Case Report

Brain and lung metastasis of alveolar echinococcosis in a refugee from a hyperendemic area

Dennis Tappe,^{1,2} David Weise,³ Uwe Ziegler,² Andreas Müller,² Wolfgang Müllges³ and August Stich²

Correspondence

Dennis Tappe
dtappe@hygiene.
uni-wuerzburg.de

¹German Consiliary Laboratory for Echinococcosis, Institute of Hygiene and Microbiology, University of Würzburg, Josef-Schneider-Strasse 2, 97080 Würzburg, Germany

²Department of Tropical Medicine, Medical Mission Hospital, Salvatorstrasse 7, 97067 Würzburg, Germany

³Department of Neurology, University Hospital of Würzburg, Josef-Scheider-Strasse 11, 97080 Würzburg, Germany

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Alveolar echinococcosis (AE) of the liver with cerebral and pulmonary metastasis was diagnosed in a Tibetan monk who initially presented with severe headache to an emergency department in Germany. Multiple lesions with perifocal oedema and severe compression of the third ventricle were seen with computed tomography (CT) of the brain. Glioma or cerebral metastasis of a hitherto undiagnosed abdominal or pulmonary malignancy was suspected. CT scans of the lung and liver demonstrated further tumorous masses. Magnetic resonance imaging of the brain revealed the cystic nature of the cerebral lesions and the patient had a highly positive serology for AE. The echinococcal aetiology of the brain lesions was confirmed by PCR for this refugee from an area where two disease entities, AE and cystic echinococcosis, are hyperendemic.

Introduction

Alveolar echinococcosis (AE) due to the larval stage of the fox tapeworm, *Echinococcus multilocularis*, is an important zoonosis endemic to the northern hemisphere. The disease has been reported in central Europe, eastern France, Turkey, North America, Japan and China. High incidences linked to close contact with dogs have been reported from human populations in the Qinghai–Tibet plateau region of China (Xiao *et al.*, 2006). The disease develops after ingestion of infective ova dispersed into the environment in the faeces of the final hosts, foxes or dogs. The incubation period is long (5–15 years; Ammann & Eckert, 1996), and the parasitic tissue grows slowly and is of the infiltrating type. The liver is the organ primarily involved. Metastasis may occur and can involve virtually any organ. In systematic surveys, metastasis to the brain was reported in only 1–3% of patients with AE (Bresson-Hadni *et al.*, 2000; Kern *et al.*, 2003). These complications are often the primary reason for medical consultation. Clinically, the disease is staged according to the World Health Organization PNM system, based on the extent of the parasitic lesions in the liver, the involvement of

neighbouring organs and metastasis (Kern *et al.*, 2006). The diagnosis is based on imaging tools, serology and, in some cases, detection of the parasite's nucleic acid by PCR (Georges *et al.*, 2004).

Here, we present a case of advanced-stage AE in a Tibetan refugee with cerebral and pulmonal metastasis. Initially, a glioma or brain metastasis of a hitherto undiagnosed primary malignancy was suspected in this patient who was from an area hyperendemic for AE and cystic echinococcosis (CE). Diagnosis of AE was established by serology and PCR.

Case report

A 47-year-old Tibetan monk, who had sought asylum in Germany after he had fled from Lhasa (Tibet Autonomous Region of China) in 2005, went to the emergency department of a German hospital in December 2007 because of severe and sudden-onset cephalgia and nausea. On examination, the patient was fully oriented and alert. There was no neck stiffness, cranial nerve palsy, paresis or sensory deficit. Right-accentuated tendon jerks were noted. During emergency cranial computed tomography (CT), the patient had an epileptic seizure. CT showed several contrast-enhancing lesions with a diameter of 1 cm, and perifocal oedema of the right frontal and parietal lobe, and

Abbreviations: AE, alveolar echinococcosis; CE, cystic echinococcosis; CSF, cerebrospinal fluid; CT, computed tomography; EVD, external ventricular drain; MRI, magnetic resonance imaging; PET, positron-emission tomography.

in the basal ganglia region of the left hemisphere. There was a midline shift to the right without signs of tentorial herniation. The third ventricle was severely compressed and the left ventricle showed compression of the anterior horn and dilatation of the posterior horn. A glioma or cranial metastasis of a pulmonary or abdominal tumour was suspected, and the patient received 40 mg dexamethasone and mannitol intravenously. A chest CT scan performed 1 day later revealed a cavernous, round lesion measuring $5 \times 3 \times 3$ cm in the upper part of the right lung. An abdominal CT scan showed a solid, partly calcified mass measuring $5 \times 6 \times 9$ cm in the right lobe of the liver. Cranial magnetic resonance imaging (MRI) showed oedema of the brain parenchyma in the affected frontal, parietal and basal ganglia regions. The cerebral lesions had a cystic and partly grape-like character, surrounded by a thin line of gadolinium enhancement (Fig. 1a, b). Glioma, cerebral metastasis, tuberculosis or parasitosis of the brain (i.e. echinococcosis, cysticercosis, coenurosis, paragonimiasis or toxoplasmosis) was suspected, and the patient was transferred to the Department of Tropical Medicine in a secondary care hospital (Medical Mission Hospital).

