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CASE REPORT

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Primary manifestation of Hodgkin's disease in the central nervous system

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Abstract A 62-year-old woman presented with loss of memory and a mild hemiparesis. Neuroradiology demonstrated a left frontoparietal tumour. Biopsy specimens of this lesion revealed intracerebral Hodgkin's lymphoma, a diagnosis supported by immunohistochemical reactions of the tumour cells for the CD30 antigen. Additional cell cycle studies revealed a high proliferative activity of the tumour cells in association with absence of apoptosis. There was no evidence that overexpression of bcl-2 or Epstein-Barr virus infection was involved in the pathogenesis of this neoplasm. Lymphomas in the lung were detected 3 months later. Following neurosurgical excision, radiotherapy, and chemotherapy, the patient had no evidence of Hodgkin's disease after 13 months of follow-up.

Key words Hodgkin's disease · Central nervous system · Proliferation · Apoptosis · bcl-2

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Introduction

The overall incidence of primary lymphomas of the central nervous system (CNS) has increased significantly over the last two decades [11, 12], and malignant non-Hodgkin's lymphomas of B cell type account for the vast majority of these tumours [11, 12]. In contrast to the highly malignant non-Hodgkin's lymphomas, Hodgkin's disease is only exceptionally manifest in the central nervous system; clinical studies of patients with Hodgkin's disease have revealed an incidence of CNS involvement of 0.2–0.5% [19, 22]. In a large series, none of 2185 patients had intracranial disease at initial presentation, and involvement of the CNS was secondary to disseminated disease outside the nervous system [19]. Moreover, presentation of Hodgkin's disease as a primary, solitary intracranial lesion is extremely rare, and only sporadic cases have been reported [2]. Indeed, most cases originally diagnosed as Hodgkin's lymphoma of the CNS in the pre-immunohistochemical era were later identified as pleomorphic B cell neoplasms following immunocytochemical reassessment [18, 23].

We describe the clinical and histopathological findings of a patient who initially presented with isolated intracranial Hodgkin's disease. At a regular 3-month follow-up a systemic manifestation of the lymphoma was detected in the mediastinum. This case indicates that in the differential diagnosis of an isolated brain tumour in an otherwise healthy patient Hodgkin's disease should be considered.

Clinical history

A 62-year old woman from the Czech Republic presented with a 3-week history of memory loss and headache. She did not complain of other symptoms and specifically said she was not experiencing fever, pain or night sweats. Her prior medical history was unremarkable with the exception of a hysterectomy at the age of 46.

On admission, general physical examination was normal. In particular, lymphadenopathy, hepatomegaly, and splenomegaly

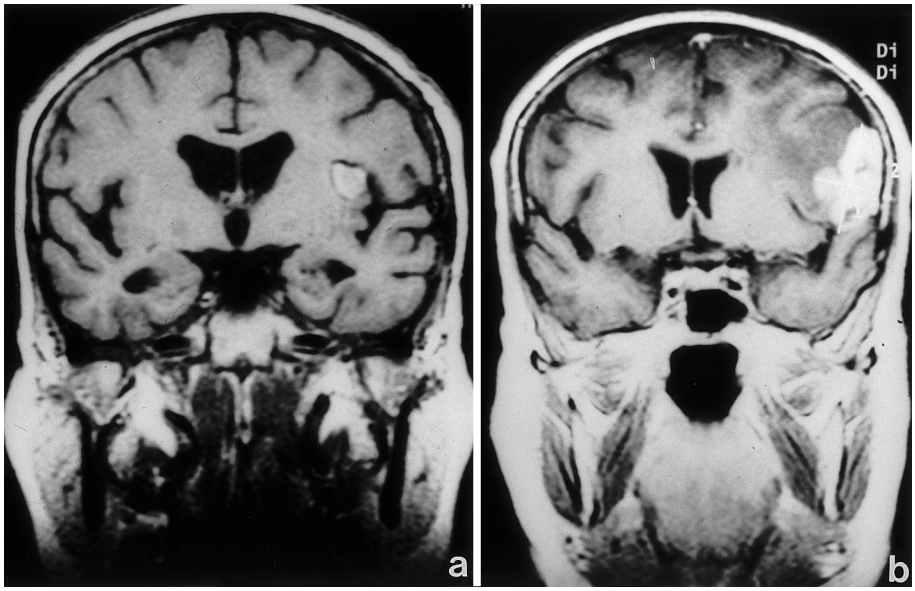

Fig. 1a, b Neuroradiological findings on admission. MRI demonstrates a large tumour in the left frontoparietal lobe. The tumour is located primarily in the cortex and the subcortical white matter (**a**, **b**). Note the hypodense centre of the lesion and the oedema-induced compression of the lateral ventricle (**b**). Coronal T1-weighted images

