CASE REPORT

Two cases of acute myelitis with idiopathic hypereosinophilic syndrome

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SUMMARY

Idiopathic hypereosinophilic syndrome (IHES) is characterised by persistent eosinophilia and organ damage after ruling out other causes. IHES is clinically and pathologically heterogeneous, and several disease mechanisms have been described. Although neurological involvement with IHES is extremely rare, we report the first cases of acute myelitis with IHES, which are confirmed using MRI, fulfil the diagnostic criteria of IHES and pathologically reveal eosinophilic tissue infiltration in the liver and skin. Patient 1 had longitudinally extensive transverse myelitis, which developed in the absence of steroid therapy. Patient 2 developed acute myelitis with two short lesions during a 3 mg/day corticosteroid treatment. Both cases had eosinophilia ($>1500/\text{mm}^3$) at the onset of myelitis. These findings suggest that earlier treatment and a sufficient dose of corticosteroids may prevent the lesional expansion in acute myelitis. Steroid therapy should be initiated early before organ involvement, because permanent neuronal damage with a larger lesion becomes more critical.

BACKGROUND

Idiopathic hypereosinophilic syndrome (IHES) was first described in 1968 by Hardy and Anderson¹ and is characterised by prolonged eosinophilia ($>1500/\text{mm}^3$ for >6 months) with evidence of organ involvement (the heart, skin, nervous system, lung, spleen, liver, eye and the gastrointestinal tract) after ruling out other causes, such as parasitic infection, allergic disorder, collagen or malignant disease, chronic eosinophilic leukaemia associated with Fip1-like1-platelet-derived growth factor receptor α (FIP1L1-PDGFRA) fusion gene, which is one of mutation in HES, or not otherwise specified, and eosinophilia by abnormal T-cell clones.^{2,3} Few cases with neurological complications have been reported in IHES, and its underlying mechanism is poorly understood.⁴ Here, we report the first cases of acute myelitis with IHES, which are confirmed using MRI, fulfil the diagnostic criteria of IHES and pathologically reveal eosinophilic tissue infiltration in the liver and skin.

CASE PRESENTATION

Case 1

A 71-year-old man presented with a 5-month history of eosinophilia and liver dysfunction. A liver biopsy showed infiltration of eosinophils, lymphocytes and histiocytes in hepatic lobules, although this resolved spontaneously. He had acute bilateral lower limb paraesthesia 10 days before admission. He subsequently developed rapidly progressive

paraplegia with absent deep tendon reflex (DTR), sensory loss below the fourth thoracic level, and urinary and faecal incontinence. He was thus hospitalised for a detailed workup. He had no history of allergic disorders. His vital signs revealed fever (38.5°C), hypertension (210/130 mm Hg), tachycardia (120/min) and hypoxia (oxygen saturation 83% at room air). Abnormality in physical findings included dyspnoea, coarse crackles in the lower lungs and generalised pruritus. Laboratory tests revealed eosinophilia ($2268/\text{mm}^3$), elevated IgE (653 IU/mL) and positive antinuclear antibody (1 : 320), but no parasitic infection was detected. Cerebrospinal fluid (CSF) analysis revealed pleocytosis (835 leucocytes/ mm^3 , 67% lymphocytes), elevated total protein (102 mg/mL) and myelin basic protein (780 pg/mL; normal <102 pg/mL). CSF cytology revealed eosinophilia and no atypical cells. CSF culture was negative for bacteria and fungus. Chest CT showed pneumonia in bilateral lower lungs. T2-weighted MRI revealed hyperintense lesions extending from the medulla oblongata to the conus medullaris (figure 1A–C) and T1-weighted MRI showed patchy gadolinium enhancement on the spinal cord surface (figure 1D).

Case 2

A 34-year-old man developed fever and swelling of the right cheek, followed by generalised pruritus and skin rash 1 year prior to admission. He had a history of bronchial asthma in childhood, which had been ameliorated for 25 years. Eosinophilia ($2268/\text{mm}^3$) and multiple granular shadows on chest X-ray were observed. These findings resolved 2 weeks after taking 25 mg/day of oral prednisolone (PSL). He was also detected to have multiple small nodules in the liver, which spontaneously resolved. After that, PSL was gradually tapered to 3 mg/day. One month prior to admission, he reported paraesthesia in the T1-weighted dermatome. Two weeks after the onset of paraesthesia, he was transferred to the emergency room with acute chest pain that lasted 15 min, but no abnormalities were detected on ECG or echocardiogram. General findings on admission revealed a 1 cm subcutaneous mass on his back, which enlarged rapidly. Lhermitte's sign and Romberg's sign were positive, but DTR was normal. Laboratory tests revealed eosinophilia ($2070/\text{mm}^3$), elevated IgE levels (965 IU/mL) and positive house dust-specific IgE, but mite antigen-specific IgE was negative. CSF analysis revealed a normal cell count and protein level, and no eosinophils or atypical cells were observed on cytology. FIP1L1-PDGFRA fusion

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Figure 1 Sagittal view of T2-weighted MRI on admission showed hyperintensity with oedema extending from the medulla oblongata to the conus medullaris (A, B, arrows). Axial view at T9 level (C, arrowheads). Patchy gadolinium enhancement on the spinal cord surface was observed on T1-weighted imaging (D, arrows).

gene was negative. T2-weighted MRI revealed hyperintensities in the posterior portion of the spinal cord at the cervical (C7) and thoracic (T2–T3) levels (figure 2A–C). A biopsy of the subcutaneous mass revealed eosinophilic infiltration in the subcutaneous fat and perivascular area, consistent with IHES (figure 3).

