

# Anhelation due to formation of tuberculomas at the medulla oblongata during chemotherapy of tuberculous meningitis

## *Duszność spowodowana gruźliczakami powstającymi w rdzeniu przedłużonym w czasie leczenia gruźliczego zapalenia opon mózgowo-rdzeniowych*

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### Abstract

Formation of tuberculoma is a rare response of neurotuberculosis in patients regularly and adequately treated with anti-tuberculous drugs. We report a 13-year-old girl with two tuberculomas which formed in the dorsal part of the medulla oblongata during chemotherapy for tuberculous meningitis. The tuberculomas were both removed via a suboccipital midline approach and were demonstrated by pathological findings but the girl died of cardiac arrest that was thought to be caused by postoperative medulla oblongata oedema. In combination with a literature review, we discuss the clinical features and treatment options of brainstem tuberculomas.

**Key words:** neurotuberculosis, formation of tuberculoma, medulla oblongata.

### Streszczenie

Tworzenie się gruźliczaka jest rzadką reakcją w przebiegu właściwie leczonej gruźlicy układu nerwowego. W pracy autorzy opisują przypadek 13-letniej dziewczynki z dwoma gruźliczakami, które utworzyły się w grzbietowej części rdzenia przedłużonego w czasie farmakologicznego leczenia gruźliczego zapalenia opon mózgowo-rdzeniowych. Oba gruźliczaki usunięto z dostępu podpotylicznego w linii środkowej i potwierdzono ich rozpoznanie w badaniu histopatologicznym, ale pacjentka zmarła w wyniku zatrzymania krążenia, przypuszczalnie wskutek pooperacyjnego obrzęku rdzenia przedłużonego. Na podstawie przedstawionego przypadku i przeglądu piśmiennictwa omówiono objawy kliniczne i możliwość leczenia gruźliczaków pnia mózgu.

**Słowa kluczowe:** gruźlica układu nerwowego, powstawanie gruźliczaka, rdzeń przedłużony.

### Introduction

Tuberculosis is a global pandemic, with 9 million new cases of the disease and approximately 2 million deaths each year [1]. It is caused by *Mycobacterium tuberculosis* and the lung is the usual location, but the highest mor-

tality and morbidity occur with tuberculous meningitis. Unlike pulmonary tuberculosis, the formation or progression of intracranial tuberculomas during the treatment of neurotuberculosis has been recognized as a rare response to anti-tuberculous chemotherapy [2-4]. Herein, we report a rare case with two medulla oblongata

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tuberculomas, both of which developed during the course of adequate and regular chemotherapy for tuberculous meningitis. With reference to the literature, we discuss the clinical features and treatment options of tuberculomas of the brainstem.

## Case report

A 13-year-old girl was hospitalized due to one-month progressive anhelation. Three months previously, she was diagnosed with tuberculous meningitis and accepted one-month anti-tuberculous treatments in our hospital. After being discharged, she continued to take rifampicin, isoniazid and pyrazinamide. However, she suffered anhelation which had worsened gradually in the last three weeks and she was readmitted to our hospital. On physical examination, we found that she had mild lip cyanosis, brisk deep tendon reflexes and positive pathological signs. Her respiration rate was 35 breaths per minute with oxygen saturation of blood 80%, and her heart rate was 125 beats per minute. No abnormalities were found on X-ray of the chest. While magnetic resonance imaging (MRI) of the head performed one month earlier showed no mass (Fig. 1A-C), MRI repeated at admission revealed two cystic lesions in the dorsal part of the medulla oblongata, one of which was  $2.6 \times 1.8$  cm and the other one was  $1.0 \text{ cm} \times 0.8$  cm. They were both hypointense on T1-weighted and FLAIR images and hyperintense on T2-weighted images (Fig. 1D-F), with wall enhancement after contrast injection (Fig. 1G-I). Therefore, her anhelation was thought to be caused by the medulla oblongata lesions and suboccipital midline craniotomy was performed.

