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Central nervous system tuberculosis with miliary tuberculomas in a child: a case report

Tuberkuloza središnjeg živčanog sustava s milijarnim tuberkulomima u djeteta: prikaz bolesnika

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Case report

Central nervous system tuberculosis is a rare form of disease that carries the high mortality and the risk of permanent neurologic sequelae if not recognized early. Clinical, laboratory and radiologic manifestations are usually nonspecific, thus postponing establishment of correct diagnosis and initiation of treatment. We report a child with central nervous system tuberculosis, which manifested with nontypical laboratory findings, as well as with the rare form of miliary intracranial tuberculomas. Signs of active tuberculosis outside the central nervous system in combination with insidious course of disease raised a suspicion on tuberculosis. Therefore, antituberculous therapy was initiated promptly, and the patient recovered completely, without permanent neurologic sequelae.

Prikaz bolesnika

Tuberkuloza središnjeg živčanog sustava je rijedak oblik bolesti s visokom smrtnosti i rizikom trajnih neuroloških posljedica, ako se ne prepozna na vrijeme. Kliničke, laboratorijske i radiološke manifestacije su obično nespecifične, što odgađa donošenje ispravne dijagnoze i početak liječenja. U radu je prikazano dijete s tuberkulozom središnjeg živčanog sustava koja se manifestirala netipičnim laboratorijskim nalazima i rijetkim milijarnim intrakranijskim tuberkulomima. Znakovi aktivne tuberkuloze izvan središnjeg živčanog sustava u kombinaciji s prikrivenim tijekom bolesti izazvali su sumnju na tuberkulozu. Antituberkulozno liječenje je odmah započeto, a bolesnica se oporavila u potpunosti, bez trajnih neuroloških posljedica.

Introduction

Central nervous system (CNS) tuberculosis (TB) is an uncommon form of disease, which develops in around 4 % of children with TB, but remains the most devastating form of disease, carrying high mortality and a distressing level of neurological morbidity [1]. Since clinical, laboratory and radiologic manifestations of CNS TB are nonspecific, early recognition of the disease is a challenge. However, it is of paramount importance because the clinical outcome depends greatly upon the stage at which therapy is initiated [2].

Here we report a case of CNS TB with rare form of miliary intracranial tuberculomas and discuss the possible clues for early diagnosis.

Case presentation

A 10-year-old girl presented with a 1-month history of dry cough, occasional low-grade fever, diarrhea, abdominal pain and weight loss of 4 kg. She was examined few times at emergency department when no abnormalities in physical examination were noticed. Laboratory findings showed elevated erythrocyte sedimentation rate (65 – 85 mm/h), normal level of C-reactive protein, unremarkable complete blood count and mildly elevated transaminases (aspartate transaminase 85 IU/L and alanine transaminase 70 IU/L). In the fourth week of disease high temperature appeared, with drowsiness, headache and photophobia, so the girl was admitted to hospital.

She was previously healthy, regularly vaccinated as provided by the Croatian National Immunization Program.

