A clinico-pathological study of adult histiocytosis X involving the brain

K Hasegawa, T Mitomi, H Kowa, T Motoori, S Yagisita

Abstract
Adult histiocytosis X involving the CNS caused progressive spastic paraparesis. The diagnosis was made by immunoreactive anti-S100 protein antibody staining and from the presence of Birbeck granules in biopsy specimens of skin lesions. Neuropathological examination showed massive proliferation and infiltration of S-100 containing histiocyte-like cells and reactive astrocytes throughout the CNS.

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The conditions which produce progressive spastic paraparesis without apparent spinal cord lesions include familial spastic paraplegia, adrenoleukodystrophy, and HTLV-I associated myelopathy (HAM). Histiocytosis X usually occurs in childhood and is rare in adults. Most patients with this disease develop masses and/or osteolytic lesions, and it is also known as an important cause of diabetes insipidus (DI) in adults.

We present a rare case of progressive spastic paraparesis due to histiocytosis X.

Case report
A male engineer, aged 45 years, had an awkward gait for six years. His gait disturbance became progressively worse, so that by the age of 41 years (in 1984) he could not walk without assistance. At the same time, he occasionally had difficulty in skilful hand movements. At the age of 42, dysarthria and dysphagia also developed, and he could not walk without using two sticks, his gait having been reduced to a scissors-type motion because of severe spasticity.

A year later, skilful hand movements had deteriorated, and all extremities had become almost completely paralysed. Dysphagia was also aggravated, and he was referred to our hospital at the age of 44. There was no relevant past or family history.

On admission xanthoma-like lesions were observed on the head and face, and a papular erythematous rash was observed over the chest. Both skin lesions were already present at the onset of gait disturbance and had gradually enlarged. He appeared malnourished and dehydrated because of dysphagia. The superficial lymph nodes were not palpable and no hepatosplenomegaly was noted. There were no abnormalities of cardiac or pulmonary function.

Neurologically, slight disorientation and dementia were noted. His dysarthria was regarded as being both pseudobulbar and cerebellar in nature. Ophthalmological examination revealed anisocoria, a rapid light reflex, and a slight restriction of vertical gaze. Horizontal movements were normal and horizontal gaze nystagmus was also observed. Moreover, the smooth pursuit eye movements showed a staircase pattern. Palatal myoclonus was noted. Projection of the tongue was impossible, although no lingual atrophy was observed. The pharyngeal reflex was normal. Spastic tetraplegia in extension was demonstrated. All deep tendon reflexes were exaggerated and pathological reflexes, such as, the snout, sucking, grasp, Babinski, Chaddock, Hoffman and Troemner reflexes, were all positive.

It was impossible to properly examine the sensory, the extrapyramidal or the cerebellar systems, but no apparent abnormalities were noted.

No abnormalities were noted on haematological, biochemical, endocrinological, or immunological examinations. The CSF was normal, as were the lysozymal enzymal activities.

In electroencephalography, the basic rhythm was found to be slow a with some θ waves. There were no sharp waves, spikes, or asymmetry. The electromyotomagography revealed downbeat nystagmus in all eye positions. The caloric test was normal. Auditory evoked potentials showed no potentials but wave I. The latency of all somatosensory evoked potentials appearing subsequent to the N1 wave was prolonged. Electromyography and nerve conduction velocity studies showed no abnormal findings. The blink reflex test revealed slight prolongation of the left R1 latency time.

Biopsies were performed of the facial xanthomas and the papular erythematous rash on the chest. The chest skin biopsy specimens showed histiocyte-like cell infiltration below the epidermis. These infiltrating cells were stained positive by anti-S100 protein
A clinicopathological study of adult histiocytosis X involving the brain

Figure 1 Pathological findings in skin biopsies. (A) Many histiocyte-like cells are seen in the upper dermis. About half of the infiltrating cells are immunoreactive; precordial skin biopsy (S100 protein immunostain × 200); (B) Three Birbeck granules are seen in a part of the cytoplasm of a histiocyte-like cell on electron microscopy (× 100,000).

Antibody (fig 1A). Ultrastructurally, histiocyte-like cells contained characteristic of Birbeck granules (fig 1B). The biopsy from the facial xanthomas showed similar findings, and so the facial eruptions were also caused by histiocytosis X, but exhibited a different expression of the same disease. The pathological findings in the skin closely resembled those of Abt-Letterer-Siwe disease.

A cranial CT scan on admission revealed disproportionate cerebral atrophy for the patient’s age. In the peri-lateral ventricular region, MRI showed a mass lesion which was considered to be either a tumour or a demyelinating focus. Disseminated small high-intensity areas were noted deep in the white matter of the cerebrum. In addition, high-intensity areas were observed in the ventral pons in T1-weighted images. However, the nature of the pontine lesions was not assessed.

