

Available at [www.sciencedirect.com](http://www.sciencedirect.com)

SciVerse ScienceDirect

journal homepage: [www.elsevier.com/locate/IJMYCO](http://www.elsevier.com/locate/IJMYCO)

## Case Report

## Delayed diagnosis of tuberculous meningitis in a pregnant Nigerian: A case report

Isa Samson Ejiji \*, Simji Gomerep, Mafuka Johnson, Achie Basil Bemgba

Department of Medicine, Jos University Teaching Hospital, Lamingo Dam Road, Plateau State, Nigeria

## ARTICLE INFO

## Article history:

Received 9 January 2013

Accepted 20 January 2013

Available online 16 February 2013

## Keywords:

Tuberculous meningitis

Pregnancy

Atypical presentation

Empirical therapy

## ABSTRACT

Tuberculous meningitis (TBM) is the most severe form of tuberculosis and is commoner in those with immunosuppression. Diagnosis continues to be difficult particularly in resource limited settings, and this may be truer in the setting of pregnancy. We report the case of a pregnant Nigerian who was diagnosed late with atypical features of TBM complicated by cerebral infarction. High index of suspicion and early administration of anti-tuberculous medications as daily therapy according to the national treatment guidelines: 600 mg Rifampicin, 300 mg Isoniazid, 1.2 g Pyrazinamide and 800 mg Ethambutol plus 50 mg pyridoxine and 0.4 mg/kg body weight/day dexamethasone which was tapered weekly led to a slow but sustained clinical improvement. The relationship between pregnancy, susceptibility to TBM and presenting features of TBM requires further exploration. Clinicians should also be aware of atypical presentation of TBM in pregnancy, and the suspicion of TBM may be sufficient grounds to initiate empirical anti-tuberculous therapy.

© 2013 Asian-African Society for Mycobacteriology. All rights reserved.

### Introduction

Tuberculosis (TB) is the third leading cause of death worldwide among women aged between 15 and 44 years and once infected, women of reproductive age are more susceptible to developing TB than men of the same age [1]. Tuberculous meningitis (TBM) accounts for about 8–14% of all cases of TB in Nigeria [2,3]. Ninety-three percent of pregnancy-related TB was located in extra pulmonary sites, and the central nervous system was involved in 69% of cases in a meta-analysis of data from 1966 to 2002 [4].

TBM is the most severe clinical presentation of tuberculosis, and it is associated with high morbidity and mortality, particularly in immunosuppressed patients [5]. Although there is no clinically identifiable immunosuppression during

pregnancy, there is, however, an ‘immune tolerant state’ caused by a down-regulation of immune mechanisms during which opportunistic infections may occur [6].

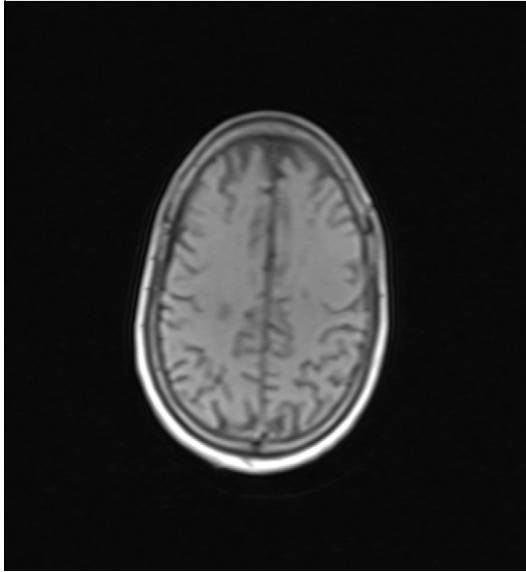
The diagnosis of TBM continues to be difficult as suggestive clinical features occur with widely variable frequencies. Fever, headache and meningeal signs as cardinal features are seen in 60–95%, 50–80% and 19–80% of cases, respectively, while focal neurologic deficits occur in 5–20% of cases [7,8]. In immunosuppressed individuals, the classic triad of headache, fever and neck stiffness is present in only 15% of cases, while headache and fever are simultaneously seen in only 60% of cases [8]. It is important to note that diagnosis in pregnancy may even be more challenging as the complaints may initially be ascribed to non-specific symptoms associated with preg-

\* Address: Department of Medicine, Jos University Teaching Hospital, Lamingo Dam Road, Jos East, Plateau State, Nigeria. Tel.: +234 802 840 2227.