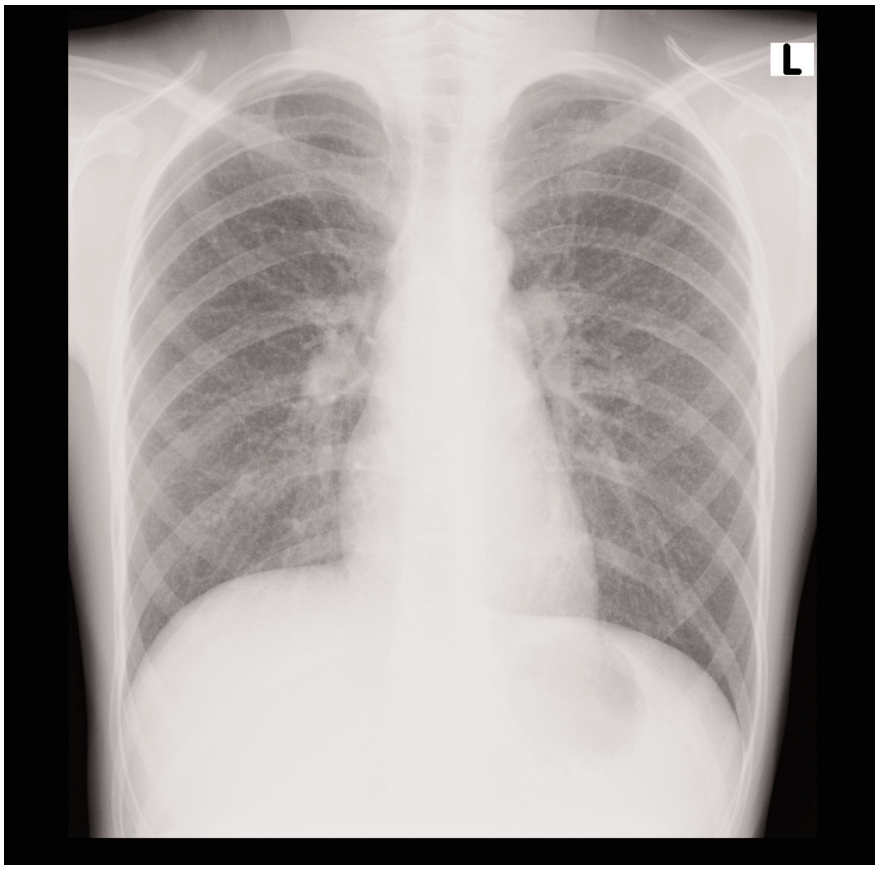

Figure 1. Initial chest x-ray shows diffuse interstitial nodular lesions

Slika 1. Inicijalni radiogram prsnog koša pokazuje difuzne intersticijske nodularne lezije

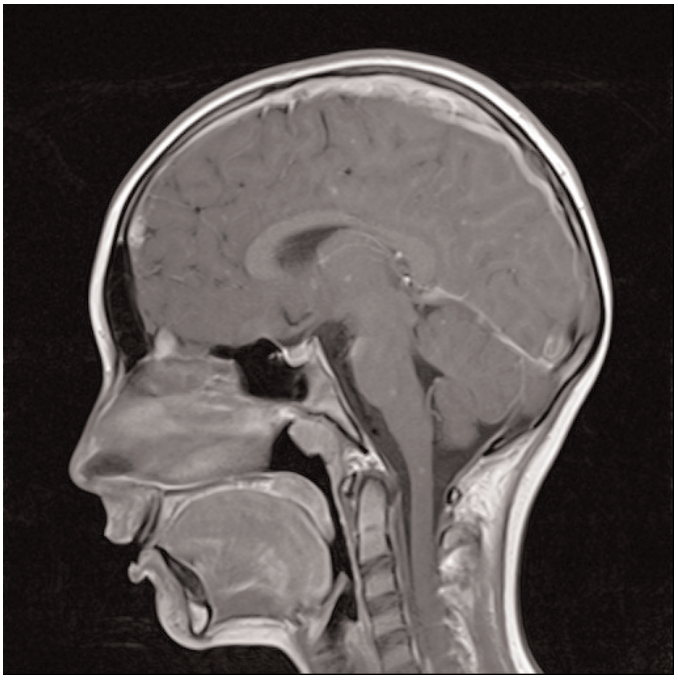

Figure 2. Brain MRI performed on hospital day 4 shows multiple tiny lesions most prominent in cerebellum, but also present in the cerebrum and brainstem

Slika 2. MR mozga učinjen 4. dan hospitalizacije pokazuje multiple sitne lezije najizraženije u malom mozgu, koje su prisutne i u velikom mozgu i moždanom deblu