TREATMENT

Both the patients were treated with intravenous methylprednisolone (1000 mg/day for 3 days) and subsequent oral PSL (1 mg/kg/day).

OUTCOME AND FOLLOW-UP

Case 1

The patient's symptoms improved. Blood and CSF eosinophilia improved and intramedullary hyperintense lesions on T2-weighted MRI disappeared. The patient developed haemorrhagic cystitis and diabetes after 3 weeks of corticosteroid therapy, and PSL was tapered to 2 mg/day, which led to recurrence of eosinophilia ($5554/\text{mm}^3$) and pruritus manifestation. Eventually, he continued taking 20 mg/day PSL and transferred to another hospital for rehabilitation.

Case 2

The patient's eosinophilia normalised. However, he reported an exacerbation of lower limb paraesthesia during walks. We added carbamazepine (200 mg/day), which eliminated the symptoms. The patient received 5 mg/day of PSL and 3 mg/day of tacrolimus and has remained free of relapse.

DISCUSSION

Significant eosinophilia and eosinophilic tissue infiltration has been associated with a variety of clinical disorders.¹ Almost all organ systems are involved with IHES, the most frequent being the heart, central and peripheral nervous system, lungs and skin.² Previous reports have also described patients with the

Figure 2 T2-weighted MRI showed mild oedema and hyperintensity in the dorsal portion of the C7 and T2–T3 levels (A) with no contrast on the T1-weighted image. Axial image at C7 (B) and T2–T3 levels (C).

histological features called chronic active hepatitis associated with eosinophilia.⁵ The longitudinally extensive transverse myelitis with eosinophils in the CSF of our case study required the exclusion of other diseases such as atopic myelitis, parasite infection, collagen disease, neuromyelitis optica and lymphoma. Although mite antigen-specific IgE and antiaquaporin-4 antibody were not tested in patient 1, he had no history of atopic disorders and developed myelitis with eosinophilia and

Figure 3 Biopsy of the subcutaneous mass that developed on the back revealed eosinophilic infiltration in the subcutaneous fat and perivascular area (bar=100 μm).

generalised pruritus that were compatible with cutaneous involvement in IHES. Patient 2 had myelitis with eosinophilia and a rapidly enlarged subcutaneous mass on his back, which was pathologically confirmed as IHES. Both cases clinically matched the diagnostic criteria of acute myelitis with IHES.² Only one case of a patient with IHES with transverse myelitis and polyneuropathy showing numbness below T10 level and lower limb weakness has been reported. In this case, somatosensory evoked potentials using tibial and median nerve stimulation revealed conduction delay in the posterior column, and spinal MRI was not performed (table 1).⁴

A recent case report described recurrent encephalomyelitis associated with eosinophilia in CSF that was responsive to steroid. However, no eosinophilia was detected in the blood.⁶

Although the mechanism of myelitis with IHES remains unclear, the following four factors define eosinophil-induced neuronal damage: (1) direct neuronal tissue infiltration⁷; (2) damage related to several neurotoxic proteins isolated from eosinophilic granules, including major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN) and eosinophil peroxidase (EPO)⁸; (3) damage related to eosinophil function by antibody-dependent cellular cytotoxicity (ADCC)⁹ and (4) embolic cerebral infarction related either to thrombi or to a generalised hypercoagulable state.¹⁰ Biopsy findings of the brain of patients with IHES with massive central nervous system inflammation have revealed ECP-positive eosinophilic and neutrophilic infiltration around the vessels.¹¹ The

effect of ECP's action on neuronal morphology in vitro is consistent with apoptosis, and the mechanism involves an increase in cell surface binding of free cytosolic Ca^{2+} , the activation of caspases-9 and the subsequent activation of pro-caspase-3 and pro-caspase-8, leading to neuronal cell apoptosis.⁸ Aggressive tissue damages in patients with IHES is caused by direct infiltration of eosinophils and increased eosinophilopoietic activity because their ECP levels are approximately 2.5 times higher than those in other eosinophilic states.¹² Therefore, determining serum ECP levels may be useful to differentiate IHES from other hyper-eosinophilic diseases. In addition, corticosteroids induce eosinopenia² and inhibit immunoglobulin-induced eosinophil degranulation and ADCC.^{9 13} Steroid therapy in patients with unknown eosinophilia without organ damage has also prevented eosinophilia-related organ dysfunction during the median follow-up period of 15 months.¹⁴ Patient 2 developed acute myelitis with two shorter lesions than patient 1 after treatment with 3 mg/day of PSL for subcutaneous, lung and hepatic lesions (table 1). It is plausible that corticosteroids decreased neurotoxic protein levels and eosinophil granule activity, and even prevented the expansion of acute myelitis lesions. Moreover, steroid therapy should be started early before organ involvement develops, because permanent neuronal damage with larger lesions may further complicate the condition.