Screening for anti-*Echinococcus* antibodies in the serum was positive using a crude *E. multilocularis* antigen-extract ELISA. The antibody index was very high (22.0, cut-off=1). Confirmatory assays for AE using an *E. multilocularis*-specific recombinant antigen, Em10 (Frosch *et al.*, 1991), and an Em2⁺ ELISA (Bordier Affinity Products) were positive with an index of 5.12 and 1.88 (cut-off=1), respectively. A commercial *Echinococcus* Western blot IgG (LDBio Diagnostics) showed a typical banding pattern for AE in the serum (Fig. 2a). A cysticercosis Western blot (LDBio Diagnostics) revealed an atypical banding pattern, indicating cross-reactivity (Fig. 2b). *Toxoplasma* serology was negative. Serology for paragonimiasis was weakly positive (1:10 by indirect haemagglutination assay), a result that was also interpreted as a serological cross-reaction. In the neurological department of a tertiary care hospital (University Hospital of Würzburg), an external ventricular drain (EVD) was inserted in the posterior horn of the left ventricle to relieve intracranial pressure. In a

Fig. 2. (a) Analysis of the patient's serum with *Echinococcus* Western blot IgG. The banding pattern is typical for AE, showing genus-specific bands at 26–28 kDa and 7 kDa and two clearly distinguishable sharp bands at 16 and 18 kDa. (b) Cysticercosis Western blot of the patient's serum. The banding pattern is not typical for cysticercosis. Cross-reactions are visible at the 6–8 kDa bands and in the 39–55 kDa area (narrow bands). (c) PCR targeting the chromosomal echinococcal spliced leader RNA gene from the CSF. An amplicon with the expected size of 110 bp is visible. +, Positive control; –, negative control; M, molecular size marker; Pt, patient's serum (a, b) or CSF (c).

cerebrospinal fluid (CSF) sample obtained from the EVD, anti-*Echinococcus* antibodies were measured and the cysticercosis blot showed cross-reactivity. However, the sample was haemorrhagic [$147\,600$ red blood cells and 1025 leukocytes ($\mu\text{l CSF}^{-1}$)] and contained tissue debris. A PCR targeting the echinococcal spliced leader RNA gene was performed as described by Brehm *et al.* (2000) on the CSF sample. An amplicon of the expected size of 110 bp was detected by agarose gel electrophoresis (Fig. 2c). Sequencing exhibited a nucleotide sequence typical for *E. multilocularis*. [^{18}F]Fluorodeoxyglucose positron-emission tomography (PET) showed increased focal tracer uptake in

Fig. 1. Coronal T2-weighted MRI of the brain (a) and frontal T1-weighted MRI with gadolinium enhancement (b). Oedema of the right frontal lobe and in the left basal ganglia area and adjoining white matter is visible (indicated by arrowheads). A cystic lesion in the left hemisphere is discernible (indicated by arrows), which has provoked a midline shift with compression of the third ventricle and dilatation of the posterior horn of the left ventricle.

the right lobe of the liver and in the right lung with central hypometabolic areas, indicative of AE lesions (Reuter *et al.*, 1999). In the brain, however, three foci with decreased tracer uptake were visible in the area of the cystic lesions, consistent with parasitic areas with lower glucose uptake than the metabolically highly active brain parenchyma (Fig. 3).

According to the World Health Organization PNM staging system, the patient was assigned to stage IV (P2N0M1). Albendazole therapy (400 mg twice daily) was commenced, and the drug was given continuously, without determination of serum levels. The EVD was removed after 6 days and low-dose oral dexamethasone was continued. As of April 2008, a 3-month follow-up was clinically uneventful, showing a marked reduction in the brain oedema and a small decrease in the cerebral lesions under anti-parasitic and anti-inflammatory chemotherapy. In the future, newly increasing intracranial pressure is anticipated and CSF

shunting will again be necessary. Surgical treatment of the cerebral lesions was not possible due to the presumed large safety margins of a resection, the multitude of lesions and the location of one lesion close to the basal ganglia. Gamma knife radiosurgery was also not considered for the latter two reasons. Because of the palliative situation, no surgical approach towards the hepatic and pulmonary lesions was contemplated.

