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Case Report

A surgical case of cerebellar tuberculoma caused by a paradoxical reaction while on therapy for tuberculosis spondylitis

Atsuhiko Ninomiya[1,2], Atsushi Saito[1], Tomohisa Ishida[1], Tomoo Inoue[1], Takashi Inoue[1], Masayuki Ezura[1], Shinsuke Suzuki[1], Hiroshi Uenohara[1], Teiji Tominaga[2]

[1]Department of Neurosurgery, Sendai Medical Centre, [2]Department of Neurosurgery, Graduate School of Medicine, Tohoku University, Sendai, Japan.

E-mail: Atsuhiko Ninomiya - ninomiya@nsg.med.tohoku.ac.jp; Atsushi Saito - satsushi2002@yahoo.co.jp; Tomohisa Ishida - tomy.ixxx4@gmail.com; Tomoo Inoue - tomoo49@gmail.com; Takashi Inoue - tainoue@snh.go.jp; Masayuki Ezura - ezura.masayuki.nz@mail.hosp.go.jp; Shinsuke Suzuki - ssuzuki@snh.go.jp; Hiroshi Uenohara - uenohara.hiroshi.dw@mail.hosp.go.jp; Teiji Tominaga - tomi@nsg.med.tohoku.ac.jp

***Corresponding author:**
Atsuhiko Ninomiya,
Department of Neurosurgery,
Tohoku University, 1-1,
Seiryo-machi, Aoba, Sendai,
Miyagi, 980-8574, Japan.

ninomiya@nsg.med.tohoku.ac.jp

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ABSTRACT

Background: A paradoxical reaction (PR) is a phenomenon in which the primary tuberculous lesion worsens or another *de novo* tuberculous lesion appears while on anti-tuberculosis therapy. Here, we report a rare case of cerebellar tuberculoma caused by a PR during therapy for lumbar tuberculous spondylitis (Pott's disease).

Case Description: A 47-year-old male with human immunodeficiency virus seronegative was diagnosed with lumber tuberculous spondylitis (Pott's disease) and prescribed anti-tuberculous agents. His lower back pain and inflammatory condition recovered after initiation of anti-tuberculous therapy. Two months later, he complained of headache, nausea, and staggering. Magnetic resonance images revealed a ring-enhanced lesion located at the cerebellar hemisphere extending to the vermis, which caused perifocal edema and bilateral ventriculomegaly. These findings were consistent with his symptoms of hydrocephalus. He did not have preceding clinical findings of meningitis, and a PR was suggested to cause *de novo* aggregation of cerebellar tuberculoma. A lesionectomy was performed, and the surgical specimen was pathologically diagnosed as a tuberculoma. He recovered well from neurological disorders after the resection.

Conclusion: *De novo* formation of intracranial tuberculoma alone caused by a PR without preceding meningitis is very rare. Lesionectomy is needed for intracranial tuberculoma, which manifests as a mass effect, as well as antituberculous therapy.

Keywords: Anti-tuberculous therapy, Cerebellar tumor, Paradoxical reaction, Pott's disease, Spinal tuberculosis, Tuberculoma

INTRODUCTION

Tuberculosis is still a high mortality disease and major public health issue even in developed countries. In Japan, 13.9 cases per 1 million persons were annually diagnosed with tuberculosis in 2016, and Japan is considered as a middle-burden country.[9,23] There were 77.2% of cases with pulmonary disease with or without concomitant extrapulmonary disease, and 22.8% of these cases had extrapulmonary disease.[24] This epidemiology coincides with that in Japan, in which extra-pulmonary disease accounts for 14.8–31.8% in all age cases.[24]

