Landouzy Sepsis (Atypical ARDS like Features) and Paradoxical Reaction of Tubercular Meningitis Complications, in a Case of Disseminated Extrapulmonary Tuberculosis

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ABSTRACT

Introduction: Disseminated tuberculosis is a form of widespread bacilli infection with typical involvement of the lungs and other extra pulmonary organs. It is a rare manifestation of mycobacterial infection and rare among immune competent individuals.

Case report: We present a case of disseminated extra pulmonary tuberculosis co-occurring tuberculous meningitis, CNS tuberculomas and Liver tuberculomas. Our patient developed atypical respiratory complications in the form of ARDS like features which also called as Landouzy Sepsis, despite apparent normal Chest x-ray following initiation of Anti Tubercular Therapy. Also patient developed paradoxical reactions to tuberculous meningitis during the treatment.

Conclusion: Awareness about paradoxical reactions in tuberculous meningitis is very much crucial as paradoxical reactions may lead to confusion about diagnostic accuracy and resistance of ATT drugs. Paradoxical reactions do not affect the outcome but require prompt treatment to the complications like hydrocephalus and respiratory distress.

Keywords: Disseminated TB, Paradoxical Reactions, ARDS, Tubercular Meningitis.

INTRODUCTION

Disseminated tuberculosis is defined as the presence of two or more non-contiguous sites resulting from haematogenous dissemination of mycobacterium tuberculosis, occurring as a result of a progressive primary infection, reactivation of a latent focus with subsequent spread.[1] Disseminated TB is a life threatening condition, especially if diagnosis and treatment are delayed. Although the primary site of infection is usually the lung, other organs may be involved either in primary or post-primary infection.[2]

In healthy individuals, this dissemination is contained by a prompt immune response, particularly cell-mediated immunity and the interferon-γ pathways, limiting the infection. Therefore, clinical disseminated disease following primary or reactivation of established latent tuberculosis is more often in relatively or absolutely compromised hosts, such as infants, patients with acquired immune deficiency syndrome(AIDS) or patients with latent infection placed on a tumour necrosis factor alpha blocker, comprising the regular immune surveillance.[1]

Paradoxical reaction, in patients with tuberculous meningitis, is characterised by either worsening of pre-existing tuberculous lesions or the appearance of new tuberculous lesions in patients who show improvement following anti tuberculous treatment. The clinical or radiological deterioration associated with such a reaction may fallaciously suggest either a drug resistant state or treatment failure, and might even prompt to look for alternative diagnosis.[3] Paradoxical reaction doesn't necessarily represent treatment failure and corticosteroids have been shown to have a beneficial effect.[4–6]

In Human Immunodeficiency Virus (HIV)-infected patients, paradoxical reactions are termed as the Immune reconstitution inflammatory syndrome (IRIS), which is a condition characterised with worsening of pre-existing infective processes, following treatment with anti-retroviral therapy. Tuberculosis associated IRIS is characterized by worsening of clinical symptoms, signs, and imaging characteristics of tuberculosis subsequent to initiation of antiretroviral therapy after initial improvement with anti-tuberculous treatment.[7,8]

We understood that patient was suffering from disseminated tuberculosis with extra-pulmonary involvement in the form of CNS tuberculomas and Granulomatous lesions in liver, although USG guided biopsy remain inconclusive however there is sufficient evidence to stamp it as component of disseminated tuberculosis as liver lesions disappeared on starting ATT, but pulmonary deterioration ARDS like symptoms probably results from miliary tuberculosis. From few case reports and series we came into conclusion that the patient might be suffering from Landouzy Sepsis also known as 'sepsis tuberculosa acutissima'[9]

CASE REPORT

A 48 year male patient presented to our hospital with on and

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How to cite this article: Vijayan Peettakkandy, Subrat Kumar Soren, Vineeth K.K., Shanavas Cholakkal. Landouzy sepsis (atypical ARDS like features) and paradoxical reaction of tubercular meningitis complications, in a case of disseminated extrapulmonary tuberculosis. International Journal of Contemporary Medical Research 2020;7(4):D1-D5.

