Title : A Family Ruined By Tuberculosis In The 21st Century

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Abstract : A 45 year old male, resident of Navi Mumbai presented with history of chronic cough. Clinico radiological features were suggestive of Pulmonary Tuberculosis. In view of multiple family members suffering from TB with bad treatment outcomes, we sent his sputum for AFB culture and drug sensitivity testing. Line Probe Assay (LiPA) revealed that he is suffering from tuberculosis with resistance to Rifampicin and Isoniazid. We present here the genesis of this case of primary drug resistant TB with special focus on drug resistance and the subsequent development of tuberculosis in family members with detailed analysis of circumstances and factors resulting in adverse outcomes.

Introduction : Tuberculosis remains one of the world's leading infectious disease with high mortality and morbidity of adults most of which are not due to multi drug resistant strains, but are due to lack of access to effective treatment for drug susceptible cases. To add to this problem, primary MDR TB is increasing morbidity & mortality leading to decreased cure rates of short course chemotherapy.

Case summary : A 45 year old male, chronic alcoholic, taxi driver, resident of Navi Mumbai and father of 4 children presented with history of chronic cough of 1 month duration for the first time. There was no history of Tuberculosis (pulmonary or extra-pulmonary), diabetes mellitus, hypertension or any other respiratory illness in the past. The patient's chest X-ray revealed a cavity in the left upper zone and infiltrates in right upper zone. Two sputum smears for mycobacterium tuberculosis was 3 + for AFB. The patient's wife and daughter were also diagnosed as drug resistant tuberculosis and were on Category IV treatment under DOTS-plus. In view of clinicoradiological presentation as well as family history of DR-TB, we sent his sputum for drug sensitivity testing. Line probe assay revealed resistance to Isoniazid & Rifampicin. The patient was diagnosed as primary drug resistant TB and started on Cat IV treatment under DOTS from DOTS plus centre.

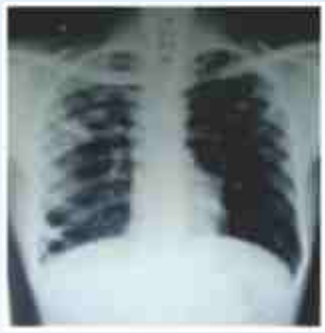

Fig 1: X-ray chest of male patient dated December 2013 showing cavity in the left upper zone and infiltrates in right upper zone

Family history:

The first family members to be affected simultaneously were two of his children (son 18 year old, daughter 20 year old) in Feb 2010, when they were diagnosed to have sputum positive TB and were started on supervised anti TB treatment under DOTS.

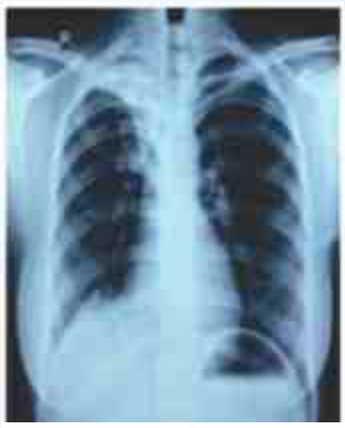

Fig 2a

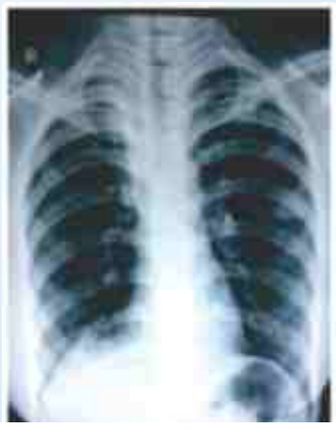

Fig 2b

Fig 2a: X ray chest of daughter dated 22/3/2011 showing right upper lobe fibrotic collapse with tenting of right diaphragm

Fig 2b: X ray chest of daughter dated 15/10/2012 showing thickened right para-tracheal stripe suggestive of right upper lobe collapse.