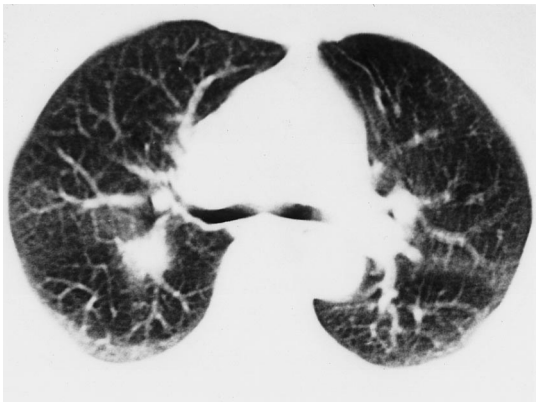

Fig. 2 Contrast-enhanced CT of the thorax at a 3-month follow-up examination. Several small hyperdense tumours are discernable in the perihilar areas of both lungs

were absent. Laboratory data were unremarkable. There was no evidence of a haematopoetic neoplasm. Radiological examination, including chest X-ray, was completely normal. Neurological examination revealed a right hemiparesis, mainly affecting the lower extremity. The EEG showed a left frontoparietal slow-wave focus. A cranial CT demonstrated a hypodense tumour in the left frontoparietal lobe. In addition, a small hypodense area in the white matter adjacent to the posterior right lateral ventricle was detected. The latter was interpreted as an old ischaemic or haemorrhagic defect with no relation to the frontal tumour. Further MRI studies revealed that the tumour was located in the cortex and subcortical white matter, had a central necrotic area and was accompanied by oedema of the surrounding brain tissue (Fig. 1a, b). On the basis of the history, the clinical and neuroradiological findings, a metastatic tumour was considered to be the most likely diagnosis, but meningioma was included in the differential diagnosis.

The patient underwent diagnostic craniotomy. A greyish tumour was detected in the left opercular gyrus immediately adjacent to the prefrontal gyrus. The lesion appeared relatively well demarcated and was firm upon palpation. A biopsy specimen of approximately 30×25×15 mm was submitted for neuropathological evaluation. Postoperatively, the patient recovered well. A mild motor aphasia was the only neurological deficit. On the basis of the neuropathological diagnosis of intracranial Hodgkin's disease, the patient was intensely followed up. CNS disease did not recur, but during a regular control examination 3 months later, chest X-ray revealed a lesion in the lung. Further CT scan analysis of the thorax confirmed this findings and demonstrated small, hyperintense tumours in both lungs in parahilar locations. They largest mass in the right perihilar region had a diameter of 22 mm (Fig. 2). These tumours were interpreted as mediastinal Hodgkin's lymphoma without biopsy verification. Otherwise, the examination was unremarkable. In particular, the remaining lymphatic system, including cervical and abdominal lymph nodes, were completely normal. In addition, there were no pathologic findings in liver or spleen. A bone marrow biopsy yielded a normal result. Furthermore, detailed serological examination was normal. Serum IgG antibodies to Epstein-Barr virus were in the normal range. There was no evidence of immunodeficiency, and the patient was HIV seronegative. A skeletal scintigraphy did not yield pathologic findings.

Chemotherapy with alexan, metothrexate, dexamethasone and leucovorin was instituted, and the patient received two cycles of this medication. With this regimen, the lung tumours resolved completely. Subsequently, the patient received radiotherapy of the brain with a dose of 45 Gy. At 13 months of follow-up, the patient is doing well with no evidence of recurrent Hodgkin's lymphoma in the CNS or at other sites. In particular, the tumours in the lungs have completely regressed, and a CT scan of the thorax was entirely normal.

