A case of Clival Tuberculosis and associated meningitis

William Peter Flynn, Yevedzo Ntuli, Henry Zhang, Simon Tiberi *

Division of Infection, Royal London Hospital, Barts Health NHS Trust, London, United Kingdom

ARTICLE INFO

Keywords:
Mycobacterium tuberculosis
Clivus
Intracranial
Meningitis
Vasculitis

ABSTRACT

Herein we report a 30-year-old man presenting with fevers, headaches and weight loss. On admission he was disorientated and demonstrated no focal signs of neurological deficit. Magnetic resonance imaging revealed a large area of abnormal bone marrow signal centred within the clivus with extension into the sphenoid sinus and signs of associated basal meningitis. A sphenoid sinus biopsy was performed and proved non diagnostic. The patient was treated empirically with antitubercular therapy (ATT). Lumbar puncture provided cerebrospinal fluid from which Mycobacterium tuberculosis (MTB) was isolated 35 days later. His clinical course was complicated by development of communicating hydrocephalus requiring placement of a ventriculoperitoneal shunt and addition of thalidomide. The patient was discharged following a ten-week admission with complete resolution of symptoms and remains well two years later.

1. Introduction

Although the overall incidence of tuberculosis in the UK is falling [1], it should remain an important differential for a wide range of presentations in those with previous residence in endemic regions, workers, refugees, previous history of incarceration and those who are immunosuppressed. Extra pulmonary manifestations of MTB occurred in 59% of infections in the UK in 2019 including 5.1% of infections involving the skeleton and 2.1% involving the meninges [1]. Skeletal MTB usually affects the spine and large joints due to the rich vascular supply of the vertebrae and long bone growth plates [2]. This case report describes a rare manifestation of tuberculous clival osteomyelitis that was found in association with tuberculous meningitis. In addition to reporting a rare case of clival Tuberculosis, this report highlights the difficulty that can be encountered in definitively diagnosing intracranial MTB and thus the importance of maintaining a high index of suspicion to facilitate early initiation of treatment and secure a better outcome.

2. Case

A 30-year-old male banker presented initially presented to his general practitioner reporting a three day history of fevers. In the absence of any localising symptoms or signs, he was prescribed oseltamivir for a suspected influenza infection. Six days later he presented to hospital with a subacute history of confusion and having lost the ability to speak English, his second language. He had not developed vomiting, neck stiffness or photophobia. He had also experienced an insidious onset of frontal headaches in the preceding month, and 12 kg of weight loss in the past four months. He did not report any history of a cough or any shortness of breath. He had moved to the UK from South Asia one year prior to presentation and had no known MTB contacts. He had previously been fit and well, taking no medications and having no history of smoking, alcohol excess or recreational drug use. On examination he appeared systemically unwell. He was pyrexial (38.9°C), tachycardic (105 bpm), and normotensive (130/65 mmHg). His respiratory rate (20 bpm) and oxygen saturation (100%) was normal on room air. He was agitated, disorientated and unable to follow commands with a GCS of 13. This made ophthalmoscopic examination of the fundii and complete neurological examination difficult. However, he moved both limbs normally, there were no obvious cranial nerve palsies. Oral examination was unremarkable with no visible inflammation of the oropharynx. Auscultation of the chest was unremarkable and there was no clubbing of the digits, rashes or cutaneous lesions.

Admission blood tests found a white cell count of 4.5 \times 10^9/L with a neutrophil count of 3.3 \times 10^9/L and lymphocyte count of 0.8 \times 10^9/L. C-reactive protein was raised at 74 mg/L. Serum markers of liver and renal function were normal. Blood-borne virus screen negative. Serum adjusted calcium was normal, and screening serum for Lyme disease and autoantibodies against ANAs, PR3, MPO, Sm, and NMDA, was negative. Blood cultures found no bacterial growth. He denied respiratory symptoms and there was no sputum produced for investigation. Initial computed tomography (CT) of the head was unremarkable. Analysis of...
Fig. 1. Sagittal T1 TIRM MRI Head. Depicts abnormal low T1 signal in the clivus and pathological tissue stranding the prepontine cistern.
Fig. 2. Transverse T2 TIRM MRI Head. Demonstrating a large abnormality centred on the clivus extending into the sphenoid sinus.
white cell count of 18 × 10^9/L, a low glucose of 0.8 mmol/L (serum 5.4 mmol/L) and a raised protein of 1672 mg/dl. CSF smear was negative for acid-fast bacilli (AFB), TB-PCR and bacterial growth at 48 h. After these initial tests he was admitted under the infectious disease team for further investigation and treatment of suspected tuberculous meningitis.

