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CASE REPORT OF PRIMARY ETHAMBUTOL RESISTANCE IN A PATIENT WITH GENITOURINARY TUBERCULOSIS AT A TERTIARY CARE HOSPITAL

Pulmonary Medicine

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ABSTRACT

Introduction: Ethambutol is one of the First line Anti Tuberculosis Drugs used for the treatment of Tuberculosis. Drug resistance to Ethambutol occurs due to point mutations in emb B gene which encodes for arabinosyl transferase enzyme involved in mycobacterial cell wall synthesis. The First National Anti-Tuberculosis Drug Resistance survey conducted by the Indian Government in collaboration with the World Health Organization and the United States Agency for International Development from 2014 to 2016 showed that Ethambutol monoresistance is around 0.21%.1 **Case:** A 13-year-old 6th standard female student from Mumbai who presented with complaints of pain in abdomen on the left flank for 2months, fever for 1 month and loss of weight (non -documented). Her urine for routine examination revealed protein 1+, pus cells 100-200/hpf, occasional RBC and bacteria +, urine culture revealed no growth. **DTPA renogram Impression-** left kidney is hydronephrotic, preserved cortical function and GFR, minimal slow drainage upper 1/3rd part of kidney and no drainage from lower 2/3rd part of kidney. She had undergone a Cystoscopy + left renal pelvis sampling + left RGP+ left DJ stenting under short GA and sample was sent for CBNAAT and serial AFB cultures. Her CBNAAT detected a positive (very low) MTB DNA. After 2 months her MGIT culture came positive and it was revealed that she was resistant to Ethambutol. **Conclusion:** All patients diagnosed with tuberculosis in any organ should undergo TB culture with Drug sensitivity testing to understand the pattern of resistance to AKT drugs. This in turn will guide us to optimise treatment, improve outcome, decrease morbidity and mortality of patients diagnosed with tuberculosis.

KEYWORDS

Ethambutol mono-resistance, tuberculosis, CBNAAT, MGIT.

INTRODUCTION

Ethambutol is a synthetic tuberculostatic drug, active against M. tuberculosis. It is commonly used as a fourth drug along with Isoniazid, Rifampicin, and Pyrazinamide in patients with drug sensitive tuberculosis.

Resistance to Ethambutol has been attributed to mutations in the *embCAB* locus encompassing 3 contiguous genes embC, embA, and embB. Ethambutol inhibits arabinosyl-tranferases embC, embA and embB involved in the synthesis of cell wall components and subsequently compromising the cell wall integrity. Drug resistance occurs due to point mutations in the emb B gene that encodes the arabinosyl transferase enzyme involved in mycobacterial cell wall synthesis.[1]

Tuberculosis (as per occurrence pulmonary tuberculosis > spine likewise) genitourinary tuberculosis is lesser-known form of Extra-pulmonary Tuberculosis. Ethambutol resistance is least common amongst the first line Anti Tuberculosis Drugs (ATT).

The term drug resistance or DR-TB was used for mono-drug resistance that is resistant to one first-line anti-tubercular drug only. The First National Anti-Tuberculosis Drug Resistance survey conducted by the Indian Government in collaboration with the World Health Organization (WHO) and the United States Agency for International Development (USAID) showed that close to 23% of new cases have resistance to any drug. Among patients previously treated for Tuberculosis, there were high levels of resistance to first-line drugs—tested Isoniazid (any 25%, monoresistance 8%) followed by resistance to Streptomycin (any 13%, monoresistance 2%), Pyrazinamide (any 9%, monoresistance 4%) Ethambutol (any 7%, monoresistance 0.21%).[2]

H.Liddicoat et al. A retrospective study was conducted on all patients with DR-TB between 2007 and 2013. 179 cases were identified: 126 patients had Isoniazid mono-resistance (H-Mono), 3 had poly-resistance including Isoniazid, and 37 patients had multi-drug resistant TB (MDR-TB). There were 6 cases of Rifampicin mono-resistance, 1 Ethambutol mono-resistance, and 6 Pyrazinamide mono-resistance.[3] Systematic review and meta-analysis by Vishal Goyal, Vijay Kadam, Prashant Narang & Vikram Singh showed that Mono-drug resistance to isoniazid and streptomycin were recorded at high levels and resistance to ethambutol alone had the least occurrence in India across both decades.[4] Mohd Javed et al. in a systematic review on Primary Ethambutol resistance found that the pooled prevalence of Primary Ethambutol resistance TB was estimated at 4.2%[5]

Case Description

Patient was a 13-year-old 6th standard female student, hailing from Mumbai. She presented with chief complaints of pain in abdomen for 2months, Fever for 1 month and Loss of weight (non - documented)

Case history

Patient was complaining of pain in abdomen on the left flank for 2 months which was insidious in onset and progressive in nature, dull aching, not associated with nausea and vomiting, loose stools, blood in stool, clay coloured stool, foul smelling stool, or constipation. She had no complaints of abdominal distension or localised swelling. She had no complaints of blood in urine, increase frequency of urination, and burning micturition. There was no radiation or referred pain. Pain was relieved temporarily on ingestion of pain killer medications. There were no aggravating factors.