DOI: http://dx.doi.org/10.21276/ijcmr.2020.7.4.6

off fever since 5 months associated with headache, abdominal pain, and minimal bilateral pedal edema. Also there is history of loss of appetite and weight. However patient did not report cough or haemoptysis, any focal neurological deficits, bony pain, generalised lymphadenopathy. Patient was an alcohol abuser before his illness but not a smoker. Patient was conscious and oriented.

Patient was admitted for the evaluation of fever, headache, occasional vomiting as his symptoms did not relieved following medications taken from local hospital. Physical examination done found to have neck stiffness and mild pedal edema. Keeping in mind provisional diagnosis as meningitis further investigation viz; routine blood, chest x-ray, LP puncture for CSF analysis and CT head, was planned. Following are the blood results revealed as TLC 7800/mm3, (L19%, N-63), Hb -13g%, Platelet 2.6Lakh/mL, ESR=100mm/hr, Blood Urea- 23mg/dL, Creatinine 0.9mg/dL, Serum electrolytes Na+ -131mEq/L, K+ -3.8mEq/L, CRP was 204 mg/dL. As neck rigidity was present, CSF analysis was done, following result revealed: OP (Opening pressure) 18 mmHg, Total count 110/mm3, DC as follows L-98, P-2, protein-1gm, sugar-42mg/dL, ADA-98U/L. HIV serology was negative. Except ESR and CRP, all other routine blood investigations was found normal. With such high values ESR, Tubercular meningitis was provisionally diagnosed and to give more support to the clinical diagnosis, Mantoux test done which again found strongly positive, post 72 hrs reading came out to be 22mm. MRI brain imaging showed multiple parenchymal lesions involving subcortical

