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TUBERCULOMA OF THE CENTRAL NERVOUS SYSTEM – A CASE REPORT

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ABSTRACT

Tuberculoma of the brain is a rare form of central nervous system (CNS) tuberculosis with non-specific clinical manifestation. Due to its similarity with many other infectious and non-infectious lesions, diagnosis is difficult. The study presents the case of a patient who developed CNS tuberculoma during the course of tuberculous meningitis.

Key words*: tuberculoma, tuberculosis, magnetic resonance imaging*

INTRODUCTION

Tuberculosis (TB) is a major global health problem, ranked as the second leading cause of death worldwide, among infectious diseases. In 2011, there were 8.7 million new cases of TB all over the world, the majority of which were identified in Asia (59%), followed by Africa (26%) and to a lesser extent in Europe (4.3%). The average incidence of TB worldwide is however slowly decreasing (1).

CASE PRESENTATION

A 38-year-old female was admitted to the Observation and Infectious Diseases Ward in the District Hospital on the 6th of February 2010, due to experience of ongoing headaches, emesis, and disorders of consciousness. On admission she was generally in a poor condition- drowsy, presenting with meningeal symptoms. She had a history of psoriasis. In November 2009, she had left-sided exudative pleuritis. She was vaccinated against TB during childhood with Calmette Guerin (BCG) vaccine, did not report any contact with TB cases and described her social condition as good. Laboratory findings on admission were as follows: RBC – $4.68x10^6$/ µl, HGB – 12.9 g/dl, HCT – 40.6%, WBC – $10.9x10^3$/µl, ESR - 19 mm/h, CRP - 10.05 mg/dl, fibrinogen – 469 mg/dl, D-dimer - 1184.8 ng/ml, Na – 137.0 mmol/l, K – 3.38 mmol/l; blood cultures - *Staphylococcus cohnii* MRCNS. Cerebrospinal fluid (CSF) obtained via lumbar puncture was colourless, transparent, cytosis – 3 cells, protein – 814.8 mg/l, glucose – 27 mg/dl (26.5% of the serum glucose), Nonne-Apelt test (-), Pandy test (-). CSF samples were taken for detecting *Mycobacterium tuberculosis*. The emergency computed tomography (CT) examination performed (without the contrast media administration) did not reveal abnormalities within the head. Ultrasonography of the liver detected a tumor after which a CT of the abdomen was ordered. The examination identified a liver haemangioma, sized 50x55mm. A chest X-ray (in posterior-anterior and lateral position) showed some reticulo-nodular opacities in the postero-inferior part of the left lung, which were assessed as post-inflammatory lesions. Whilst in hospital the patient presented with subfebrile body temperature. There was a short period of improvement after which the patient's condition worsened. Upon examination the patient had anisocoria, difficulties in swallowing, right hemiparesis and positive left Babinski reflex. She was drowsy and unable to communicate. Follow-up CT performed on the 16th of February did not reveal any lesions in the CNS. The following treatment course started at the beginning of hospitalization included empiric therapy: mannitol, dexamethasone, ciprofloxacin, ceftriaxone, rifampicin, gentamicin, metoclopramide, and diazepam.

On the 19th of February the patient was transferred to the Department of Infectious Diseases and Neuroinfections at the University Hospital. On admission the patient's condition was bad, she was excessively drowsy only periodically being able to answer ques-

tions logically. The patient reported headaches in the frontal part of the head and memory disorders. A physical examination revealed slow motion, positive Brudzinski neck sign, positive neck stiffness – 3cm, anisocoria (L>R) and massive right hemiparesis, body temperature 38.5°C, BP 110/70. Laboratory findings: RBC – $4.56x10^6$/µl, HGB – 13.0 g/dl, HCT - 37.2%, WBC – $9.38x10^3$/µl, a peripheral blood smear was normal, ESR – 24 mm/h, CRP - 13.2 mg/l, Na – 122 mmol/l, Cl – 89 mmol/l, K – 4.13 mmol/l, Ca – 1.96 mmol/l, AST – 28 U/l, ALT – 39 U/l, creatinine – 0.56 mg/dl, fibrinogen – 500.1 mg/dl, D-dimer – 7.32 mg/l. CSF culture using BACTEC MGIT 960 TB system revealed acid-resistant bacillus. The positive culture was obtained 22 days after CSF examination. DNA of the bacilli was found in CSF using PCR. Serological examinations for human immunodeficiency virus (HIV), herpes simplex virus (HSV), tick-borne encephalitis (TBE), syphilis, cysticercosis, echinococcosis were negative. Magnetic resonance imaging (MRI) examination of the head performed on the 23th of February was of limited value, due to the movement of artifacts. A non-homogenous, mostly cystic lesion within the deep structures of the left hemisphere, sized 30x17mm was identified. The lesion presented with a slightly mass effect with III ventricle compression and lack of enhancement after contrast media administration (Fig.1)

A diagnosis of tuberculoma or cysticercosis was proposed, however neoplasmatic lesion could not be excluded. The combined treatment of rifampicin, isoniazide, ethambutol, pyrazinamide was administered on the first day of hospitalization. Additional pharmacotherapy included: dexamethasone, mannitol, furosemide, ketoprofen and omeprazole.

