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ORIGINAL PAPER

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Signs of rapidly progressive dementia in a case of intravascular lymphomatosis

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Abstract Intravascular lymphomatosis (IVL), a rare type of non-Hodgkin's lymphoma, is an uncommon cause of progressive dementia, usually followed by death within a few months of onset of clinical disease. Often this aggressive tumor is only diagnosed at autopsy, because of misleading clinical features mimicking a broad spectrum of syndromes and the absence of circulating lympoma cells in the blood, bone marrow or cerebrospinal fluid in many cases. Here we present IVL in a 78-year-old woman with findings leading to the clinical diagnosis of vascular dementia with sudden beginning and positive 14-3-3 protein in the CSF, commonly reported in Creutzfeldt-Jakob disease (CJD).

Key words dementia · intravascular lymphomatosis · non-Hodgkin's lymphoma · primary angiitis of the CNS · Creutzfeldt-Jakob disease

Introduction

Intravascular lymphomatosis (IVL) is a rare, high-grade non-Hodgkin's lymphoma with a propensity for systemic dissemination [5] and poor prognosis [1]. Single cases show a restriction of the tumor process limited to the CNS [9]. Usually, the clinical course of this disease is followed by death within a few months, even with treatment [4]. Originally, intravascular lymphomatosis [17], also known as angiotropic large cell lymphoma [6, 23], was considered to be of endothelial origin and therefore was called neoplastic angioendotheliomatosis [8] or neoplastic angioendotheliosis [10, 26]. Recent studies [2, 3, 17, 19, 23] provide evidence that this tumor is of lymphocytic origin, most often of B-cell lineage [4], but T-cell origin has been reported [5, 22, 27].

Usually IVL occurs in middle-aged and elderly individuals with a range from 12 to 87 years [4]. One case of IVL was reported in a stillborn infant [27]. The male to female ratio is 2:1 [4]. Here we describe a case presenting signs of rapidly progressive dementia and IVL. The clinical findings led to a diagnosis of vascular dementia with sudden beginning and a differential diagnosis of primary angiitis of the CNS was discussed. The 14-3-3 protein commonly observed in the CSF of patients with Creutzfeldt-Jakob disease also tested positive in the case presented here.

Case report

A 78-year-old woman with no preceding psychiatric history had presented no clear hints of dementia in the past. Two months before her death short-term disorientation occurred followed by anxiety, mistrust and paranoid ideas. At that time she was treated for depression in the hospital and a medication with benzodiazepines was implemented. Four weeks after her release she again developed short phases with psychotic symptoms such as imagining she was being mugged, not recognizing her daughter and attacking her while crying for help. Therefore she was hospitalized again presenting paranoid ideas and anxiety, disorientation concerning time and place, symptoms of motor and sensory aphasia and a depressed mood. At first, this was thought to be a delirious episode since her treatment with benzodiazepine (2 mg lorazepam per day) had been discontinued abruptly and she was monitored during withdrawal treatment. During the following days, paramnesia, memory and language disorder were noticed and she scored 16 out of 30

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on mini-mental state examination. The laboratory findings revealed a leukocyte count of 8.31/nl, the hematocrit was 39 %. In the EEG a generalized slowing was observed with parieto-temporal Theta-Delta foci in both hemispheres. Cerebral CT showed multiple low density areas in the white matter and several remote infarct-like lesions. Magnetic resonance imaging showed multiple lesions of different stages widespread throughout the white matter. Radiologically, the differential diagnosis of vasculitis was discussed but since internal and neurological consultations revealed no certain symptoms for cerebral or peripheral vasculitis no cortisone was prescribed. An echocardiography was done to exclude endocarditis. Cerebrospinal fluid protein was increased to 78.6 mg/dl and 14-3-3 proteins were tested positive. No tumor cells were detected in the CSF. A clinical diagnosis of vascular dementia with sudden beginning was suspected since typical signs were observed such as sudden beginning of intellectual decline, transient episodes with delirious symptoms, lability of affect, neurological symptoms (aphasia), and vascular cerebral lesions revealed in CT and MRT. However, the clinical time course of 6 month duration required for a reliable diagnosis of dementia according to ICD-10 and DSM-IV criteria was not reached.