CT of the chest, abdomen and pelvis was performed to search for sites of granulomatous, lymphoproliferative or malignant disease. Calcified mesenteric, mediastinal and hilar lymph nodes were found in keeping with previous granulomatous disease but there was no evidence of active infection. In the absence of pulmonary symptoms, signs or radiological findings of active infection, bronchoscopy with bronchoalveolar lavage was not performed. Magnetic resonance imaging (MRI) of the brain revealed a region of abnormal marrow signal (MRI) of the brain revealed a region of abnormal marrow signal affecting the osseous basiphenoïd-basiocipital clivus (Fig. 1) with extension into the petrous apices and the sphenoid sinus where there was also evidence of chronic mucosal inflammatory change (Fig. 2). This was associated with basal meningitis of the retro-clival dura and basal pontine leptomeninges. Perineural enhancement was apparent bilaterally in the oculomotor, trigeminal and abducens nerves (Fig. 3) although no cranial nerve palsies were elicited clinically.

A young man presenting subacutely with headaches, fevers and weight loss with previous residence in a TB endemic region is a classical presentation for tuberculous meningitis on the 17th of June. He was started on intravenous (IV) rifampicin 600 mg OD (later increased to 1200 mg due to low drug levels), IV isoniazid 300 mg, IV levofloxacin 500 mg BD, oral pyrazinamide 2 g OD and IV dexamethasone 0.3 mg/kg/day. The patient improved clinically, with return to full cognition and ability to speak English. Following four weeks of treatment the patient developed auditory and visual hallucinations and became confused. Repeat MRI of the head found more widespread leptomeningeal enhancement now involving cranial nerves II, III, V, VII/VIII with perivascular enhancement of anterior cerebral, middle cerebral and basilar arteries. Early signs of a communicating hydrocephalus could also be seen. Repeat lumbar puncture on the 22nd of July revealed CSF with a rising protein count, low glucose and a raised white cell count of predominantly neutrophils and was culture negative for standard microbiology, mycology and mycobacterial culture, immunophenotyping of the CSF showed a mixed population of cells, no sign of lymphoproliferative disease and no CD4-CD8 inversion to suggest neurosarcoidosis. These findings and the clinical picture were in keeping with the development of paradoxical reaction reaction to ATT which can complicate a third of MTB meningitis cases [3]. This was managed with unlicensed repurposed thalidomide 100 mg BD, increasing doses of steroids, and aspirin to treat any MTB associated cerebral vasculitis [4]. One week after this worsening episode the patient developed vomiting and seizures, and a CT head demonstrated worsening communicating hydrocephalus. Neurosurgical input was sought and a ventriculoperitoneal shunt was inserted on the 6th of August, further biopsies and cultures were taken which were negative for Mycobacterium tuberculosis. Following this he began to improve steadily, with no further headaches, vomiting or seizures. Levofloxacin as considered potentially epileptogenic was swapped with linezolid 600 mg OD but later re-added, given rifampicin therapy can reduce linezolid levels, therapeutic drug monitoring was performed after 14 days and then monthly thereafter and linezolid was reduced to 600 mg OD given adequate levels. From the 26th of September thalidomide was weaned by 50 mg every 3 days until cessation, while steroids were continued, and weaned gradually till month 5.

