Case report

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Acute disseminated encephalitis in an adult patient addicted to heroin. Neuropathological, neuroradiological and clinical features

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Abstract

Acute disseminated encephalomyelitis (ADEM) is an immune demyelinating central nervous system (CNS) disorder, characterized by monophasic new onset neurological symptoms including encephalopathy, combined with neuroradiological evidence of multifocal demyelination. ADEM is extremely rarely diagnosed and is much more common in children and adolescents than in adults. The aim of this study is to present an extremely rare case of ADEM in a heroin-addicted patient with a very difficult diagnostic course. The results of the magnetic resonance imaging (MRI) examination in this patient were inconclusive. Fungal abscesses or inflammatory lesions of an unclear nature were suspected especially in a patient with impaired immunodeficiency. In view of the constantly deteriorating condition of the patient with disturbed consciousness and the unclear aetiology, the lack of effective treatment, a decision was made to perform a bilateral stereotactic biopsy and aspiration of brain abnormalities in order to obtain a neuropathological specimen and begin with the causal treatment. Neuropathological examination revealed the presence of Creutzfeldt-Peters cells characteristic of ADEM. Treatment with methylprednisolone significantly improved the patient's general and neurological condition.

To our knowledge, the above case is the first in the world literature in which ADEM has been confirmed by bilateral stereotaxic aspiration for the treatment of symptoms of increased intracranial pressure as a lifesaving procedure. Neuropathological confirmation allowed for the implementation of appropriate treatment, which resulted in complete recovery. Moreover, this case is interesting because ADEM was diagnosed in a patient addicted to heroin, where opportunistic inflammation of a fungal aetiology was considered in the first place.

Key words: *acute disseminated encephalomyelitis, stereotactic biopsy, Creutzfeldt-Peters cells, increased intracranial pressure.*

Introduction

Acute disseminated encephalomyelitis (ADEM) is an immune demyelinating central nervous system (CNS) disorder, characterized by new onset neurologic symptoms including encephalopathy [2,3]. ADEM is classically considered a monophasic illness, with the highest incidence in early childhood. The first description of an ADEM-like disorder with recognition of a temporary relationship to infection dates back to the 18th century [20]. The association of ADEM with vaccines or triggering infection is well recognized [20]. ADEM continues to be among the most frequent demyelinating disorders in childhood [4]. It is diagnosed extremely rarely in adults, especially with no history of bacterial or viral infections [2,3].

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In this article we report a rare case of ADEM diagnosed in a patient addicted to heroin, where opportunistic inflammation of a fungal aetiology was considered in the first place. Moreover, the presented case is unique because bilateral stereotactic biopsy was done to reduce the symptoms of increased intracranial pressure and obtain brain tissue to introduce the appropriate treatment.

Case description

A 33-year-old woman was referred to our hospital because of left hemiparesis and severe dysarthria of 6 hours' duration. The patient had a history of intravenous opioid use treated with methadone maintenance therapy for about 15 months at our institution. She denied any infection, vaccination or illicit opioid use in the months preceding hospitalization. The patient's only medication was methadone hydrochloride syrup (90 mg per day) and she had no known comorbidities. Neurological examination revealed severe central left facial nerve paresis, mild left masseter muscle weakness, bilateral decreased gag reflex and palatine reflex, severe left upper extremity weakness, mild left lower extremity weakness and a prominent left-sided Babinski sign. The patient did not speak – she could mumble very quietly with no discernible words or syllables but answered questions correctly by gestures and writing. The patient had dysarthria with severe hypophonia. Psychogenic mutism or motor aphasia were excluded (because the patient correctly used the Polish language while writing).

