

Case Report

Tumefactive eosinophil-rich non-granulomatous small vessel vasculitis in the cerebrum in a patient with idiopathic hypereosinophilic syndrome

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The definite diagnosis of central nervous system vasculitis requires pathological verification by biopsy or surgical resection of the lesion, which may not always be feasible. A 74-year-old woman with a history of allergic rhinitis, but not asthma, presented with slowly progressive left hemiparesis. Magnetic resonance imaging of the head revealed a heterogeneously enhancing mass involving the right internal capsule and corona radiata. Histological examination of the resected specimen revealed eosinophil-rich non-granulomatous small vessel vasculitis with no neutrophil infiltration or foci of microbial infection. Epstein–Barr virus *in situ* hybridization was negative, and polymerase chain reaction tests for both T-cell receptor gamma and immunoglobulin heavy-chain variable region genes did not show rearrangements, excluding the possibility of lymphoma and lymphoproliferative disorders. Blood hypereosinophilia and elevated erythrocyte sedimentation rate were observed; however, anti-neutrophil cytoplasmic antibodies were not detected. A biopsy of the erythema in the hips and thighs revealed perivasculitis with eosinophilic infiltration within the dermis. Chest computed tomography revealed multiple small nodules in the lungs. Her symptoms, aside from hemiparesis, disappeared after corticosteroid administration. The clinicopathological features were similar to eosinophilic granulomatosis with polyangiitis but did not meet its current classification

criteria and definition. This patient is the first reported case of idiopathic eosinophilic vasculitis or idiopathic hypereosinophilic syndrome-associated vasculitis affecting the small vessels in the brain. Further clinicopathological studies enrolling similar cases are necessary to establish the disease concept and unravel the underlying pathogenesis.

Key words: biopsy, central nervous system, hypereosinophilic syndrome, small vessel, vasculitis.

INTRODUCTION

Central nervous system (CNS) vasculitis can occur as either an isolated lesion or one manifestation of systemic vasculitis. Clinical signs and symptoms are non-specific in patients with CNS vasculitis, including headache and cognitive decline, and focal neurologic deficits, such as aphasia and paralysis, with the onset of these symptoms varying from acute, subacute, and chronic.¹ A definite diagnosis of CNS vasculitis usually requires pathological verification by biopsy or surgical resection of the lesion, which may not always be feasible. The 2012 revised International Chapel Hill Consensus Conference nomenclature (CHCC2012) provided mutually exclusive clinicopathological definitions for primary vasculitides based on the size of affected vessels.² We encountered an elderly patient presenting with slowly progressive hemiparesis associated with a heterogeneously enhanced tumor-like lesion on brain magnetic resonance imaging (MRI); histopathological examination of the resected specimen revealed eosinophil-rich lymphocytic vasculitis, requiring differential diagnoses from lymphoma, lymphoproliferative disorders, and other non-neoplastic lesions. However, the clinicopathological features did not meet any established disease definitions in the present case.

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CLINICAL SUMMARY

A 74-year-old Japanese woman with a clinical history of colon cancer and hypertension had difficulty moving her left upper limb and gradual weakening of the ipsilateral lower limb. One month after the symptom onset, she had left paresis with inarticulate speech. Her height was 142 cm, and her body weight was 36 kg; she had lost 6 kg in the preceding few months. She was afebrile, and no gastrointestinal tract symptoms were observed. Brain MRI revealed a heterogeneously enhancing mass involving the right internal capsule and corona radiata (Fig. 1). The patient underwent mass removal under the diagnosis of a suspected malignant glioma. However, intraoperative frozen-section diagnosis was inconclusive, and histological examination of the paraffin sections revealed eosinophil-rich vasculitis.

Repeated checking of her medical history revealed allergic rhinitis but no asthma. Blood tests revealed eosinophil counts over $1.5 \times 10^9/L$ (24.6% of 6100 white blood cells), high IgE levels (1740 IU/mL) including those specific for the pollen of cedar and Japanese cypress, elevated β 2-microglobulin (2.4 mg/L), and soluble interleukin-2 receptor (sIL-2R) (1350 U/mL), as well as elevated erythrocyte sedimentation rate (38 mm/h). Serum myeloperoxidase-anti-neutrophil cytoplasmic antibody

