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Case Report

Disseminated tuberculosis masquerading as Tolosa-Hunt syndrome in initial presentation: A case report with literature review ☆,☆☆

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ABSTRACT

Tolosa-Hunt syndrome (THS) is a painful ophthalmoplegia due to non-specific granulomatous inflammation in the cavernous sinus region. It is diagnosed by the International Classification of Headache Disorders (ICHD)-3 criteria. We report the case of a young lady who presented with a right-sided headache for 2 weeks, followed by right-sided diplopia for 4 days. Clinical examination revealed right trochlear nerve palsy. Magnetic resonance imaging (MRI) of her brain showed abnormal thickening and postcontrast enhancement of the right orbital apex and superior orbital fissure, suggesting THS. Examination of cerebrospinal fluid (CSF) ruled out intracranial infection. The initial presentation satisfied the ICHD-3 criteria. Further imaging revealed cervical, axillary, and intra-abdominal lymphadenopathy with granulomatous lesions in the spleen and right kidney. Ultrasound (US)-guided axillary lymph node biopsy was positive for *Mycobacterium tuberculosis*. QuantiFERON TB gold plus test from serum was positive. Based on radiological and histopathological findings, a diagnosis of disseminated tuberculosis involving lymph nodes, kidneys, spleen, and lungs was made. THS is a diagnosis of exclusion. This case signifies that patients diagnosed with THS based on ICHD-3 criteria should be extensively evaluated to rule out granulomatous infections such as tuberculosis. Typical THS symptoms with granulomatous inflammation can give false reassurance to clinicians and prevent investigation for more dangerous etiologies. As painful ophthalmoplegia can arise secondary to a myriad of pathologies, diagnostic workups for all possibilities should be exhausted before arriving at a diagnosis of THS. Regardless of MRI findings, workups for tuberculosis and fungal infections should be completed.

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Introduction

Tolosa-Hunt syndrome (THS) is a painful ophthalmoplegia characterized by episodes of orbital pain associated with paralysis of one or more of the extra-ocular cranial nerves [1]. The most typical clinical manifestations of THS are unilateral orbital pain and ipsilateral third nerve palsy [2]. It is recognized as a rare disorder by the National Organization for Rare Disorders and as one of the painful cranial neuropathies by the International Headache Society. It was first described in 1954 by Dr. Eduardo Tolosa, a Spanish neurosurgeon [1]. The exact cause of THS is unknown and is thought to be from non-specific inflammation in the cavernous sinus region or superior orbital fissure. The annual global estimated incidence is one case per million per year [1]. A retrospective study from Qatar showed that the incidence of THS over 5 years from 2015 to 2020 was 31 cases [2]. International Headache Society has proposed diagnostic criteria for THS, with high sensitivity (95%-100%) but low specificity (approximately 50%). The criteria include unilateral headache, granulomatous inflammation of the cavernous sinus, superior orbital fissure or orbit (on MRI or biopsy), and ipsilateral III, IV, or VI cranial nerve palsies. Ophthalmoplegia should have occurred within 2 weeks of the onset of the headache, which should be localized around the ipsilateral eye [3]. THS is mostly unilateral (bilateral in 5% of cases), occurs equally in men and women, and has no age predisposition [4]. Though there is no established auto-immune etiology for THS, it has been reported as the presenting complaint of some systemic auto-immune inflammatory conditions such as systemic lupus erythematosus [5], sarcoidosis [6], and Wegener's granulomatosis [7]. Only one out of 31, THS patients analyzed in Qatar had a history of an auto-immune disease [2]. There is no proven association of THS with any infectious agent. A literature search showed one reported case of THS in a patient with latent tuberculosis [8]. We report the case of a young lady who presented with a right-sided headache and diplopia. Magnetic resonance imaging (MRI) evaluation of her brain showed abnormal thickening and postcontrast enhancement of the right orbital apex and superior orbital fissure, suggestive of THS. Examination of cerebrospinal fluid (CSF) ruled out intracranial infection. Initial presentation satisfied the International Classification of Headache Disorders (ICHD)-3 diagnostic criteria [3] for THS. Further imaging revealed cervical, axillary, and intra-abdominal lymphadenopathy with granulomatous lesions in spleen and right kidney. Ultrasound (US)-guided biopsy of axillary lymph node was positive for *Mycobacterium tuberculosis*. THS is a diagnosis of exclusion. This case signifies that patients diagnosed as THS based on ICHD-3 criteria should be extensively evaluated to rule out granulomatous infections such as tuberculosis.