Discussion

Metastasis of parasitic tissue from the liver (or secondarily from the lung) to the brain is a rare event and occurs in 1–3 % of patients with AE (Bresson-Hadni *et al.*, 2000; Kern *et al.*, 2003). Brain metastasis is considered a sign of the terminal phase of the disease (Barjhoux *et al.*, 1970; Bresson-Hadni *et al.*, 2000) and could simply be a matter of time during the course of AE. Metastasis to the lung occurs more often (in 7–20 % of patients infected; Bresson-Hadni *et al.*, 2000; Kern *et al.*, 2003) and may be a prerequisite for brain metastasis in some cases. Pregnancy (Yang *et al.*, 2005) has been proposed to play a role as a predisposing factor for cerebral metastasis in AE. Few reports on the rare primary infections of the brain have been published (Aydin *et al.*, 1986; Qiu *et al.*, 1986). The clinical symptoms of cerebral AE depend on the localization of the lesions within the central nervous system. Interestingly, despite the multitude and size of the cerebral lesions, our patient presented almost without any focal neurological deficits. Instead, signs of increased intracranial pressure led to his hospitalization. On MRI scans, cerebral AE lesions are cystic and often multilobular, grape-like masses with definite margins and surrounding contrast enhancement. Calcifications and oedema are common (Algros *et al.*, 2003). Cerebral metastasis of primary hepatic AE is often multifocal, as also seen in our patient. The differential diagnosis encompasses coenurosis (a single, large grape-like mass in the brain without other organ involvement), cysticercosis (small cysts in multiple brain locations and in the muscles, the grape-like racemose type in the cisternae), brain paragonimiasis, toxoplasmosis, glioma and cerebral metastasis of malignant neoplasias. In the case presented, the cerebral lesions were not biopsied due to their location. In order to confirm the assumed echinococcal aetiology of these lesions, we used a specialized PCR with primers directed against the spliced leader RNA gene in chromosomal echinococcal DNA on a CSF sample of the patient. *Trans*-splicing is a typical feature of tapeworm transcription, requiring a small multicopy gene (the spliced leader RNA gene) in the parasite's chromosomal DNA (Brehm *et al.*, 2000). In a recent report, *E. multilocularis* was successfully distinguished from *Echinococcus granulosus* in a patient with subcutaneous and osseous lesions by this method (Scheuring *et al.*, 2003). PCR has been used to confirm the echinococcal aetiology of lesions in unusual locations. Diverse protocols have been developed to detect

Fig. 3. (a, b) Coronal (a) and transversal (b) PET of the brain. Tracer uptake is decreased in the area of the parasitic lesions (indicated by filled arrowheads). (c, d) Coronal PET/CT of the trunk. Increased tracer uptake is shown in the right lung (indicated by arrows) and in the right lobe of the liver (indicated by open arrowheads). The lesions are centrally hypometabolic. The kidneys and the urinary bladder show normal tracer excretion.

echinococcal nucleic acids in biological samples, and PCR is increasingly being accepted as a complementary diagnostic tool for echinococcosis (Georges *et al.*, 2004; Scheuring *et al.*, 2003).

This report indicates that immigrants who present with unknown tumours in any organ should be screened serologically for parasitic diseases endemic to their place of origin. Blood eosinophilia is not a reliable marker for chronic infections with tissue-invasive metazoan parasites, especially not for echinococcosis. However, serological test results should be interpreted with caution if unusual banding patterns are present in Western blot analyses. Serological cross-reactions between various cestodes, and between cestodes and the phylogenetically related trematodes may occur. In the case described, the patient grew up in the Qinghai–Tibet plateau region, an area hyperendemic for AE and CE. Dogs are the final hosts for *E. multilocularis* and *E. granulosus*, and close contact with dogs, as also reported by our patient from the monk's temple area, is a known risk factor for both AE and CE (Tiaoying *et al.*, 2005). Interestingly, dogs seem to be non-suitable final hosts for *Echinococcus shiquicus*, a novel echinococcal species endemic to the Qinghai–Tibet plateau (Xiao *et al.*, 2006). *E. shiquicus* is a species with unknown potential to infect humans, but unusual sonograph findings inconsistent with both AE and CE have been reported in some patients (Xiao *et al.*, 2006). In our patient, the PCR results showed clear features of *E. multilocularis* infection. As in many patients with AE, a complication of the advanced stage of the disease was the reason for medical consultation in the case presented. As many organ systems may be involved during the natural history of AE, a multi-disciplinary approach is necessary to treat the disease. Currently, there is no consensus on the treatment of cerebral lesions, but a surgical approach should be considered whenever possible (Algros *et al.*, 2003). Radical resection of hepatic and other lesions is the treatment of choice (Ammann & Eckert, 1996); however, most patients are inoperable at the time of diagnosis (Reuter *et al.*, 2004). Schmid *et al.* (1998) described the successful treatment of a single, large, cerebral lesion with gamma knife radiotherapy. In our patient, the extent of the cerebral lesions and the neurological deficits to be expected after an intervention did not allow radical resection or radiosurgery. Thus, long-term benzimidazole chemotherapy remained the only therapeutic option in this case. However, this drug is merely parasitostatic in most patients and does not significantly improve the poor prognosis of cerebral AE.

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