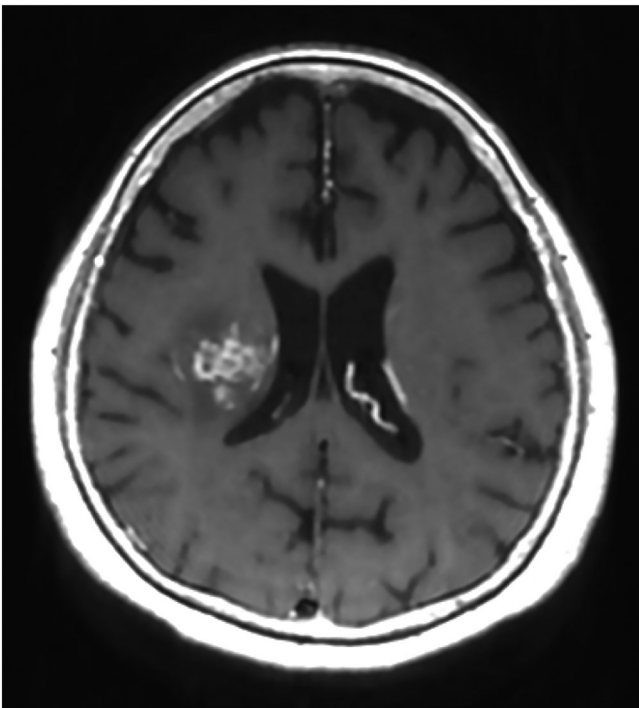


Fig 1 Preoperative MRI findings of the brain. A preoperative gadolinium-contrast axial T1-weighted image shows a heterogeneously and curvilinearly enhancing mass with perifocal edema involving the right internal capsule and corona radiata.

(ANCA), proteinase 3-ANCA, and rheumatoid factor were negative, and C-reactive protein (CRP) levels were within normal range. No abnormalities were observed in the hepatic and renal functions. The cerebrospinal fluid examination results were unremarkable. Immediately before surgery, multiple foci of erythema appeared in the bilateral hips and thighs; one of the lesions was biopsied after brain surgery. Head computed tomography (CT) and MRI also demonstrated nasal mucosal thickening and fluid retention in the paranasal sinuses. Chest CT revealed multiple foci of small nodules in both lungs. Her symptoms, including erythema, rhinitis, paranasitis, and pulmonary lesions on chest CT, disappeared after corticosteroid administration with no enhancing brain lesion on follow-up MRI; however, erythema recurred three weeks later. She had no signs or symptoms of peripheral neuropathy. The patient was transferred for rehabilitation.

This study was approved by the ethics committee of Akita Cerebrospinal and Cardiovascular Center and was conducted in accordance with the Declaration of Helsinki (as revised in Brazil 2013).

PATHOLOGICAL FINDINGS

Histological examination of formalin-fixed, paraffin-embedded sections from the resected specimen on hematoxylin and eosin (HE) revealed perivascular mononuclear cell infiltration containing abundant eosinophils and plasma cells (Fig. 2A). Transmural mononuclear cell infiltration with destructive or occlusive changes (Fig. 2B) and concentric arrangement of reticular fibers (Fig. 2C) was also noted in the venous vessels, which infiltrated the brain parenchyma together with eosinophils. Plasma cells of different sizes with occasional binucleation were found in areas distant from the blood vessels (Fig. 2D). There was no granulomatous inflammation, neutrophil infiltration, fibrinoid necrosis of vessel walls, thrombotic obstruction, or infectious lesions by microorganisms such as bacteria, fungi, parasites, and protozoa. Immunohistochemically, the infiltrating mononuclear cells consisted of a central area mainly containing CD3-positive T-cells (Fig. 2E) with a subset of CD8-positive cells, surrounded by a peripheral area containing abundant CD138-positive plasma cells (Fig. 2F), a few CD20-positive B-cells (Fig. 2G), and rare CD1a-positive dendritic cells. These inflammatory cells, including eosinophils, also infiltrated the surrounding brain parenchyma, showing marked reactive astrogliosis and macrophage/microglial infiltration (Fig. 2A, D, H). Ki-67-positive nuclei were found in both lymphocytes and plasma cells (Fig. 2I). No immunoreactivity for amyloid- β was observed throughout the specimen. Epstein-Barr virus *in situ* hybridization was