During the course of her disease temperatures up to 38.5 °C were recorded, and interpreted as being due to a urinary tract infection which was treated intravenously with antibiotics. Increased serum levels were detected for C-reactive protein varying between 21 and 101 mg/l, lactate dehydrogenase (269 UL) and antinuclear antibodies (1:160, reference < 1: 80) showing a "speckled" pattern. Anemia was observed and the leukocyte count rose to a maximum of 19.06/nl one day before her death. In the differential leukocyte count remarkable lymphocytes were described but without suspicion to be neoplastic cells four days before her death. Three days later the internal consultant was called again. He found the infection of the urinary tract to be treated well now but electrolytes were out of balance and she had constipation. Therefore he recommended the patient to be moved to another hospital with a ward for internal medicine. One day later she died. An autopsy was performed to clarify the diagnosis.

Materials and methods

The brain was fixed in 4 % buffered formalin for 3 weeks. Small tissue blocks were pretreated with formic acid for one hour, postfixed in formalin and embedded in paraffin. Histological sections were stained with hematoxylin and eosin. Immunohistochemistry was performed for several regions of the brain using the alkaline phosphatase red detection kit (Ventana, USA). Primary antibodies used in this study included LCA (leukocyte common antigen) (CD45; Dako), CD3 (Dako), CD20 and CD79a (Dako), CD31 (Dako), factor VIII (Dako), and cytokeratin (Immunotech). Furthermore, 3F4 (Dako) and L42 directed against the prion protein were used.

Pathological findings

Gross examination of the brain and the circulus arteriosus Willisii revealed several small lesions within the white matter of the cerebrum and cerebellum that were confirmed histologically as recent and remote infarcts. Microscopically the small blood vessels were packed with large, atypical lymphoid cells with bizarre nuclear features and numerous mitotic figures (Fig. 1). These neoplastic cells were detected within capillaries, arterioles and venules in all areas of the brain. Immunohistochemically LCA, CD20 (Fig. 2) and CD79a were positive. In contrast, CD3, CD31, factor VIII and cytokeratin were negative. There were no spongiform changes typical of CJD in the brain; immunohistochemistry for the prion protein was negative.

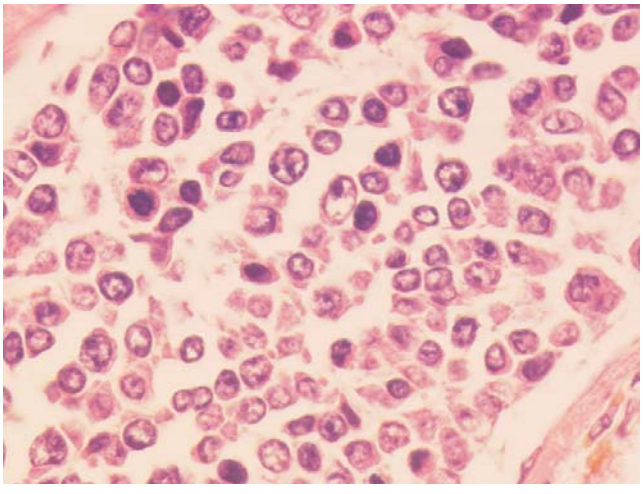

Fig. 1 Intracerebral blood vessel packed with atypical lymphoid cells showing mitotic figures (H. E., x 400)

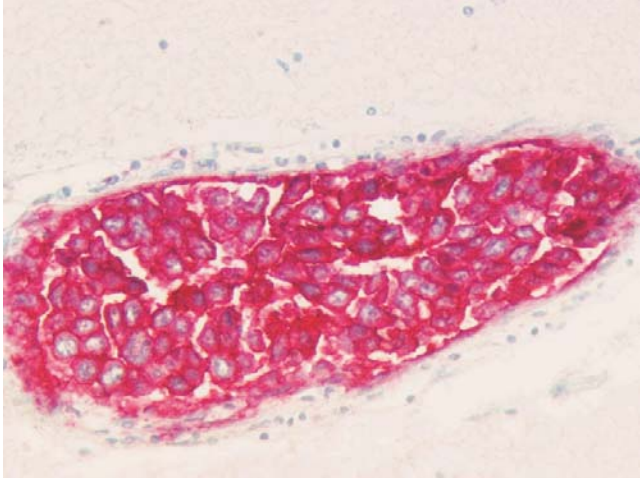

Fig. 2 Intravascular tumor cells staining positive with antibody CD 20 (x 200)