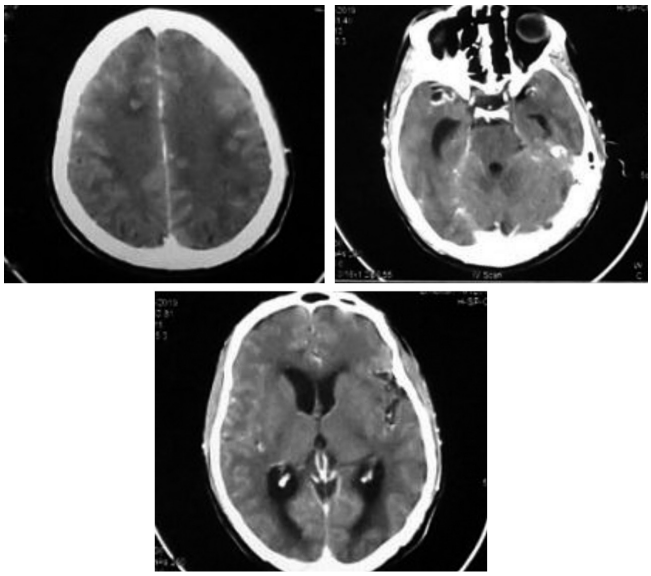

Figure-1, 2 & 3: CT head shows multiple tuberculomas at initial presentation,

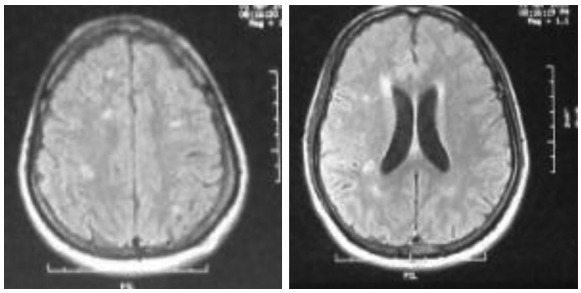

Figure-4,5: MRI brain images as part of diagnosis,

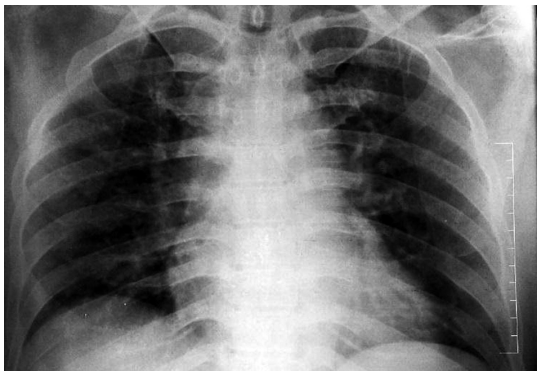

Figure-6: Normal chest Xray

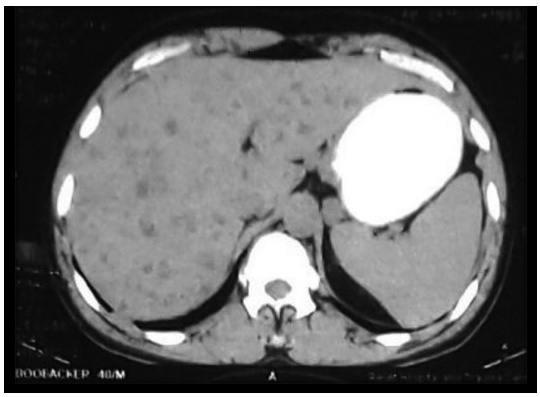

Figure-7: CECT contrast abdomen showing multiple liver tuberculomas

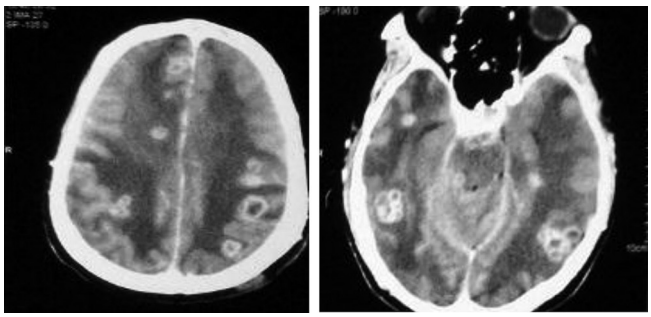

Figure-8,9: Paradoxical reactions CT head contrast showing increased tuberculomas

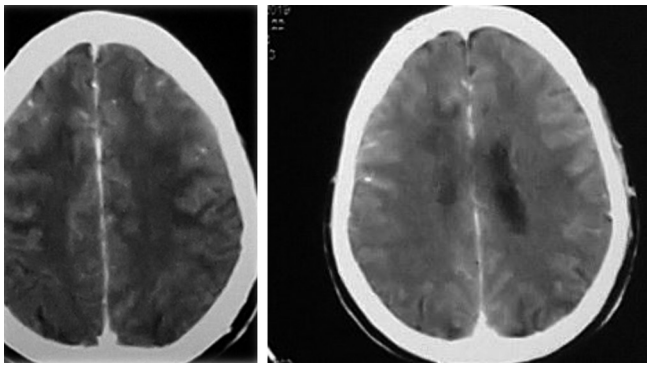

Figure-10,11: Repeat Contrast CT head shows resolving tuberculomas

and periventricular white matter (figure 1,2,3 and 4,5) and also whole spine screening done found to be normal. Chest X-ray within normal limit (figure-6). As patient was too complaining of abdominal pain, Ultra sound of abdomen and pelvis was advised and found multiple hypoechoic lesions in liver and enlarged para aortic lymph nodes. So further Contrast CT abdomen and thorax was been done to diagnose and confirm radiologically disseminated tuberculosis. CECT abdomen reported as multiple hypodense lesion in both lobes of liver giving the imaging impression as metastasis or granulomatous foci (figure-7). To confirm the liver lesion we made USG guided biopsy from liver but results were in conclusive. CECT thorax grossly appears to be normal except few enlarged mediastinal lymph nodes. After summating all reports finally diagnosed to be disseminated extra pulmonary TB manifested as tubercular meningitis with CNS tuberculoma and Liver tuberculoma.