A paradoxical reaction (PR) is a phenomenon in which the primary tuberculous lesion worsens or another *de novo* tuberculous lesion appears during anti-tuberculous therapy although clinical symptoms improve initially after antituberculous therapy.[1,5,7,11] The mechanism of a PR is neither a therapeutic failure nor drug resistance to *Mycobacterium tuberculosis* but rather an exaggerated immune reaction. The incidence of cases with a PR is higher in patients with an extrapulmonary lesion (82% of all cases) compared to that of patients with a pulmonary lesion.[2] For intracranial tuberculosis, 56% of tuberculous meningitis patients had a PR, and 20–56% of these patients had a complicated *de novo* tuberculoma.[6,22] Tuberculoma may occur followed by tuberculous meningitis, and the incidence of tuberculoma alone with a PR is rare.[2,20]

Hereby, we experienced a rare surgical case of cerebellar tuberculoma caused by a PR during antituberculous therapy for tuberculous spondylitis. We report clinical characteristics of this patient and describe this case compared to previous studies.

CASE REPORT

A 47-year-old male with seronegative human immunodeficiency virus (HIV) and diabetes mellitus suffered from lower back pain. He was diagnosed with bacterial spondylitis and iliopsoas abscess [Figure 1a]. Multiple antibacterial agents were prescribed, but the lesion did not disappear. *M. tuberculosis* was detected from the abscess, and caseous granuloma was identified pathologically in surgical specimens of the intervertebral disk [Figure 1b]. He was prescribed the antituberculous agents which were isoniazid 300 mg, rifampicin 600 mg, ethambutol 1000 mg, and pyrazinamide 1500 mg/day. His lower back pain and inflammatory findings improved by the antituberculous therapy.

Two months after starting the antituberculous therapy, he complained of headache, nausea, and staggering. Physical findings on admission were that he was afebrile and did not have stiff neck. A right coordination deficit was identified, and other neurological deficits did not exist. Laboratory findings did not show inflammatory reaction. Chest computed tomography (CT) did not show any cavity lesions. Magnetic resonance (MR) images revealed a nodular enhanced lesion in the right cerebellar hemisphere extending to the vermis associated perifocal edema and bilateral ventriculomegaly [Figure 2]. The lesion showed hypointensity by diffusion-attenuated, weighted images.

Tuberculoma was suspected which appeared *de novo* or enlarged during the antituberculous therapy that was suggested to be a PR. The therapeutic strategy was a lesionectomy because he presented noncommunicating hydrocephalus, and malignant glioma could not be ruled out completely. Lesionectomy would be thought to relief noncommunicating hydrocephalus, and we did not plan to perform ventricular shunt.

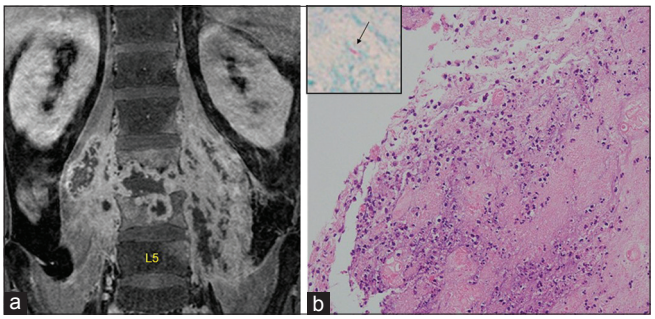

Figure 1: (a) Gadolinium contrast-enhanced magnetic resonance imaging demonstrated inflammation of vertebral body at L3 and L4 with bilateral iliopsoas abscesses. (b) Microscopy of the surgical specimen of the vertebral interbody revealed granuloma aggregating of histiocytes by hematoxylin and eosin staining at low magnification. A punctured specimen from the abscess of iliopsoas muscle demonstrated *Mycobacterium tuberculosis* in the Ziehl–Neelsen stain at high magnification (left upper).

