Sequential Magnetic Resonance Features of Encephalopathy Induced by Systemic Mastocytosis

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A 37-year-old man developed encephalopathy with prominent eosinophilia. Magnetic resonance imaging (MRI) revealed multiple T2-weighted high signal intensity lesions with dimeglumine gadopentetate (Gd-DTPA) enhancement on T1-weighted images, which were distributed in the cerebral cortex, thalamus, deep white matter and cerebellum. He was diagnosed as having systemic mastocytosis on the basis of proliferating mast cells in the bone marrow and peripheral eosinophilia. Following steroid administration, there was a rapid improvement of his symptoms and laboratory data. To our knowledge, this was the first reported case of systemic mastocytosis provoking encephalopathy with serial MRI findings.

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Introduction

Systemic mastocytosis is a rare disease entity characteristic of primary mast cell proliferation, and involves the systemic organs such as skin, liver, spleen, lung, heart, lymph nodes and bone marrow (1-4). This disease is known to exhibit various kinds of clinical manifestations, but no central nervous system involvement had been confirmed radiologically. We present a rare case of encephalopathy associated with systemic mastocytosis showing peculiar magnetic resonance imaging (MRI) findings.

Case Report

A 37-year-old male patient, with an approximately twenty-year history of hypereosinophilic syndrome (HES), showed symptoms of gradual consciousness impairment and fever. The patient had often suffered from urticaria since his childhood, irrespective of diet. Three days prior to admission, he was febrile at 39°C but did not show flu-like symptoms or headache. The patient was admitted to Hokuyukai Neurological Hospital with suspected acute exacerbation of hypereosinophilic syndrome, as the peripheral white blood cell (WBC) count was 23,300/mm³ with 7% segmented cells, 4% lymphocytes and 87% eosinophils. Neurologically, he was somnolent and could be aroused by painful stimuli but soon drifted back to sleep. In addition, slight nuchal rigidity was noted as well as slight tremors in the jaws. Cerebrospinal fluid (CSF) examination revealed pleocytosis of 19 cells/mm³, protein 0.51 g/L and glucose 0.53 g/L. Electroencephalogram (EEG) was markedly abnormal, showing poor background of alpha-rhythm with prominent diffuse slowing, but no epileptiform discharges were observed. T2-weighted MRI exhibited multiple high signal intensity lesions in the basal ganglia, cerebral deep white matter and cerebellum (Fig. 1a). Methylprednisolone 1 g was administered for three days and then the patient was transferred to our neurological service for further evaluation and treatment.

On admission, the patient was lethargic and disoriented as to time and place. The cranial nerves were intact, and the muscle tone was increased in all four extremities. The deep tendon reflexes were symmetrically hyperactive and the plantar responses were extensor bilaterally. Coordination was intact. No sensory abnormalities were noted. WBC in peripheral blood was 10,100/mm³ with 13% eosinophils. IgE and vitamin B12 rose to 28,620 IU/ML (normal 250 IU/ML), and 1,790 pg/ml (normal 210-1,200 pg/ml), respectively. Plasma histamine level was 0.9 µg/dl (normal 0.8 µg/dl>). Tumor markers and auto-antibodies were all within normal limits. Significantly elevated viral antibodies against herpes simplex virus, cytomegalovirus, Epstein-Barr virus and other viruses were not...
detected. CSF revealed: glucose 0.60 g/L, protein 0.41 g/L and 
4 cells/mm³. Cultures of the CSF yielded no growth of bacteria 
or fungi. No oligoclonal bands were demonstrated. IgG index 
was 0.53. Cytologic examination showed slight atypical 
mononuclear cells resembling eosinophils and was determined 
as Class III. Results of karyotype analysis were completely 
normal. Abdominal CT scans showed slight hepatomegaly and 
splenomegaly, but mediastinal or visceral lymphadenopathy 
was not found. The scintigrams of the bone with ⁹⁹ᵐTc and of 
the whole body with ⁶⁷Ga exhibited focal uptake in the clivus, 
but no other skeletal activity. T2-weighted MRI revealed mul-
tiple high signal intensity areas in the cerebral cortex, cerebral 
deep white matter, thalamus and cerebellum (Fig. 1b).

Following the administration of dimeglumine gadopentetate 
(Gd-DTPA), some of these lesions were highly enhanced (Fig. 
1c). Moreover, there was an enhanced lesion in the clivus 
compatible with scintigraphical findings (data not shown). 
Bone marrow examination showed an increased number of 
mast cells with mature eosinophils presumably reactive to mast 
cell proliferation (Fig. 2).

Several days after steroid treatment, the patient became alert 
and responded normally to questions and commands. EEG 
showed nearly normal findings in accordance with his improve-
ment. Peripheral eosinophilia was also diminished. Vitamin 
B12 and plasma histamine levels decreased to 693 pg/ml 
(normal 210–1,200 pg/ml) and 0.46 μg/dl (normal 0.8 μg/dl>), 
respectively. T2-weighted MRI showed that high signal inten-
sity areas in the cerebral cortex, cerebral deep white matter, 
thalamus and cerebellum still remained (Fig. 1d), whereas 
enhancement of the T1-weighted MRI with Gd-DTPA could
Cranial MRI of Systemic Mastocytosis

Fig. 1. Continued.

