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A Rare Case of Tuberculosis Meningitis in Immunocompromised Patient on Rituximab.

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Summary

A 66-year-old patient of Asian background from the US was admitted with confusion and behavioral changes for the last 10 days. The patient was on rituximab for RA. He had a normal CT head and blood tests showed hyponatremia, acute kidney injury. CSF showed a raised protein and considerably high lymphocyte count. Mycobacteria tuberculous was isolated from one of her sputum cultures after having several negative sputum cultures, and consequently, the patient was treated for tuberculous meningitis. During admission, he had worsening of GCS, and he was admitted to ITU where he developed acute ischaemic stroke. He was treated for acute infarct and Tb meningitis and was discharged on anti-tuberculous medications. It was a unique presentation in an immunocompromised patient with sudden deterioration and confusion, however, without neck stiffness or typical meningitis features. His condition was improved with the commencement of the anti-tuberculosis therapy and was discharged from the hospital, and the patient traveled back to the US following discharge. While his stay, he was started on anti-tuberculous therapy early on due to high suspicion. The positive sputum culture was reported only after he had traveled back to the US and the same was conveyed to the patient's GP in the US.

Background

Tuberculosis meningitis is an uncommon presentation and can vary from changes in behavior to neurological symptoms, including photophobia, headache, neck stiffness, limb weakness. It is relatively more common in patients who are immunocompromised, HIV patients, and patients from high risk such as TB. One-third of the world's population is infected with latent Tb, and these individuals carry only a 10% risk of developing the active disease in their lifetime. TB is a leading cause of death in HIV patients with resulting mortality of about 15% to 40% or 1-2 in 5 cases (up to date).

Tuberculosis meningitis patients usually present with typical symptoms, including headache, neck stiffness, and fever, with onset weeks to months, before the onset, although typical meningeal signs may be absent initially. Some patients may present with very low GCS <10, while other patients may have neurological features such as cranial nerve palsies, hemiparesis, paraparesis, and seizures.

Early diagnosis is crucial, and in case of high suspicion of tuberculosis meningitis, the treatment needs to be commenced on anti TB therapy immediately as the outcomes are significantly influenced by the stage of tuberculosis meningitis when treatment was commenced.

Case Presentation

A 66-year-old patient of Asian origin who has been living in the US for the last few decades, traveled to the UK to see her family. The patient was on Rituximab for Rheumatoid Arthritis and also has had type 2 diabetes, ischaemic heart disease, and hypothyroidism. She presented with confusion and behavioral changes for the last 10 days. Physical examination was unremarkable besides a low GCS of 14/15. Additionally, the blood results were normal except for slightly elevated CRP 7, Creatinine 113, urea 9.4 and notably low Na level of 115, and CRP was increased to 71 during admission. A CT head was normal, but his lumbar puncture showed Protein > 2.0, glucose 1.4, WCC 22.3 with 80% lymphocytes and 20% polymorphs.

Consequently, he was started on IV antibiotics as per microbiology advice. An MRI head showed a small vessels disease and mild brain atrophy. On 3rd day of his admission, he developed left-sided weakness, and a repeat CT head showed an ischaemic infarct of the right basal ganglia, and accordingly, he was transferred to ITU due to further deterioration of GCS. He was intubated and an NG tube was inserted. A CT thorax illustrated tree bud appearance in lungs consistent with bronchiolitis or TB and a CT venogram showed a small area of established infarct involving right periventricular coronal radiate. An echocardiogram was unremarkable.

The sputum cultures revealed candida Albicans, however, the blood cultures were negative. As a result, he was commenced on the anti-tuberculosis therapy and Dexamethasone with regards to her high risk

of Tb meningitis and was also commenced on high dose aspirin for ischaemic infarct. He also developed swallowing issues initially because of stroke, for which he was seen by speech and language therapists. Subsequently, he was also started on thickened fluids, an NG tube was also removed.