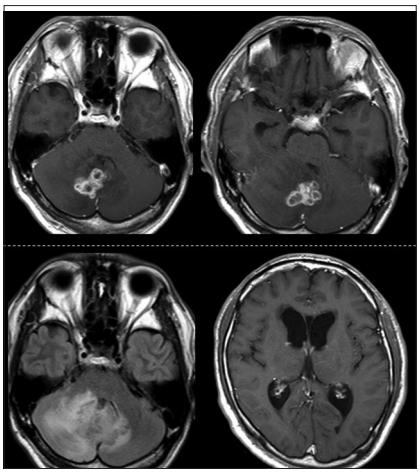

Figure 2: Magnetic resonance images showed a nodular lesion with ring enhancement by gadolinium contrast medium in the cerebellar hemisphere extending to the vermis, compressing fourth ventricle (upper 2 slides). The lesion was associated with perifocal edema and bilateral ventriculomegaly (lower 2 slides).

Surgery was performed by a midline occipital approach. A well-circumscribed mass with gray color was identified by opening the cerebellomedullary fissure [Figure 3]. A mass of 3.5 cm was extracted [Figures 3 and 4]. Pathology revealed a caseous granulomatosis at low-power magnification and invasion of lymphocytes and macrophages at high-power magnification [Figure 4a], and those were suggestive findings of past infection of *M. tuberculosis*. *M. tuberculosis* was not identified by Ziehl–Neelsen stain. These findings lead to

a definitive diagnosis of tuberculoma. Postoperative MR images revealed total removal of the lesion [Figure 4b]. He recovered well from nausea and staggering and was discharged 3 weeks after the operation. He was prescribed antituberculous agents which were isoniazid, rifampicin, ethambutol, and pyrazinamide for the first 2 months and then isoniazid and rifampicin for up to 10 months according to the guideline for the treatment of tuberculosis of central nervous system.[23]

DISCUSSION

The pathological mechanism of a PR is an exaggerated immunological reaction to viable microbes and debris of microbes destroyed by antituberculous therapy. This mechanism has been studied among patients who are coinfected with HIV and *M. tuberculosis* and received antiretroviral therapy (ART) and is relevant to the pathology of immune reconstitution inflammatory disease.[5,12,15] Although a PR is less frequent in HIV-seronegative patients compared to HIV-positive patients receiving ART,[16] immune-competent patients may have a PR induced by antituberculous therapy through an exaggerated immune reaction to a latent tuberculous lesion involving production of pro-inflammatory cytokines.[21]

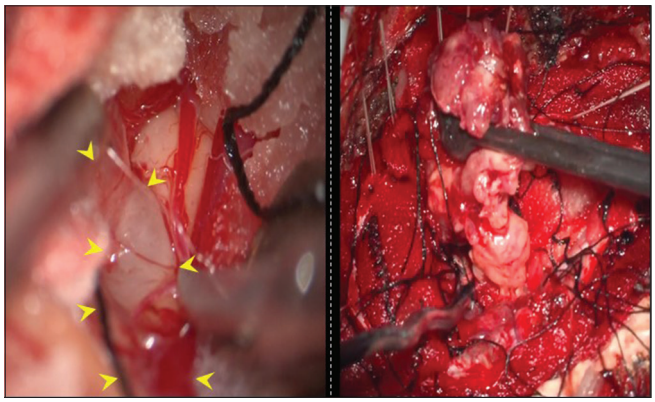

Figure 3: Operative view: A lesionectomy was performed by opening the cerebellomedullary fissure, and a well-circumscribed mass with gray color encircled by arrowhead was identified (left). Total mass resection was performed (right).

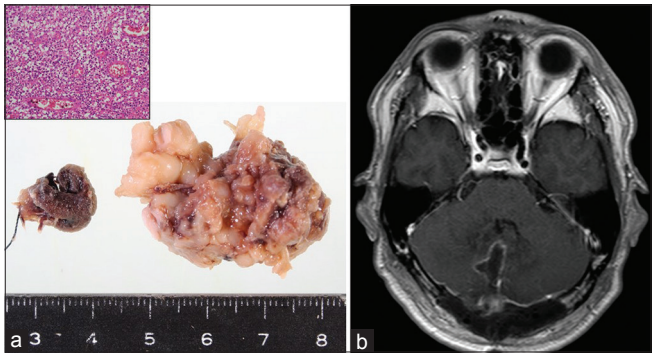

Figure 4: (a) Operative view: A lesionectomy was performed by opening the cerebellomedullary fissure, and a well-circumscribed mass with gray color encircled by arrowhead was identified (left). Total mass resection was performed (right). The size of the extracted mass was 3.5 cm. Pathology of the lesion revealed lymphocytes, macrophages, plasmacytes, and neutrophils aggregated around the tuberculoma by hematoxylin and eosin staining at 200-fold magnification (upper left). (b) Postoperative MRI showed a total mass resection.