Patient was started anti tubercular treatment on dated 17-03-2019 with four drugs regimen viz-Isoniazid(H), Rifampicin(R), Pyrazinamide(Z) and Ethambutol(E) administered three days per week according to RNTCP(Revised national tuberculosis control programme, Government of India programme) schedule as Category I,HRZE as intensive phase(IP) for 2 months and HRE for next 10 months although RNTCP recommends total durations of 9 months for extra-pulmonary TB but after reviewing guidelines for CNS TB management we chose to advice to take total 12 months. Also added steroid and pyridoxine to his treatment. After 10 days of taking ATT medications patient noticed yellowish discolouration of eyes. Patient again visited us for jaundice and was been advised blood test for LFT and results found to be altered liver enzymes. We thought it could be ATT drug induced so Rifampicin, Pyrazinamide and INH Stopped and then Streptomycin, Ethambutol and levofloxacin been started for 2 weeks and allowed to settle his jaundice with serial monitoring of LFT. Subsequent testing of blood revealed normal LFT at the end of 2 weeks of stopping hepatotoxic ATT drugs. Again first line ATT drugs was been resumed and streptomycin and levofloxacin was omitted along with dexamethasone. Patient was doing well for around 1 month, but again he landed to our hospital with more severe symptoms viz; high grade fever, mild disorientation, walking difficulties and severe breathlessness. Immediately Chest X-ray was advised but no gross pathology noted except bilateral reticulonodular shadows. Also clinically detected there is facial deviation with right facial palsy. In view of severe breathlessness, CTPA (Computed Tomography Pulmonary Angiography) was done to rule out any possibility of pulmonary embolism but found negative. Since patient symptoms getting worsened, patient was shifted to Intensive care unit. ABG(Arterial Blood Gas Analysis) showed Respiratory alkalosis which was been corrected. After 24 hours of ICU care patient becomes severe breathless and desaturated, so patient was put on NIV(Non Invasive Ventillation). Clinically patient was diagnosed as pneumonia with sepsis as there was hypotension. We stepped up injectable antibiotics viz; Piperacillin tazobactum and Linezolid and Clindamycin had been started along with antiviral Tamiflu. Resuscitation and low dose Ionotropes support for hypotension initiated. Antiviral has been added thinking viral pneumonia, as there is not much blood parameter results suggestive of bacterial pneumonia. Over 48 hours past, patient was not responding to antibiotics, diagnosis has been revised and antifungal coverage was also advised as patient was put on steroid (dexamethasone) for longer duration as part of CNS tuberculosis. However after 5 days of treatment fever subsided and sensorium slowly improved and better, and patient was undergone repeat CT head and chest X-ray. CT head doesn't show any evidence of fresh lesions and previous hydrocephalus was improved but multiple ring enhancing lesions persisting. Strict glycaemic controlled (Dexamethasone induced diabetes) done with insulin. Slowly patient recovered and been discharged following 2 weeks. Finally dexamethasone has been tapered and stopped over next 1 month

On dated 16-7-2019, patient had fallen from chair at home and there is loss of consciousness probably had attack of GTCS(Generalized Tonic-Clonic seizure) as no one has attended during the ictus. Patient was again hospitalized for the same and again evaluated. Repeat CT head with contrast was done and found there is increase of tuberculoma lesions, edema and hydrocephalus (Figure-8,9). Patient was treated with antiedema measures viz; mannitol, furosemide and Diamox and AED has been stepped up to Eptoin, levetiracetam and clobazam. Patient becomes apparently normal after 48 hours able to talk and recognise his wife. Now there is dilemma in treatment regimen whether ATT(Antitubercular therapy) drugs became resistant and results of which there is aggravated increase numbers of CNS tuberculoma, edema and hydrocephalus. We kept reserve alternative CSF diversion procedures either VP shunt or Endoscopic third ventriculostomy. As sensorium of the patients improved we continued the conservative management of acute CNS pathological sequelae. Next we planned for isolation of organism and undergone sensitivity testing of ATT drugs. Patient underwent craniotomy and excisional biopsy. Tissue sample sent for AFB stain and mycobacterial agent was identified, GeneXpart doesn't show resistance to Rifampicin and later on culture was too proved, lack of resistance to Isoniazid and Rifampicin. We continued ATT and patient now completed 9 months and to be continued for another 3 months to complete 12 months of treatment. Patient is on follow up, clinically improved and repeat CT head shows improvement of brain radiological conditions. (Figure 10,11)