A quick stroke magnetic resonance imaging (MRI) examination of the head was performed upon admittance to the emergency room. The MRI was performed without contrast and revealed two large focal brain lesions with peripherally restricted diffusion (Fig. 1). The lesion located in the left frontal lobe produced mass effect and midline shift of 5 mm to the right. Physical examination showed multiple burn-like scars on the patient's neck and back, needle marks on upper extremities, and a wound on the patient's right anterior shin of 1 cm depth with no apparent signs of active infection. Blood tests at presentation showed moderate microcytic anaemia and hypoferraemia. Psychiatrists supervising the patient's methadone maintenance therapy noted that the patient had lost considerable weight during two weeks that preceded this patient's admission. They confirmed that the patient had spoken fluently in recent months. The patient underwent brain MRI which revealed multiple white matter lesions with an open-ring pattern of contrast enhancement and diffusion restriction in both hemispheres, in the left optic nerve and cervical spine according to the reporting radiologist, suggesting in the first place demyelinating foci with vast differential diagnosis of abscesses (including fungal), metastasis, glioblastoma, cysticercosis and tuberculoma (Figs. 1-5). Two other radiologists, as well as neurosurgeons and neuroinfectious disease specialists involved in the case suggested an atypical infection, possibly aspergilloma – a plausible explanation given the patient's history of intravenous drug abuse. Because of the danger of high-dose intravenous steroid administration in a patient with a possible invasive CNS fungal infection, a lumbar puncture was performed despite the mass effect noted on brain MRI. The opening pressure during the lumbar puncture was elevated. Cerebrospinal fluid (CSF) examination showed normal white blood cell count, mild hyperproteinrrhachia – 48.5 mg/dl (with a normal value range between 15 and 45 mg/dl) and no signs of intrathecal antibody production. Blood tests showed no presence

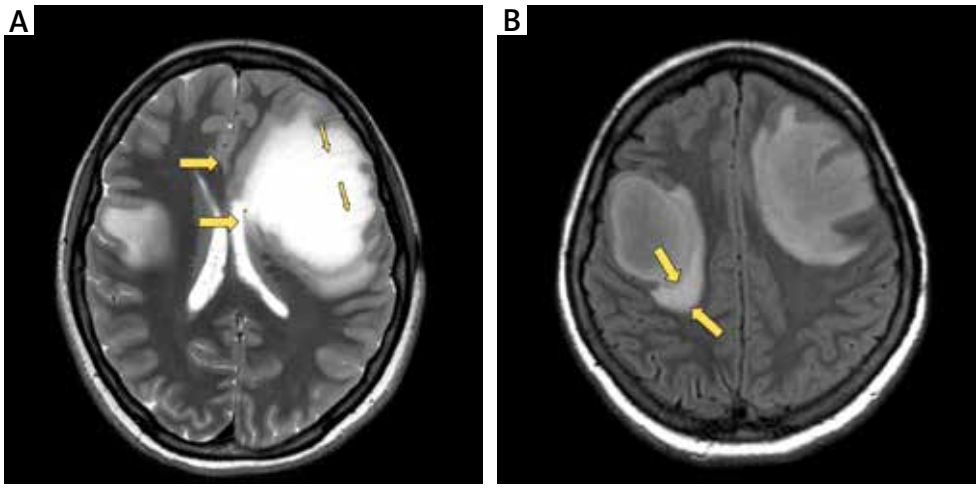

Fig. 1. T2W image (**A**) and FLAIR image (**B**) show the two largest hyperintense lesions. Note mass effect causing a little midline shift to the right and compressing anterior horn of lateral ventricle accompanied by little peripheral oedema (FLAIR image arrows). T2W image (**A**) reveals also dilated veins (thin arrows) located centrally within the lesion.