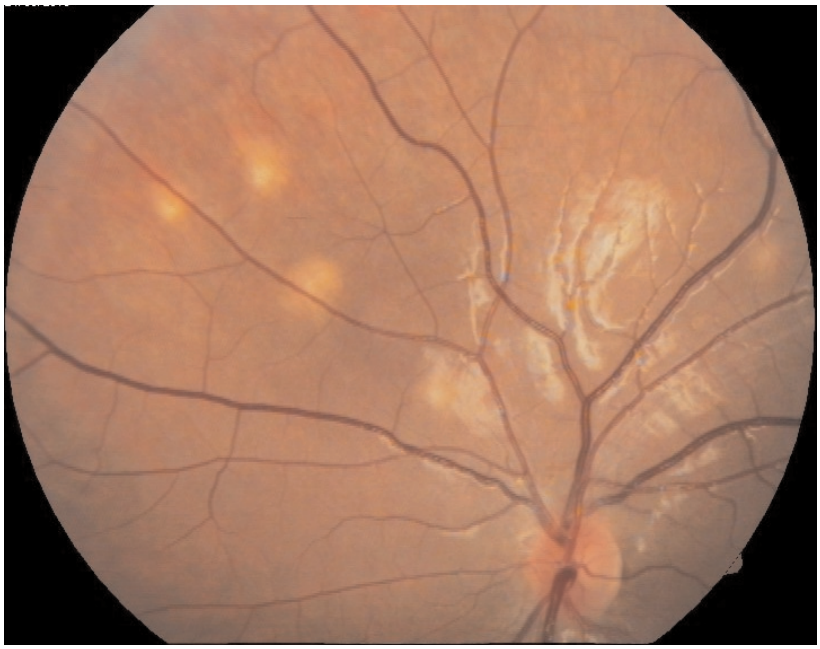

Figure 3. Initial funduscopic examination reveals disseminated chorioretinitis of both eyes
Slika 3. Inicijalni pregled fundusa oka pokazuje diseminirani korioretinitis oba oka

