Case Report

Concurrent Tuberculoma of Medulla Oblongata and Tuberculosis of Bone Marrow: A First Case Report and Literature Review

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The authors reported a first case of concurrent tuberculoma of medulla oblongata and tuberculosis of bone marrow. The patient presented with vertigo, vomiting, and headache for two months. Magnetic resonance imaging (MRI) showed irregular ring enhancing lesion at medulla and magnetic resonance spectroscopy (MRS) showed increased lipid peak in central area of lesion. The patient's diagnosis was tuberculoma. In addition, bone marrow biopsy was done because of leukocytosis and thrombocytosis. The pathological results showed granulomatous inflammation and positive polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* complex. The patient was treated with anti-tuberculous drugs for 18 months, and MRI follow-up revealed disappearance of the lesions, including clinical improvement.

Keywords: Tuberculoma, Tuberculosis, Medulla oblongata, Bone marrow

J Med Assoc Thai 2019;102(2):222-6
Website: http://www.jmatonline.com

Tuberculosis is more commonly found in developing countries. Tuberculosis of the central nervous system (CNS) is a life-threatening condition and occurs in about 5% to 10% of extrapulmonary tuberculosis cases[1]. The most common clinical manifestation is tuberculous meningitis[2]. Moreover, tuberculoma and tuberculous abscess are also presented. Brainstem tuberculoma is difficult to diagnose and biopsy may risk developing complications[3]. Meanwhile, tuberculosis of bone marrow is the most common diagnosis by bone marrow examinations for fever of unknown origin[4]. To the best of the authors' knowledge, this is the first case report of patient who had tuberculoma of medulla oblongata and concurrent with tuberculosis of bone marrow.

Case Report

A 48-year-old male presented with vertigo, nausea, vomiting, and headache for two months. He was afebrile. There was no history of contact with tuberculosis. His symptoms progressed and he developed right hemianesthesia, dysphagia, and hoarseness of voice. The examination revealed that he was fully conscious and could orientate to time, place, and person. The left side gag reflex was impaired suggesting glossopharyngeal and vagus nerve palsies. Other cranial nerves examinations remained intact including the hypoglossal examination. No motor weakness was detected. The right side of the face, arm, body, and leg had decrease pinprick sensation suggesting trigeminothalamic and spinothalamic tracts involvement. The otolaryngologist found that the left true vocal cord paralysis was due to central pathology from the flexible laryngoscopy. The clinical diagnosis was brainstem lesion.

Computer tomography scan (CT) with contrast media showed a thick peripheral rim-enhancing lesion size of 1×0.8 cm at the left side of the medulla oblongata. He was treated with Ceftriaxone and Metronidazole as bacterial brain abscess at a provincial hospital for two weeks, but his symptoms and signs were not improved. All culture specimens' results were negative. Therefore, he was referred to the authors hospital. His Magnetic resonance imaging (MRI) showed irregular thickening ring enhancement of 1.3×1.3×1.2 cm in size at the left side of the medulla oblongata, which was larger than in the previous CT

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How to cite this article: Jiranukool J, Thiarawat P. Concurrent Tuberculoma of Medulla Oblongata and Tuberculosis of Bone Marrow: A First Case Report and Literature Review. J Med Assoc Thai 2019;102:222-6.