There is currently no established consensus for the maintenance dose of corticosteroids to prevent the recurrences of IHES. Patient 1 developed several side effects after 3 weeks of steroid

Table 1 Clinical features of acute myelitis with IHES

	Patient 1	Patient 2	Tsai <i>et al</i>
Sex	M	M	F
Age at onset (years)	71	34	76
Eo count at onset (mm ³)	2268	2070	2310
Organ involvement	Liver, skin, spinal cord	Skin, lung, liver, spinal cord	Spinal cord
Treatment at onset of myelitis	None	Oral PSL (3 mg/day)	None
General appearance	Dyspnoea, generalised pruritus	Subcutaneous mass on the back	None
Neurological findings	Paraplegia, absent DTR in lower limbs, bilateral pansensory loss below T4 level, bladder and rectal disturbances	Lhermitte's sign, Romberg's sign	Weakness of lower limbs, pansensory loss below T10, spastic gait, increased DTR, Babinski's signs
Location of the lesion at MRI	From the medulla to conus	C7 and T2–T3 levels	NA
CSF abnormalities	Preocytosis, protein↑, MBP↑ (780 pg/mL) eosinophils in cytology	Normal	Normal
Lab abnormalities	IgE↑ (653 IU/mL) house dust-specific IgE↑ ANA (1 : 320)	IgE↑ (965 IU/mL)	IgE↑ (2823 IU/mL)
Bone marrow examination	No atypical cells	NA	NA
FIP1L1-PDGFRα fusion gene	NA	Negative	NA
Biopsy site	Liver	Skin	NA
Initial treatment	IVMP (1 g/day for 3 days), oral PSL (60 mg/day)	IVMP (1 g/day for 3 days), oral taper from 60 mg of PSL	Oral PSL (20 mg/day)
Response to treatment, course	Moderate improvement. Complicated by haemorrhagic cystitis, and diabetes mellitus within 3 weeks after steroid therapy Recurrent eosinophilia and pruritus at 2 mg/day of PSL	Rapid improvement. Paraesthesia worsened 2 weeks after taper	
Maintenance management	Oral PSL of 20 mg/day	Oral PSL of 5 mg/day 3 mg/day of tacrolimus 200 mg/day of CBZ	

↑, elevated; ANA, antinuclear antibody; C, cervical; CBZ, carbamazepine; CSF, cerebrospinal fluid; DTR, deep tendon reflex; Eo, eosinophil; F, female; IVMP, intravenous methylprednisolone; Lab, laboratory; M, male; MBP, major basic protein; NA, not available; PSL, prednisolone; T, thoracic.

therapy, and also suffered a relapse of eosinophilia during steroid tapering (table 1). In a multicentre retrospective analysis of 188 patients with IHES,¹⁵ 72% patients were maintained on corticosteroids from 2 months to 20 years, with a median maintenance dose of 10 mg/day. Some patients were administered a combination therapy of agents such as hydroxyurea and interferon- α because of the possibility of relapse or adverse events with corticosteroids, whereas others were switched to imatinib or anti-interleukin-5 antibody because of poor drug response. It is necessary to determine whether the additional drugs can decrease the use of steroids and result in a favourable prognosis.

Reports on myelitis with IHES are limited and this further impedes investigations into its underlying pathology. We should continue the treatment with periodic monitoring of the eosinophil count. Although it could not be examined because of the limited materials, we believe that elevated levels of serum and CSF eosinophil granule proteins such as MBP, ECP, EDN and EPO in suspected cases are significant and that these proteins as well as the eosinophil count could be used as disease markers of acute myelitis with IHES. Furthermore, investigating the relationship between corticosteroid therapy and ECP activity in eosinophils may result in a better understanding of the pathological processes and clinical manifestations of myelitis with IHES. This will facilitate the development of better treatment regimens.

Learning points

- ▶ Idiopathic hypereosinophilic syndrome (IHES) must be considered in the patient with longitudinally extensive transverse myelitis and eosinophilia in the peripheral blood and cerebrospinal fluid.
- ▶ Steroid therapy should be started early before organ involvement develops, because permanent neuronal damage with larger lesions may further complicate the condition.
- ▶ We should continue the treatment of acute myelitis with IHES with periodic monitoring of the eosinophil count.

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