The patient made a full recovery with complete resolution of symptoms following a ten week-long hospital stay and has since made a good recovery. A repeat MRI brain has been reported significant resolution in the basal cistern enhancement, residual enhancement along the posterior aspect of the clivus but no narrow abnormality in the clivus and he successfully completed a year and a half of TB therapy which was comprised of a prolonged intensive phase with isoniazid, rifampicin, pyrazinamide, levofloxacin and linezolid for 4 months (he developed initial signs of peripheral neuropathy and elevated uric acid at month 4 for which linezolid and pyrazinamide were stopped) followed by isoniazid, rifampicin and levofloxacin for an additional 13 months). The patient resumed work 4 months after admission and now at 24 months he patient continues to remain well and has started reducing the dose of his levetiracetam.
Fig. 4. Endoscopic images of sphenoid sinuses. Images taken following take-down of the intersphenoid septum. A yellowish, friable lesion was found in the inferior left sphenoid sinus which was tethered to the septum. (ICA - Internal Carotid Artery).
therapeutic drug monitoring. We describe the successful management of MTB; intensifying treatment with IV ATT; high dose steroids and definitive diagnosis is commonly encountered in cases of MTB CNS reaction and cerebral vasculitis using unlicensed medications aspirin complications of intracranial MTB including suspected ATT paradoxical [9]. The difficulty experienced by the treating team in obtaining a subsequently died due to infectious vasculitis causing basal ganglia infarcts and thalamic or inflammatory? Pediatr Neurosurg 2018;53(4):280–1. https://doi.org/10.1055/s-0036-1588032.
[9] Sagar P. Tubercular osteomyelitis of the clivus. Tr-ENT 2018;28(1):44–7. https://doi.org/10.5606/Tr-ENT.2018.49932.
[10] Tiberi S, Payen MC, Manika K, et al. Clinical cases in tuberculosis. Eur Respir Monogr 2018;82:446–60.

3. Patients perspective

“I have found myself very fortunate that I have been treated in England for this uncommon problem. Sincere thanks to all the doctors and nurses who have given me right treatment and made me well and fit. I feel very proud to share that I am now medically fit and fine and have not experienced any issue or symptoms again. Thank you once again for everything and saving my life.”