The daughter was declared cured after 6 months of

Category I treatment under DOTS

However his son relapsed and hence was started on Cat II treatment under DOTS in June 2011. Health authorities continued him on Cat II despite lack of improvement. However Patient succumbed to his illness. Drug resistance testing was not done.

In November 2010, His wife was started on anti-tubercular treatment by a private practitioner for tubercular pleural effusion. The patient received 5 drug regimen consisting of INH, Rifampicin, Ethambutol, Pyrazinamide and Levofloxacin. Unable to buy the drug the patient went to DOTS centre where she was started on Cat I regimen. 6 months after completing her treatment (fully compliant) patient became symptomatic again and was diagnosed with the relapse with sputum positive pulmonary tuberculosis. She was put on Cat II regimen against the advice of pulmonologist, who were strongly suspecting drug resistant tuberculosis. Even after completing Cat II regimen her sputum was 3+ for AFB. Moreover having forced the patient to go through the RNTCP routine of Category - II treatment the patient was finally diagnosed to have Drug Resistant Tuberculosis. Currently she is on Cat IV treatment under DOTS plus which is "supervised" treatment.

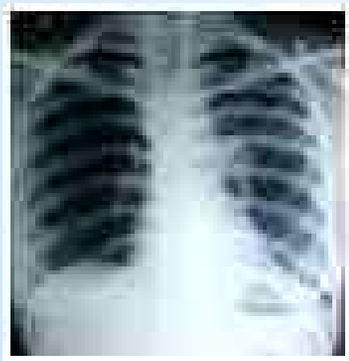

Fig 3a

Fig 3b

Fig 3a: X ray chest of wife dated 07/08/2011 showing left perihilar infiltrates and fibrosis

Fig 3b: X ray chest of wife dated 17/01/2012 showing left upper zone consolidation with cavity Fig 3c: X ray chest of wife dated 11/12/2013 showing consolidation involving whole of left lung Fig 3d: X ray chest dated 14-7-14 shows partial resolution after 6 months of treatment In February 2012 the youngest daughter, aged 13 years also developed sputum positive pulmonary tuberculosis. She was started on Category – I treatment. After 5 months of treatment she remained sputum positive. Sputum sent for Drug Sensitivity Testing by LiPA revealed resistance to INH & Rifampicin. She was diagnosed to have Drug Resistant Tuberculosis (MDR TB). Two weeks after the diagnosis of drug resistant tuberculosis she was started on Cat IV treatment in August 2012 -2013. Her school contacts have not been investigated. Currently she is on supervised Category IV treatment under DOTS PLUS.

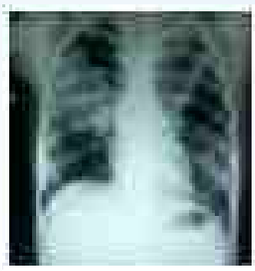

Fig. 4A

Fig. 4B

Fig. 4C

Fig 4a: X ray chest of youngest daughter dated 24/02/2012 showing consolidation in left upper zone and right upper & mid zone with bilateral hilar prominence.

Fig 4b: X ray chest youngest daughter dated 15/06/2012 showing left lung consolidation with breakdown and right upper & midzone consolidation with cavitation.

Fig 4c: X ray chest youngest daughter dated 27/01/2014 showing right upper zone consolidation, significantly better after Cat IV treatment.

Discussion : Development of drug resistance is largely a reflection of poor management of tuberculosis cases and poses a threat to tuberculosis control in India. We focus on the following factors that have contributed to the genesis of two cases of primary MDR tuberculosis , one acquired MDR tuberculosis and one death related to tuberculosis in this unfortunate family.

Delayed diagnosis: All family members were diagnosed when the disease was in fairly advanced stage. Case finding in DOTS center is a passive process. Delay in diagnosis adds to frustration and

bad outcome of patient. Only smear microscopy is used for diagnosis of tuberculosis at DOTS Centre and can affect treatment decisions.Microscopy is less sensitive and misses 40-60% of cases. Moreover its performance is worse in immunosuppressed patients. Large numbers of patients are likely to remain undiagnosed unless they also undergo chest X-ray examination or evaluation by pulmonologist in the same visit. Availability of both is questionable in rural and semi urban areas.