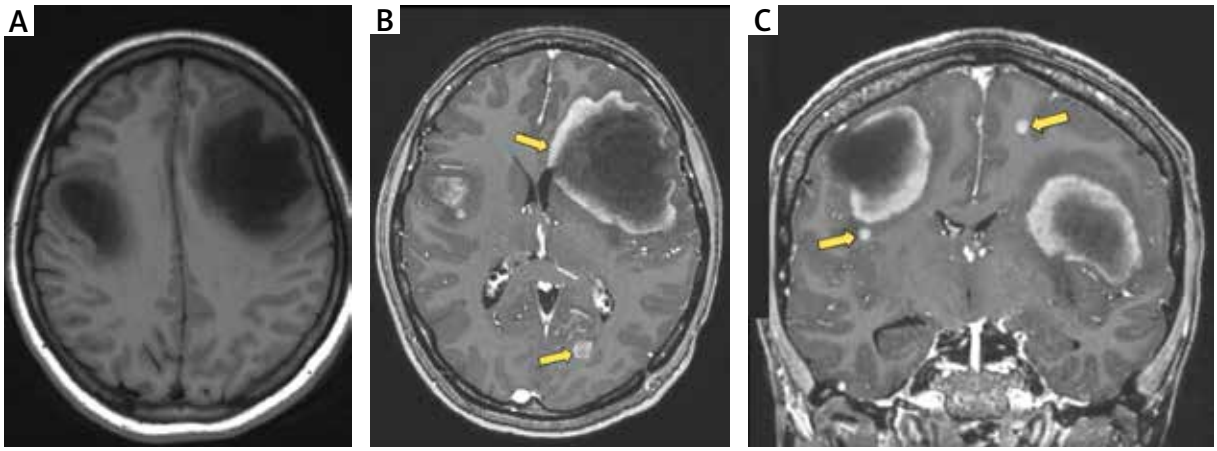

Fig. 2. Non-contrast enhanced T1W image (**A**) shows obvious large hypointense masses. Contrast administration reveals more small enhancing lesions at MPRAGE T1W images (**B**, **C**).

of antibodies to aquaporin-4 or myelin-oligodendrocyte glycoprotein antibodies. Due to unremarkable CSF analysis, it was decided to perform a stereotaxic brain biopsy of both lesions.

A blood test showed active hepatitis C virus infection while the test for human immunodeficiency virus infection was negative. Two generalized tonic-clonic seizures of 2 minutes' duration were observed on the fourth day of hospital stay while the patient was awaiting brain biopsy. Also on the fourth day of hospitalization, local deterioration of the wound on the right shin was noted with a simultaneous increase in C-reactive protein from 2.2 mg/l to 23.5 mg/l in 12 hours. Intravenous antibiotics (linesolide and meropenem) were started as well as intravenous fluconazole while awaiting access to voriconazole for possible invasive *Aspergillus* spp. infection.

On the fifth day of hospitalization, a significant neurological deterioration was noted: severe anopsia of the left eye, paresis of the adduction of the right

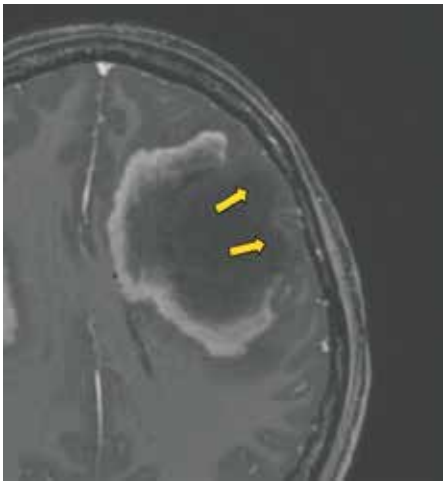

Fig. 3. Contrast-enhanced T1W image showing the enhancement pattern in the form of an open ring with the incomplete portion of the ring on the grey matter side of the lesion (arrows).

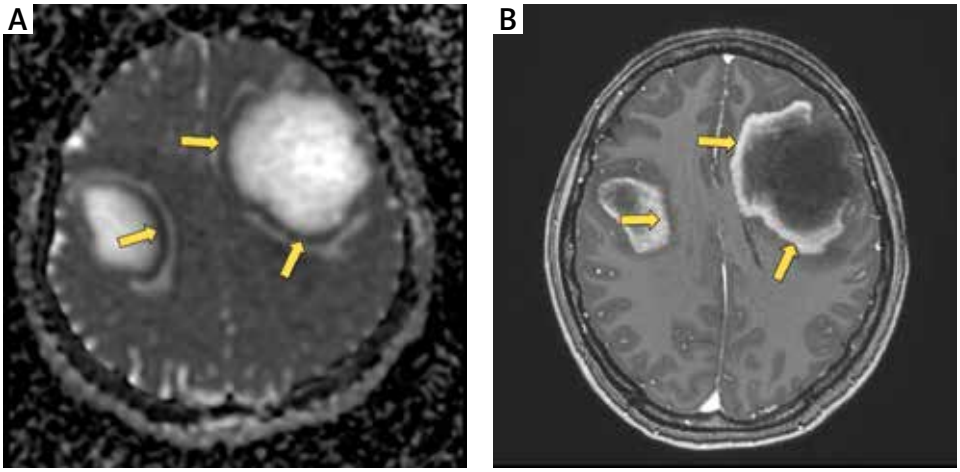

Fig. 4. ADC map (**A**) and corresponding T1W MPRAGE image after gadolinium injection (**B**). Restricted diffusion bands (black bands on ADC map – arrows) matching areas of contrast enhancement corresponding with the leading edge of most active demyelination.