It was strongly suspected that a disease of the CNS had been induced by histiocytosis X. The main lesions in the CNS were considered to be located in the pons and upper medulla since palatal myoclonus, downbeat nystagmus in all eye positions, and spastic paraplegia were cardinal clinical features.

After the tentative diagnosis of histiocytosis X, in order to treat the disease and prevent its spread from the ventral part of the pons to other parts of the CNS, we tried γ-interferon therapy, which has recently been reported to be effective against malignant lymphoma and poorly differentiated malignant tumours, because conventional chemotherapies are at present usually considered ineffective against this disease. The chest and the facial xanthomas were transiently reduced after two months of γ-interferon therapy.

In 1988, however, when the patient was 45 years old, his level of consciousness deteriorated, and abnormal eye movements, such as, ocular bobbing developed, accompanied by bilateral lateral gaze palsy.

A high-intensity area mainly situated in the pons but extending to the midbrain, cerebellar peduncles and medulla, was seen on T1-weighted MRI (fig 2). The top of this lesion was thought to have reached the thalamus. Moreover, a round mass was also found in the left caudate nucleus, protruding into the lateral ventricle, and disseminated small

Figure 2 MRI findings of the brain. T1-weighted MRI image (parasagittal plane). The high-intensity area in the pons is seen extending into the cerebellum.
Figure 3. Macroscopic findings in the CNS. (A) Marked swelling of the brainstem, especially the pons. Prominent lesions extend from the medulla to the diencephalon. (B) Disseminated masses involving the pons to spinal cord.

high-intensity foci were also noted in the cerebral white matter on T2-weighted MRI. Diabetes insipidus and optic neuritis developed later. Electrophysiological and radiological findings suggested that the brainstem lesion had grown into the thalamus, hypothalamus and optic nerves. The patient's condition deteriorated and in 1988 he died.

Pathological findings

No gross abnormalities other than the skin lesions were revealed by general pathological examination. There was no macroscopic tumour infiltration into the visceral organs or the bones. On microscopic examination, histiocytosis X tumour cells were found to have invaded the base of the skull and the spleen.

The brain weighed 1440g. Marked swelling of the brainstem, especially of the pons, was noted (Fig 3A). The optic nerves, medulla, and cerebellar hemispheres were also grossly swollen. Some tumefactions were observed in the spinal nerve roots, especially at the cauda equina. In cross sections, a number of tumorous lesions were also observed from the basal ganglia to the cerebellum and spinal cord (Fig 3B). A tumour mass was revealed in the left caudate nucleus. It was 1 cm in diameter and protruded into the lateral ventricle.

Microscopically, most tumour cells had abundant homogeneous eosinophilic cytoplasm, and presumably originated from the reticuloendothelial system, infiltrated the brainstem diffusely, accompanied by reactive astrocytosis (GFAP positive) and Langerhans type giant cells (Fig 4). There were both degenerating and normal appearing nerve cells together with the tumour cells as a situa-
A study of adult histiocytosis X involving the brain

Age of presentation:
- Waldrom: 7 years
- Yamaguchi: 12 months
- Drolshagen: 12 months
- Present case: 39 years

Discussion

The term "histiocytosis X" was proposed by Lichtenstein to serve as a unifying name for a group of pathological conditions. The basic pathological feature of this disease is to form tumour masses or granulomatosis with destruction of the surrounding tissues. Histiocytosis X may be associated with CNS involvement, which is usually limited to the hypothalamus or posterior pituitary gland. While granulomatous lesions have been reported in the brainstem, spinal cord, spinal nerve roots and cauda equina, the most common site for extracranial involvement appears to be the cerebellum. The table lists the reported cases with no symptoms of either diabetes insipidus nor exophthalmos.

This case was characterised by the confinement of symptoms and signs to the motor system and the skin for the first seven years. Gradually, in the late stage, pontine neurological symptoms and signs became apparent. And diffuse swelling in the brainstem was observed at the same time without radiological evidence of mass formation. It is rare for mass formation not to occur in histiocytosis X. Only three cases are reported with a pathology similar to our case: Feigin's case 2, the case reported by both Hirai et al. and Yamaguchi et al., and case 3 of Kepes et al. The neuropathology of these cases and of ours was granulomatosis of the brainstem with invasion of the cerebellum and diencephalon. We believe that a brainstem variant of histiocytosis X should be recognised.

Although there was no pathological continuity between the skin lesions and the CNS lesions, it is reasonable to consider that they were another expression of the same disease process. Unfortunately, we could not demonstrate Birbeck granules in the tumour cells in the CNS, but only two cases with Birbeck granules have been reported. The skin lesions in our case were histologically similar to those in Letterer-Siwe disease, whose pathological process is thought to be infiltrative and destructive, and the tumours we found in the CNS were also infiltrative. Moreover, fatty degeneration of the neoplastic cells was observed in the brainstem in this case, so it is plausible that the tumour cells are less mature histiocytes than are usually seen. This also supports our notion that the skin and CNS involvement were different expressions of the same disease. Histologically, eosinophilic plasma-rich monocytes and giant cells tend to proliferate in histiocytic granulomatosis. In addition, normal appearing nerve cells were also sporadically observed. These remaining neurons suggest that the neurological symptoms should have been relatively mild.