DISCUSSION

Disseminated TB with normal chest radiograph is labelled by some authors as "cryptic tuberculosis".[10] It's presentation is insidious and mainly affects middle aged and the elderly. Diagnosing disseminated tuberculosis in such patients is still a dilemma, from both clinical and laboratory prospective, because of the lack of localizing signs, absence of choroidal tubercles, normal chest x-rays, and negative tuberculin test.[11]

Therefore, disseminated tuberculosis should be suspected in immunocompromised patients and in those from endemic areas who have prolonged pyrexia of unknown origin, weight loss, lassitude, hepatomegaly, splenomegaly, liver function abnormalities, and abnormal haematological indices. However in our case patient was HIV seronegative and no evidence of definite immunocompromised except history of alcohol abuse. Initially patient was diagnosed extra pulmonary TB as tubercular meningitis associated with multiple tuberculomas complicated with hydrocephalus. There is no chest symptoms and preliminary chest x-ray suggest within normal limit. Also patient complains of abdominal pain CECT abdomen and thorax had been advised and found to had multiple hypodense lesions in liver and hepatomegaly.With context of proven tubercular meningitis and liver lesions are provisionally impressed as tubercular lesions which resolves on anti tubercular treatment, although USG guided FNAC results were inconclusive. So final diagnosis was made disseminated extra-pulmonary TB Involving CNS and liver and abdominal lymphnodes. Patient was been started on dated 17-03-2019 with ATT 4drugs regimen with coverage of steroid (Dexamethasone). Initially patients improves but following 1 month patient`s respiratory function deteriorated acutely for which patient was put under NIV ventilation for 72 hrs and high grade fever has been managed symptomatically and empirical antibiotics covering gram positive, gram negative and anaerobes, started. Also empirical antiviral medications had been administered. Keeping in mind pneumonia with sepsis, as there is no definite evidence of Pneumonitic lung and bronchioalveolar lavage was negative for TB. Bilateral reticulonodular shadows on chest Xray, probable cause in this case might be due to miliary TB or shedding of mycobacterial protein products. Pulmonary embolism had been ruled out with CTPA(Computed Tomography Pulmonary Angiography). So retrospectically analysed the situations and reviewed different literatures, we concluded that patient was either because of miliary spreading of tuberculosis or because of concomitant sepsis which also called as Landouzy sepsis. This is a rare entity, described first at the end of 19th century, and was also called "sepsis tuberculosa acutissima". It presents with three pattern of evolution: first, a typhoid septic form with early exitus; second, a typhoid sepsis followed by a short symptoms-free interval, followed by multiorgan failure with exitus and a third pattern, a septic presentation followed by a complete recovery.[9]

In the majority of the cases reported in the literature, the diagnosis has been made only post mortem confirming the confusing clinical picture of the disease.[12,13]

Murray et al described three cases with a fulminant pneumonia but all cases started with primary infection.[14] another presented a case with miliary TB, initially without affecting the lungs but later on, complicated by an ARDS.

This seems to be one of the rare cases having an ARDS as a complication of miliary TB without having any other co-morbidity. In other reports, patient with miliary tuberculosis and ARDS almost had predisposing factors such as alcohol abuse, diabetes, hepatic cirrhosis etc. High mortality rates have been reported in patients with acute respiratory failure on the background of pulmonary TB.

The transient elevated liver enzymes following about one week of taking ATT might be due to the effect of hepatotoxic drug themselves. The latter scenario was less convincible because the enzymes normalized despite permanent hepatotoxic ATT drugs therapy. Miliary TB is more probable because it has been shown that hepatic TB is usually present in all miliary TB cases.[15] It has been found in 80-100% of autopsied patients with disseminated pulmonary TB.