E-mail address: [ejijisa@yahoo.com](mailto:ejijisa@yahoo.com) (I. Samson Ejiji).

2212-5531/\$ - see front matter © 2013 Asian-African Society for Mycobacteriology. All rights reserved.

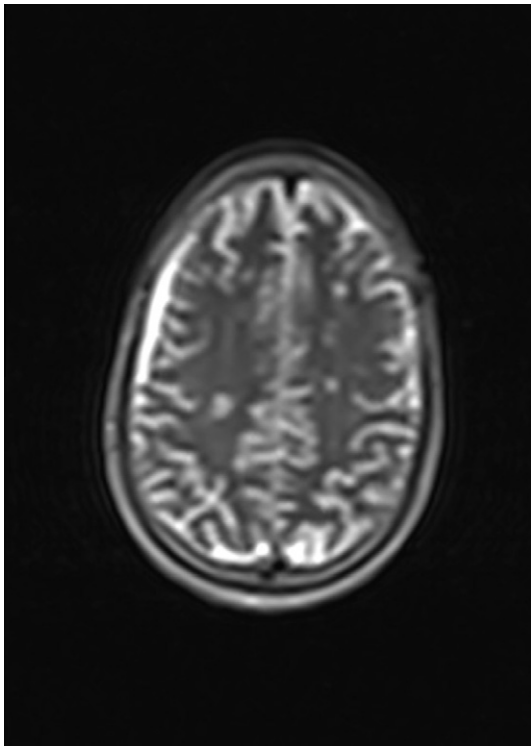
<http://dx.doi.org/10.1016/j.ijmyco.2013.01.003>



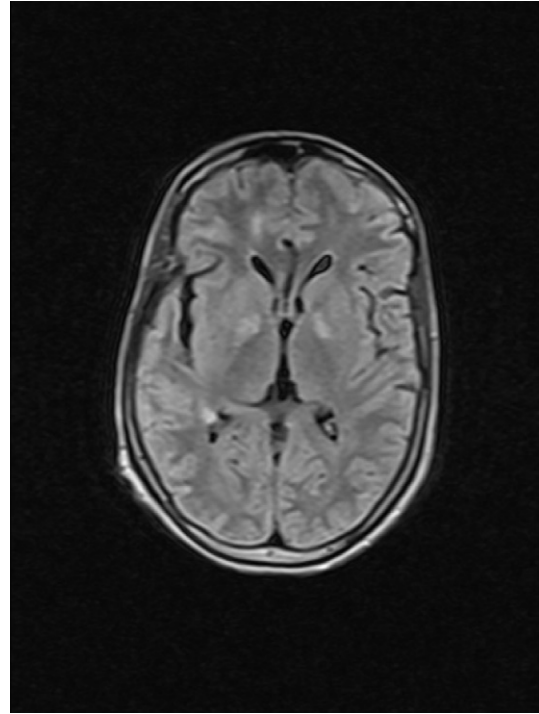
**Fig. 1 – T1W multiple fairly oval areas of low signal intensity.**

nancy, and weight loss associated with TBM may be temporarily masked by the normal weight gain in pregnancy.

Although the consensus case definition and scoring system [9] which utilizes clinical, laboratory and imaging parameters may be useful for diagnosis with about 95% sensitivity and 81% specificity, clinical features and cerebrospinal fluid (CSF) abnormalities alone usually determine the initiation of



**Fig. 2 – T2W images showing multiple fairly oval hyperintense lesions on both cerebral hemispheres at a level above the ventricles.**



**Fig. 3 – Post-contrast T1W image showing enhancing lesions in the right basal ganglia and left internal capsule.**

empirical treatment in routine clinical practice [10]. This report highlights the case of a pregnant HIV-negative woman with a three-month history of insidious headaches and fevers. She presented acutely at the gynaecology emergency unit because of features suggestive of urinary tract infection, and subsequently lost consciousness with associated focal neurological deficits. Early suspicion of TBM and institution of empirical anti-tuberculous therapy led to demonstrable improvement in her clinical state and the maintenance of fetal viability.

