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Case Report

Radiological Follow-up of a Cerebral Tuberculoma with a Paradoxical Response Mimicking a Brain Tumor

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We report a case of a paradoxical response of a tuberculoma in the brain mimicking a brain tumor. A 76-year-old woman presented with a 2 week history of headache, dysarthia, and orthopnea. Brain magnetic resonance images (MRI) revealed two rim-enhancing lesions on the pons and occipital lobe, and chest computed tomography showed randomly distributed miliary nodules. The tentative diagnosis was tuberculosis (TB) of the brain and lung. She complained of right hemiparesis and worsening general weakness after taking the anti-TB medication. On the monthly follow-up images, the enhanced lesions were enlarged with increased perfusion and choline/creatinine ratio, suggesting a high grade glioma. A surgical resection was completed to diagnose the occipital lesion, and the tuberculoma was pathologically confirmed by a positive TB-polymerase chain reaction. The anti-TB medication was continued for 13 months. A follow-up MRI showed decreased size of the brain lesions associated with perilesional edema, and the clinical symptoms had improved. Brain tuberculoma could be aggravated mimicking brain malignancy during administration of anti-TB medication. This paradoxical response can be effectively managed by continuing the anti-TB drugs.

Key Words : Brain · Paradoxical · Tuberculoma · Tumor.

INTRODUCTION

Tuberculosis (TB) is common disease in developing and developed countries caused by various strains of mycobacteria, usually *Mycobacterium tuberculosis* (*M. tuberculosis*)[14]. Appropriate treatment before any neurologic deficits appear usually results in a good outcome. The most common initial infection site is the lung, but the brain can be infected by hematogenous transmission. TB meningitis and tuberculoma are the two most common forms of TB of the central nervous system. Tuberculoma of the brain can be solitary or multiple[18]. Surgical treatment is only recommended when medical therapy fails, decompression is necessary, or the diagnosis is uncertain[9,15].

Transient worsening, appearance of new symptoms, or radiological manifestations of TB can develop after initiating of anti-TB medication[4]. These paradoxical responses are not uncommon in human immunodeficiency virus-negative patients and have been observed in 6–30% of patients with a TB infection[6,7]. These episodes of paradoxical deterioration are commonly associated with extrapulmonary TB and the central nervous system is the most common location for this presentation. Our case of cerebral tuberculoma showed typical radiological findings of cerebral tuberculoma. However the lesion revealed indistinguishable radiological findings of a malignant intracranial tumor such as a high grade glioma after anti-TB treatment. We describe the radiological findings of the paradoxical response of a cerebral tuberculoma mimicking a malignant brain tumor.

CASE REPORT

A 76-year-old woman developed orthopnea. She underwent a chest computed tomography (CT), which showed minimal cardiac fluid collection with pleural effusion but without pleural enhancement or thickening. She underwent a thoracentesis. The pleural fluid was an exudate, with a white blood cell count of 907/mm^3 and 30% lymphocytes. The Quantiferon TB and immunoglobulin M for the Ebstein-Barr virus capsid antigen was positive. The adenosine deaminase level in the pleural fluid was 54.6 IU/L. The tentative diagnosis was TB or viral pericarditis. She refused anti-TB medication, and her symptoms im-

