SHORT REPORT

Atypical form of non-Langerhans histiocytosis with disseminated brain and leptomeningeal lesions

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Abstract

An 18 year old girl presented with acute visual loss. T2 weighted brain MRI showed areas of hyperintensities in the thalamic nuclei, internal capsule, lentiform nuclei, the subarachnoidal spaces, and a retrobulbar infiltration. Analysis of CSF showed numerous foamy histiocytes without malignant cells, raised protein, and depressed glucose concentration. Biopsy of the right thalamus demonstrated aggregates of histiocytes with immunohistological and ultrastructural characteristics of non-Langerhans cell histiocytosis. The patient improved with chemotherapy and corticosteroids. After 3 months of treatment, CSF analysis showed no more histiocytes. Cytological examination of CSF can be helpful for the management of patients with extensive histiocytic infiltration.

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Histiocytosis is a rare and heterogeneous group of disorders currently classified on immunohistological, ultrastructural, and biochemical data. The contemporary classification of histiocytic disorders, based on the lineage of lesional cells, has disclosed three types of histiocytosis.¹ The first group belongs to the dendritic cell lineage and includes Langerhans cell histiocytosis or histiocytosis X, Hand-Schüller-Christian disease, and Letterer-Siwe disease. The second group, also called non-Langerhans cell histiocytosis, derives from monocytemacrophage cells and includes different diseases such as haemophagocytic lymphohistiocytosis, histiocytosis with massive lymphadenopathy, and Erdheim-Chester disease. The third group is characterised by malignant histiocytosis which has in the past, been confused with T cell lymphoma due to the lack of monoclonal antibodies specific to histiocytes. Langerhans cell histiocytosis, by contrast with non-Langerhans cell histiocytosis, presents S-100 immunoreactivity and contains Birbeck granules in the cytoplasm, also called X bodies.¹ Neurological manifestations

are often observed in non-Langerhans cell histiocytosis such as Erdheim-Chester disease. To date, more than 60 cases of Erdheim-Chester disease have been reported in the literature but neurological manifestations remain rare.² Among these, analysis of CSF, where performed, is normal or can show increased protein concentrations. We report on an 18 year old girl with atypical non-Langerhans systemic histiocytosis involving brain and long bones and whose CSF demonstrated a marked hypoglycorachia.

Case report

An 18 year old girl was admitted in July 1996 for acute loss of vision. She had neither personal nor familial history and no alcohol or drug misuse. Her neurological examination was normal. Visual acuity was less than 20/200 in both eyes and a papillary oedema was present. Latency of visual evoked potentials, obtained only by flashes, was significantly prolonged, consistent with a pattern of bilateral and severe optic neuritis. Brain MRI showed, on T2 weighted images, abnormal foci of increased signal intensity in the thalamus, internal capsule, and subarachnoidal spaces. None of these lesions was enhanced by gadolinium. Infiltration of the frontal sinus and dura showing intense gadolinium uptake was particularly noticeable. The optic nerves were enlarged and infiltrated (data not shown). The first CSF analysis showed 7 white cells/mm³, a normal protein concentration, and severe hypoglycorachia with a glucose concentration of less than 0.10 mg/dl. Intensive research for malignant cells performed on four successive CSF samples was negative. One month later, the CSF contained 50 cells/mm³ among which atypical histiocytes characterised by large and irregular nucleus, were seen. Protein electrophoresis of the CSF disclosed no oligoclonal bands. Complete blood count, routine biochemistry, serum immunoglobulin protein electrophoresis, rheumatic factor, thyroid hormone concentration, erythrocyte sedimentation rate, serum and CSF β 2-microglobulin, antinuclear and anti-DNA antibodies, complement, angiotensin-converting enzyme, and lysosomal enzyme activity were all normal.

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Hypoglycorachia suggested a CNS infection but all bacteriological, including mycobacterium tuberculosis, and mycological and parasitological cultures remained negative. Serologies for human immunodeficiency virus, *Treponema pallidum*, *Borrelia burgdorferi*, *Cryptococcus neoformans*, *Toxoplasma gondii*, *Histoplasma capsulatum* and *Aspergillus fumigatus* were also negative. Thoracoabdominal CT was normal. Gynaecological and dermatological examination disclosed no lesions. Tumour markers such as CA125, CA15-3, CA19-9,

Figure 1 Axial T2 weighted MRI showing increased signal intensity in the thalamic nuclei, internal capsule, lentiform nuclei, and also in the frontal sinus (arrow).

Figure 2 x Ray film of right humerus demonstrating osteolytic lesions of the metaphysis.

carcinoembryonic antigen, α -foetoprotein, β -human chorionic gonadotrophin, and thyroglobulin were all within the normal range. The patient was treated with high doses of intravenous corticosteroids (1 g/day for 3 days) without any improvement.