### Case report

A 38-year-old housewife gravida-6 Para 5<sup>+0</sup> (5 alive) with estimated gestational age at presentation of 27 weeks was brought to the gynaecological emergency unit with a three-month history of persistent throbbing frontal headaches associated with low grade fever. No history of neck stiffness, seizures, irrational speech, cough, weight loss and drenching night sweats or close contact with a known tuberculosis case. There was also a history of frequent passage of loose stools and dysuria associated with loin pain which began about 3 days prior to presentation. Her current and past obstetrical and gynaecological history was unremarkable and she was never diagnosed with TB in the past. She has not been on any regular medication other than multivitamins for her pregnancy, but admitted using short courses of medications dispensed over the counter and sometimes prescribed at some health facilities since she became ill. She does not smoke cigarettes, drink alcohol or use recreational drugs.

On examination she was found to be febrile with an axillary temperature of 38 °C, mildly pale, grade 2 digital clubbing, no significant lymphadenopathy and mild pitting ankle oedema bilaterally. Her pulse rate was 112 beats/min and blood pressure was 116/70 mmHg. She was conscious but lethargic and there were no signs of meningeal irritation or focal neurological deficit. Her respiratory rate was 30 cycles/min with vesicular breath sounds in all lung fields on auscultation. Abdominal examination revealed a full abdomen without areas of tenderness, organomegaly or ascites. She had a symphysis-fundal height of 26 cm and normal fetal heart sounds. The clinical diagnosis at presentation was urinary tract infection to rule out malaria, and samples were collected for investigations while the patient was commenced empirically on intramuscular Artemether and intravenous Augmentin.

On the third day of admission, the patient's conscious level rapidly deteriorated to a Glasgow Coma Score of 6/15 (E<sub>2</sub>M<sub>3</sub>V<sub>1</sub>). She had also developed anisocoria, peri-orbital oedema with conjunctival suffusion, and signs of meningeal irritation. The patient was only able to move her left upper and lower limbs in response to painful stimuli. A clinical diagnosis of tuberculous meningitis with right-sided spastic hemiplegia was made and the patient was commenced on daily fixed dose combination of first line antituberculous therapy according to the national treatment guidelines: 600 mg Rifampicin, 300 mg Isoniazid, 1.2 g Pyrazinamide and 800 mg Ethambutol plus 50 mg pyridoxine and 0.4 mg/kg body weight/day dexamethasone which was tapered weekly.

The results of investigations revealed a negative HIV test, full blood count (FBC) showed leukocytosis of  $33 \times 10^6/\mu\text{L}$  with relative lymphocytosis of 66%, hematocrit of 25%, platelet counts of  $230 \times 10^6/\mu\text{L}$  with blood picture showing polychromasia, ovalocytosis, burr cells, reactive lymphocytes and left shift with neutrophilic toxic granulations. Her CD4+ count was 1715/ $\mu\text{L}$  while the electrolytes, urea and liver function results remained normal on repeated sampling.

The cerebrospinal fluid (CSF) had an opening pressure of 300 mm of water. The sample was clear and colorless. The CSF protein was 1.1 g/L and glucose was 2.1 mmol/L while the concurrent random blood glucose was 5.9 mmol/l. The CSF white and red cell counts were <5 cells/ $\mu\text{L}$ . Direct gram stain for bacteria and Ziehl-Neelsen stain for Acid Fast Bacilli (AFB) showed no organisms, and Indian ink stain for cryptococcal species revealed no encapsulated organisms. The CSF culture for bacteria yielded no growth after 48 h. Blood cultures were negative for any growth after 1st, 2nd and 3rd sub-culture on MacConkey, chocolate and sabouraud agar. There was no abnormality in the urine m/c/s, and the Rheumatoid factor and VDRL tests were both negative. Abdominal ultrasonography showed no abnormality with a normal singleton active fetus at 26 weeks gestational age with adequate liquor, and normal kidneys and urinary tract. Brain MRI revealed multiple fairly oval areas of low signal intensity on T1 W (Fig. 1) and high signal intensity on T2 W (Fig. 2) of varying sizes in the region of the basal ganglia, frontal lobes and parietal lobes while the post contrast image (Fig. 3) showed enhancing lesions in the left basal ganglia and the left internal capsule. However, the ventricles and basal cisterns are within normal limits.