Materials and methods

Surgically removed CNS tissue was fixed in 4% buffered formalin and embedded in paraffin, and 4-μm paraffin sections were used for H&E, Giemsa and reticulin fibre stains. In addition, an immunohistochemical analysis was performed. The following monoclonal mouse anti-human antibodies were used for phenotypic characterisation of the tumour cells (all from Dakopatts, Hamburg, Germany): CD45 (LCA), CD20 (L26), CD45RO (UCHL-1), CD30, and CD68 (KP1). In addition, monoclonal mouse anti-human bcl-2 (Novocastra, Heidelberg, Germany), monoclonal mouse anti-human Ki-67 (MIB-1, Dakopatts), monoclonal mouse anti-Epstein-Barr virus, LMP (Dakopatts), and polyclonal swine anti-rabbit GFAP (Dakopatts) were applied as primary antibodies. The expression of all antigens was demonstrated in an ABC protocol [10] using 3,3'-diaminobenzidine and H_2O_2 as cosubstrate. The sections were lightly counterstained with haemalum, dehydrated in

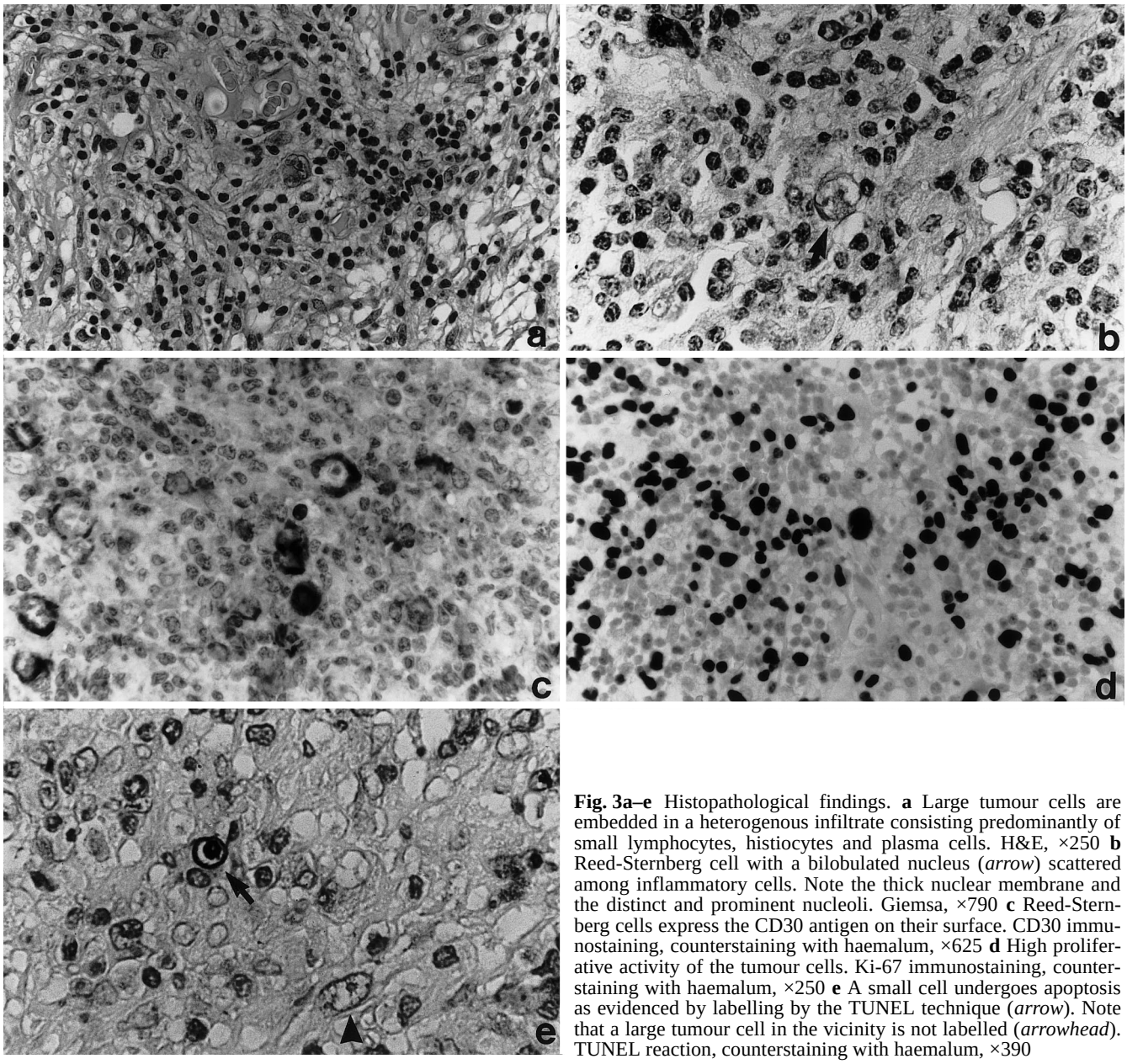

Fig. 3a–e Histopathological findings. **a** Large tumour cells are embedded in a heterogenous infiltrate consisting predominantly of small lymphocytes, histiocytes and plasma cells. H&E, ×250 **b** Reed-Sternberg cell with a bilobulated nucleus (*arrow*) scattered among inflammatory cells. Note the thick nuclear membrane and the distinct and prominent nucleoli. Giemsa, ×790 **c** Reed-Sternberg cells express the CD30 antigen on their surface. CD30 immunostaining, counterstaining with haemalum, ×625 **d** High proliferative activity of the tumour cells. Ki-67 immunostaining, counterstaining with haemalum, ×250 **e** A small cell undergoes apoptosis as evidenced by labelling by the TUNEL technique (*arrow*). Note that a large tumour cell in the vicinity is not labelled (*arrowhead*). TUNEL reaction, counterstaining with haemalum, ×390

graded alcohols and xylol (Merck, Darmstadt, Germany) and mounted in Corbit-Balsam (Hecht, Kiel, Germany). For each antibody, positive and negative controls were included. Negative controls included omission of the primary antibody and use of an irrelevant isotype-matched control antibody.

For demonstration of apoptotic cells, the TUNEL technique was applied. The TUNEL kit (Boehringer, Mannheim, Germany) was used according to the manufacturer's instructions. In negative controls, the reaction was performed without terminal transferase.

Pathological findings