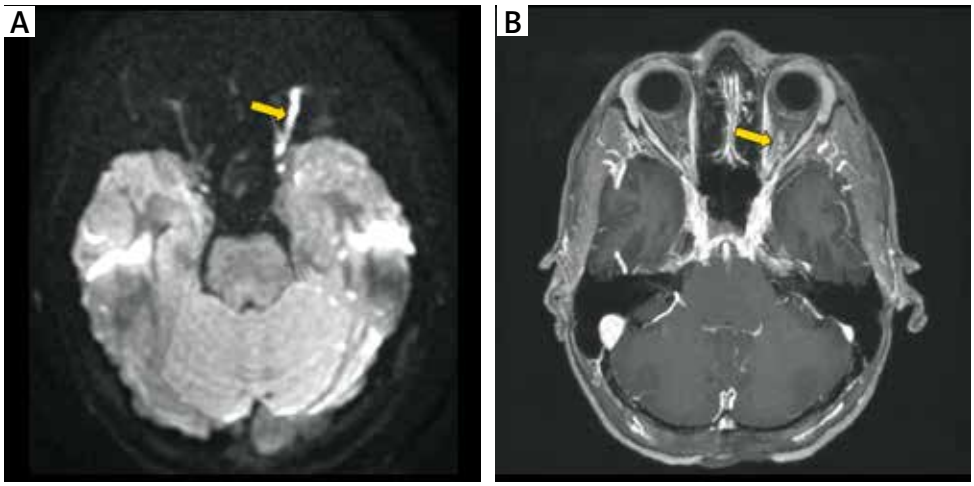

Fig. 5. A) DWI MIP image; image depicts restricted diffusion within the left optic nerve, what corresponds with enhancement at the image (**B**): T1W MPRAGE MIP image; revealing active demyelination. Note the pattern of its involvement: sparing of the retrobulbar optic nerve and chiasm which is more commonly seen in MS (than in other demyelinating entities e.g. ADEM or neuromyelitis optica spectrum disorder).

eye, almost complete palsy of the left upper extremity, worsening of the paresis of the left lower extremity and a pseudobulbar palsy presenting as a hypoglossal nerve paresis on both sides, swallowing difficulty requiring nasogastric tube placement, lack of gag and palatal reflexes and hypoesthesia of the left cheek. The ophthalmologic examination revealed mild papilledema. The computed tomography (CT) examination showed massive brain oedema with nearly total disappearance of cerebrospinal fluid spaces over cerebral hemispheres.

The patient was transferred to the Department of Neurosurgery where bilateral stereotactic biopsy in general anaesthesia was performed. Additionally, 20 ml of light yellow fluid was evacuated from the lesion in the left frontal area and 5 ml from the lesion in the right parietal area. Postoperative brain CT showed remarkable midline shift reduction from 7 mm to 3 mm. The perilesional brain oedema also subsided significantly. However, no clinical improvement was observed in the first two postoperative days.

Microbiological studies of the biopsy specimen showed no evidence of infection. The neuropathological examination of the brain specimens showed areas of focal demyelination and strong macrophage proliferation, presence of Creutzfeldt-Peters cells (CPC) and reactive astroglial formation – in correlation with the clinical picture most likely corresponding to a diagnosis of tumefactive demyelinating lesion (TDL) with neuropathological characteristics of acute disseminated encephalomyelitis (ADEM). Such a lesion mimics a tumour mostly because of its mass effect with surrounding oedema. TDL is a radiological diagnosis.

Two days after the stereotactic biopsy the patient was retransferred to the Department of Neurology where methylprednisolone was reintroduced (1 g daily for 7 days). The patient gradually improved followed re-initiation of steroid treatment – mainly regaining the ability to walk and talk. MRI of the cervical spine with the administration of contrast material was done and revealed on the left on the level of C1-C3, a focal intramedullary lesion of 30 mm length, partially enhancing peripherally, supporting a diagnosis of active demyelinating process (Fig. 6).