In 1955, a paradoxical response under TB treatment was first identified by Choremis and his friends on lung graph imaging results of a child who was being treated for TB.

In 1974, Thrush and Barwick, for the first time, documented paradoxical reaction in a patient with CNS TB, who had multiple tuberculomas and developed a new tuberculoma during treatment with anti TB drugs.

Paradoxical deterioration mostly occurs in patients with extra pulmonary and disseminated TB, like miliary TB and TB meningitis. The CNS and the respiratory system remain the most common sites of involvement during paradoxical deterioration as we had diagnosed in our case. For the CNS manifestation patient had headache, mental confusion, focal seizures, cranial nerve palsies and cortical signs such as hemiparesis, para paresis and hemianaesthesia as a result of the enlargement or development of intracranial tuberculomas and hydrocephalus. Our patient presented with headache, doubtful seizure as there was no attender when there was ictus, Right facial palsy and there was new CNS tuberculomas, the exact reason is not being known but most acceptable explanation for paradoxical reaction is interplay between host`s immune response an direct effect of mycobacterial antigen. A paradoxical response can occur 3-12 weeks after the initiation of TB treatment; however it can take as long as 18 months. It was seen in our patients about 3 months after the ATT treatment.

A paradoxical response is commonly seen in 6-30% of patients being treated for TB, particularly in adults and immunocompromised patients however in our case patient was immunocompetent. This situation is seen very rarely in children and the earliest age at which it occurred was 21 day old child who was treated for congenital lung TB.

It is not necessary to change or stop ATT, when a paradoxical response develops. Also, 95% of mycobacteria are sensitive to the treatments, but the resistance to Anti TB drugs is still important, especially in our country like India where proliferation of resistant TB strain is ongoing process.

Paradoxical reactions are treated with systemic corticosteroids and/ or surgery. Beside this, the differential diagnosis of a paradoxical reaction may also pose a serious challenge. A wrong diagnosis, possibility of treatment failure, multidrug resistance, atypical mycobacterial infection, drug toxicity, or clinical deterioration due to some unrelated cause should always be co-considered.

Corticosteroids decrease intracranial pressure by decreasing brain edema which is helpful in diminishing neurological

symptoms. Systemic steroids had been added in our case with good clinical responses and we also controlled blood sugar level which was steroid induced.

Despite appropriate treatment, the cause of the paradoxical response in TB patients is not clear. As a result, new antibiotic were added to the treatment. Subsequently brain biopsy was been done and found sensitive to isoniazid and rifampicin and again continued the treatment according to RNTCP protocol.

CONCLUSION

We report a patient with disseminated extrapulmonary TB manifesting as TB meningitis, CNS tuberculoma, multiple liver tuberculomas, who subsequently developed paradoxical reactions in the brain and ARDS features in lungs during appropriate ATT and steroid therapy. This paradoxical reaction manifested with clinical deterioration in the form of altered consciousness, seizure, cranial nerve palsy and features of hydrocephalus and changes in radiological features. While multiple studies have found that some paradoxical reactions in extra pulmonary TB don't adversely affect clinical outcome. CNS lesions always have a potential threat for grave consequences so requires more vigilant and prompt diagnosis of complications and its management as tubercular meningitis having more paradoxical reactions and mortality. There is always a question of drug resistant TB when there is worsening of the patient clinical conditions and often paradoxical reaction leads to appropriate increment or addition of more toxic newer anti tubercular drugs with several adverse reactions. Finally we concluded that patient also had developed a tuberculous sepsis (third pattern)but still a miliary course complicated by a paradoxical reaction to the drug was possible.

To differentiate further may be looked for additional factors that might influence the evolution of our patients disease such as genetic strain of TB, geographical location of the patient, and the vitamin D level.

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Source of Support: Nil; **Conflict of Interest:** None

Submitted: 07-02-2020; **Accepted:** 16-03-2020; **Published:** 14-04-2020