Neuropathological evaluation showed a highly cellular tumour which was predominantly located in the cortex. It extended into the subcortical white matter and showed focal infiltration of the adjacent leptomeninges. Large tumour cells were embedded in a heterogenous infiltrate consisting of numerous small lymphocytes, histiocytes, and plasma cells (Fig. 3a). The neoplastic cells exhibited a homogeneous, amphophilic cytoplasm and a vesicular nucleus with finely dispersed chromatin granules. Occasional bilobar nuclei were seen. The nuclear membrane was prominent, and a distinct, acidophilic nucleolus was located in the centre of the nucleus (Fig. 3b). Immunohistochemistry demonstrated that the large cells were CD30 positive, but CD45, CD45RO, and CD20 negative (Fig. 3c). On the basis of their morphology and their immunohistochemical profile they were classified as Reed-Sternberg cells. The surrounding CD45 positive leucocytes consisted predominantly of CD45RO-positive T lymphocytes and, to a lesser extent, CD20-positive B cells. Whereas the T cells were also scattered throughout the tumour, the B cells resided predominantly in perivascular

cuffs. In addition, CD68-positive macrophages were distributed throughout the tumour. Many large tumour cells were MIB-1 positive, and regionally, more than 50% of the cells were labelled by this antibody (Fig. 3d). A significant number of small cells was labelled in the TUNEL reaction, and many of these cells exhibited morphological features of apoptotic cells with a condensed, shrunken nucleus. In contrast, Reed-Sternberg cells did not undergo apoptosis and were not labelled in the TUNEL reaction (Fig. 3e). In addition, they expressed neither the bcl-2 protein nor the Epstein-Barr virus late membrane antigen. Small groups of tumour cells were surrounded by reticulin fibres, but the blood vessel walls were rarely split by layers of tumour cells. There was severe oedema of the surrounding brain parenchyma with the formation of bizarre, sometimes multinucleated gemistocytic astrocytes.

Discussion

In contrast to non-Hodgkin's lymphomas, in Hodgkin's disease primary or secondary involvement of the brain is exceptional [1, 3, 5, 8, 11, 19]. The diagnosis of cerebral Hodgkin's lymphoma therefore met with scepticism. However, a detailed histopathological and immunohistochemical analysis confirmed this classification in the present case. The expression of the CD30 antigen identified the large tumour cells as Reed-Sternberg cells. CD30 is generally viewed as the most specific Hodgkin's disease-associated antigen, and it reliably detects Reed-Sternberg cells with a sensitivity of more than 90% [7, 21]. The mixed-cellularity type, as in our patient, and the lymphocyte-depleted subtypes prevail according to most case reports in the literature [2, 6].