The patient continued her rehabilitation program improving in all aspects of neurological symptoms including vision and partial regaining of the left upper extremity strength. Three months after emergency hospital admission the patient's neurological examination was unremarkable. The clinical improvement correlated with the resolution of intracranial lesions found in this patient. A two-month MRI follow-up with contrast showed no enhancement of the lesions (Fig. 7), just as the 11-month MRI follow-up showed only residual lesions without mass effect or new lesions (Fig. 8).

Neuropathological findings

Brain tissue for neuropathological examination was obtained during bilateral stereotactic biopsy performed in general anaesthesia. Formalin-fixed, paraffin-embedded tissue sections were stained histologically with haematoxylin and eosin, periodic acid-Schiff, Klüver-Barrera,

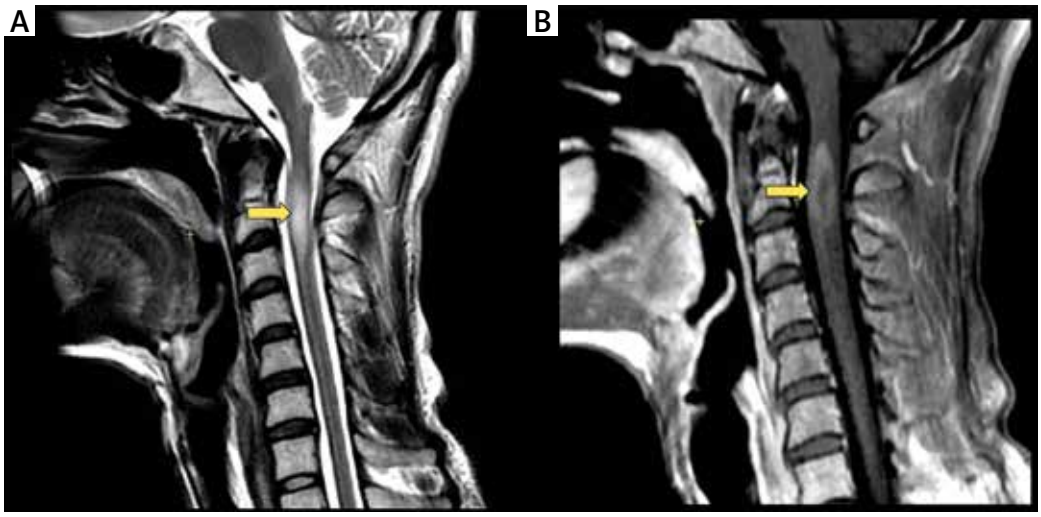

Fig. 6. T2W image on the (**A**) demonstrates a short segment (less than 2 segments) of the spinal cord lesion at the level of C2. After gadolinium application (**B**) peripheral enhancement is seen.

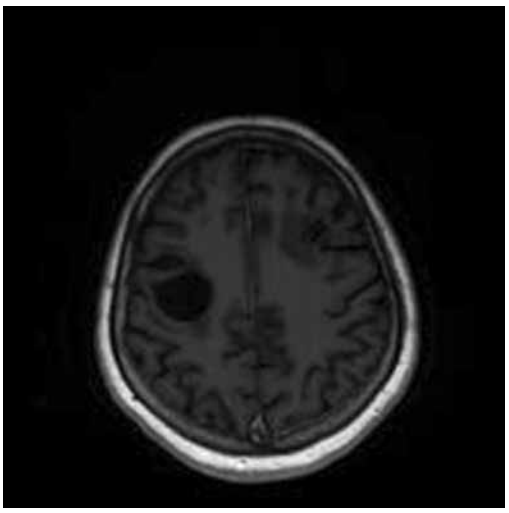

Fig. 7. Contrast administration reveals no enhancing lesions at T1 images performed 2 months after bilateral stereotactic biopsy.