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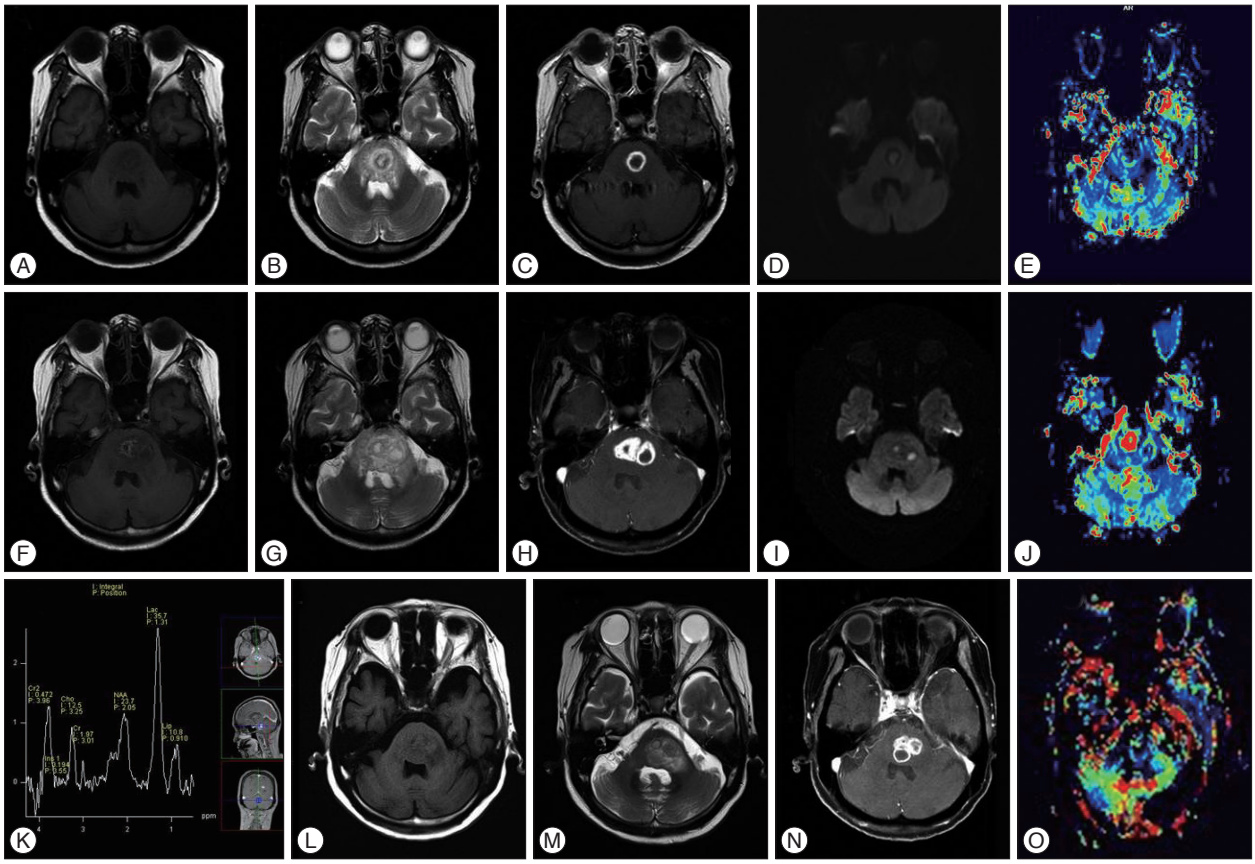

Fig. 1. Radiological findings. The lesions were hypointense on T1-weighted images, and iso-intense with a central hyper-signal on T2-weighted images associated with perilesional edema and rim-enhancement after contrast administration (A, B, and C). The diffusion images showed diffusion restriction in the central area but no increased cerebral blood volume on MR perfusion images (D and E). At the one month follow-up, the thickened peripheral enhanced lesion was enlarged and associated with aggravated perilesional edema (F, G, and H). The lesion showed increased perfusion and restricted diffusion (I and J). Magnetic resonance spectroscopy revealed an increased choline/creatine ratio of 6.35 and a lactate and lipid peak (K). The lesion decreased in size with less perilesional edema (L, M, and N), and perfusion decreased after 13 months (O).

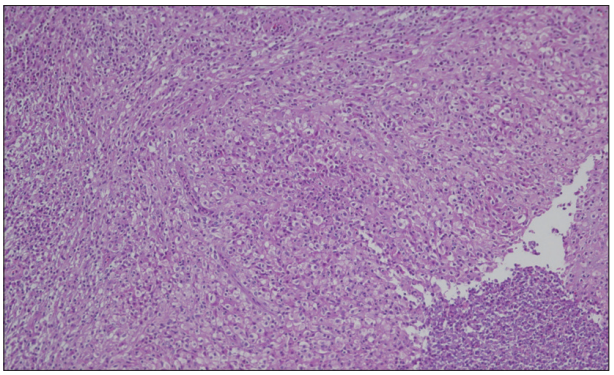

Fig. 2. Pathologic findings. The biopsy showed chronic granulomatous inflammation with focal necrosis (hematoxylin and eosin staining, original magnification, ×100).

proved after aspirin and steroid treatment.

Intermittent headache and dysarthria had occurred for 2 weeks at the follow up. Brain magnetic resonance images (MRI) showed 18 mm and 6 mm sized lesions on the pons and occipital lobe, respectively. The lesions were hypointense on T1-weighted images, and iso-intense with a central hyper-signal on T2-weighted images associated with perilesional edema and rim-enhancement after contrast administration (Fig. 1A, B, C). The diffusion images showed diffusion restriction in the central area but no increased cerebral blood volume on MR perfusion images (Fig. 1D, E). A follow-up chest CT showed randomly distributed miliary nodules and mixed small centrilobular nodules, suggesting pulmonary TB with miliary dissemination. The diagnostic impression was TB of the brain and lung. Anti-TB medication was started with isoniazid, rifampicin, ethambutol, and pyridoxine. However, her general condition deteriorated, and right hemiparesis developed. At the 1 month follow-up, the thickened, peripherally enhanced lesions were enlarged and associated with aggravated perilesional edema (Fig. 1F, G, H). The lesions showed increased perfusion and restricted diffusion (Fig. 1I, J). ^{1}H MR spectroscopy revealed increased choline, lactate and lipid peak, and reduced N-acetyl aspartate and creatine, suggesting a high grade glioma rather than tuberculoma (Fig. 1K). The polymerase chain reaction (PCR) for TB on blood was negative.