Investigations

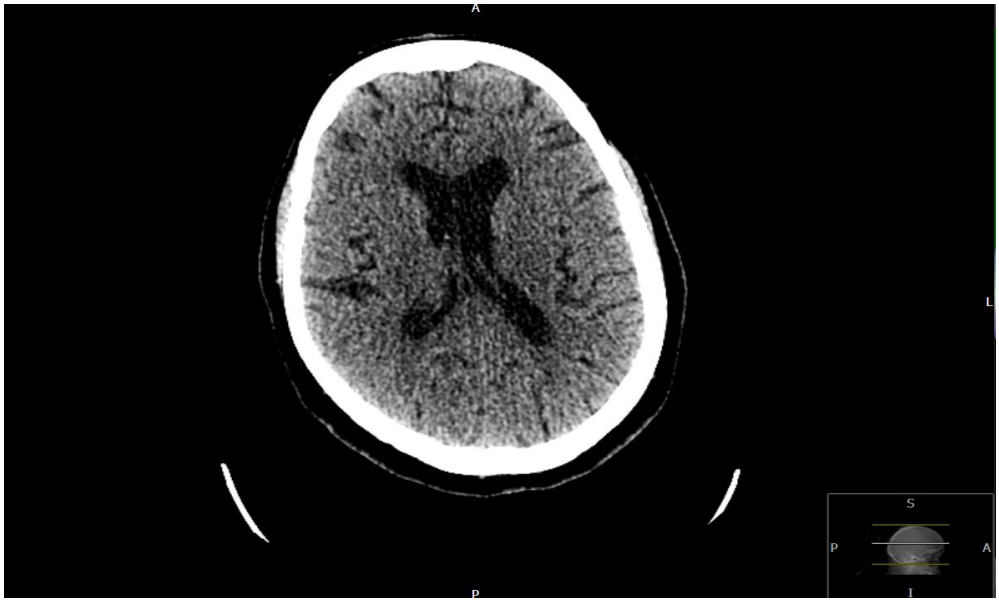

Figure 1. CT head on admission. Small vessels disease only.

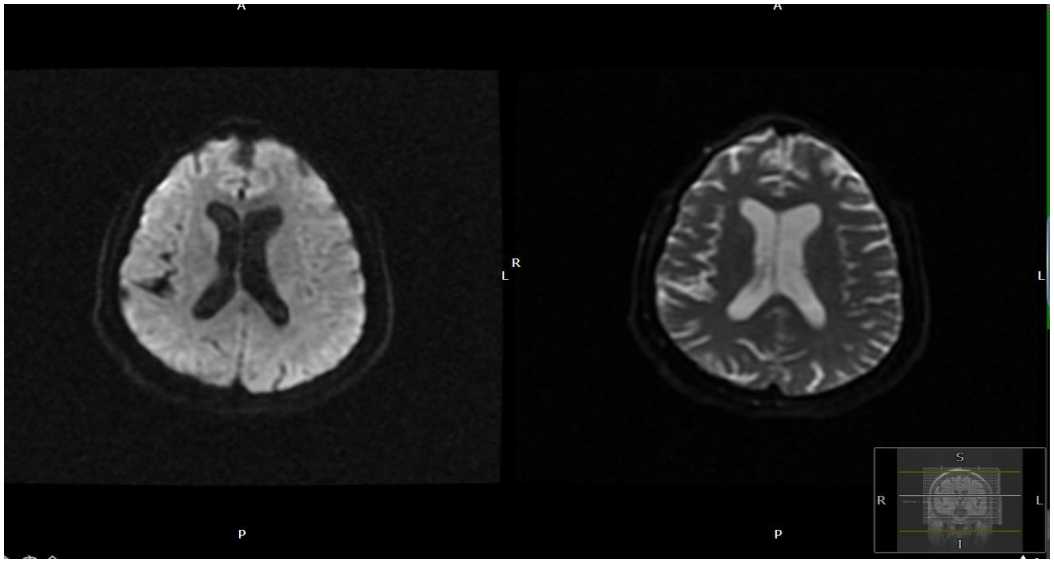

Figure 2. MRI head 2 days after admission. Small vessels disease only, No tuberculoma.

Figure 3. CT head on day 3. Patient developed right basal ganglion infarct.