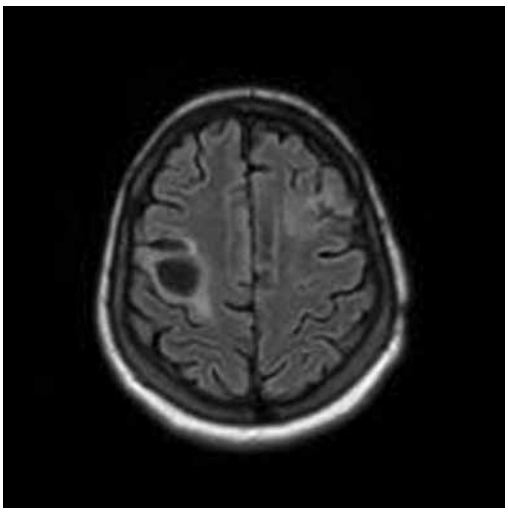

Fig. 8. T2 FLAIR image performed 11 months after bilateral stereotactic biopsy showing residual lesions without mass effect and no signs of new brain lesions.

Bielschowsky methods and immunohistochemically with GFAP (1 : 500, Bio-Rad, Hercules, USA), CD3 (1 : 100, GenomeMe, Richmond BC, Canada), CD68 (1 : 250, Cell Marque, Rocklin, USA), LCA (1 : 75, Cell Marque, Rocklin, USA), Ki67 (1 : 75, Thermo Fisher Scientific, Waltham, USA), anti-*Toxoplasma gondii* (1 : 20, Leica Biosystems, Newcastle, UK) and anti-*Borrelia burgdorferi* (1 : 100, Hercules, USA) antibodies. Microscopic examination showed a confluent, well-demarcated demyelination with diffuse, severe, parenchymal macrophage infiltration, mild, perivascular T-cell accumulation, reactive astrogliosis and reactive astrocytes with concomitant presence of nuclei with 'granular mitosis', typical of CPC (Figs. 9-12). Neither signs of viral or bacterial infection, nor for CNS vasculitis or lymphoma were revealed.

Discussion

This illustrated case represents diagnosis difficulties found in an adult patient with confirmatory neuropathological findings of ADEM obtained by urgent bilateral stereotactic biopsy. The challenging confounding factors in this patient were as follows: a recent rapid weight loss (body mass index of 17.1) with evident

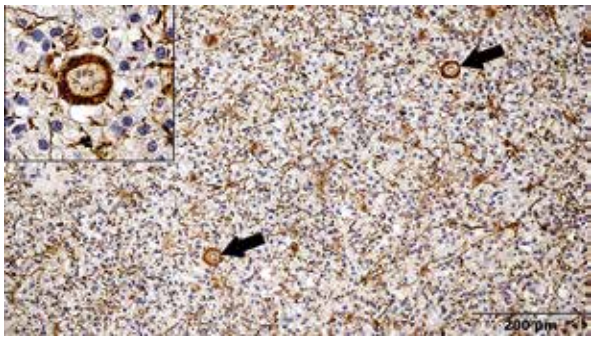

Fig. 9. Microscopic findings. Immunohistochemical staining for glial fibrillary acidic protein (GFAP) showed diffuse, parenchymal inflammation with astrogliosis and reactive astrocytes with typical for Creutzfeldt-Peters cells nuclei with 'granular mitosis' (arrows, insert).

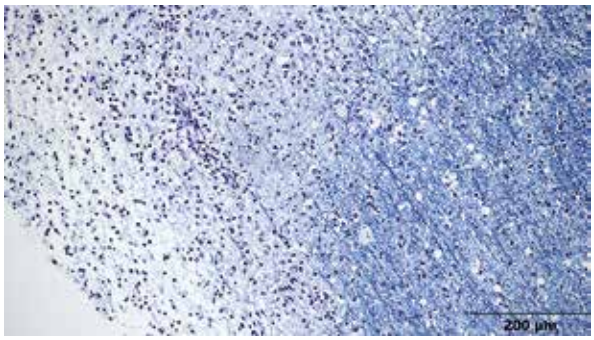

Fig. 10. Microscopic findings. The Klüver-Barrera staining revealed severe, well-demarcated loss of myelination.