On the 2nd of March the patient was transferred to the Neurosurgery Department at the University Hospital to perform a stereotactic biopsy of the lesion. Necrotic tissue was obtained during the procedure.

During the hospitalization the patient's condition improved, the paresis abated, consciousness disorders lessened and biochemistry parameters improved (ESR -12mm/h, CRP - 2.2 mg/l, WBC– $5.21x10^3$/µl, Na – 137 mmol/l, Cl – 98 mmol/l). Follow-up CSF examination revealed normalization of parameters. Follow-up CSF culture did not show the presence of acid-resistant bacilli. Follow-up MRI examination performed on the 22nd of March revealed a lesion similar in size and morphology to the one previously detected. On the 2nd of April the patient was discharged and asked to continue treatment in the outpatient clinic.

During the follow-up hospitalization on the 7th of June the physical examination revealed slight right-sided hemiparesis. The patient's general condition was better in comparison to that documented during previous hospitalization. Her consciousness was normal and she was moving unaided. Laboratory findings were normal. However follow-up MRI examination showed hydrocephalus and massive nodular enhancement of the meninges of the suprasellar cister, Sylvian fissures (mostly on the left side) and in front of the brain stem

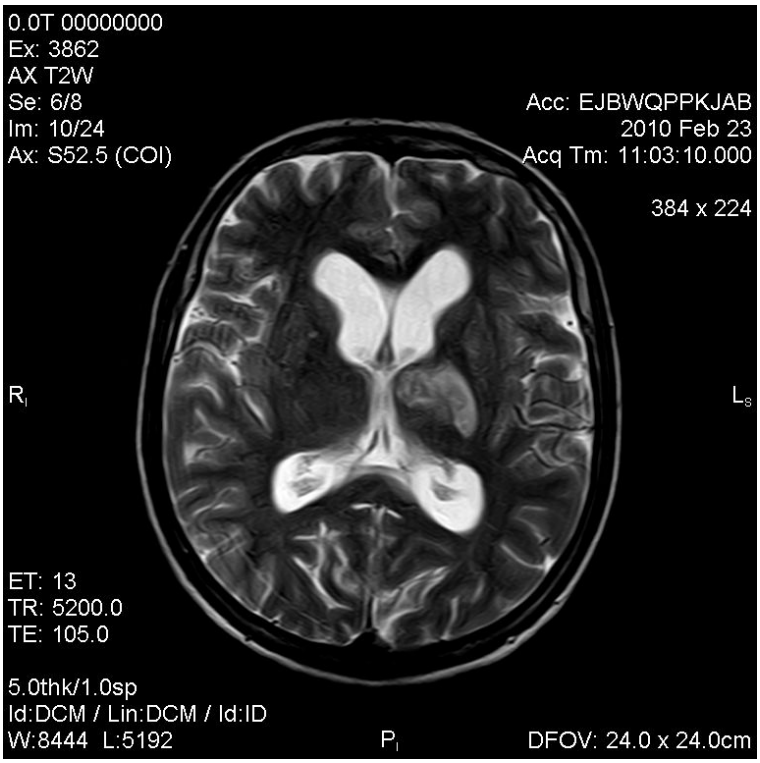

Fig. 1. Magnetic resonance imaging examination, T2-weighted image: hyperintens lesion in deep structures of the left hemisphere.