Case report

A 39-year-old lady of Philipino nationality presented to our emergency department with a 4-day history of double vision, which worsened on looking toward her right side. It was present with both eyes open and left eye closed but absent when the right eye was closed. She reported associated 2-week history of right-sided frontal and peri-orbital headaches. There was no history of fever, chills, headache, photophobia, dysphagia, neck pain, or vomiting. There was no significant medical or surgical history, medications, allergies, sick contacts, and similar illness in friends or family. Clinical examination showed normal visual acuity and intraocular pressure in both eyes. The sclera, conjunctiva, cornea, anterior chamber, iris, lens, and fundus were bilaterally normal. The pupil was equal, round, and reactive on both sides, with no afferent pupillary defect. Examination of extraocular muscles (EOMs) showed limited adduction and depression of the right eye with inferior oblique overaction. Left EOMs were normal. The rest of the neurological examination and other systemic examinations were normal except for multiple matted lymph nodes of size approximately 1 cm in the left axilla. Her blood works, including complete blood count, comprehensive metabolic panel, and C-reactive protein, were unremarkable. Autoimmune workup such as anti-nuclear antibodies (ANA), antineutrophil cytoplasmic antibodies, C3, C4, rheumatoid factor, anti-double-stranded DNA, and other extractable nuclear antigen antibodies Panel were negative. Thyroid function test and vitamin B12 levels were normal. An initial non-contrast CT head showed no abnormalities. CSF analysis showed no white or red cells, normal protein and glucose, negative viral panel, cryptococcal antigen, bacterial, TB, and fungal cultures. An MRI brain with an MR angiogram of the head and neck was done for further evaluation, which showed abnormal thickening and postcontrast enhancement of the right orbital apex and superior orbital fissure with possible extension to the anterior aspect of the right cavernous sinus (Fig. 1). Major intracranial and neck arteries were normal without any vessel wall enhancement. Enlarged bilateral cervical lymph nodes were incidentally noted, with the largest one in the right upper jugular region measuring 25 × 8 mm. PAN CT scan done for evaluation of lymphadenopathy showed multiple enlarged necrotic lymph nodes in the left axilla, few prominent necrotic lymph nodes in the porta hepatis, bilateral posterior basal mosaic attenuation of the lungs, multiple small hypodense foci in the spleen suggestive of granulomas, multifocal hypo enhancing and hypoattenuating areas involving the right kidney and mild circumferential wall thickening of the infrarenal abdominal aorta (Fig. 2). US-guided core needle biopsy of the left axillary lymph node showed necrotizing granulomatous lymphadenitis with positive TB PCR. TB smear and PCR from sputum were negative. QuantiFERON TB gold plus test from serum was positive. Based on radiological and histopathological findings, a diagnosis of disseminated tuberculosis involving lymph nodes, kidneys, spleen, and lungs was made. She was immediately started on oral steroids (prednisolone 1 mg/kg/ day) with first-line anti-TB medications (Rifampicin, Isoniazid, Pyrazinamide, and ethambutol with pyridoxine). The prednisolone dose was gradually tapered (10 mg weekly) over the next 6 weeks. At the 6-week follow-up, the diplopia and headache had completely resolved. Clinical examination showed full power of EOMs of the right eye. Axillary and cervical lymphadenopathy could not be appreciated. TB culture from the lymph node grew *M. tuberculosis* fully sensitive to first-line agents. Anti TB regimen was shifted to maintenance therapy (Isoniazid, Rifampicin,