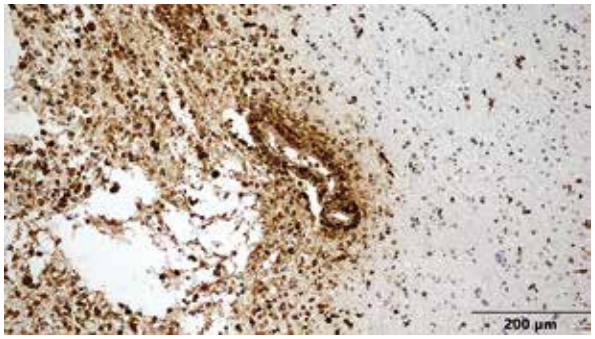

Fig. 11. Microscopic findings. Immunohistochemical staining for CD68 showed massive parenchymal and perivascular macrophage infiltration.

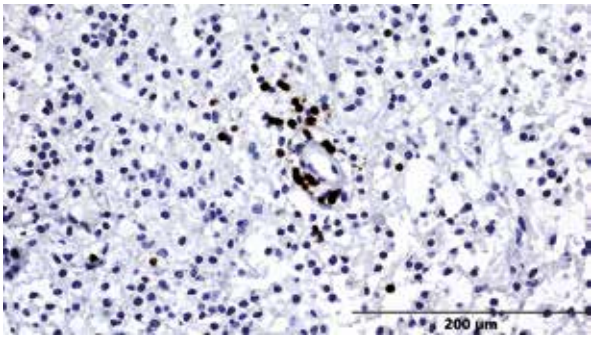

Fig. 12. Microscopic findings. CD3 immunohistochemistry revealed mild perivascular T-cell accumulation.

malnutrition, positive history of intravenous drug abuse, hepatitis C virus infection with suspected encephalitis or encephalomyelitis.

Diagnosis of ADEM based on imaging is difficult since there are no defining MRI criteria [5]. The MRI abnormalities are most frequently identified on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences as poorly marginated areas of increased signal intensity [25]. Lesions in ADEM are typically large, multiple, and asymmetric [5,25,27]. These lesions are located usually subcortically, or at the grey-white matter junction. In the presented case, the patterns of MRI findings were related to large, confluent, tumefactive demyelinating lesions. These lesions were large causing mass effect with relatively small surrounding oedema. Moreover, this case illustrates also difficulty in diagnosing a rare disease in the presence of a highly specific but not pathognomonic sign, as the open ring sign for tumefactive demyelinating lesions seen on contrast-enhanced T1-weighted images [16,17]. Prevalence of tumefactive demyelinating lesions is estimated to be 1-3 per 1000 cases of multiple sclerosis (MS) with an annual incidence of 0.3 per 100,000 while the proportion of ADEM presenting as a TDL is unknown [3].

It should be noted that the incidence of gadolinium enhancing lesions in ADEM on T1-weighted images may depend on the stage of inflammation. Specific patterns of lesions enhancement are present in 30% to 100% in described cases of ADEM [7,23,25]. Ring enhancement may be complete but also incomplete at the grey matter side of the lesion as seen in our case. Given the much higher incidence of neoplasm and infections, these lesions are still frequently responsible for open-ring enhancement [9].

Smaller multiple inflammation lesions may show ring-like or homogenous enhancement like seen in our case in the white matter of both hemispheres. When

lesions are solitary, the suspicion of high-grade glioma or lymphoma should be taken into consideration. In these cases using dynamic susceptibility contrast MR perfusion may be recommended. An especially useful parameter is relative cerebral blood volume as within tumefactive demyelinating lesions it has been found to be lower than in high-grade gliomas and lymphomas [9,19].

Another helpful sequence may be diffusion-weighted imaging (DWI). Gliomas, lymphomas and cerebral abscesses demonstrate a restricted diffusion pattern of signal changes. For example, in gliomas there will be observed multiple foci of restricted diffusion within the lesion, whereas in lymphomas it will rather be described as an "area". In the cerebral abscesses there will be centrally restricted diffusion within capsulated mass accompanied by large oedema. In the presented case, we observed a band of restricted diffusion on the periphery of large lesions which was corresponding to the enhancing area after contrast application. These are known to be regions of the most active demyelination process (so called leading edge) heading towards grey matter [7].

Susceptibility-weighted imaging (SWI) may also be helpful in differentiating pyogenic abscess from necrotic glioblastomas and the dual rim sign is the most specific [26].