Discussion

The clinical diagnosis of IVL may be difficult. Only 18 of 66 patients reported in the scientific literature were diagnosed correctly ante mortem [4]. Initial manifestations often occur in the absence of circulating lymphoma cells in the blood [9], cerebrospinal fluid [4] or bone marrow [9, 11, 21], although they have been reported to be detected in each of these three localizations in single cases [2, 18, 28]. Usually neoplastic cells are located within the lumina of small blood vessels only [9]. The extent of organ involvement [22], the distribution [28] and the territories of occluded vessels [24] with tissue infarction [25] may sometimes result in a confusing array of clinical signs and symptoms [28, 29].

In the case presented here lymphoma as a pathophysiological cause for the ambiguous psychopathological syndrome was not suspected clinically. In contrast, due to the positive finding of protein 14-3-3 a differential diagnosis of CJD was discussed. Therefore, the autopsy was limited to the brain. With the knowledge about the results of the autopsy, the clinically unspecific mental disturbances such as short-term disorientations and paranoid ideas occurring in phases must be interpreted as the initial manifestations of IVL presumably due to involvement or occlusion of small cerebral vessels by tumor cells. Cerebral CT findings showing multiple low density areas and infarct-like lesions and MR imaging appearance were the reason why an early state of vascular dementia with sudden beginning was suspected although the time criteria according to ICD-10 and DSM-IV were not fulfilled. In the scientific literature the psychopathological abnormalities suggesting a diagnosis of dementia with a time course less than 6 months duration of the disease is described in cases with IVL [14] and CJD. Sporadic CJD presents signs of rapidly progressive dementia and death often follows within 2 or 3 months [20]. Of these patients, 70 % are reported to die within 6 months. Therefore time criteria in cases with rapidly progressive dementia like IVL and CJD seem to be problematic, and distinction from confusional states with mental state deterioration may be difficult. In our case vascular dementia, the second most common dementia after Alzheimer's disease [16], was suggested clinically at first. Vascular dementia often presents with unspecific signs. This diagnosis was supported by the finding of increased antinuclear antibodies reported to be present in about 60 % of vascular dementia patients [15]. A differential diagnosis of CNS vasculitis was discussed; indeed, vasculitis may be similar to IVL [13] in neuroimaging studies [25]. On the other hand the signs of rapidly progressive dementia and the positive result of the CSF14-3-3 test were thought to be typical of Creutzfeldt-Jakob disease. This protein is reported to be released into the CSF as a consequence of extensive destruction of the brain tissue. However, it is not thought to be specific for any one disease process as illustrated by our case [12]. In the absence of periodic sharp wave complexes in the EEG, myoclonus, visual and/or cerebellar symptoms, pyramidal and/or extrapyramidal signs, and akinetic mutism, it was not possible to make a clinical diagnosis of probable or possible CJD according to WHO criteria, even though the 14-3-3 proteins were positive. The detection of 14-3-3 protein in patients with IVL is reported in single cases only, showing lesions in the cortex, leptomeningeal and cortical enhancement [12].

In conclusion, our case presented here should alert clinicians to think of IVL in cases of progressive encephalopathy with mental changes ranging from acute disorientation to rapid progressive dementia [4] and imaging characteristics of CNS vasculitis or lesions consistent with cerebral infarctions. Constellations of fever of unknown origin [4], anemia, increased RBC sedimentation rate, LDH, CSF protein [4, 9] and antinuclear antibodies showing a "speckled" pattern increase the probability of IVL [9]. Careful examination of peripheral blood smear is recommended according to Glass et al. [9].

Because of the plurivalent interpretation of the reported features the diagnosis should be established by biopsy of an affected site, such as brain tissue or another organ in cases of systemic involvement, like the skin [7].

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