Clinical improvement was observed with her temperature dropping to normal by the tenth day, gradual but full recovery of consciousness by the twentieth day and 4/5 power restored in the right limbs by the fortieth day of anti-tuberculous therapy. The patient's condition continued to improve despite the appearance of right-sided III and VII cranial nerve palsies that became obvious at the time of this report.

## Discussion

While pregnancy has not been demonstrated to be a risk factor for tuberculosis, advancement of infection may be facilitated by the down-regulated Th1 lymphocyte surveillance that might contribute to an overall decline in immune function [11,12]. Therefore, frequent and consecutive pregnancies, as was the case in this multi-gravida may promote reactivation of latent tuberculosis.

The diagnostic challenge of TBM may be accentuated in pregnancy as initial symptoms are usually constitutional and can easily be dismissed as due to pregnancy. The mean duration of presentation to hospital after onset of symptoms among unselected Nigerian patients is 3.7 weeks and neurological signs become apparent a few days to weeks after onset of symptoms [13]. This pregnant patient presented to us about 3 months after the onset of illness and developed abnormal neurology shortly afterwards. She apparently had ineffective intermittent treatments for her symptoms at several health posts and was thought to have either a urinary tract infection or malaria when she presented to our hospital.

In addition to the clinical features, the patient's laboratory and imaging results met the consensus case definition and scoring system [9] for TBM. Although she presented acutely with symptoms suggestive of a UTI accompanied by a left shift and neutrophil toxic granulation on blood film, the urine was sterile and without pyuria. Whether the acute event was an intercurrent UTI or due to tuberculosis dissemination may be difficult to disentangle, more so that she had already taken antibiotics before urine and blood samples were sent to the laboratory.

The patient's FBC result revealed a relative lymphocytosis of 66% and hematocrit of 25% in keeping with TBM. Although anaemia is associated with pregnancy in resource-limited settings, it also indicates poor general health, and it is frequently described in neurological diseases [14]. This patient also had a CSF protein of about three times the upper limit of normal at 1.1 g/l and a low CSF glucose at 2.1 mmol/l which was less than two-thirds of the blood glucose, but she did not have CSF pleocytosis as would be expected in TBM. The combination of CSF findings typical of TBM including pleocytosis (>5 cells/ $\mu\text{L}$ ), increased protein levels (>45 mg/dL), and low glucose levels (<45 mg/dL) are not always seen [15], as was the case in this patient. Although the sighting of AFB in the CSF allows for definite diagnosis and early initiation of therapy, AFBs were isolated in only 5-30% of Nigerian patients, and therefore not surprising that this patient's CSF was negative on the Ziehl-Neelsen stain of CSF sediment [13].

The radiologic findings commonly seen in TBM are hydrocephalus and basal contrast enhancing exudates which occur in about 40% of adults [16]. Cerebral infarct is seen in only

about 20% [16] of patients and result from a necrotising pan-arteritis with secondary thrombosis and vessel occlusion involving the small and medium-sized vessels in the brain. This patient had infarcts; the largest was at the basal ganglia and is in keeping with the occlusion of the small lenticulostriate arteries at the base of the brain. In direct contrast to a CSF pressure of 300 mm of H<sub>2</sub>O in this patient, there were no MRI findings consistent with tuberculomas or other space occupying lesions which may cause raised intracranial pressure.

In conclusion, the relationship between ‘immune tolerant state’ of pregnancy and TBM requires exploration, and a high index of suspicion for TBM even in those without obvious immunosuppression should be maintained by clinicians. In addition, early administration of anti-tuberculous drugs can improve patient outcome such that empirical therapy must not be delayed in severely sick patients who may present with atypical features of TBM.

