patient refused to continue treatment after development of serious side effects.

There is growing evidence of successful treatment with second line ATT in HIV negative patients with pulmonary XDR TB (Sotgiu *et al.,* 2009). So medical therapy and multidisciplinary care with involvement of histo-pathologist, specialist nurse, social worker and pulmonologist is prudent. Moreover patient's education regarding good compliance and identification of adverse effects is also very important for successful treatment of XDR TB.

But it also raises a very important question regarding management of patients who have got limited bone disease without pulmonary involvement. Would it be enough to do surgical debridement only without complicated drug regime and save patient from un-necessary side effects or will this approach left patient on risk of developing disseminated disease in future and there will also a risk of spread of this resistant bacterium in community.

***Conclusion***

In conclusion high suspicion index for diagnosis of primary cases of Drug resistant TB in endemic areas is needed with immediate investigations and appropriate management of patients.

This case serves to emphasize that some guidance in form of guidelines regarding management of extra pulmonary drug resistant TB is also needed. This case report should be of interest not only to pulmonologist but also the general practitioners and internist, as a big percentage of patients first present to them for assessment of their non specific symptoms.

***Consent***

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

***Competing Interests***

All authors clearly declare that they have no competing interests.

***Abbreviations***

MDR TB: Multi Drug Resistant Tuberculosis
XDR TB: Extensive Drug Resistant Tuberculosis
HIV: Human Immunodeficiency Virus.
AIDS: Acquired Immunodeficiency Syndrome.
CT: Computed Tomography.

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