In resource constrained settings with high prevalence of TB & HIV infection, an estimated of 30 % of all patients with TB & more than 90% of those with MDR TB do not receive diagnosis [1,2,3] . Diagnostic strategies should also move beyond smear microscopy to include access to drug susceptibility testing as suggested in the recent WHO guidelines.

Diagnostic test which is more sensitive, accurate and deployable at the "point of care" is to be used. Grant et. al[4] from South Africa have reported that use of X pert-MTB/RIF testing for tuberculosis in primary care setting resulted in more patients starting same day treatment, more culture positive patients starting treatment and shorter time to treatment. In view of the fact that upto 40% of patients who test positive for sputum AFB examination do not return for their results in endemic settings [5,6,7] and non availability of expert in real world context an urgent policy change decision is needed. RNTCP aims at achieving more than 70% diagnostic and more than 85% therapeutic success. High diagnostic success is the first step in determining ultimate success, a reduction in drop –outs would be a major step in that direction, by leading to higher rates of treatment initiation, lower rates of true positive patient drop –outs and lower rates of empirical treatment. In a study in India, patients with failure to the category I regimen have been noted to have a 17% prevalence of MDR –TB[8] subjecting such patients to drug susceptibility testing only after they do not convert to smear negativity after 4 months of a category II regimen, as suggested by the DOT- plus initiative of the RNTCP, will introduce further delays in their access to effective therapy.[9]

CAT-2 Regimen: Patient's wife had to go through the RNTCP routine of Category - II treatment. Nearly 0.2 million category II patients with tuberculosis, often treated by one or more healthcare providers, are registered by the RNTCP every year.[10] They comprise 26 % of the smear –positive patients reported annually[11] and constitute a major public health risk as they form the reservoir of drug –resistant tuberculosis including multidrug –resistant (MDR) tuberculosis. Prevalence of INHresistance in this group ranges from 47.7% to 87.1 % while resistance to both INH and Rifampicin (i.e. of MDR tuberculosis) in this group has ranged from 8.1 %to 80.6%. [11,12]

Studies have shown that patients with treatment failure are most likely to harbor MDR-TB strains while those with default or relapse have a lower rate of MDR –TB and may well have drug sensitive strains if the infecting strain was drug sensitive at the onset of therapy. [13]

The 2003 WHO guidelines have correctly separated category II patients with a history of default or relapse from those with treatment failure and suggested different treatment regimens and strategies for the two groups. [14] The present provision of a single regimen for all patients in category II is against the basic principles of tuberculosis chemotherapy in patients with treatment failure i.e. to never add a single new drug to a failing regimen. [15]

The end of treatment outcomes of category II patients has been suboptimal with the treatment regimens administered by DOTS and the RNTCP- much below the global target cure rate of 85 %.A study of treatment outcomes has shown that only about half of re-treatment patients and only a quarter of MDR-TB patients were cured successfully with the current standardized short course therapy under DOTS across 6 nations.[16]The results of treatment in an urban as well as a rural cohort from southern India were both below 50% with a default rate exceeding 40%.[17,18] While DOTS is an excellent means of preventing acquired resistance ,it is not an effective means of treating patients with resistant tuberculosis.[19]Poor outcomes of patients with treatment failure by cat 2 regimens have been well documented also from Peru.[20] In a systematic review of 7 studies from India published in 2012 [21] high relapse rate of 10% was found under RNTCP programmes. Risk factors for relapse like drug irregularity, initial drug resistance, smoking &

alcoholism are controllable if not totally preventable.[22]

Use of suboptimal [fully intermittent] regimens: The efficacy of treatment regimens in tuberculosis is judged by a low relapse rate on follow up and not only by high cure rate. In a departure from previous recommendations, WHO now recommends daily administration as the preferred dosing schedule for all categories of patients, and considers intermittent regimens optional[14] A single regimen has now been recommended for all new cases, irrespective of the site of disease or status of the sputum smear. Published evidence has consistently suggested that the risk of relapse has been higher than acceptable in patients who receive fully intermittent thrice-weekly or twice-weekly regiment in trial and in programme conditions. [23,24,25]