She underwent craniotomy and occipital lesion mass removal for a definitive diagnosis. The biopsy showed chronic granulomatous inflammation with focal necrosis (Fig. 2), and PCR for

TB was positive. Her medication was changed to isoniazid, rifampicin and ethambutol. After 13 months of medication, the right hemiparesis improved and the lesion had decreased in size with decreased perilesional edema (Fig. 1L, M, N). Perfusion had decreased (Fig. 1O). A chest CT showed improvement in the pulmonary TB with remaining activity. She continued the anti-TB medication to treat the remaining lung and brain lesions.

DISCUSSION

Involvement of the central nervous system (CNS) is the most severe form of TB[11]. A ring-enhancing lesion can be seen in intracranial infections or tumors such as tuberculomas, neurocysticercosis, bacterial cerebral abscesses, neurosarcoidosis, cerebral metastases, glioblastomas, and CNS lymphomas[8]. A tuberculoma with ring enhancement reveals various radiological findings[10]. A caseating tuberculoma with a solid center shows ring and central heterogeneous enhancement and is iso- to hypointense on T1- and T2-weighted MRI. A caseating lesion with a liquid center shows ring enhancement and is hypointense on T1- and hyperintense on T2-weighted MRI. Intense focal gyral enhancement can be seen, and a secondary cerebral infarction from obliterative end arteritis can be associated with intracranial TB[16]. A tuberculoma with liquid necrosis shows restricted diffusion with a low apparent diffusion coefficient, whereas those with solid necrosis do not. ^{1}H MR spectroscopy of the lesion reveals lipid with increased choline and reduced N-acetyl aspartate and creatine[12]. MR perfusion also shows increased cerebral blood volume on initial images, which gradually normalize with treatment, suggesting healing of the lesion[12].

TB can be treated medically after the diagnosis[11]. The diagnosis is established based on the pathology results of a biopsy or detecting *M. tuberculosis* DNA in a PCR study[2]. Treatment of a tuberculoma is based on anti-TB treatment regimens, which include two important antibiotic agents[10]. Isoniazid and rifampicin can be used for several months with combinations of other agents due to bacteria resistance. The initial treatment of extrapulmonary TB includes these two agents and the brain is not an exception.

Expansion of an intracerebral tuberculoma or newly detected lesions can be seen on follow up images after anti-TB medication, which is called a paradoxical response or paradoxical progression[5,17]. The tuberculomas increase in size at 1–7 months after starting chemotherapy. The explanation for this paradoxical response during therapy remains unclear, but it may be related with local tissue reactivity[17]. The brain is known as 'immunologically privileged', meaning that immune reactivity in brain is selective and modified. Foreign antigens including pathogens deposited in the brain parenchyma are not detected efficiently by the immune system in the CNS. The experimental data showed that peripheral immune sensitization can result in the immune-mediated delayed-type hypersensitivity response, which can be used to explain 'paradoxical reaction' of intracranial tuberculoma[3].

Once the active TB is under control with chemotherapy, enhanced delayed type hypersensitivity can cause activation and accumulation of lymphocytes and macrophages at the site of bacillary deposition or toxin production[1]. These phenomena occur in a limited number of cases. Therefore, many factors may combine to produce the paradoxical response, which might be related to a host immune response, virulence of the tubercle bacilli, the infection site, antigen load, or the effects of chemotherapy. These aggravated lesions can be misdiagnosed as treatment failure or other tumorous pathology. In our case, the initial radiological diagnosis was cerebral tuberculoma combined with proven pulmonary TB. After 1 month of treatment, our patient developed worsening symptoms, radiological aggravation with tumoral spectrum on ^{1}H MR spectroscopy, and increased blood volume on MR perfusion. These findings mimicked a high grade glioma even if this center of the lesion with liquid necrosis showed a diffusion restriction. We performed a biopsy for another lesion, and the tuberculoma was confirmed. The benign paradoxical response usually does not require changing therapy[1,9,13]. Initial improvement followed by deterioration despite adequate diagnosis and treatment is strong evidence to suspect the paradoxical response on clinical grounds. The response can be effectively managed by continuing the anti-TB drugs, and eventual clinical improvement is observed in almost all reported cases. Systemic corticosteroids are probably indicated to manage symptoms and cerebral edema for most patients with a cerebral paradoxical response. However, careful consideration of corticosteroid administration must be given due to possible complicating factors such as the host's immune status or the presence of concomitant infections. Surgical intervention should be considered for patients with increased intracranial pressure or an uncertain diagnosis.

CONCLUSION

Brain tuberculoma could be aggravated mimicking brain malignancy during administration of anti-TB medication. This paradoxical response can be effectively managed by continuing the anti-TB drugs with careful radiologic follow-up.

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