As she progressively developed deafness of a sensorineural type, she was readmitted in March 1997. She had marked loss of weight and complained of headaches, vomiting, and diffuse arthralgia. Bilateral exophthalmos was found. A new brain MRI was performed, which showed, on T2 weighted images, an increased number of hyperintense lesions widespread in the thalamic nuclei, internal and external capsules, lentiform nuclei (fig 1), brainstem, and cerebellum. Radiological studies disclosed lytic lesions of the long tubular bone metaphysis (fig 2) and of the frontal bone. Analysis of CSF disclosed 14 white cells/mm³ and numerous foamy histiocytes (fig 3 A). Protein concentration in CSF was 100 mg/dl and the glucose concentration was less than 0.10 mg/dl. These histiocytes stained positively with antibodies to CD68 and negatively for glial fibrillary acidic protein and for CD20. A bone marrow biopsy showed no clonal proliferation and less than 5% of histiocytes without erythrophagocytosis. Caryotype analysis on bone marrow cells was normal. Stereotaxic biopsy of the right thalamus showed a huge proliferation of histiocytes in perivascular areas (fig 3 B). These cells were CD68 positive, CD1a negative and, in few cases, S100 positive. Immunostaining for CD79 and CR45R0, which are respectively B and T cell markers, was negative. Immunostaining for CD3 was negative. Ultrastructural study of the biopsy showed no Birbeck granules.

The patient was treated by intravenous vepeside, corticosteroids, and intrathecal injections of aracytine and methotrexate. One week later, pain and signs of intracranial hypertension decreased but blindness did not regress. Three months after the onset of the treatment, CSF analysis showed no more histiocytes but the glucose concentration was still depressed.

Discussion

Although the initial clinical presentation and brain MRI did not suggest a histiocytosis, the CSF analysis and the biopsy of the thalamus confirmed a huge proliferation of histiocytes. The occurrence of exophthalmos due to retro-orbital infiltration and later, osteosclerosis of long bones suggested the diagnosis of a systemic non-Langerhans histiocytosis such as Erdheim-Chester disease. This is a rare systemic histiocytosis usually affecting adult patients aged between 26 to 78 years with clinical features of diabetes insipidus, painful bones, skin nodules, and exophthalmos² caused, as in our case, by xanthogranulomatous retrobulbar infiltrate leading to a rapid loss of vision.³ Deafness, although not clearly demonstrated by brain MRI, may also be the consequence of a granulomatous infiltrate involving the cochlear nerve. Although brain

Figure 3 (A) CSF cytology illustrating a group of foamy cells belonging to the monocyte-macrophage lineage (haematoxylin and eosin staining; original magnification $\times 400$). (B) Thalamus biopsy, stained with haematoxylin-eosin, showing diffuse infiltrate of large and round histiocytes with foamy cytoplasm and ovoid nuclei, surrounding a small vessel (original magnification $\times 300$).

MRI findings in histiocytosis, may occasionally show periventricular, hemispheric and brain-stem hyperintense T2 lesions,^{4,5} peculiar lesions first infiltrating the thalamus and later the other nuclei were predominantly observed in our case.

Characteristics of CSF in Erdheim-Chester disease are seldom reported in the literature. When performed, CSF analysis is normal⁶ or may show a raised protein concentration.⁷ Depressed glucose content and pleocytosis in the CSF have never been reported in Erdheim-Chester disease. Atypical histiocytes in the CSF with high phagocytic activity have been described in malignant histiocytosis.⁸ However, our patient did not fulfil the criteria for malignant histiocytosis, as she did not have splenomegaly, hepatomegaly, lymphadenopathy, or hemophagocytosis, which are the common features of malignant histiocytosis.⁹ Moreover, on bone marrow biopsy, there was no clonal proliferation and no breakpoint on chromosome 5, which represents the hallmark of malignant histiocytosis.⁹ Besides malignant histiocytosis, atypical histiocytes have also been

reported in CSF in Hand-Schüller-Christian disease and Letterer-Siwe disease, in the second case showing depressed glucose concentration and more atypical histiocytes than those found in malignant histiocytosis.¹⁰ At necropsy, these cases demonstrated involvement of the leptomeninges and brain by histiocytic proliferation. As pointed out by Hamilton *et al.*,¹⁰ a wide range of cellular atypicality was seen in the CSF of histiocytic proliferative disorders which did not seem to be related to the classification of histiocytic disorders. The depressed CSF glucose concentration could also be the consequence of an increased glucose metabolism due to an active inflammatory reaction with histiocytes, as reported previously.⁶

Besides the peculiar characteristics of the CSF, diagnosis of non-Langerhans cell histiocytosis was also difficult to assess as other cardinal symptoms such as exophthalmos and painful bones appeared later. Moreover x ray of the long bones disclosed osteolytic lesions, which are more commonly seen in eosinophilic granuloma and Langerhans cell histiocytosis.² Observations of osteosclerotic lesions with pathological results of Langerhans cell histiocytosis¹¹ or osteolytic lesions with histological features of Erdheim-Chester disease¹² have already been reported. The variability of radiological features in Erdheim-Chester disease and the histopathological overlap between Erdheim-Chester disease and Langerhans cell histiocytosis may argue for a transformation of Langerhans cells into cells of monocyte-macrophage lineage.¹³

The classification of histiocytic proliferative disorders remains controversial but progress in molecular biology currently allows a reasonable classification. Based on the ultrastructural characteristics of histiocytes and the absence of clonal proliferation, our case seems to belong to an atypical form of non-Langerhans histiocytic disorder. We think that our patient has an intermediate form of histiocytosis, as the required criteria for malignant histiocytosis such as monoclonality, cytogenetic abnormality, and malignant histomorphology,¹ were absent. Moreover, the long course of the disease, and the lack of pancytopenia and hepatosplenomegaly argues against a malignant disease. Analysis of CSF, although of limited value in the classification of histiocytic disorders, provides a reliable documentation to determine the leptomeningeal involvement and should be considered in therapeutic approaches.

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