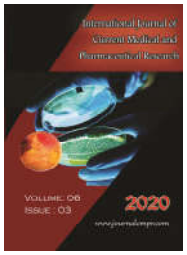
INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND PHARMACEUTICAL RESEARCH
ISSN: 2395-6429, Impact Factor: 4.656
Available Online at www.journalcmpr.com
Volume 6; Issue 03(A); March 2020; Page No.5025-5027
DOI: http://dx.doi.org/10.24327/23956429.ijcmpr202003855



Research Article

PREGNANCY WITH BRAIN TUBERCULOMA WITH SEVERE HEPATOTOXICITY – A CASE REPORT

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ARTICLE INFO

Article History:
Received 10th December, 2019
Received in revised form 2nd January, 2020
Accepted 26th February, 2020
Published online 28th March, 2020

Key words:
Hepatotoxicity, liver injury, brain tuberculoma, anti-tubercular treatment (ATT)

ABSTRACT

We report the case of a 25-year-old patient on anti-tuberculartreatment (ATT) who presented to our OPD for the first time at eight months pregnancy, with jaundice, loss of appetite, pruritis, and decreased urinary output. The patient was diagnosed as pregnancy with ATT induced acute liver injury and was admitted. The patient had earlier reported to a private clinic in the first trimester of the index pregnancy with persistent headache, and was evaluated and initiated on ATT. She went for follow up visits at the private clinic for only two months. Subsequently, she did no regular medical follow up until month eight of her pregnancy, when she first visited our OPD. Despite immediately admitting her, discontinuing ATT and instituting necessary management, the patient ultimately went into hepatic encephalopathy. Strict monitoring and regular follow up by both the physician and the patient (including family) need to be emphasized and are critical in preventing avoidable morbidity and mortality.

INTRODUCTION

Tuberculosis remains one of the world's biggest health problems. Worldwide, ~10 million new cases and 1.6 million deaths occur annually[1]. India accounts for a quarter of the global burden, with 2.8 million cases annually and 850,000 cases that are undetected and untreated[2]. Pulmonary tuberculosis is the commonest form. Extra pulmonary tuberculosis accounts for 14-40% of all tuberculosis cases of which 5-10%[3, 4] involve the central nervous system. Liver disease can be co-incidental or unique to pregnancy or predate pregnancy. We present the case of a third trimester pregnancy, with brain tuberculoma, with ATT-induced fatal hepatotoxicity.

Case Report

A 25-year-old woman, reported to the Obstetrics & Gynaecology OPD of Era Lucknow Medical College and Hospital on 29th March 2019 with amenorrhea of eight months, and complaints of weakness, body aches, yellowish skin for one month; vomiting, generalized itching and swelling for 15 days; fever and decreased urinary output for three days.

Earlier in October 2018, in her late first trimester, the patient visited a private hospital complaining of persistent headache. An MRI showed multiple granular tuberculomas of the brain (Exhibit 1). Accordingly, anti-tuberculosis treatment (ATT i.e. isonex, rifampicin, pyrazinamide and ethambutol)was started and on follow up in December 2018 pyrazinamide was omitted as per records.

Three months later, she reported to our OPD on 29th March2019. She was a non-smoker and a non-alcoholic. Her period of gestation by her LMP was 35 weeks.

On clinical examination, there was severe jaundice, generalized edema, pulse 92 beats per minute (bpm), and blood pressure120/80 mmHg. The chest examination was unremarkable. The abdominal wall was edematous, the uterus was at 34 weeks, with cephalic presentation, adequate liquor and FHS 138 bpm. On vaginal examination, the cervix was uneffaced, and closed. The Obstetric USG was unremarkable. The clinical diagnosis was Gravida 2, Para 1 at 34 weeks of pregnancy with severe jaundice, ATT induced.

She was admitted. Isoniazid and rifampicin were discontinued immediately and relevant lab investigations sent (Table-1). Under consultation with the Department of General Medicine she was put on ethambutol, intravenous (I/V) antibiotics (cefoperazone and sulbactum 1.5gm 12-hourly), furosemide 20mg 8-hourly, Vitamin K1 12-hourly I/M, and albumin infusion 15gm/50 ml once a day).

Fetal surveillance was done and standard steroid coverage for fetal lung maturity was given.

A week after admission, the patient went into spontaneous labour. Her lab investigations at the onset of labor were repeated (Table-1).The patient's progress of labor, general condition and vital parameters were closely monitored along with fetal surveillance.