Cox [26] reviewed the results of long term outcome of DOTS regimen and found wide variation in relapse rates prompting them to question the ability of standard DOTS to produce lasting cure under routine programmatic conditions. The problem with higher relapse rates with fully intermittent therapy assume even greater importance in the Indian context where initial drug resistance to a key drug such as INH is expected to be 20%-25% in programme conditions.[27] Fully intermittent regimens have been advocated as they lower total cost and make direct observation of drug intake easier .Yet, if they compromise the longer term outcomes of therapy, and lead to higher and unacceptable relapse rates, especially in a setting of INH resistance, their disadvantages may well outweigh the benefits of ease of direct observation of each dose.

While fully intermittent dosing is still an option in the treatment of patients with susceptible bacilli, there is a consensus among guidelines against their use in the treatment of drug-resistant tuberculosis.[28] The **American Thoracic Society** guidelines state; Intermittent therapy should not be used in the treatment of the drug-resistant –tuberculosis, except perhaps for injectable agents after an initial phase (usually 2-3 months) of daily therapy.

Inadequate supervision of treatment : Although the entire family was under supervised treatment from DOTS, actual drug administration may not have been supervised. Directly observed therapy is the most important component of DOTS but practically it is not vigorously followed. A balsubramanian et all[29] has concluded that that although all patients in DOTS programme were recorded as having received DOT, 26.5 % did not actually receive it. Obviously they had high treatment failure or relapse rate of 45% compared to those who had actually received DOTS

Lack of coordination between private practitioners & DOTS centre : Private practitioners are reluctant to refer patients to DOTS centre till patients can no more afford for drugs and consultation. Treatment is often not according to standard guidelines. Upalekar and Rangan[30] have reported 80 different kinds of prescriptions by private practitioners from a slum of Mumbai. As in case of the patient's wife fluoroquinolones are often used as 5th ant-TB drug. Fluoroquinolones are widely used in treatment of LRTIs. In such settings prevalence of DR-TB is substantial. It is already a cause for concern in some areas. Similarly misuse of Amikacin for lower respiratory tract infection and suboptimal use in drug resistant tuberculosis(DR-TB) can worsen DR-TB epidemic.

Accountability of TB centers : No active efforts were made on the part of DOTS programme staff to do contact tracing. Despite the wife being under Cat IV treatment, both primary MDR TB cases were discovered in advanced stages & through the efforts of non DOTS programme HCWs.

Stigmatization associated with TB : Also contributed to the delayed diagnosis. Patient himself and his family preferred to hide their illness due to fear of social boycott. In fact the family faced social boycott after HCWs were sent to the locality for contact tracing. Control of tuberculosis is difficult due to the stigma that tuberculosis is incurable & is a hereditary disease.

Negative opinion about government health facilities: In India 80% of households use private sector for treatment of minor illnesses and 75% of households use private sector for major illnesses.[31] There are many reasons for this. In a rural cohort of patients from the RNTCP, 42% of patients as well as 34% of their DOTS providers cited drug-related side effect as the leading cause of non-compliance with

treatment. [32] There is no provision for symptomatic treatment from DOTS centre for such patients.Besides inconvenient clinic timings, long waiting hours, impolite behavior of DOTS staff also contribute to this phenomenon.