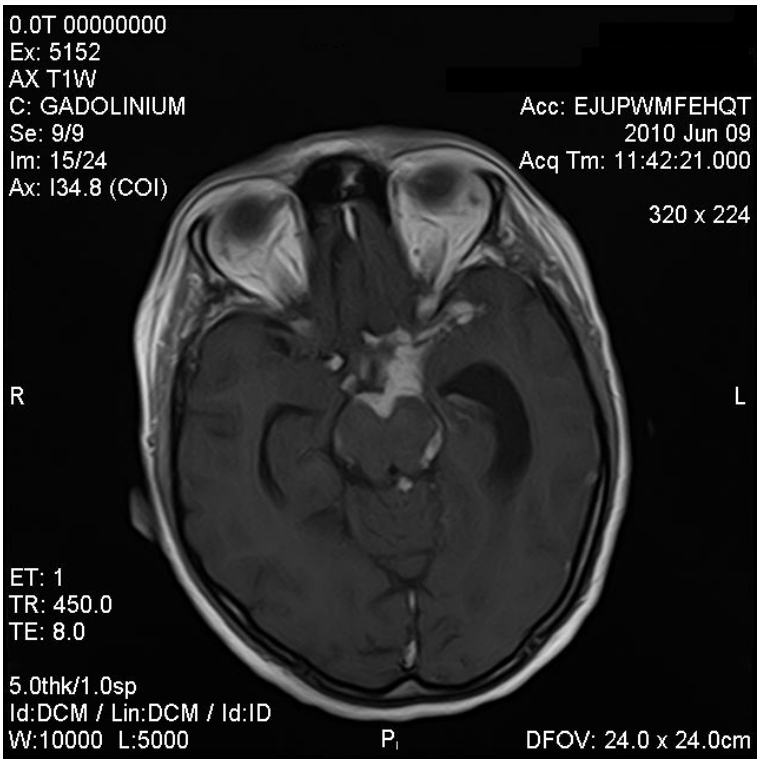

Fig. 2. Magnetic resonance imaging examination, T1-weighted image after the contrast media administration. Nodular enhancement of meninges of the suprasellar area and in front to the brain stem.

(Fig.2). Hydrocephalus did not require specific treatment. Neurological and pulmonological consultations excluded neurosarcoidosis. The treatment with tuberculostatics was continued. The patient was discharged in a good general condition and was given instructions to continue tuberculostatic treatment and follow-up at the Neurological and Neurosurgical Outpatients Clinic.

On the 9th of November 2010 the patient was admitted to our Department again. On admission her condition was quite good, she was able to communicate and no quality deficits were present. Physical examination revealed slight right-sided hemiparesis. Laboratory findings showed leucopenia ($2.8x10^3/\mu l$) and increased aminotransferases activity (ALT – 79 U/l, AST – 43 U/l). Reactive phase parameters were normal. Follow-up CSF examination showed cytosis of 13 cells, and decreased glucose concentration - 40 mg/dl. Follow-up MRI examinations revealed regression of the inflammatory process. Hydrocephalus disappeared. The antituberculotic treatment was continued. The patient was discharged and recommended to continue treatment in the outpatient clinic.

DISCUSSION

CNS TB is the most serious form of disease caused by *M. tuberculosis*. It can present in the form of tuberculous meningitis (TBM) and/or intracranial tuberculoma. The bacteria reached the CNS via hematogenous spread, where the formation of tubercles initiated, which later became surrounded by the fibrous capsule (the so-called Rich focus) within the oedematic zone. During inflammation reactivation of the Rich focus may burst, with its capacity moving towards the subarachnoidal zone or ventricular system of the brain leading to the TBM (2,3). In other cases the enlarging tubercles, which constitute the Rich focus, form a tuberculoma. In our patient tuberculoma developed during the course of TBM. Both types of CNS TB are reported in about 50% of cases (4). In adults, tuberculomas are most often located in the supratentorial area, within the frontal or parietal lobes of the brain, usually in parasagittal areas (3,5). In our patient the tuberculoma was located in the deep structures of the left hemisphere: thalamus and internal capsule.

Clinical manifestations of the tuberculoma are differentiated. They result from the irritation of brain structures and the increase of intracranial pressure, which causes difficulties in the diagnostic work-up. The most common symptoms are: headaches, nausea, emesis, fits, focal neurological symptoms, optic disc oedema, hypersomnia, fever-like status or less often fever up to 39°C. Around 25% of patients experience paresis and paralysis of the cranial nerves (most often nerve VI) (2,3,6). CSF does not present with abnormalities if the tuberculoma is not associated with TBM (3). Otherwise CSF presents with lymphocytic pleocytosis of 50-500 cells/mm^3 in 2/3 of cases (7), an increase of protein concentration, whilst glucose concentration

(<50% of the serum glucose concentration) and chloride concentration decrease. In the early phase, neutrophils may dominate (2,8). In patients with impaired cellular immunity, the number of leucocytes in the CSF may be normal (8).

During the treatment of our patient we observed hyponatremia and hypochloremia. Generally, it is assumed that electrolyte disorders are caused by the dysfunction of the hypothalamus and pituitary gland system and SIADH (syndrome of inappropriate antidiuretic hormone hypersecretion). Hyponatremia and hypochloremia are observed in around 50% of patients with TBM (2,7). Moreover, we observed an increase in CRP and ESR, these values are usually only slightly increased. The number of leukocytes most often remains within normal ranges and the peripheral blood smear is usually normal. Tuberculin skin test (TST) is not of diagnostic significance (2). However, a positive TST can help in the decision to include antimycobacterial drugs pending the results of CSF culture.