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Six hours after the onset of labor, the membranes spontaneously ruptured. At this time, FHS was 110bpm, and the CTG trace showed poor variability. Her vital parameters were maintained, uterus was mildly acting and relaxing well; vaginal examination revealed thick meconium, cervical dilatation of 3cm and Bishop cervical score wasfour.

After reviewing lab results (Table-1) fresh frozen plasma (FFP) was started.

Decision for LSCS was taken and pregnancy surgically terminated. Intraoperatively the uterus and placenta were deeply stained yellow; the liquor was thick meconiumstained. Intraoperatively, there was moderate PPH, which was controlled with oxytocics, uterine massage; and one unit each of FFP and blood.

A live male baby of 2.603 kg was delivered with Apgar score five at five minutes. Meconium aspiration for the baby was immediately done and the baby shifted to NICU and put on ventilatory support.

Post operatively, the patient was shifted to the ICU. Her vital parameters were stable and lab investigations repeated (Table1).

Her postoperative management included ventilatory support, I/V fluids,I/V antibiotics (ceftriaxone 1gm 12-hourly, metronidazole 100mg 8-hourly, gentamycin 80mcg 12-hourly, ranitidine 150mg 12-hourly, metoclopromide 10mg 12-hourly, Hepamerz 2 amp in 500ml, (L ornithine- L Aspartate 10gm in 500ml of 5%dextrose), rifamycin 550mg per rectum 12-hourly, and syrup lactulose 30ml through Ryles tube. Strict input output was maintained.

Lab investigations on the first post-operative day (Table-1) reflected deterioration in liver function tests with bilirubin at 21mg/dl, and further increased levels of liver enzymes and worsening of prothrombin time and INR.

The patient developed fever on the third postoperative day. Ceftriaxone was replaced with Teicoplannin 400mg I/V loading dose with maintenance dose of 200mg I/V daily.

Lab investigations were monitored daily.

Her renal function tests deteriorated from the fifth post-operative day with blood urea rising to 68mg/dl and creatinine to1.5mg/dl (Table-1).Hydrocortisone 100mg I/V 8-hourly was added.

By the sixth postoperative day serum bilirubin was 29mg/dl, PT33.6, INR was 3.14 and the total serum proteins 2.2g% (Table-1).Post operatively uterus remained well contracted with no significant vaginal bleeding.

The patient was under intensive care and had by then received a total of five-units of blood transfusion, eight units of fresh frozen plasma, five-units of intravenous albumin, and antibiotics. Despite all these measures, liver functions continued to deteriorate followed by deterioration in renal functions.

On the sixth day, in view of the grave prognosis and critical condition, and on request from relatives, the patient was discharged against medical advice. She died the following day as learnt on telephonic enquiry. Though pathological postmortem could not be done, the clinical picture and progression of the case suggested hepatic toxicity that was ATT induced as the primary cause of death.