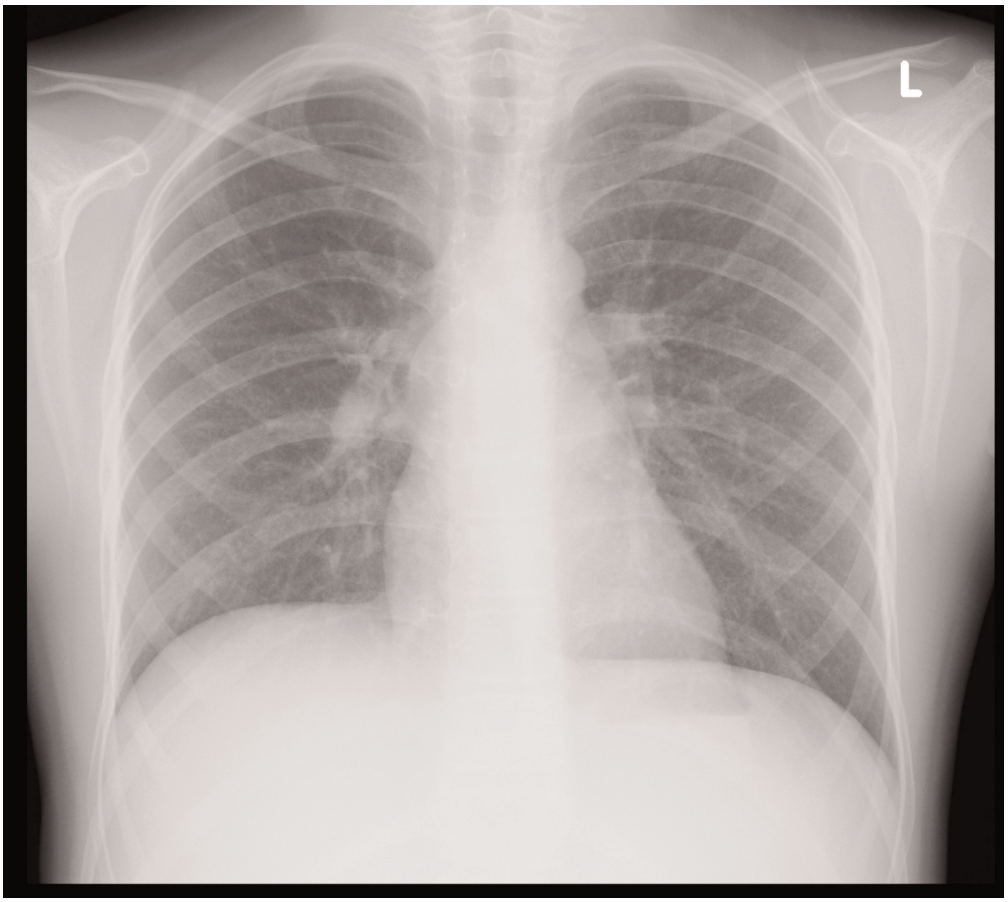

Figure 4. Control chest x-ray 3 weeks after initiation of antituberculous therapy shows almost complete resolution of infiltrates
Slika 4. Kontrolni radiogram prsnog koša nakon početka primjene antituberkulotske terapije pokazuje gotovo potpuni nestanak infiltrata

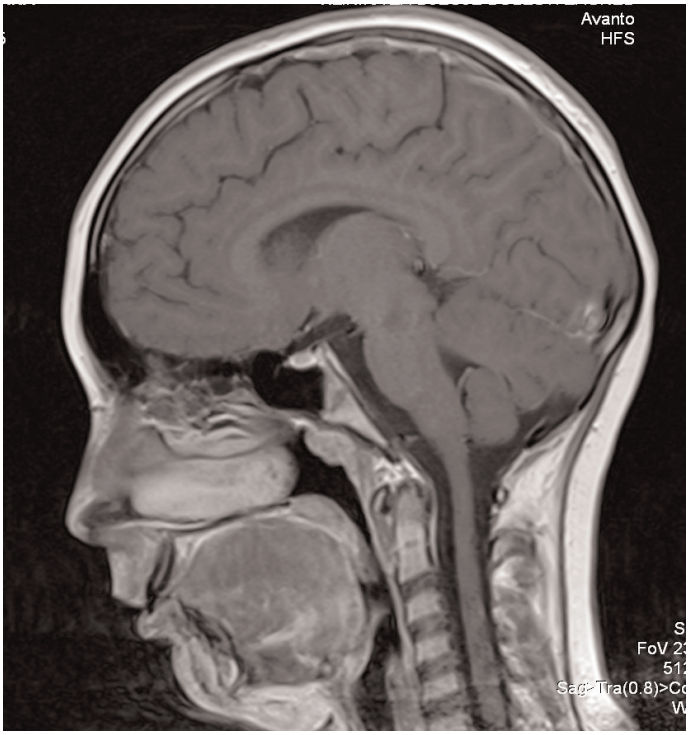

Figure 5. Brain MRI reveals significant reduction of the miliary tuberculomas 1 month after initiation of antituberculous therapy
Slika 5. MR mozga pokazuje značajnu redukciju milijarnih tuberkuloma mjesec dana nakon početka antituberkulotskog liječenja

According to her mother's statement, the contacts were healthy, although we later found out the grandmother was in observation because of lung infiltrate with hilar lymphadenopathy.

On admission neurologic examination revealed nuchal rigidity, but no focal neurologic deficits were detected. Laboratory tests showed similar findings as previously mentioned. Because of the dry cough in anamnesis, chest x-ray was performed on admission and revealed bilateral nodular infiltrates, highly suggestive of miliary TB (Figure 1).