### Acknowledgments

We wish to thank the obstetricians who invited us to manage the patient. We also wish to thank the Radiologist, Dr. Charles Ani who assisted with the interpretation of the MRI scan and the Clinical Microbiology Team’s interest in investigating the patient.

### REFERENCES

- [1] World Health Organization, Stop TB partnership 2009 tuberculosis, Women and TB WHO. <[www.stoptb.org/assets/documents/resources/factsheets/womenandtb.pdf](http://www.stoptb.org/assets/documents/resources/factsheets/womenandtb.pdf)>, 2009. (downloaded 08.12.12).
- [2] O.M. Ige, O.M. Sogaolu, O.A. Ogunlade, Pattern of presentation of TB and hospital prevalence of TB and HIV co-infection at UCH, Ibadan: a review of 5 years, *Afr. J. Med. Sci.* 34 (2005) 329–333.
- [3] G.E. Erhabor, O.O. Adewole, O. Ogunlade, A 5 year review of tuberculosis mortality amongst hospitalized patients in Ile-Ife, *Indian J. Chest Dis. Allied Sci.* 48 (2006) 253–256.
- [4] V.C. Cheng, P.C. Woo, S.K. Lau, et al, Peripartum tuberculosis as a form of immunorestitution disease, *Eur. J. Clin. Microbiol. Infect. Dis.* 22 (2003) 313–317.
- [5] G.E. Thwaites, B.N. Duc, D.N. Huy, et al, The influence of HIV infection on clinical presentation, response to treatment and outcome in adults with tuberculosis meningitis, *J. Infect. Dis.* 192 (2005) 2134–2141.
- [6] M.A. LaGatta, C. Jordan, W. Khan, et al, Isolated pulmonary cryptococcosis in pregnancy, *Obstet. Gynecol.* 92 (1998) 682–684.
- [7] T. Guy, F. Martin, H. Cheryl, et al, British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children, *JIF* 59 (2009) 167–187.
- [8] G.C. Mariana, E.V. Jose, V.H. Adrian, et al, Tuberculous meningitis in HIV-infected patients in Brazil: clinical and laboratory characteristics and factors associated with mortality, *IJID* 14 (2010) e586–e591.
- [9] S. Marais, G. Thwaites, J.F. Schoeman, et al, Tuberculous meningitis: a uniform case definition for use in clinical research, *Lancet Infect. Dis.* 10 (2010) 803–812.
- [10] G.E. Thwaites, T.T. Chau, K. Stepniewska, et al, Diagnosis of adult tuberculous meningitis by use of clinical and laboratory feature, *Lancet* 360 (2002) 1287–1292.
- [11] O.M. Petrucco, R.F. Seamark, K. Holmes, et al, Changes in lymphocyte function during pregnancy, *Br. J. Obstet. Gynaecol.* 83 (1976) 245–250.
- [12] S. Vaquer, A. de la Hera, J. Jorda, et al, Diminished natural killer activity in pregnancy: modulation by interleukin 2 and interferon gamma, *Scand. J. Immunol.* 26 (1987) 691–698.
- [13] B.O. Osuntokun, Tuberculous meningitis in Nigerians: a study of 194 patients, *Trop. Geogr. Med.* 23 (1971) 225–231.
- [14] J.G. Hakim, I.T. Gangaidzo, R.S. Heyderman, et al, Impact of HIV infection on meningitis in Harare, Zimbabwe: a prospective study of 406 predominantly adult patients, *AIDS* 14 (2000) 1401–1407.
- [15] D. Cecchini, J. Ambrosioni, C. Brezzo, et al, Tuberculous meningitis in HIV-infected and non-infected patients: comparison of cerebrospinal fluid findings, *Int. J. Tuberc. Lung Dis.* 13 (2009) 269–271.
- [16] S.B. Koh, B.J. Kim, M.H. Park, et al, Clinical and laboratory characteristics of cerebral infarction in tuberculous meningitis: a comparative study, *J. Clin. Neurosci.* 14 (2007) 1073e7.