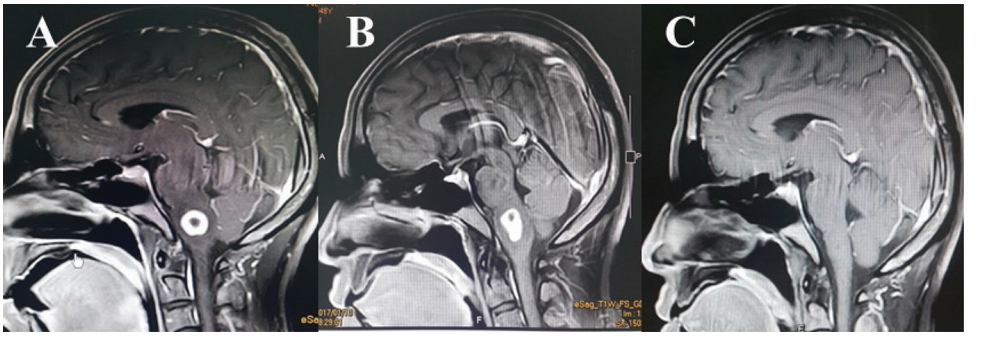

Figure 1. (A) T1-weight Gd-enhanced sagittal MRI showed lesion at medulla. (B) T1-weight Gd-enhanced sagittal MRI at 4 months showed enlargement of lesions. (C) T1-weight Gd-enhanced sagittal MRI after complete treatment showed disappearance of lesion.

(Figure 1A). The diffusion-weighted images (DWI) showed restricted diffusion, and magnetic resonance spectroscopy (MRS) showed increased lipid peak in central area of the lesion. The provisional diagnosis was tuberculoma. His complete blood counts showed leukocytosis (white blood cell [WBC] 27,430 cells/mcL) and thrombocytosis (platelets count 1,151,000 cells/mcL). Thus, bone marrow aspiration and biopsy were done. In addition, the serum JAK2 mutation and polymerase chain reaction (PCR) for BCR/ABL gene were positive. Hematologist diagnosed myeloproliferative neoplasm. However, the pathological results showed granulomatous inflammation and positive PCR for *Mycobacterium tuberculosis* complex. The patient was treated with corticosteroids (dexamethasone 16 mg/day) for cerebral edema and four anti-tuberculous drugs (rifampicin, isoniazid, pyrazinamide, and ethambutol). After two weeks of treatment, the symptoms improved, and he was discharged. Treatment was reduced to isoniazid and rifampicin after two months.

At the 4-month-follow-up, the MRI findings of the lesion were 2.1×1.7×1.3 cm, which showed an increased diameter, with perilesional vasogenic edema despite that his symptoms were improving (Figure 1B). Hoarseness of voice and dysphagia were resolved. Only the right arm and leg numbness remained. Therefore, the patient was continued on isoniazid and rifampicin. At the nine months follow-up, the brain MRI showed that the lesion decreased in size to 0.4×0.4×0.2 cm and there was no vasogenic edema. His MRI showed complete resolution at fourteenth months. Treatment was continued for 18 months (Figure 1C).

Discussion

M. tuberculosis is the cause of tuberculosis. The most common presentation is pulmonary tuberculosis. Tuberculosis is transmitted by droplets that contain *M. tuberculosis* through coughing or sneezing. The CNS tuberculosis primarily affects the lungs and spreads by lymphatic or hematogenous dissemination. However, chest radiography may be abnormal or normal[2]. Some cases have evidence of systemic tubercular infection[3]. The most common manifestation of CNS tuberculosis is tuberculous meningitis. Moreover, space occupying lesions (tuberculoma and tubercular abscess) and disseminated miliary lesions are also found[2,6].

Tuberculomas are found in about 7.6% to 9% of CNS tuberculosis depending on the country[7,8]. Currently, the incidences have probably increased due to more immune-compromised host. Tuberculomas are commonly found in the frontoparietal region and basal ganglia, but rarely found in cerebellar hemisphere and brainstem. For brainstem tuberculomas, Pons is the most common location[7]. Tuberculomas may occur with or without meningeal involvement. Multiple tuberculomas are more common than solitary lesion[7]. The clinical manifestation of tuberculoma is similar to other space occupying lesions[2,9].