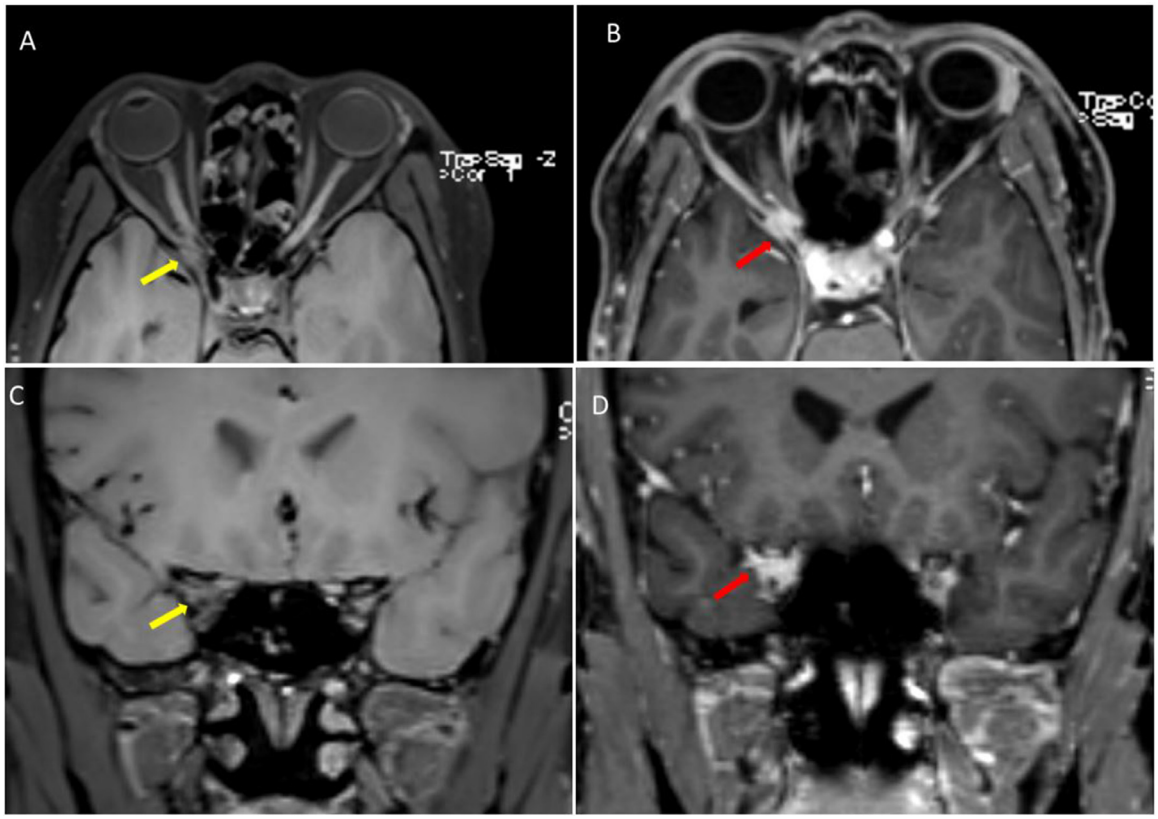

Fig. 1 – MRA Head [(A) T1 axial, (B) T1 axial postcontrast, (C) coronal T1, and (D) coronal T1 postcontrast] showing abnormal thickening (yellow arrows), and postcontrast enhancement (red arrows) in the right orbital apex, with possible extension to the anterior aspect of the right cavernous sinus.