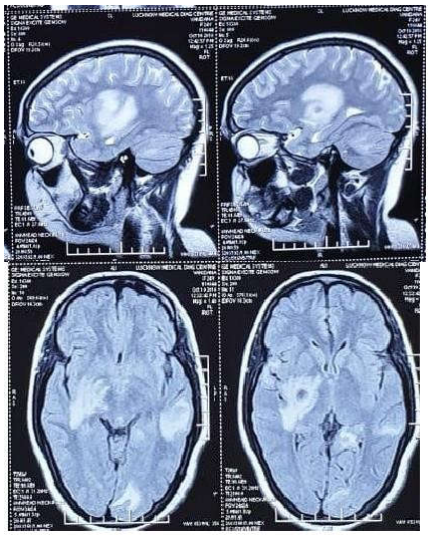

Exhibit 1 MRI scan

Table 1 Laboratory investigations

Date -	29/3/19 (On Admission)	5/4/19 (On Onset of Labor)	6/4/19 (Immediate Post-operative)	7/4/19 (Post-operative Day 1)	11/4/19 (Post-operative Day 5)
Hemoglobin (g/dL)	8.6	8	7.6	5.9	9.3
TLC (cells/mm^3)	10,600	16,500	16500	27500	15000
DLC (Neutrophils/ Lymphocytes/ Eosinophil/ Monocytes/ Basophils)	70/16/12/2	66/15/15/4	66/15/15/4	90/8/02/0	88/10/1/1
Platelets	2 Lakhs	1.8 Lakhs	1.8 Lakhs	2.2 Lakhs	1.5 Lakhs
Total bilirubin (mg/dL)	19.2	19.0	17.9	21.7	29.2
SGOT (U/L)	155	155	154	99	59
SGPT (U/L)	82	75	46	46	30
ALP (U/L)	272	250	215	157	88
Hepatitis A	Non-reactive				
Hepatitis B	Non-reactive				
Hepatitis C	Non-reactive				
Hepatitis E	Non-reactive				
Anticardiolipin antibody	Negative				
Antiphospholipid antibody	Negative				
PT (sec)	42.7	27.9	26.6	26.3	33.6
INR	4.01	2.56	2.43	2.41	3.14
Urea (mg/dL)	29	30	32	32	93
Creatinine (mg/dL)	0.9	0.9	1.1	1.1	1.4
Serum sodium (mmol/L)	138	137	140	140	141
Serum potassium (mmol/L)	4.9	4.8	4.3	4.3	3.4
Total Protein (g/dL)	4.8	4.8	4.2	4.2	5.2
Serum albumin (g/dL)	2.1	2.1	1.9	1.9	2.7

DISCUSSION

Tuberculosis of the CNS manifests as meningitis/ meningoencephalitis with brain tuberculomas. Clinically, a patient with brain tuberculoma may present with seizures or signs of raised intracranial pressure, localized neurological deficits or even behavioral problems[3,4].

Pregnancy with brain tuberculoma is both rare and a diagnostic and therapeutic challenge although MRI has revolutionized the diagnosis of brain tuberculomas[3].

In our case,the MRI (Exhibit 1) revealed multiple tuberculomas involving the cerebral and cerebellar hemisphere based on which the patient was administered ATT by the private health facility expert, six months prior to admission to our institution.

The risk of hepatotoxicity from ATT drugs is approximately 5-28%[5]. Pregnancy is an immunosuppressive state and coupled with stress and poor nutrition could lead to an exaggerated form of tuberculosis and its complications[4].

Also, in pregnancy, there is a 2.5 times higher risk of developing ATT induced hepatitis because pregnancy also encourages cholestasis.

Clinically, hepatic toxicity has a variable presentation.Nausea, vomiting, and abdominal pain are seen in 50-75% of patients with severe illness, whereas fever is noted in 10% and rash in 5% of patients. Overt jaundice, dark urine, and clay-colored stools are late signs of clinical worsening. Coagulopathy, hypoalbuminemia, and hypoglycemia signify life-threatening hepatic dysfunction[6].The regression of isoniazid hepatotoxicity usually takes weeks. Recovery is complete in most after discontinuation of isoniazid

Our patient belonged to a relatively poor socio-economic status so she was possibly anaemic and malnourished when ATT was started. She was a non-alcoholic, non-smoker; hence liver pathology prior to commencing the ATT was unlikely. Further in our case Hepatitis A,B,C and E were ruled out by serological tests.

Normal platelets count and absence of hypertension excluded preeclampsia and HELLP syndrome. Acute fatty liver (AFL) unique to pregnancy was excluded as there was no hypoglycaemia. Also, Swansea's six criteria for diagnosing AFL were unfulfilled[7,8]. Therefore, our case was pregnancy with drug induced liver injury (DILI), which continued to progress to severe hepatic toxicity and hepatic encephalopathy, to which the patient succumbed despite intensive care.

CONCLUSION

We reported the case of a 25-year-old pregnant female with brain tuberculoma and ATT induced fatal hepatotoxicity. The case illustrates that it is not enough to just diagnose and start ATT. It is important to counsel and emphasize strict follow up not just for the initial few weeks but till completion of ATT. Further, it is imperative to alert the patient and family about signs and symptoms of hepatotoxicity so that patient reports early when hepatotoxicity is mild and can be reverted.

Our case exemplifies that patients and families need to also take responsibility to follow-up regularly during the full course of ATT. Had our patient reported a month earlier when hepatic toxicity was mild, stopping the hepatotoxic drugs could have possibly reversed the hepatic damage and prevented the maternal mortality.

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How to cite this article:

Dr. Savita Chandra, Dr. Garima Maurya and Dr. Swapnil Agrahari (2020) 'Pregnancy With Brain Tuberculoma With Severe Hepatotoxicity – A Case Report', *International Journal of Current Medical and Pharmaceutical Research,* 06(03), pp 5025-5027.

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