Lumbar puncture demonstrated moderate pleocytosis of 270 white cells/μL (neutrophils 55 %), mildly elevated protein level (0.83 g/L) and cerebrospinal fluid (CSF)/serum glucose ratio of 0.35. The patient was immediately started on antituberculous treatment with isoniazid, rifampicin, ethambutol and pyrazinamide. Dexamethasone was also added as adjunctive therapy. Lumbar puncture was repeated three days later, when antituberculous therapy was already initiated. Acid-fast staining, culture and polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* remained negative from both CSF samples. The magnetic resonance imaging (MRI) of brain demonstrated multiple, contrast enhanced tiny nodules in cerebellum, cerebrum and brain stem, without signs of basal meningitis. This finding highly suggested the miliary pattern of brain tuberculomas (Figure 2).

Active searching for other signs of active TB outside the CNS revealed disseminated chorioretinitis of both eyes (Figure 3).

Our struggle to detect mycobacteria from other samples beside the CSF (i.e. bronchoalveolar lavage fluid, urine, stool) unfortunately wasn't successful. Only blood IFN-γ releasing assay (IGRA) came positive. Although etiologic diagnosis wasn't confirmed, there was significant clinical and radiologic improvement on treatment (Figures 4, 5). Repeated lumbar puncture also showed improvement of CSF analysis.

HIV test, as well as immunologic screening for possible immunodeficiencies were negative.

The patient was treated with 4-drug regimen mentioned above for two months, followed by ten months of isoniazid and rifampicin. Dexamethasone was added to therapy for ten weeks. No toxic side effects of therapy were noticed.

Chest x-ray showed complete resolution of nodules two months after initiation of therapy, and brain MRI performed six months after admission to hospital demonstrated no pathology. On follow-up one year later, the patient was in good clinical condition and no neurological sequelae were reported.

Discussion

With an overall mortality rate of almost 15 % and permanent neurological sequelae occurring in around half of patients, CNS TB remains a devastating infection in childhood [3].

Early recognition of CNS TB is difficult because clinical and laboratory manifestations can mimic many infectious and noninfectious diseases. Our patient presented with 1-month history of occasional low-grade fever with abdominal pain, diarrhea, cough and weight loss. Laboratory findings of elevated erythrocyte sedimentation rate and slightly elevated transaminases were also nonspecific.

Children with CNS TB often initially present with abdominal symptoms such as nausea and vomiting. The disease is typically subacute and progresses through three phases: the prodromal, meningitic and paralytic phase. The prodromal phase, lasting two to three weeks, is characterized by nonspecific symptoms such as malaise, lassitude, headache or low-grade fever. The meningitic phase follows with more pronounced neurologic features, such as meningismus, protracted headache, vomiting, lethargy, confusion, and cranial nerve and long-tract signs. The paralytic phase is characterized by confusion which progresses to stupor and coma, seizures, and often hemiparesis [3, 4].

The diagnosis of CNS TB was suspected in our patient in meningitic phase, having in mind one-month history of nonspecific symptoms and finding of small nodules on chest x-ray performed on admission.

It's important to emphasize that abnormalities on chest radiograph may be seen only in half of CNS TB cases, ranging from focal lesions to a subtle miliary pattern [5]. Other sighs of active TB outside the CNS, such as choroidal tubercles, as seen in our patient, are of diagnostic import if present.

Although the typical analysis of CSF from patients with CNS TB demonstrates lymphocytic pleocytosis, low glucose level and elevated protein level, there are many atypical presentations with normal protein or glucose level or normal white blood cell count. There even may be a predominance of polymorphonuclear cells rather than lymphocytes in the CSF [6]. Similarly, CSF analysis of our patient wasn't typical for TB: mild pleocytosis with polymorphonuclear cell predominance (55 %), only slightly elevated protein level (0.83 g/L) and relative hypoglycorachia (1.7 mmol/L or 35 % of blood glucose level).