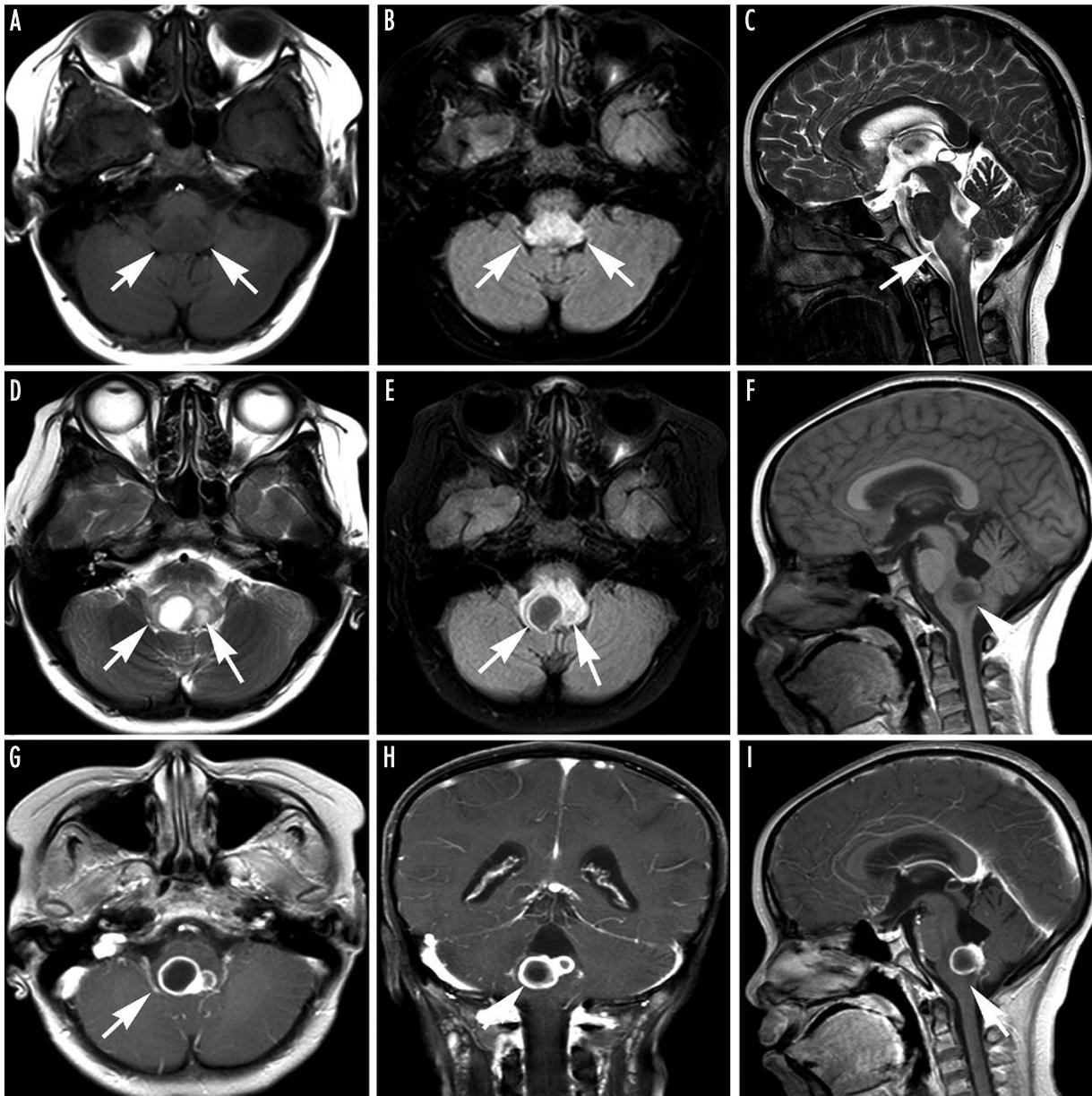
At surgery, we found that the lesions were pink and soft, connecting loosely with surrounding tissue but their roots were sticking tightly with the dorsal surface of the medulla oblongata (Fig. 2A-B). We first evacuated the pus-like content from the lesions with a syringe to shrink them, and then isolated their roots from the surface of the medulla oblongata with an electrocauterizer and micro-scissors. During the course of dissection, her heart rate changed markedly from 90 beats to 30 beats per minute. Postoperatively, she recovered smoothly in the first two days, but on the third day, she felt anhelation again and apnoea ensued. She was intubated emergently with an endotracheal tube to enable her blood oxygen saturation to be maintained normally via a ventilator. Meanwhile, she was given corticosteroid and human albumin. Unfor-

tunately, she died of cardiac arrest on the fourth day and her family refused an autopsy. Histological findings demonstrated that removed tissues were tuberculomas, because they had granulomatous lesions with Langhans giant cells, epithelioid histiocytes and mature lymphocytes (Fig. 2C-D).