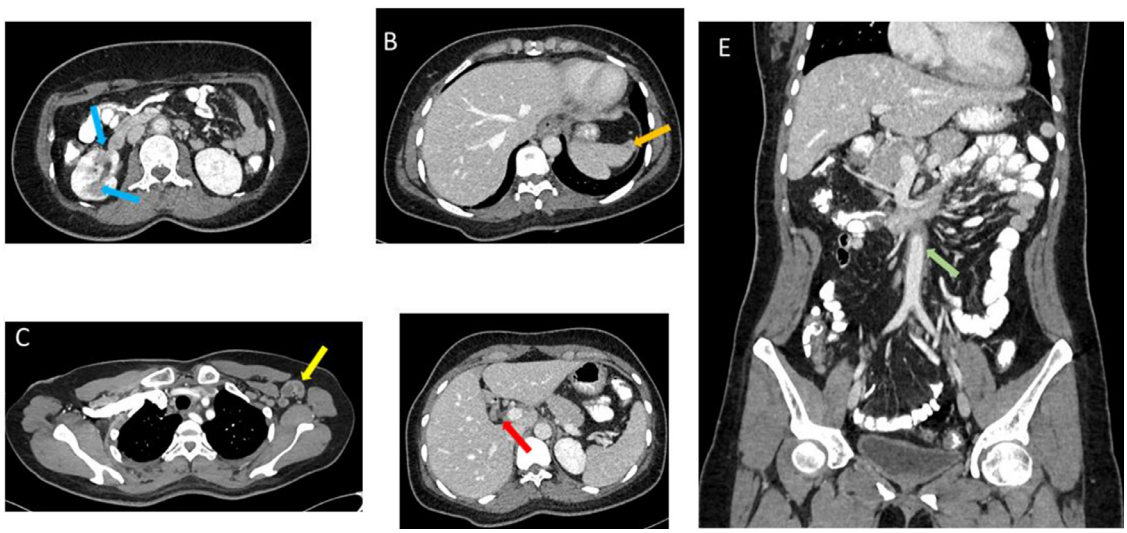

Fig. 2 – CT abdomen and pelvis with intravenous contrast (A-D) axial, and (E) coronal reformatted images showing multifocal hypo enhancing areas involving the right kidney (blue arrows), slight parenchymal heterogenicity with tiny hypodense foci in the spleen (orange arrow), mild circumferential wall thickening of the infrarenal abdominal aorta (green arrow), multiple enlarged necrotic lymph nodes in the left axilla (yellow arrow), and few prominent necrotic portal hepatis lymph nodes (red arrow).

and Pyridoxine) after 8 weeks. A follow-up PAN CT after 4 months of treatment showed near-total resolution of all previously noted lesions and lymphadenopathy.

Discussion

THS is unilateral orbital pain associated with paresis of third, fourth, or sixth cranial nerves caused by granulomatous inflammation in the cavernous sinus, superior orbital fissure, or orbit. Diagnosis is made by the ICHD-3 diagnostic criteria [3]:

A. Unilateral headache fulfilling criterion C
B. Both of the following:
   1. granulomatous inflammation of the cavernous sinus, superior orbital fissure, or orbit, demonstrated by MRI or biopsy
   2. paresis of one or more of the ipsilateral third, fourth, or sixth cranial nerves
C. Evidence of causation demonstrated by both of the following:
   1. headache has preceded paresis of the third, fourth, or sixth nerves by 2 weeks or developed with it
   2. headache is localized around the ipsilateral brow and eye
D. Not better accounted for by another ICHD-3 diagnosis [3].

Our patient was diagnosed with definite THS based on the above criteria. Some reported cases of THS also involved the ophthalmic branch of the trigeminal nerve, optic, facial or auditory nerves. Sympathetic innervation of the pupil is occasionally affected [3]; however, it was spared in our patient. In some biopsied cases, THS is caused by granulomatous material in the cavernous sinus, superior orbital fissure, or orbit. Biopsy of the cavernous sinus is a sophisticated procedure that an experienced neurosurgeon can only perform, and often risks outweigh the benefit, limiting its utility for diagnosis [9]. No cavernous sinus biopsy was done on our patient; however, MRI suggested granulomatous thickening in these areas. There was no evidence of other causes of painful ophthalmoplegia, such as tumors, vasculitis, basal meningitis, sarcoid, or diabetes mellitus. A normal CSF examination and lack of radiological features of meningoencephalitis ruled out CNS infection in our patient.