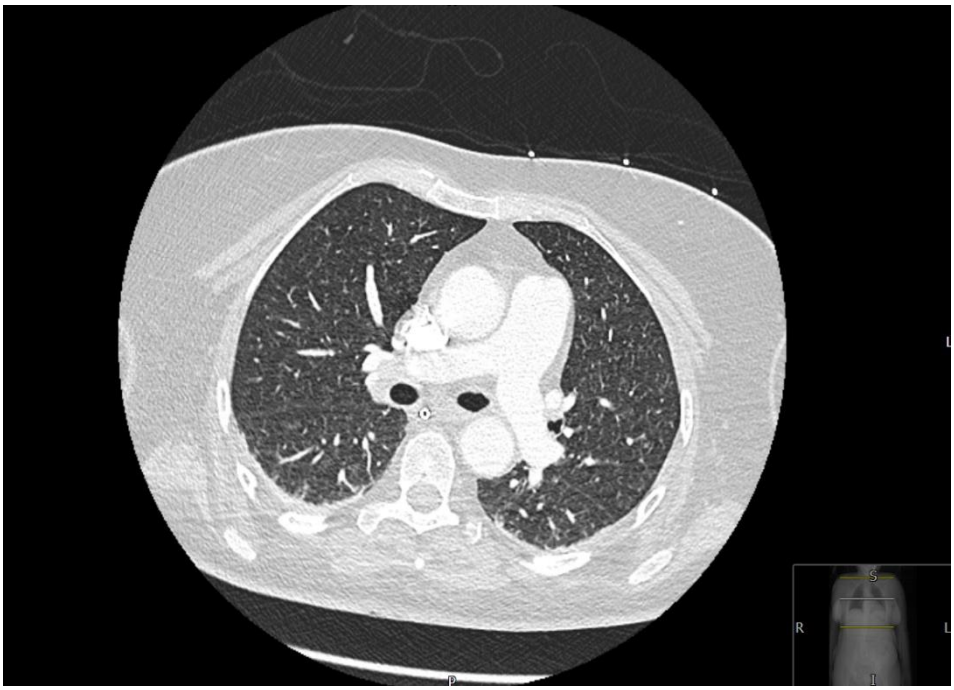

Figure 4. CT CAP during admission to ITU suggesting possible bronchiolitis/TB

Table 01. CSF results.

CSF Results	Value
CSF total protein	* >2.00 g/L (0.15 - 0.45)
WCC	22.3
CSF glucose	1.4 mmol/L
RBC	4
Adenosine Deaminase	7.7 IU/L (0.0 - 6.0)
Percentage Polymorphs	20
Percentage Lymphocytes	80

CSF Microbiology	Value
Gram stain	No organisms seen
Herpes Simplex Virus	Not detected
VZV virus	Not detected
Retrovirus	Not detected

Table 02. Blood results

Bloods	01/06/2019	05/06/2019	24/06/2019
CRP	07	71	06
WCC	8.0	10.2	4.8
Neutrophils	6.32	9.51	3.77
Urea	9.4	13.4	10.7
Creatinine	113	135	75
Sodium	115	127	136
Potassium	3.7	4.3	3.9
Hb	120	110	102

Differential Diagnosis

1. Tuberculosis meningitis
2. Viral meningitis

3. Intracranial bleed
4. Encephalitis
5. Infection/Sepsis
6. Confusion secondary to Hyponatraemia
7. Cerebral salt losing syndrome

Treatment

Initially, the patient was treated for meningitis with antibiotics, including Ceftriaxone, Acyclovir and Amoxicillin as advised by microbiology. Despite the treatment, he had a sudden onset left-sided weakness on day 3 and his GCS was 9/15. A CT head revealed right basal ganglia infarct and was started on Aspirin 300 mg OD accordingly. All blood cultures and sputum cultures were negative except two sputum samples which demonstrated candida Albicans and mycobacterium tuberculosis respectively. He has also commenced on Dexamethasone 8 mg OD on tapering dose along with Rifater (Rifampicin, Isoniazid, and Pyrazinamide) and Ethambutol. The patient had a 21-day course of anti-tuberculosis therapy at the time of discharge and was advised to continue the treatment. He also had physiotherapy and was also seen by speech and language therapists for swallowing difficulty during admission. His GCS was improved to 15/15 at the time of discharge.

In conclusion, this 66-year-old patient presented with low GCS and confusion had significant hyponatremia on admission with acute kidney injury and CSF samples were suggestive of tuberculosis meningitis and had a positive sputum culture after several negative cultures.

Outcome and Follow-Up

Unfortunately, it was not possible to follow up with this patient due to his overseas residence, however, it was confirmed from family members and next of kin that patient was doing well and was getting better.

Discussion

Most TB meningitis cases are noted in Southeast Asia, the Western Pacific and African regions.

The most common presenting features include headache, fever, neck stiffness, and the duration of symptoms onset can vary from days to months. TBM Patients usually present with low GCS in areas with poor resources and symptoms such as cranial nerve palsies, hemiparesis, paraparesis and seizures

should raise the possibility of TBM in patients, whereas some patients present with multiple cranial nerve palsies with the most involved cranial nerves being cranial nerves 3, 6 and 7.

We were not able to find any reported cases of tuberculosis meningitis in patients on rituximab despite an extensive search. There are few cases of Tb meningitis, however, reported in patients on adalimumab and infliximab. A case report authored by Cristina Castro Marquez et al on a patient 53 years old who was diagnosed with Crohn's disease, for which he was initially on Azathioprine and then commenced on Infliximab for repeated flare-ups, and subsequently commenced on Adalimumab after having surgery due to emergency admission. The patient then presented a month and a half after with a frontoparietal headache, constitutional symptoms including nausea, fever and vomiting and CT head confirmed dilated right ventricle. A subsequent MRI head showed dilated left ventricle and the patient was diagnosed with hydrocephalus. As a result, a ventriculoparietal shun was inserted, which was changed to a ventriculoatrial shunt. The patient had a positive Mantoux test and was treated with Pyrazinamide, rifampicin and Ethambutol. Our patient presentation was different as compared to this patient as our patient presented with confusion and behavioral changes, and our patient was on rituximab for several years for RA.