Additional cell cycle studies demonstrated a high proliferative activity of the tumour cells, but no significant apoptosis. These observations are in line with Lorenzen et al. [16], who also failed to detect TUNEL labelling of Hodgkin and Reed-Sternberg cells in a series of extracranial Hodgkin's lymphoma cases. Interestingly, as observed in our study, TUNEL-positive apoptotic cells were confined exclusively to the non-neoplastic cellular background [16]. There is increasing evidence that impairment of apoptotic pathways is of critical relevance in the pathogenesis of a variety of lymphomas. In particular, overexpression of the proto-oncogene bcl-2, a powerful inhibitor of apoptosis, has been noted in a variety of lymphomas and linked to their pathogenesis [15, 17]. To our knowledge, bcl-2 expression has not yet been assessed in intracranial Hodgkin's disease. The observation that bcl-2 protein was not detectable may indicate that overexpression of this oncogene was not involved in the pathogenesis of the lymphoma in our patient. However, bcl-2 protein may show a nonhomogeneous expression in Hodgkin's lymphoma in the CNS, as has recently been described for extracerebral Hodgkin's disease [9]; analysis of a large series of cases will be required to assess this possibility.

In addition, infections with Epstein-Barr virus have been implicated in the pathogenesis of a subset of patients with Hodgkin's disease [13, 14]. Since our patient had normal serum IgG levels to the Epstein-Barr virus, and the late membrane antigen of the Epstein-Barr virus was not detectable on the tumour cells, there is no evidence for an Epstein-Barr virus infection as a critical pathogenic factor. Furthermore, our patient was not immunosuppressed. Although both primary non-Hodgkin's lymphomas of the CNS and extracerebral Hodgkin's lymphoma can be associated with a variety of congenital and acquired immunodeficiency states, a clear relationship between immunodeficiency conditions and intracranial Hodgkin's disease has not been established [6].

The clinical course of our patient, in whom Hodgkin's disease of the lung was detected 3 months after the initial presentation of the intracerebral lymphoma, raised the question as to whether the intracerebral tumour was the primary lesion or the result of a secondary dissemination of the lung disease to the CNS. The age of the patient (62 years), the symptoms of an altered mental status and a motor deficit, the primary intraparenchymatous location of the large solitary tumour and the satisfactory response to therapy and the favourable course of the disease argue for a primary CNS tumour rather than for secondary involvement of the brain. Thus, our patient with primary presentation of intracranial disease differs from patients with secondary CNS involvement. Secondary intracranial Hodgkin's disease has mostly become manifest in patients who were significantly younger at inital presentation (mean age 21 years) and following multiple relapses [18]. The median interval from the initial presentation to intracranial disease was 57 months [18]. In these patients, the supraclavicular lymph nodes were usually involved on one or both sides [18, 20]. In most reported cases, tumour cells were confined to the lumina of dural and leptomeningeal vessels [4, 18]. Correspondingly, the most common clinical symptom was cranial nerve palsy, followed in frequency by headache and motor deficit [18]. Involvement of the brain parenchyma by secondary Hodgkin's disease has been reported only in terminally ill patients with disseminated, advanced disease, who also showed involvement of multiple extranodal sites, including the bone marrow [18, 24]. In addition, response to therapy is usually poor in these patients [18]. Taken together, the clinical, neuroradiological and neuropathological findings in our patient would be uncommon in the case of a secondary manifestation of Hodgkin's disease. However, the possibility that the lung tumour preceded the intracerebral lymphoma and initially escaped detection cannot be definitively ruled out.

Secondary involvement of the brain is interpreted as the result of haematogenous metastasis [18, 20]. The pathogenesis of primary Hodgkin's disease of the CNS is still poorly understood, but the hypothesis that lymphatic cells undergo malignant transformation in the brain is attractive. However, to gain more insight into the pathogenesis of cerebral Hodgkin's disease, detailed clinical

and neuropathological studies of larger clinical series and an experimental model are required.

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