Neglect of MDR tuberculosis patients--MDR-TB has been documented in India since the 1980 but there has been a continued lack of provision of treatment regimens effective against it in the national programme.DOTS-PLUS programme covers only a minority of our current MDR population. Unless urgent action is taken, a large number of patients will continue to be deprived of access to effective therapy and will propagate multiple drug resistance, before dying a premature death. As farmer et al. have noted, the arguments against aggressive treatment of MDR-TB in resource – poor countries are flawed on clinical, epidemiological, analytical and moral grounds, and that 'It is too expensive not to treat MDR-TB now, when only a small fraction of all TB cases are resistant to our best drugs.[33]

Poverty: Poverty leading to tuberculosis and Tuberculosis leading to poverty is a vicious cycle. Poor patients are less educated, live in crowded conditions, are malnourished, are less aware of health and disease. Acquisition of tuberculosis perpetuates and exacerbates poverty. Poverty even affects the health – seeking behavior of the patient due to cost of transportation and loss of wages. The patient, a taxi driver by occupation, was the sole bread-winner of the family and had five dependants.

Nearly two decades after WHO declared tuberculosis a global health emergency,[34] it remains a significant and a serious health problem atleast in developing countries as described by WHO in 2013.Alimuddin Zamda and others [35] have made a strong case for finding the missing 3 million T.B. patients who are either not diagnosed or unreported and continue to spread and left to die premature death at a productive age. Tuberculosis as a disease has been neglected when compared with other diseases like HIV AIDS, cardio-vascular diseases and obesity.

In India the print media is more vocal and active about tuberculosis than the medical fraternity. Rising to the challenge of tuberculosis is the responsibility of all medical professionals.Tuberculosis has not spared anyone since history including statesmen, physicians and scientists. Lately it is taking toll on young healthcare professionals as well in public health care institutions. Our patient's family suffered despite of being compliant with the RNTCP program.It is high time that we as Chest Physicians become more proactive in decision and policy making.

While DOTS may prevent the development of drug resistance, its efficacy is diminished where significant drug resistance is already present. DOT regimen can amplify the number of drugs to which bacteria are resistant. Once drug resistance is established DOTS alone will never suffice. DOTS plus for MDR TB provides treatment based on culture and sensitivity testing and has been shown to provide good cure rates where effective DOTS infrastructure is present. Guidelines and control programmes for TB are based on scientific and social back grounds but also need to be individualized for the patients .Local pulmonologist must be given enough freedom and not be forced to follow these guide lines and programmes .We have not been convinced that the so called supervised treatment was actually supervised .If it is expected that DOTS Plus be implemented using the same infrastructure ,we fear similar outcomes for many like our patients. It is important to accept that under programme conditions patients continue to have long waiting period even after confirmed diagnosis of DR-TB and the drug resistant strains may be passed between the family members as in our cases leading to high morbidity and mortality.

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FUNCTIONAL TYPES OF AMBULANCE

Ambulances can be grouped into types depending on whether or not they transport patients, and under what conditions. In some cases, ambulances may fulfil more than one function (such as combining emergency ambulance care with patient transport).

Emergency ambulance – The most common type of ambulance, which provide care to patients with an acute illness or injury. These can be road-going vans, boats, helicopters, fixed-wing aircraft (known as air ambulances) or even converted vehicles such as golf carts.

Patient transport ambulance – A vehicle, which has the job of transporting patients to, from or between places of medical treatment, such as hospital or dialysis center, for non-urgent care. These can be vans, buses or other vehicles.

Response unit – Also known as a fly-car or a [Quick Response Vehicle], which is a vehicle which is used to reach an acutely ill patient quickly, and provide on scene care, but lacks the capacity to transport the patient from the scene. Response units may be backed up by an emergency ambulance which can transport the patient, or may deal with the problem on scene, with no requirement for a transport ambulance. These can be a wide variety of vehicles, from standard cars, to modified vans, motorcycles, pedal cycles, quad bikes or horses. These units can function as a vehicle for officers or supervisors (similar to a fire chief's vehicle, but for ambulance services).

Charity ambulance – A special type of patient transport ambulance is provided by a charity for the purpose of taking sick children or adults on trips or vacations away from hospitals, hospices or care homes where they are in long term care. Examples include the United Kingdom's 'Jumbulance' project. These are usually based on a bus.

Bariatric ambulance – A special type of patient transport ambulance designed for extremely obese patients equipped with the appropriate tools to move and manage these patients.

(source: http://en.wikipedia.org/wiki/Ambulance)