IGRAs (Interferon-Gamma Release Assays) tests, based on the measurement of IFN-g secretion by T-specific lymphocytes stimulated by *M. tuberculosis* specific antigens and few other tuberculi species (*M. kansasi, M. szulgai, M. microti*), may be helpful (9). *Kim et al*. found that their sensitivity and specificity in CSF for the diagnosis of TBM was 59% and 89% (10). The IGRAs test do not have a significant advantage over TST. Direct examination and CSF culture for mycobacteria in patients with tuberculoma without concomitant TBM are usually negative. In the case of concomitant TBM direct microbiological examination of CSF may present mycobacteria in <20% (3), and CSF culture in 25-70% cases (sensitivity is directly proportional to the number of cultures and the amount of CSF). Nevertheless the expected time taken to culture CSF for *M. tuberculosis,* remains unsatisfactory (4-8 weeks) (3,7). The BACTEC system yields positive cultures within a shorter period of time than conventional methods. In the case of tuberculoma without coexisting TBM or in the case of negative CSF cultures, PCR, with its 30-100% sensitivity and 80-100% specificity, seems to be a helpful diagnostic method (11-13). PCR can yield a result on the day of CSF examination and a positive result in a patient during tuberculostatic treatment (7). Definitive diagnosis of CNS TB is through detection of mycobacteria in the CSF (3).

Neuroimaging techniques (e.g. CT, MRI) are the leading tools used to diagnose TB infection of the CNS. MRI has a higher resolution and tissue contrast, in comparison to CT and is therefore the preferred technique and should be ordered. Such differences were noted during this study where the CT examinations performed at point of admission did not pick up any abnormalities, whilst MRI examination performed after 7 days showed the lesion. MRI allows imaging most often of the isointense core surrounded with hypointense rim on T1-weighted scans and hypointense core with hyperintense rim on T2-weighted images. Smaller tuberculomas are isointense on T1-weighted images and hyperintense on T2-weighted images (4,5). The characteristic neuroradiological findings in TBM on MRI and CT are thickening and intense enhancement of meninges, especially in basilarregion and hydrocepalus regions (3).

Among histopathological examinations, brain biopsies remain the subject of debate. *Wasay et al.* (4) analyzed 100 patients with tuberculoma, using histopathological examination diagnosis was confirmed in only 19 patients. In the case of diagnostic difficulties (especially if the tuberculoma is not associated with the primary lesion in the lungs) biopsy is necessary as it allows the differentiation of tuberculoma from focal lesions of other etiology, infectious or neoplastic. The indications for biopsy must be considered individually (14). Biopsy specimens should be cultured. Concurrent neurological and respiratory symptoms e.g. pleuritis observed in our patient, facilitated diagnosis. In a group of 12 patients with brain tuberculoma described by *Thonell et al.* (15) X-ray examination showed specific lesions in the lungs resembling TB in all the patients. Our patient had a history of exudative pleuritis, which may have been of tuberculous etiology. This information made the diagnosis easier.

The treatment of tuberculoma is similar to the treatment of other forms of CNS TB. Initially 2-month therapy with rifampicin (10 mg/kg body weight), isoniazid (5 mg/kg body weight), etambutol (15 mg/kg body weight) and pirazynamide (25 mg/kg body weight) is recommended, followed by therapy with isoniazid and rifampicin for 7-10 months (the total period of treatment should be 9-12 months). Such a schedule of treatment was given to our patient. The patient experienced a short period of improvement, during the first hospitalization. This was probably related to treatment with ciprofloxacin and rifampicin, which show antimycobacterial activity. Additional supplementation of vitamin B6 is recommended as isoniazid might lead to peripheral neuropathy due to the piridoxine deficiency (2,6,8,11,16). Due to the presence of the increased intracranial pressure the patients should also be treated with dexamethasone in the first 1-2 months of therapy. Corticosteroids also reduce risk of death and permanent neurological impairment. The recommended dose of dexamethasone is 12 mg/day for adults (2,6,8). Antimycobacterial drugs should be given despite a negative TST, if there is a high risk of TB.

Unrecognized and untreated CNS TB is always fatal. Even though the treatment has been started, the mortality rate remains high. The survivors often expe-

rience some form of neurological impairment such as blindness, deafness, hemiparesis or mental retardation (3,6).

CONCLUSION

Despite the fact that CNS TB is a rare disease in developed countries it must be always considered during differential diagnosis, especially in patients with the history of TB or people travelling to endemic countries. A history of BCG vaccination does not eliminate the need to investigate the possibility of tuberculoma, which can be challenging to diagnose, even in well equipped clinics. A task that is particularly difficult is proving the presence of *M. tuberculosis* in neither direct nor indirect way.

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