Fig. 1. Serial magnetic resonance imaging (MRI) findings. Before the steroid treatment, axial T2-weighted MRI (0.5 Tesla, 2,000/10:TR/TE) revealed high signal lesions in cerebral deep white matter, cerebral cortex, basal ganglia and cerebellum (a). In spite of the administration of 1 g methylprednisolone for three days, axial T2-weighted MRI (1.5 Tesla, 3,000/90:TR/TE) exhibited high signal intensity in the cerebral white matter, thalamus and cerebellum (b). These lesions were highly enhanced with dimeglumine gadopentetate (Gd-DTPA) (1.5 Tesla, T1-weighted image, 600/15:TR/TE) (c). Five weeks after admission, axial T2-weighted MRI (1.5 Tesla, 3,000/90:TR/TE) was still unchanged (d), but enhancements with Gd-DTPA (1.5 Tesla, T1-weighted image, 600/15:TR/TE) were diminished in accordance with clinical improvements (e). Some T1-weighted low signal intensity lesions were also identified (e).

Fig. 2. Increased number of spindle-shaped mast cells in the bone marrow. Many eosinophils without cellular atypia were also present (Paraffin-embedded tissue, Giemsa staining, ×200).

Subsequently, the steroid was tapered and he was discharged with minimal steroid intake to suppress the abnormalities in the blood examinations. Since being discharged, the patient has exhibited no evidence of recurrence.

Discussion

The most characteristic finding of our case was the encephalopathy with prominent eosinophilia. In general, peripheral eosinophilia is associated with various kinds of disorders such as parasitic or bacterial infection, allergic disease, neoplasms, skin disease, hematological disease, and collagen-vasculitis disease. Additionally, except for those well-known causes, Hardy and Anderson introduced the term “hypereosinophilic syndrome (HES)” in 1968 (5) and subsequently Chusid and colleagues proposed its diagnostic criteria (6).

Despite full examinations for an enlarged lymph node 20 years prior, the primary cause could not be found and the present patient was diagnosed as HES. However at that time, we were able to establish a diagnosis of systemic mastocytosis because bone marrow examinations revealed an increased number of mast cells and presumed reactive mature eosinophils.
If, on the other hand, the patient had exhibited a different clinical phase of systemic mastocytosis and only a few mast cells had remained in the bone marrow, they may have been overlooked. The possible effect of the corticosteroid prescribed prior to the bone marrow examination should also be considered. Although a large number of eosinophils could also have induced most of his clinical symptoms, we considered that his primary pathogenetic event was the abnormally proliferating mast cells, partly because marked eosinophilia had rapidly decreased following the steroid treatment.

Our speculation was supported by previous reports which have shown that mast cells can secrete chemical mediators such as eosinophil-chemotactic-factor (ECF) and eosinophils can proliferate in response to those mediators (7). Since both the proliferating eosinophils and mast cells were mature and not showing a malignant appearance, we excluded the possibilities of eosinophilic leukemia and mast cell leukemia. The results of the karyotype analysis also supported our evaluation. Apart from encephalopathy, clinical features including frequent urticaria, hepatosplenomegaly, peripheral eosinophilia, elevated plasma histamine and IgE were all consistent with systemic mastocytosis. Since the increased level of histamine in the first examination was relatively low, the administration of corticosteroid had probably affected the value. Compared with the second examination, the increase of histamine in the first examination was considered to be significant.

To our knowledge, central nervous system (CNS) dysfunction is quite rare in systemic mastocytosis and there has only been one autopsied case of cerebellar hemorrhage due to mast cell infiltration (8). We suspected that the multiple intracranial lesions showing T2-weighted high signal intensity with T1-weighted Gd-DTPA enhancement implied a regionally active inflammatory process. In these lesions, the blood-brain barrier must be destroyed.

Additionally, T2-high signal intracranial lesions could not account for his consciousness disturbance. Moreover, as CSF did not show prominent pleocytosis, we may be able to disregard the direct neurocytopathic effects caused by infiltrating cells. Subsequently, we suspected other mechanisms, possibly that of soluble factors secreted by eosinophils and mast cells, had provoked encephalopathy. Previous reports have described eosinophil-derived neurotoxin or other toxic eosinophil products as capable of inducing encephalopathy (9). With regards to the mast cell derived factors, little is known except that histamine may be neurotoxic. On the other hand, we should consider other diagnostic possibilities such as infections, collagen-vascularitis disorders and demyelinating diseases. Laboratory data could exclude the possibility of infections and autoimmune diseases. Additionally, the clivus and some cerebral cortices were unlikely to have been involved by demyelinating diseases. ABR and SEP which have been often utilized to reveal latent lesions, especially in demyelinating disease, showed no abnormalities in the present patient.

No evidence of peripheral neuropathy was uncovered in the present case. Peripheral neuropathy has been observed in 52% of HES cases (10), a literature search revealed very few previous cases of peripheral neuropathy accompanied by systemic mastocytosis. Moreover, encephalopathy induced by systemic mastocytosis had rarely been reported, although 15% of all HES cases exhibited CNS dysfunction.

These facts may indicate the differences in neurotoxic mechanisms between systemic mastocytosis and HES.

In summary, further attention must be paid to mast cells in the broad range of diseases diagnosed as HES, both clinically and in research. Systemic mastocytosis should be included in the differential diagnosis when multiple enhanced lesions are encountered on MRI of patients diagnosed as HES.

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References