Intracranial tuberculoma occurs in 1% of tuberculous patients.[10] The causative mechanism of the development of intracranial tuberculoma is hematogenous infection from distant tuberculous lesions or a PR of preceding tuberculous meningitis.[8] The incidence of tuberculoma without preceding meningitis is 5% among intracranial tuberculosis, and few papers report PR of tuberculoma alone.[2,6] The standard management of intracranial tuberculosis is the initiation of antituberculous therapy for 12 months based on a regimen for pulmonary tuberculosis. In particular, isoniazid and pyradinamide may pass the blood–brain barrier. The optimal duration for antituberculous therapy for patients with PR of tuberculosis of central nervous system is not reported. We referred to the guideline published by British Infection Society and decide to continue antituberculous therapy for 12 months, permitting another additional 6 months according to their response.[3,23] Concurrent use of corticosteroids is beneficial for pediatric and adult patients who are HIV seronegative and recommended because it suppresses exaggerated immune reactions and improves perilesional brain edema which leads to diminish neurological symptoms.[14,18,23] Surgery is also considered for cases with both primary intracranial tuberculosis and an intracranial tuberculous lesion caused by a PR in case of serial complications of hydrocephalus and a mass effect.[17] Shunt implantation and endoscopic third ventriculostomy are a therapeutic option for hydrocephalus.[19] Lesionectomy is also another therapeutic option for patients not effectively treated by antituberculous therapy, but only a few surgical cases have been reported.[4,16]

Here, we treated an immune-competent case with cerebellar tuberculoma caused by a PR during the therapy for tuberculous spondylitis. The cerebellar tuberculoma was suggested to be formed by PR against the preceding nonsymptomatic *M. tuberculosis* lesion in the cerebellum hematogenously infected from tuberculous spondylitis. He did not have a preceding clinical history of meningitis. Although the symptoms and clinical findings of tuberculous spondylitis markedly recovered after antituberculous therapy, annual neurological symptoms occurred after 2 months. The initiation of antituberculous therapy may induce the enlargement of the cerebellar lesion, which

is considered a PR. Recently, it is reported that vertebral involvement of *M. tuberculosis* infection is a risk factor for PR of tuberculosis in central nervous system, which would support the clinical features of this case.[13] Furthermore, a pathological finding from the surgical specimen, which showed an aggregation of inflammatory cells with caseous granuloma and lack of *M. tuberculosis*, suggested that the mass was formed by an inflammatory process and neither by active tuberculous activity, drug resistance nor difficulties about drug delivery of antituberculous agents.[18] In our case, it was obvious that the cerebellar lesion caused the obstruction of the fourth ventricle, and he presented with symptoms of hydrocephalus. Lesionectomy was effective to improve his neurological symptoms caused by noncommunicating hydrocephalus and contributed to the precise pathological diagnosis.

Limitations of the present case were that the patient had not taken brain CT scans or MR images ahead of antituberculous therapy, and we could not identify when the lesion formed. However, he did not show any neurological symptoms before antituberculous therapy and enlargement of the lesion produced neurological disorders after the initiation of antituberculous therapy.

CONCLUSION

We treated a patient who had cerebellar tuberculoma caused by a PR and presented with neurological disorders during therapy for tuberculous spondylitis. Antituberculous therapy is the first choice for tuberculoma manifesting PR. Concurrent use of corticosteroids is recommended because of suppressing exaggerated immune reaction in tuberculoma causing PR and reducing perilesional brain edema. Surgery is considered for localized tuberculoma causing neurological symptoms.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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