Before the ICHD-3 criteria were established, granuloma on imaging or biopsy was not essential to diagnose THS. According to La Mantia et al. [10], 50% of THS patients had no evidence of granuloma and were classified as benign THS. Those with granulomas on imaging or biopsy were grouped as inflammatory THS [10]. Demographics from Qatar showed that 20 out of 31 cases were inflammatory THS, and 85% satisfied the ICHD-3 criteria. MRI brain with contrast helps exclude other disease processes that produce painful ophthalmoplegia. Classical MRI finding in THS is the thickening of the cavernous sinus because of abnormal soft tissue, which is isointense on T1, iso or hypointense on T2, and enhances with contrast [1]. Similar findings were seen in our patient (Fig. 1). When there is suspicion of THS on clinical presentation and MRI, blood and CSF studies should be performed to rule out other causes of painful ophthalmoplegia [1]. In a retrospective cohort of THS patients from Qatar, the commonest symptoms were visual disturbance (96%), headache (80.6%), partial third nerve palsy (54.8%), sixth and fourth cranial nerve palsy (54.8% and 25.8%), complete third nerve palsy (16.1%) and trigeminal (V1) nerve involvement (12.9%). All the patients had normal CSF analysis, and the median C-reactive protein was 1.75 mg/L [2]. MRI-confirmed granulomatous inflammation in the cavernous sinus region can cause THS-like symptoms in patients with other pathologies of neoplastic or infectious origin [9].

Glucocorticoids are the mainstay in the treatment of THS [11]. There are no clear guidelines regarding the effective dose, route, and duration of steroid therapy in THS [11]. Orbital pain has been proven to improve quickly with glucocorticoids, but there is no clear evidence regarding cranial nerve palsies [12]. Most studies recommend starting with oral prednisolone 80 mg to 100 mg (or 1 mg/kg) for the first 3 days to 1 week, followed by a gradual taper over the next 6 weeks [13,14]. Most patients who present with painful ophthalmoplegia may not have THS. Painful ophthalmoplegia is due to a mass effect in the cavernous sinus, which many other pathologies can cause. These pathologies can also respond favorably to corticosteroid therapy, leading to misdiagnosis. THS is ultimately a diagnosis of exclusion [9]. There are reports of cases that presented like definite THS with MRI findings fulfilling ICHD-3 criteria but were later attributed to different pathologies, such as lymphoma [15] and cryopyrin-associated periodic fever [16]. Mandrioli et al. [17] reported an infectious etiology that presented and was initially diagnosed as THS. A middle-aged man presented with left-sided retro-orbital pain and sixth nerve palsy; MRI revealed a lesion in the cavernous sinus. After 4 months of corticosteroid therapy, the patient had no response clinically or radiologically. Biopsy revealed actinomycetes colonies, and the patient responded to antibiotic therapy [17].

Conclusion

THS is a diagnosis of exclusion. This case signifies that patients diagnosed with THS based on ICHD-3 criteria should be extensively evaluated to rule out granulomatous infections such as tuberculosis. Typical THS symptoms with granulomatous inflammation can give false reassurance to clinicians and prevent investigation for more dangerous etiologies. As painful ophthalmoplegia can arise secondary to a myriad of pathologies, diagnostic workups for all possibilities should be exhausted before arriving at a diagnosis of THS. Regardless of MRI findings, workups for tuberculosis and fungal infections should be completed.

Data availability

Data supporting the conclusions of the study are all available free of cost through open access journals and websites.

Statement of ethics

The manuscript of this case report was approved by Institutional Review Board (IRB), Medical Research Centre (IRB) of Hamad Medical Corporation. Approval number: MRC-04-22-663.

Patient consent

A written, and informed consent was obtained from the patient for publication of his case information and images and is available with the corresponding author. This consent can be provided on request from the journal editor.

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