Our patient had a positive history of heroin addiction which directed the suspicion of atypical neuroinfectious disease, including in the first place fungal abscesses caused by aspergilloma but also cysticercosis, tuberculoma, and less likely metastasis or CNS lymphoma. The coincidence of simultaneous different aetiologies was also taken into consideration. Despite the above-described findings with inconclusive CSF examination, the diagnostic uncertainty necessitated the stereotactic brain biopsy. This neurosurgical treatment was even accelerated by worsening of our patient's neurological status and consciousness state despite intravenous antibiotic and antifungal treatment. The bilateral stereotactic biopsy with aspiration of intralesional fluid from the largest lesions decreased the intracranial pressure and enabled the final diagnosis which initiated urgent high-dose steroid treatment. The patient received methylprednisolone with continued clinical improvement.

The stereotactic brain biopsy in clinically uncertain cases remains the only way to establish the final diagnosis. In our case the neuropathological findings revealed the presence of CPCs. These CPCs are reactive astrocytes with fragmented nuclear inclusions (micronuclei) that are associated with inflammation and demyelination, routinely seen in MS or ADEM [4,22] Micronuclei originate from chromosomes that do not attach properly to the spindle apparatus during mitosis and fail to be included in the daughter nuclei, but are enclosed by the nuclear membrane [3,18,19]. Interestingly, CPCs are frequent in active MS lesions and absent in neuromyelitis optica, which may suggest different inflammatory or oxidative environments in these conditions; CPC in MS may reflect astrocyte proliferation, whereas their absence may result in astrocyte death or compromise [4].

Our case is also rare as ADEM is much more common in children or young adults [2,3,14]. One of the largest studies to date describing 40 adult patients meeting ADEM criteria was presented by Schwarz *et al*. [21]. Brain biopsy was performed in 4 patients to rule out CNS lymphoma, and 1 patient was diagnosed after death [21]. In another study involving 5 adult patients with neuropathologically confirmed ADEM or ADEM-like disease, 3 patients were diagnosed on the basis of brain biopsy and 2 postmortem [13]. Also, children in whom ADEM is much more often diagnosed on the basis of clinical and radiological results, are extremely rarely undergoing a stereotaxic brain biopsy [11] or other forms of neurosurgical treatment, such as decompressive craniectomy [2,8,10].

The diagnosis of ADEM can be difficult as shown in this patient. The main confounding factor was heroin addiction without prior infection or vaccination. The first treatment was directed against a possible neuroinfectious disease or an active fungal infection of the CNS. Stereotactic brain biopsy with aspiration of the fluid components of the brain lesions had two possible lifesaving effects. First, it sufficiently diminished the signs of increased intracranial pressure and promoted effective steroid therapy in high doses, resulting in a full recovery. We advocate an invasive but effective method of obtaining tissue to establish the final diagnosis.

This challenging case was finally diagnosed as ADEM based on clinical, neuroradiological, and finally neuropathological findings. It was the most plausible diagnosis on account of the patient presented with rapid multifocal neurologic deficits without any prior history of neurological dysfunction. Additionally, we considered a Marburg variant of MS. This variant may present clinically as a pseudotumour form of MS, although Marburg variant has a very fulminant clinical course with very high morbidity and mortality rates [15]. In Marburg variant of MS even immunosuppressive treatments including high doses of corticosteroids may not provide clinical improvement [1,6,12,24]. On the contrary, in our patient when corticosteroid treatment was started, the improvement was noticed within a short time. Furthermore, ADEM has a more favourable clinical outcome when compared to Marburg variant of MS [1,3,5,6,24]. This is confirmed also by our

presented case. Moreover, the follow-up MRI examination done 2 and 11 months after stereotactic biopsy showed absence of any new lesions.

Conclusions

Confirming ADEM is a diagnostic challenge that requires extensive differential diagnosis and a series of neuroimaging, clinical and CSF studies that can often be inconclusive. Adult heroin addicts are highly sensitive individuals who develop opportunistic diseases, including neuroinfections or fungal infections of the CNS. We support the position that neuropathological examination should be the gold standard in such difficult diagnostic cases. Moreover, it is the first report that a bilateral biopsy has been performed in an adult ADEM patient who would have undoubtedly died from large TDL, and possibly postmortem examination should be conclusive.

Disclosure

The authors report no conflict of interest.

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