She also had low grade fever more in the evening not associated with chills and rigors. Her fever was relieved temporarily on taking antipyretic medications. She had loss of weight (undocumented) and loss of appetite. She had no active respiratory complaints. Her mother had taken AKT for 6 months for clinic radiologically diagnosed Tuberculosis 12 years ago. She had no previous history of pulmonary tuberculosis. She had no known comorbidities. On general

examination, patient was vitally stable, afebrile, oxygen saturation of 98% on room air. Weight 40kgs, height 149cm and BMI of 18kg/m2. On auscultation, bilateral normal vesicular breath sounds. Per abdominal examination was soft, no tenderness, no organomegaly.

Patient visited local private doctor with above complaints and was diagnosed as acute febrile illness and was started on tab Cefixime 200 mg twice daily for 5 days along with symptomatic treatment. CBC (Hb 9.3, WBC 10,300, platelet 5,07,000) and fever profile was sent (Widal's test, malaria, Leptospirosis, and Dengue profile) was negative. Urine routine examination revealed protein 1+, pus cells 100-200/ hpf, occasional RBC, 2-3 epithelial cells, bacteria present. Urine culture revealed no growth on culture. CT KUB: Suggestive of right mild dilatation of pelvicalyceal system. Left bulky kidney with hydroureter. No renal or ureteric calculus.

Patient was then referred to Sir JJ group of hospitals to Urology OPD and was advised urine for DNA TB PCR which was negative and Urine culture which had no growth.

DTPA renogram of Left kidney showed a flat curve with no cortical peak and Right kidney showed preserved cortical peak with down sloping curve. Impression- left kidney is hydronephrotic, preserved cortical function and GFR, minimal slow drainage upper 1/3rd part of kidney and no drainage from lower 2/3rd part of kidney. Right side has good parenchymal function and GFR and non-obstructed drainage pattern.

She had undergone a Cystoscopy + left renal pelvis sampling + left RGP+ left DJ stenting under short general anaesthesia which showed evidence of multiple flakes of pus in the bladder and sample was sent for Cartridge Based Nucleic Acid Amplification Test (CBNAAT) and serial TB cultures.

Her CBNAAT report detected a positive (very low) MTB DNA. Patient was started on first line ATT as fixed dose combination under NTEP as per her weight.

After 2 months her MGIT culture came positive and it was revealed that she was resistant to Ethambutol.

MGIT of urine -1st line drugs- sensitive to Isoniazid, Rifampin, Streptomycin, Pyrazinamide and resistant to Ethambutol. 2nd line drugs- sensitive to Ethionamide, PAS, Cycloserine*, Kanamycin, Ciprofloxacin, Clarithromycin*, Rifabutin*, Amikacin.

In view of Resistance to Ethambutol, Fixed dose combination was stopped and she was shifted to loose drugs as Isoniazid, Rifampicin, Pyrazinamide and Levofloxacin. On routine follow up after 3 months, patient was symptomatically better, no fever episodes, decreased pain in left flank. She had Weight gain of 5 kgs and her appetite improved. USG KUB after 3 months showed mild to moderate left hydronephrosis with left sided DJ stent in situ.

Plan was to complete full 18 months of ATT with regular follow-ups both at Urology for DJ stent replacement every 3 months and in Pulmonary Medicine.

DISCUSSION:

Ethambutol is one of the key components of the first-line anti-TB drugs and is added to the current treatment regimen for TB as a protection against unrecognized resistance to other core drugs (INH, RIF, and PZA) [Horsburgh et al. 2015][5]. Increasing resistance to EMB is associated with increased risk of unsuccessful TB treatment outcome and acquiring resistance to other anti-TB drugs [WHO, 2011][6]. Therefore, understanding the current situation of primary EMB-resistant TB is necessary for the programmatic management of TB cases.

CONCLUSION:

All patients diagnosed with tuberculosis at any organ should undergo TB culture with Drug sensitivity testing to understand the pattern of resistance to ATT. This in turn will guide us to optimise treatment, improve outcome, decrease morbidity and mortality of patients diagnosed with tuberculosis.

Abbreviations

CT KUB- Computed Tomography of Kidneys, Ureters and Bladder.
DTPA- Diethylenetriamine Pentaacetate.
PCR- Polymerase Chain Reaction.
CBNAAT- Cartridge Based Nucleic Acid Amplification Test
PAS- Para-amino salicylic acid.
INH- Isoniazid
RIF- Rifampicin
PZA- Pyrazinamide

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