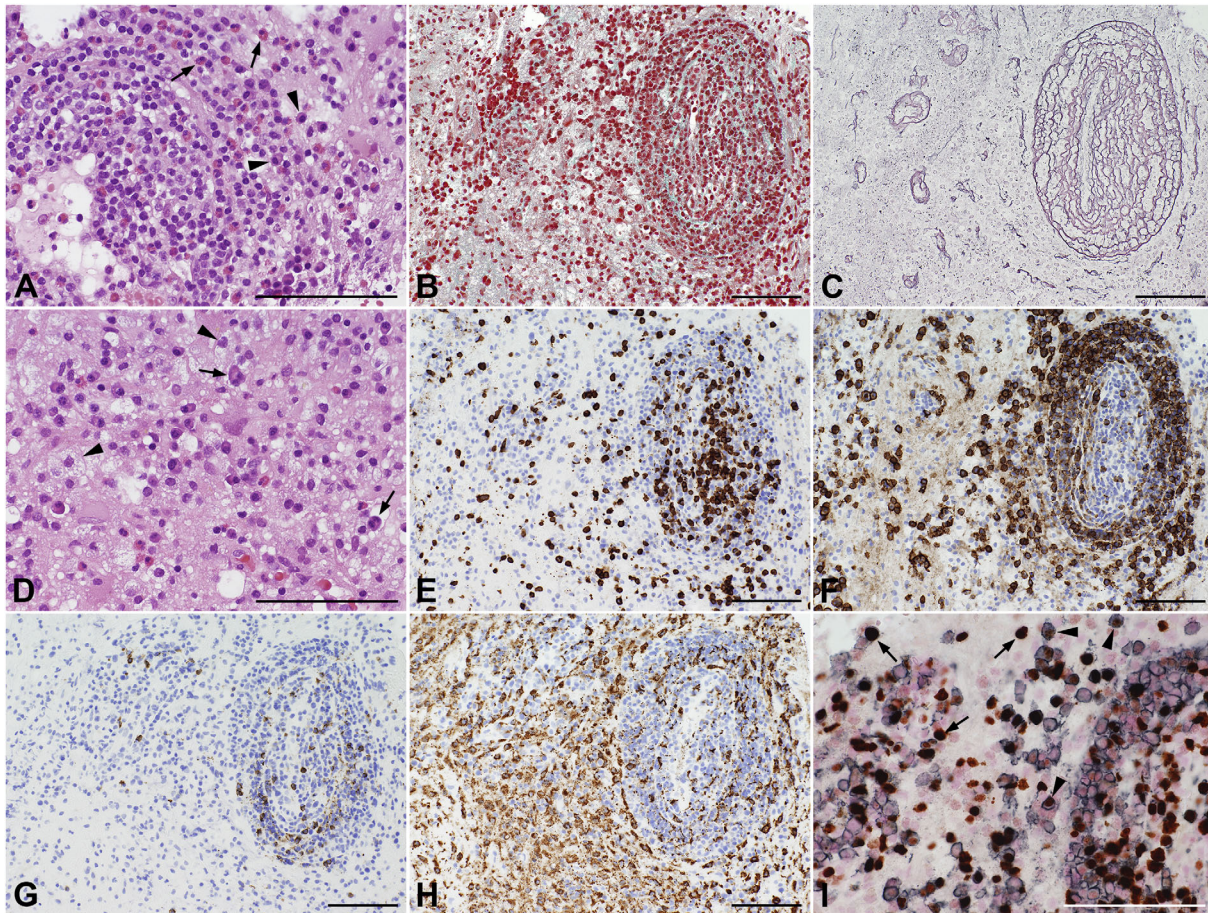


Fig 2 Microscopic findings of the resection specimen from the brain lesion. (A) Numerous mononuclear cells, including lymphocytes, eosinophils (arrows), and plasma cells (arrowheads), infiltrate the parenchymal vein and surrounding brain parenchyma with marked edema and reactive astroglia. (B) Destructive change of an affected venous vessel is evident. (C) Vascular mononuclear cell infiltration is associated with the concentric proliferation of reticulin fibers. (D) Plasma cells of different sizes with occasional binucleation (arrows) were found in the brain parenchyma showing marked reactive astroglia and macrophage infiltration (arrowheads). (E) Infiltrating T-cells are distributed in the relative inner area of vascular inflammation and surrounding brain parenchyma. (F) Abundant plasma cells infiltrate the relative outer area of vascular inflammation and surrounding brain parenchyma. (G) A small number of B-cells are observed in part of the plasma cell infiltration area. (H) Monocyte/macrophage and microglial cells are mainly observed in the brain parenchyma. There are no multinucleated giant cells within the inflammatory lesion. (I) Ki-67-positive nuclei are observed in both lymphocytes (arrows) and plasma cells (arrowheads). Panels B, C, and E–H represent the same area at the same magnification. HE (A, D), Elastic–Masson (B), reticulin silver impregnation (C), immunohistochemistry for CD3 (E), CD138 (F), CD20 (G), and CD68 (H) performed by the polymer-immunocomplex method (BOND Polymer Refine Detection, Leica Biosystems, Newcastle Upon Tyne, UK) with 3–3' diaminobenzidine (DAB) as the chromogen and hematoxylin as the counterstain (E–H). Double-labeling immunohistochemistry for Ki-67 (DAB) and CD138 (HistoGreen, AbCys S.A., Paris, France) with nuclear fast red (Vector Laboratories, Burlingame, CA, USA) counterstain (I). Scale bars: 100 μ m (A–I).

negative, and polymerase chain reaction tests for both T-cell receptor gamma and immunoglobulin heavy-chain variable region genes did not show rearrangements. These results excluded the possibility of lymphoma and lymphomatoid granulomatosis. Together with these findings, a histological diagnosis of eosinophilic CNS vasculitis was made. Histological examination of the biopsy specimen from the erythema revealed perivasculitis with eosinophilic infiltration within the dermis (Fig. 3). Primary antibodies used for immunohistochemistry are listed in Table 1.