Definitive diagnosis of CNS TB is based on the detection of the tubercle bacilli in the CSF, either by smear examination or by bacterial culture. However, the demonstration of mycobacteria in the CNS is not always possible. It is known that the sensitivity of acid-fast staining and TB culture of CSF is directly dependent on the number and volume of CSF samples examined. That's why repeat lumbar puncture, meticulous microscopy and culture of a large volume (> 6 mL) of CSF are recommended [7]. Unfortunately, mycobacteria weren't confirmed in CSF samples of our patient, probably because one sample was taken on admission, and second three days later, when therapy was already initiated.

Because of the limitations of conventional tests, the commercial nucleic acid amplification test and other PCR-based assays have emerged as an alternative diagnostic tool. The Xpert MTB/RIF used in this case is reported to have sensitivity of almost 60 % in the diagnosis of CNS TB [8].

We used blood IGRA as a supportive method for diagnosing CNS TB, although it is reported to have limited diagnostic value and negative results cannot entirely exclude the disease. As with the tuberculin skin test, IGRAs cannot distinguish latent tuberculosis infection from active disease. The sensitivity of IGRA assays in patients with miliary tuberculosis is reported to be 68 – 93 % [9, 10].

CNS TB has various imaging appearances, including meningitis, tuberculoma, miliary tuberculosis, abscess, cerebritis and encephalopathy. Although meningitis is the most common radiologic manifestation of CNS TB, seen most frequently in the children and adolescents [11], our patient's brain MRI didn't show signs of meningeal enhancement or other radiologic manifestations of possible TB meningitis complications (progressive hydrocephalus, vasculitis, infarction or cranial neuropathies) [12]. On the contrary, MRI showed contrast-enhanced tiny lesions in cerebrum, cerebellum and brainstem. This imaging suggested the miliary pattern of intracranial tuberculomas, rare parenchymal form of CNS TB, seen mostly in severely immunocompromised patients [13]. These lesions are usually located at the corticomedullary junctions, are tiny (2 – 3 mm in diameter) and may be invisible on noncontrast MR sequenced. Postcontrast, T1-weighted MR images reveal numerous, round, small, homogeneous, enhancing (usually ring enhancement) lesions [14].

Since our patient raised a high index of suspicion on CNS TB, empiric antituberculous therapy with 4-drug regimen was promptly initiated, with significant resolution of symptoms and improvement of chest x-ray and brain MRI. Dexamethasone was also added to therapy regimen as adjunctive therapy. Because of the relative rarity of TBM and the difficulty of early diagnosis no randomized controlled trial has established an optimal regimen and course for CNS TB. Nevertheless, our patient was treated with an initial 2-month induction therapy regimen including isoniazid, rifampicin, pyrazinamide and ethambutol, followed by 10 additional months of isoniazid and rifampicin as

maintenance therapy, as suggested by most guidelines [15]. The use of steroid therapy as an adjunctive therapy is also approved by guidelines, and the mechanism for survival benefit may come from reducing hydrocephalus and preventing infarction [16].

Our patient recovered completely, without neurologic sequelae. One of the reasons is early recognition and prompt initiation of treatment. Namely, the overall mortality from CNS TB may be greater than 50 % in those patients recognized late in the course of disease. A large proportion of these patients also suffer from severe sequelae [3]. The other reason for good outcome is probably Bacillus Calmette-Guérin (BCG) vaccine, which is a part of national immunization program in Croatia and is given to all newborns. BCG is thought to be 52 – 86 % protective against developing the severe complications of TB such as miliary TB and CNS TB [17], but in cases of CNS TB it protects against a fatal outcome and severe sequelae [3].

In conclusion, we reported a case of CNS TB with rare form of miliary intracranial tuberculomas. Although the etiology wasn't confirmed since the CSF cultures and acid-fast stain remained negative, clinical presentation, epidemiological history, signs of TB outside the CNS and good clinical and radiologic response to antituberculous treatment indicated the diagnosis.

CNS TB continues to be a condition which carries significant morbidity and mortality. Early diagnosis and prompt initiation of treatment are essential to improve the poor outcome.

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