In our case, symptoms other than the neurological ones, particularly the papular erythematous rash in the precordial region, served as keys to the diagnosis. If a definite diagnosis of the disease had not been made, application would be impossible to make.

Summary of atypical reported cases of histiocytosis X without diabetes insipidus or exophthalmos

<table>
<thead>
<tr>
<th>Author</th>
<th>Age of onset</th>
<th>Duration</th>
<th>Clinical symptoms</th>
<th>Onsetysis</th>
<th>Neuropathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feigin case 2</td>
<td>11 Years</td>
<td>?</td>
<td>fever, quadriplegia</td>
<td>-</td>
<td>brainstem granulomatosis</td>
</tr>
<tr>
<td>Rube case 1</td>
<td>20 Months</td>
<td>?</td>
<td>ICP ?</td>
<td>+</td>
<td>leptomeningeal granulomatosis</td>
</tr>
<tr>
<td>Rube case 2</td>
<td>30 Months</td>
<td>?</td>
<td>ICP ?</td>
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<td>leptomeningeal granulomatosis</td>
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<tr>
<td>Elkan case 2</td>
<td>36 Months</td>
<td>?</td>
<td>lymphadenopathy rash</td>
<td>-</td>
<td>leptomeningeal granulomatosis</td>
</tr>
<tr>
<td>Elkan case 3</td>
<td>37 Years</td>
<td>4-5 Years</td>
<td>ataxia</td>
<td>+</td>
<td>multiple dural mass</td>
</tr>
<tr>
<td>Hirai and</td>
<td>31 Years</td>
<td>3 Years</td>
<td>epilepsy, xanthomas</td>
<td>+</td>
<td>brainstem granulomatosis</td>
</tr>
<tr>
<td>Yamaguchi case 2</td>
<td>12 Years</td>
<td>6 Weeks</td>
<td>cerebellar signs</td>
<td>?</td>
<td>temporal mass</td>
</tr>
<tr>
<td>Kepes case 3</td>
<td>11 Years</td>
<td>9-5 Years</td>
<td>ICP ?</td>
<td>?</td>
<td>temporal mass</td>
</tr>
<tr>
<td>Kepes case 4</td>
<td>26 Years</td>
<td>1 Year</td>
<td>hemiparesis, ICP ?</td>
<td>?</td>
<td>frontal mass</td>
</tr>
<tr>
<td>Salcman case 1</td>
<td>7 Years</td>
<td>?</td>
<td>paraparesis, lymphadenopathy</td>
<td>+</td>
<td>spinal epidural mass</td>
</tr>
<tr>
<td>Hewlett case 2</td>
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<td>?</td>
<td>paraparesis</td>
<td>+</td>
<td>spinal dural mass</td>
</tr>
<tr>
<td>Sivalenty case 2</td>
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<td>?</td>
<td>epilepsy</td>
<td>+</td>
<td>temporal mass</td>
</tr>
<tr>
<td>Cerda-Nicolas case 35</td>
<td>35 Years</td>
<td>?</td>
<td>hemiparesis</td>
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<td>frontal mass</td>
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<tr>
<td>Greenhood case 2</td>
<td>14 Years</td>
<td>2 Years</td>
<td>epilepsy, ICP ?</td>
<td>-</td>
<td>temporal mass</td>
</tr>
<tr>
<td>Camilleri</td>
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<td>paraparesis</td>
<td>+</td>
<td>brainstem granulomatosis</td>
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<tr>
<td>Waldrom case 2</td>
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<td>+</td>
<td>frontal mass</td>
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<tr>
<td>Geoffray case 2</td>
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<td>6 Months</td>
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<td>multiple mass</td>
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<tr>
<td>Yamak case 2</td>
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<td>+</td>
<td>spinal tumour</td>
</tr>
<tr>
<td>Al-Rodhan case 2</td>
<td>1 Year</td>
<td>?</td>
<td>paraparesis, fever, lymphadenopathy?</td>
<td>+</td>
<td>spinal tumour</td>
</tr>
<tr>
<td>Drosdagen case 2</td>
<td>12 Months</td>
<td>?</td>
<td>hemiparesis</td>
<td>+</td>
<td>cervical tumour</td>
</tr>
<tr>
<td>Present case</td>
<td>39 Years</td>
<td>?</td>
<td>quadriplegia, pontine syndrome, rash</td>
<td>+</td>
<td>brainstem granulomatosis</td>
</tr>
</tbody>
</table>

ICP, intracranial pressure.
on the basis of the skin biopsies, diagnosis from the postmortem histology alone would have been very difficult. Thus patients with spastic paraplegia of unknown cause should be suspected of having this disease. Even minor organic lesions warrant careful attention.

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