The diagnosis of tuberculoma may be made relying on clinical, imaging features, response to treatment, and biopsy[2,3,8,9]. Cerebrospinal fluid (CSF) can be collected for examination. However, tuberculoma is less commonly found *Mycobacterium* both acid-fast bacilli (AFB) and culture, compare to tuberculous meningitis[2,9]. Sadashiva et al reported that CSF examination was of little aid in the diagnosis of brainstem tuberculoma[3]. The tuberculin skin test (TST) demonstrates prior *M. tuberculosis* exposure but does not necessarily indicate active disease[2]. The diagnostic utility is highly variable. Ten to 95% of CNS tuberculosis patients are TST positive[2,9,16]. The

patients from high prevalence areas are more likely to have positive tests with an unrelated illness[9,16]. In the present case, the authors decided not to perform the test because it was already suspected of tuberculoma from the MRI, and in high prevalence areas.

Non-contrast CT may show isodense, hyperdense, or mixed density. Contrast CT may show nodular, ring, or irregular heterogeneous enhancing lesions. However, it is difficult to distinguish tuberculoma from other causes of ring enhancing lesions, especially bacterial abscess, neoplasm, toxoplasmosis, or neurocysticercosis[2,9,17,18]. The characteristics of MRI findings depend on the stage of maturation but may be classified into three stages. First, tuberculoma with non-caseating granuloma shows iso-hypointense in T1 weighted image (T1WI), hyperintense in T2WI, and homogenous nodular contrast enhancement. Second, tuberculoma with caseating and solid center shows iso-hypointense in T1WI, hypointense in T2WI, and rim enhancement. T2 hypo-intensity is represented by dense cellularity of the central core of the tuberculoma. Third, tuberculoma with caseating with liquid center shows hypointense in T1WI, hyperintense in T2WI with a peripheral hypointense rim that represents collagenous capsule, and rim enhancement. A variable degree of vasogenic oedema may be presented in the three stages[2,3,10,18]. However, MRI features of tuberculoma may overlap others intracranial focal lesions, for example, neurocysticercosis, metastasis, lymphoma, and fungal infections[10,18]. The characteristic "target sign", an isointense region surrounded by a rim enhancement with central nidus of calcification, is recent and not a specific feature of tuberculoma, but is highly suggestive of tuberculoma[2,18]. DWI will exhibit restricted diffusion only tuberculoma in caseating with a liquid center. There is no restriction of DWI in caseating with a solid center[2,10,18]. On MRS, tuberculoma shows lipid peak at 0.9 and 1.3 ppm in hypointense T2WI. It is highly specific for tuberculoma[2,3,10,18,19]. In the authors' case, the MRI showed as tuberculoma with caseating liquid center.

PCR techniques assay is a new method for the diagnosis of tuberculosis, especially extrapulmonary tuberculosis. The problems of diagnosis of extra-pulmonary tuberculosis are paucibacillary nature of the specimens, lack of adequate clinical sample volume, including difficult to access. The main advantage of PCR test is their rapid turnaround time and reliability for an early detection[13,22]. In the authors' case, PCR result from bone marrow aspiration showed positive.

The main treatment of tuberculoma is anti-tuberculosis drugs. First line drugs consist of isoniazid, rifampicin, pyrazinamide, and either ethambutol or streptomycin. In case of multiple drug resistance (MDR), second-line drugs such as ethionamide, kanamycin, cycloserine, and para-amino-salicylic acid, should be considered for treatment[2,3,8,9]. Complete resolution of intracranial tuberculoma has been reported in 57% to 87% after treatment with anti-tuberculosis drugs[2,3,12]. The various reports may depend on the duration of treatment, drug resistance, and compliance. The duration of treatment ranges from 9 to 18 months or may be extended until radiographic resolution[2,3,6,8,9]. Mostly, the duration of treatment is four drugs (IRZE) for initial two months and two drugs (IR) for additional seven to 16 months[2,3,8,9]. Some report starts four drugs for the initial three to four months[6]. British Infection Society guideline recommended that first-line treatment regimen for all forms of CNS tuberculosis was two IRZE and ten IR, and patient should be treated for a minimum of 12 months[9]. Continuation of drugs beyond 18 months in tuberculoma patients that persist for two years or longer provides no additional benefit[14]. Paradoxical tuberculoma enlargement or development of the new tuberculoma during medical treatment may occur in up to 25%. These phenomena generally appear within three months after starting therapy. The most likely explanation is an interaction between the host's immune response and the direct effects of *Mycobacterium* products. The present patient was treated with an initial of two IRZE and additional 16 IR. The additional treatments are adjunctive steroids or surgery[14,20]. Corticosteroids are not routinely used but may improve outcome by modulating inflammation and reducing cerebral edema. The patients whose symptoms are not improved or are worsening after anti-tuberculosis therapy, may benefit from corticosteroids. The duration of corticosteroids ranges from two to six weeks or until the patients have clinical recovery[2,3,6,9]. The authors' patient received dexamethasone 16 mg/day for about one week only due to clinical improvement and reducing cerebral edema from MRI.