Zumrut Sahbudak Bal et al, 2017 reported a 13-year-old juvenile with idiopathic arthritis treated with methotrexate and steroids initially, then switched to steroids and Adalimumab, and was then switched over abatercept as he did not respond to the above treatments. He was then treated for pneumonia and pleural effusions followed by further admission for abdominal pain and subsequently underwent appendectomy. Intestinal lymph nodes biopsies showed granulomatous tissues and possible differentials including Crohn's disease and tuberculosis lymphadenitis. The patient became agitated on the 2nd of admission and an MR Head and MR venogram showed basilar meningeal contrast enhancement and contrast-enhanced nodular lesions. CSF samples showed high protein, high glucose contents and cells were mainly lymphocytes (90%). Both CSF and sputum samples were negative for Tb, however, ADA levels were raised, and he was commenced on anti-Tb therapy. He was admitted to intensive care on the day after developing refractory status epilepticus and right-sided hemiplegia and required mechanical ventilation. Intestinal lymph nodes revealed granulomatous inflammation with caseation and LP was repeated and CSF showed high protein, glucose and lymphocytes but was negative for Tb again. He was commenced on anti-Tb therapy and 06 weeks after admission, CSF analysis Mycobacterium tuberculosis which was susceptible to all anti-Tb drugs. The patient, unfortunately, passed away 21 days after admission to ITU despite appropriate anti-Tb therapy. It’s important to mention that anti-Tb therapy in this patient was commenced on day 10 whereas our patient was commenced on anti-Tb therapy early on during admission which could be a reason for a better outcome in our patient. Our patient also developed weakness and a decline in GCS and CT venogram confirmed an infarct in our patient also which is likely due to vasculitis in patients with tuberculous meningitis.

Youn Ho Kim et al, 2007 reported a case of tuberculous meningitis in patients on infliximab for Crohn's disease. The article is unfortunately not fully accessible to gain full details of the presentation of the patient. The presentation of Tb meningitis may vary however it should always be considered in patients on biologics or immunosuppressants as delay in initiation of treatment in these patients can prove fatal. The overall outcome is better if anti-Tb therapy is initiated early on, and the prognosis is poor with delay in treatment.

Hyponatremia is common in patients with Tb meningitis, and it was reported to be present in 44% of patients in a study reported by Usha K Misra et al 2016 and classified into three severe categories (<120mEq/L), moderate (120-129mEq/L), or mild (130-134mEq/L). Our patient had severe hyponatremia with a sodium level of 113. The two most common causes of hyponatremia in TBM patients were cerebral salt wasting and syndrome of inappropriate anti-diuretic hormone secretion (SIADH) and cerebral salt wasting was the more common of the two and was related to the severity of TBM.

In conclusion, Tuberculosis meningitis is rare, however, it can present in high-risk patients and patients with an immigrant background from certain regions and early initiation of treatment is of paramount importance in these patients as the disease can prove fatal. The use of glucocorticoids is recommended early in the disease onset and these patients are at high risk of strokes due to vasculitis.

Learning Points/Take Home Messages

- Any patient presenting with confusion and low GCS, we should always keep tuberculosis meningitis in our differentials.
- Commencement of early treatment in tuberculosis meningitis leads to better outcome.
- Mortality is significantly high in tuberculosis meningitis with rates between 15% to 40% and very high in HIV positive patients
- We should always consider tuberculosis meningitis in patients presenting with meningeal symptoms, including altered behaviour that are from high-risk areas or immunosuppressed.
- Steroids and anti-tuberculosis therapy should be commenced early in these patients.
- Consider MRI brain and CT CAP in these patients in order to look for brain tuberculoma and pulmonary TB, and LP should be done in these patients.
- Tuberculosis meningitis patients may present differently, and presentation varies from patients to patients and time of onset of symptoms may vary from days to weeks to months.
- Treatment should be continued for at least 7 to 10 months in tuberculosis meningitis and up to 18 months in presence of intracerebral tuberculoma.

Patient's Perspective

I am so grateful to God for my mom's miracles recovery. My mom had received excellent care in hospital when she fell ill during her visit to the UK. The Hospital staff kept us informed throughout her recovery process and provided her undivided attention along with support throughout her stay in ICU and then general ward. The only concerning issue I felt that could have been addressed in a better was her initial visit to the ER with the symptoms of vomiting and unconsciousness, where the amount of time it took to establish her diagnosis could be shortened if only the procedures expedited because of her age and history of health. Nevertheless, I am also very thankful to doctors especially Dr. Zahid Khan and many others in ICU including the nursing staff for their support.

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