## Discussion

The paradoxical formation or progression of intracranial tuberculomas during the treatment of neurotuberculosis was first described as a rare response to antituberculous chemotherapy by Thrush and Barwick in 1974 [5]. Statistically, the patient age ranged from 4 months to 75 years with a median age of 20 years, and the interval between the onset of anti-tuberculous therapy and the paradoxical response was from 1 to 116 weeks with a median interval of 12 weeks [6]. In paediatric patients, the incidence was about 18% and was higher in boys than that in girls [7]. Moreover, it was found that solitary or multiple tuberculomas could occur within the cranium as a response to the treatment of intracranial or extracranial tuberculosis [2,8]. For our patient, two tuberculomas that developed at the back of the medulla oblongata were found at three months after she started to take regular anti-tuberculous drugs, consistent with the above description of the development of tuberculomas.

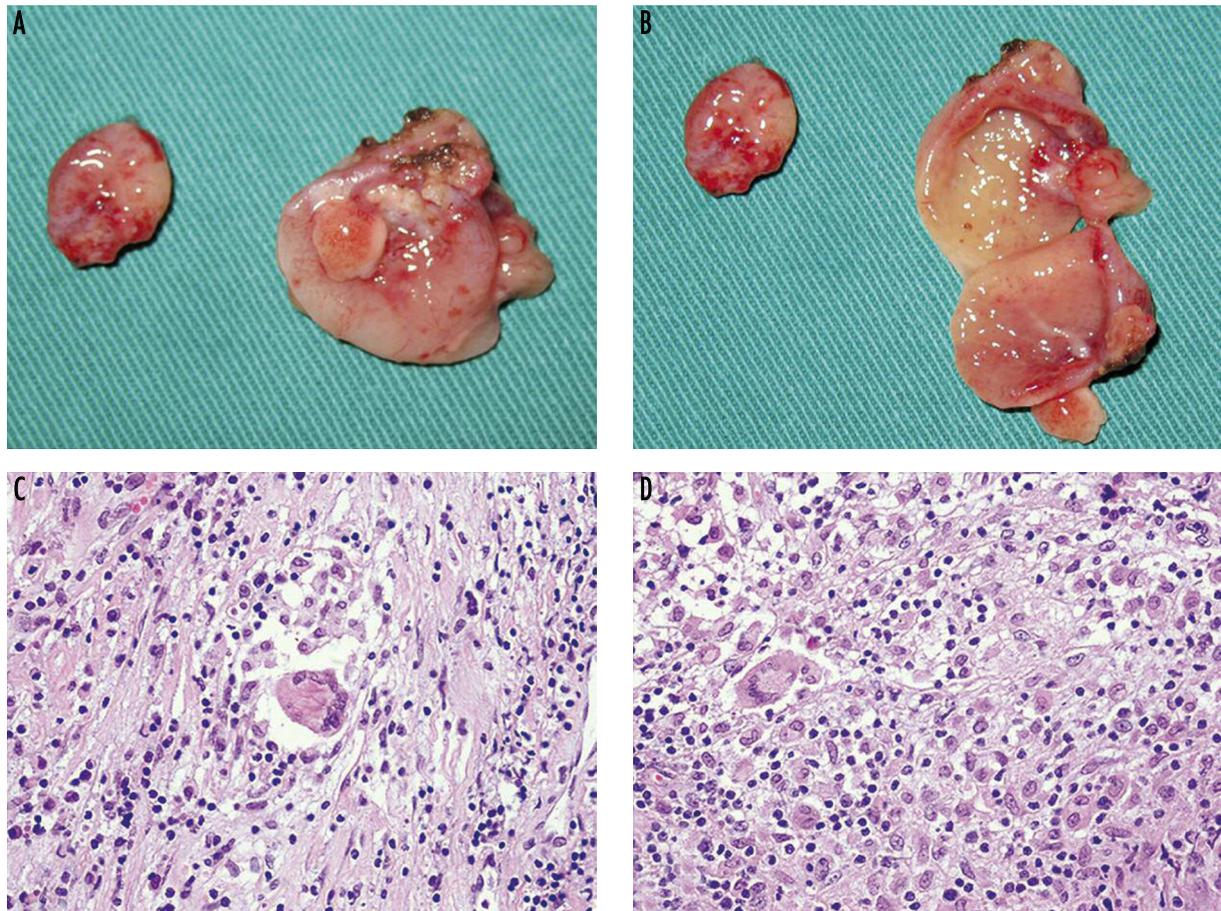
The common symptoms caused by brainstem tuberculomas include cranial nerve palsy and communicating hydrocephalus. In paediatric patients, when the cranial nerves were compressed by tuberculomas or entrapped by basal exudes, nerve palsy ensued and would occur in the third, sixth, seventh, ninth and tenth cranial nerve. Concomitantly, pyramidal signs could also be found [7]. Communicating hydrocephalus was thought to be caused by basilar arachnoiditis or aqueductal compression [9]. Additionally, some rare signs or syndromes such as horizontal gaze palsy [10], nystagmus [11], Millard-Gubler syndrome [12], one-and-a-half-syndrome [13], and eight-and-a-half syndrome [14] were all reported to occur in patients with brainstem tuberculomas. However, neither cranial nerve palsy nor communicating hydrocephalus was found in our patient, but anhelation presented as the main complaint when she was readmitted to hospital. Since the respiratory centre is located within the medulla oblongata, we thought her respiratory dysfunction was caused by tuberculomas' compression on the medulla oblongata.