The surgical treatment of tuberculoma is performed in patients with increased intracranial pressure despite the medical treatment or the uncertain diagnosis. The brain biopsy can provide the definitive treatment. The alternative methods are a stereotactic biopsy or a surgical resection[2,3,8,9]. Previously, a stereotactic biopsy at the brainstem was a high-risk procedure, but those were small and outdated

series. A recent meta-analysis of Kickingereder et al involving 1,480 cases concluded that diagnostic success is 96.2% with a low rate of procedure-related complications[21], with an overall morbidity of 7.8%, permanent morbidity of 1.7%, and mortality of 0.9%. The stereotactic biopsy of lesions at the medulla oblongata is preferred to the transcerebellar approach. Moreover, Gurjar et al reported on the surgery of the large pontine tubercular abscess. The midline suboccipital craniotomy and the splitting of the lower part of the vermis through a floor of the fourth ventricle were performed, then intraoperative ultrasound was used to localize the thinnest part of the ventricular floor and abscess[6]. The authors did not perform a biopsy because the provisional diagnosis from the MRI was tuberculoma and the PCR tuberculosis from the bone marrow was positive.

Bone marrow is one of the involved sites in disseminated mycobacterial infections. The clinical diagnosis may present with fever of unknown origin. Other characteristic clinical presentations, such as miliary pattern, fibrocavitary, nodular or bronchiectatic lesions on the chest radiographs, and presence of lymphocytosis in pleural fluid or CSF may be found[4]. The mycobacterial bone marrow infection is diagnosed by histopathological demonstration of the granulomatous changes, AFB positive, PCR positive, and culture positive. However, the gold standard for diagnosis is a positive culture[4,15]. The main treatment is anti-tuberculosis drugs.

Conclusion

CNS tuberculoma rarely occurs at the medulla oblongata and is commonly due to disseminated hematogenous spread. Bone marrow is one of the involved sites in disseminated mycobacterial infection. The definite diagnosis of CNS tuberculoma is tissue culture and tissue biopsy. These could be safely done under stereotactic techniques. Biopsy is usually unnecessary if imaging findings suspected of tuberculoma or other sites show tuberculosis infection. Anti-tuberculosis drugs can be started early, and clinical response can be followed.

What is already known on this topic?

The gold standard of diagnosis of CNS tuberculoma is positive culture *M. tuberculosis*. However, biopsy cannot be performed in every case, especially those located in the medulla oblongata. The other methods for diagnosis are the imaging features and response to medications. Tuberculosis of bone marrow can be found in patient with fever of unknown origin and disseminated mycobacterial infection. The main treatment of tuberculosis is anti-tuberculosis drugs.

What this study adds?

This study reported the first case of concurrent tuberculoma at the medulla oblongata and tuberculosis of bone marrow. This study also reviewed and updated the diagnosis and treatment of tuberculoma at medulla oblongata.

Conflicts of interest

The authors declare no conflict of interest.

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