4. Discussion

Tuberculosis of the clivus and skull base is very rare even in endemic regions, and usually occurs as extension of cranio-vertebral junction (CVJ) infection [5]. Extensive literature review found six cases of clival tuberculosis without involvement of the CVJ [7–12]. Patients were typically immunocompetent young adults presenting with 1–3 months duration of headaches or facial pain, diplopia and weight loss in the absence of respiratory symptoms. Five of the six were found to have lateral rectus palsies on admission. One patient had clinical and radiological evidence of associated meningitis. Imaging revealed involvement of the sphenoid sinuses in three cases [6,7,9] and nasopharyngeal extension [6,9] in two of these cases. In all cases lesions were biopsied, and histological examination found epithelioid and giant cells typical of granulomatous infection, however in only 1 case were AFB identified [11]. Typically empirical ATT led to full recovery. One patient developed meningitis and hydrocephalus similarly to our case and subsequently died due to infectious vasculitis causing basal ganglia infarcts [9]. The difficulty experienced by the treating team in obtaining a definitive diagnosis is commonly encountered in cases of MTB CNS infection [12]. A prolonged period of diagnostic uncertainty caused a significant amount of anxiety for the patient and his family. A positive outcome resulted from empirical ATT based on a high index of suspicion of MTB; intensifying treatment with IV ATT; high dose steroids and therapeutic drug monitoring. We describe the successful management of complications of intracranial MTB including suspected ATT paradoxical reaction and cerebral vasculitis using unlicensed medications aspirin and thalidomide in the setting of steroid refractory disease; and neuro-surgical control of hydrocephalus with VP shunt insertion.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Tuberculosis in England 2019 report: presenting data to end of 2018. Public Health England 2019. URL: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/821334/Tuberculosis_in_England_annual_report_2019.pdf (accessed 1st October 2019).
[2] Pigrau-Serrallach C, Rodríguez-Pardó D. Bone and joint tuberculosis. Eur Spine J 2013;22(4):556–66. https://doi.org/10.1007/s00586-012-2331-y.
[3] Singh AK, Malhotra HS, Garg RK, Jain A, Kumar N, Kohli N, et al. Paradoxical reaction in tuberculosis meningitis: presentation, predictors and impact on prognosis. BMC Infect Dis 2016;16(1). https://doi.org/10.1186/s12879-016-1625-9.
[4] Mai NTH, Dobbs N, Phu TH, Thuong NTT, et al. A randomised double blind placebo controlled phase 2 trial of adjunctive aspirin for tuberculosis meningitis in HIV-uninfected adults. Elife 2018;7. https://doi.org/10.7554/eLife.33478.
[5] Nayak B, Patnaik S, Sahoo PK, Biswal D. Cranio-cervical junction tuberculosis: Usual pathology at an unusual site. Surg Neurol Int 2015;6(1):115. https://doi.org/10.4103/2152-7806.159835.
[6] Shenoy SN, Raja A. Tuberculous granuloma of the sphenoid-clival region. Neurol India 2004;52(1):129–30.
[7] Bhavanam HS, Rajesh A, Uppin MS. Tubercular osteomyelitis of sphenoid-clival region presenting with lateral rectus palsy. Neurol India 2014;62:198–200. https://doi.org/10.4103/0028-3886.132400.
[8] Joshi V, Valsangkar S, Valsangkar A, Dehke A, Nivargi S, Agrawal A. Tuberculosis of the Clivus. JNS 2017;06(01):072–5. https://doi.org/10.4103/jnns.jnns_1588032.
[9] Sagar P. Tubercular osteomyelitis of the clivus. Tr-ENT 2018;28(1):44–7. https://doi.org/10.5606/Tr-ENT.2018.49932.
[10] Shashidar A, Bharath R, Rao M, Arivazhagan A. Clival lesion in a young girl: neoplastic or inflammatory? Pediatr Neurosurg 2018;53(4):280–1. https://doi.org/10.1159/000489011.
[11] Selvapandian S, Chandy MJ. Tuberculous granuloma of the clivus. Br J Neurosurg 1993;7(5):581–2.
[12] Tiberi S, Poyen MC, Manika K, et al. Clinical cases in tuberculosis. Eur Respir Monogr 2018;82:446–60.

Table 1

| Clival Tuberculosis cases | Gender | Age | Presenting symptoms | Diagnosis | Treatment | Outcome |
|--------------------------|--------|-----|---------------------|-----------|-----------|---------|
| Bhavanam HS et al. [7]   | Male   | 20  | Headache, emesis, fever, diplopia, 6th cranial nerve palsy | Histological, caseating necrosis with well-formed granulomas, TB culture negative. | Resection of clival lesion and 18 months of standard anti TB medications | Full recovery |
| Joshi V et al. [8]       | Male   | 40  | Right-sided trigeminal neuralgia | Histological, epithelioid histolytic granulomas showing central caseation necrosis. TB culture not available. | Right retrosigmoid craniotomy and near-total resection of the lesion. Standard TB treatment | Full recovery |
| Sagar P. et al. [9]      | Female | 24  | Headache and diplopia | Histology suggestive of Tuberculosis | Nasopharyngeal biopsy. Standard TB treatment | Full recovery |
| Shahidhara, et al. [10]  | Female | 13  | Diplopia | Clinico-radiological suspicion, lesion improved on anti-Tuberculous medication given for 18 months. | Lesion improved on anti TB medications (18 months course), planned transphenoidal biopsy not performed. | Patient succumbed, basal ganglia and thalamic infarcts and respiratory arrest. |
| Selvapandian S et al. [11]| Male   | 53  | Headache, vomiting and cranial nerve involvement | Biopsy of lesion was culture positive with Mycobacterium tuberculosis | Limited excision biopsy and standard anti TB medications | Full recovery |
| Tiberi S, et al. [12]    | Male   | 28  | Right-sided facial tumefaction and TMJ involvement | TB culture grew fully-sensitive Mycobacterium tuberculosis | Limited excision biopsy and standard anti TB medications for 12 months | Full recovery but had a paradoxical reaction. |