**Fig. 1.** MR scanning showed no significant abnormality one month before the patient was admitted to hospital. A (Axial T1W image), B (Axial FLAIR image) and C (Sagittal T2W image) revealed oedema-like abnormal signal within brainstem. The second MR imaging revealed that cystic lesions were located at the back of the medulla oblongata, with enhancement in the walls. D (Axial T2W image), E (Axial FLAIR image) and F (Sagittal T1W image). Contrast imaging (G, H and I)

The precise mechanism underlying the formation of tuberculomas remains unclear, but an enhanced immune response is thought to be responsible in patients receiving anti-tuberculous treatment. Recent findings showed that prolonged use of anti-tuberculous drugs in combination with 3–4 months use of steroids could resolve the newly formed tuberculomas [3]. This indicates that additional use of steroids on the basis of regular anti-tuberculous drugs benefited the prognosis of the patients

with formation of tuberculomas. For tuberculous meningitis, the Infectious Disease Society of America, Centers for Disease Control and Prevention, and American Thoracic Society guidelines recommend an initial 2-month induction therapy with isoniazid, rifampicin, pyrazinamide and ethambutol, followed by 7 to 10 months of additional isoniazid and rifampin. According to this guideline, our patient did not receive efficient treatment, which might be the cause of the formation of tuberculomas.



**Fig. 2.** Macroscopic and microscopic imaging of the removed lesions. A) and B) were the macroscopic imaging, which showed the exterior (A) and interior (B) aspects of the removed lesions. C) and D) were the microscopic imaging, which revealed Langhans giant cells, epithelioid histiocytes and mature lymphocytes within the lesions

Although drug therapy proved effective in patients with tuberculomas, for patients with worsening neurological symptoms or mass effect produced by tuberculomas, surgical procedures should be considered. Donmez *et al.* [15] reported a 70-year-old woman, who recovered uneventfully after her medulla oblongata tuberculoma was removed totally. By contrast, Tegeris *et al.* reported an 18-year-old girl with a solitary tuberculoma in the medulla oblongata, who died suddenly at 24 hours after the tuberculoma was subtotally removed via craniotomy [16]. In our case, the patient felt progressive anhelation and her oxygen saturation of blood was significantly lower than the normal value, which made us decide to perform surgical removal. Although her tuberculomas were removed totally, she suffered transient anhelation and apnoea on the third day and died of cardiac arrest on the fourth day. Given that dorsolateral medullary infarction could lead to recurrent cardiac arrest [17] and the tuberculomas in our case

were located at the back of the medulla oblongata, we thought postoperative oedema in the medulla oblongata might be the reason for the cardiac arrest in our patient.

Due to the risk of total removal, subtotal removal or content evacuation are thought to be good options as well. They could effectively relieve the patients' symptoms and make time for future use of anti-tuberculous drugs. Kumar *et al.* reported a 12-year-old boy with a paradoxical tuberculoma extending from the pons to the medulla oblongata [4]. Although the upper solid part of his tuberculoma was removed sub-totally and the lower cystic part was shrunk via evacuation, the boy improved gradually via postoperative treatment with anti-tuberculous drugs. Therefore, for patients with brainstem tuberculomas, how to select the surgery method should be considered perioperatively. Moreover, many more cases are needed for further evaluation of the effectiveness and safety of surgery. Particularly,

prospective studies are also required to define better selection criteria for medical treatment for patients with brainstem tuberculomas.

In summary, we have reported a girl with progressive anhelation produced by tuberculomas formation at the medulla oblongata when she was receiving routine anti-tuberculous chemotherapy. For patients who need surgery, it should be considered carefully to choose total or subtotal removal before the operation.

## Disclosure

Authors report no conflict of interest.

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