DISCUSSION

The present case was clinically characterized by a cerebral tumefactive lesion on MRI and multiple foci of erythema histologically showing eosinophil-rich non-granulomatous small vessel vasculitis and dermal eosinophilic infiltration in an ANCA-negative and asthma-free patient with hypereosinophilia. In addition, the patient had a clinical history of allergic rhinitis and paranasitis, and her symptoms, including recurrent erythema and multiple foci of bilateral pulmonary small nodules on chest CT, disappeared after corticosteroid administration. These

clinicopathological features were similar, at least in part, to eosinophilic granulomatosis with polyangiitis (EGPA) or formerly Churg–Strauss Syndrome (CSS).

Currently, there are no established diagnostic criteria for EGPA with an international consensus. In the past, CSS was defined as a disease characterized by hyper-eosinophilia (peak blood eosinophil counts exceeding $1.5 \times 10^9/L$) and systemic vasculitis involving two or more extra-pulmonary organs in patients with asthma and allergic rhinitis.³ Conversely, four or more of the six items were required to evaluate a given patient with angiitis as having CSS in the subsequent American College of Rheumatology (ACR) 1990 classification criteria.⁴ The association with asthma was also specified in the definition of EGPA by the CHCC2012.² Accordingly, based on the absence of a history of asthma and satisfying only three of the six ACR criteria, the present case fulfills neither the

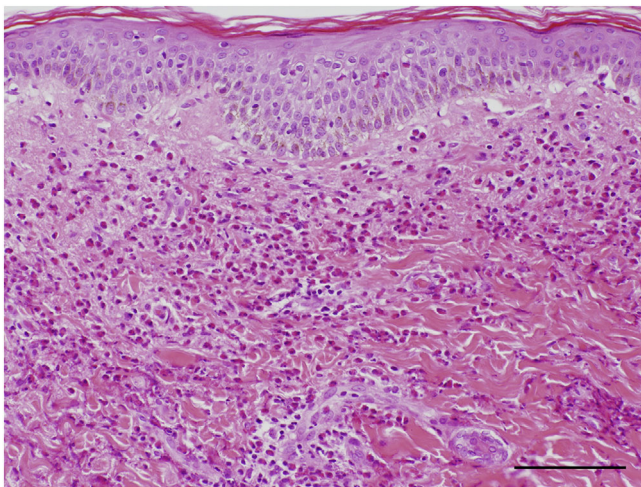


Fig 3 Microscopic finding of the biopsy specimen from the erythema. An HE-stained section shows perivascularitis with eosinophilic infiltration within the dermis. Scale bar: 100 μ m.

Lanham diagnostic nor ACR classification criteria nor the definition of EGPA by the CHCC2012. However, it remains to be solved whether the pathological condition in the present case can be interpreted as a spectrum of EGPA even without asthma or another distinct eosinophil-associated disease concept. Another possible interpretation of the histopathological findings is that eosinophils are bystanders intermingled with lymphocytic vasculitis lesions due to peripheral blood hyper-eosinophilia. However, biopsy-proven lymphocytic CNS vasculitis lacking eosinophil infiltration has also been described in a single patient with severe peripheral blood hyper-eosinophilia.⁵ Detailed mechanisms for eosinophil infiltration are yet to be determined; eosinophils induce tissue inflammation through three major degranulation mechanisms: exocytosis, piecemeal degranulation, and cytolytic degranulation.^{6,7} Therefore, the eosinophil count in inflammatory lesions may not necessarily reflect the intensity of eosinophilic inflammation. Lack of or subtle eosinophil infiltration in the cerebral vasculitis lesion in a setting of peripheral blood hyper-eosinophilia may not necessarily rule out the possibility of eosinophilic inflammation and suggests a possible involvement of cytolytic degranulation in the pathomechanism of vasculitis.

Hypereosinophilic syndrome (HES) appears to be an important differential diagnosis in the present case. The term hypereosinophilia (HE) refers to the conditions with a blood eosinophil count exceeding $1.5 \times 10^9/L$ and/or histologically confirmed tissue eosinophilia; and HES is defined by (i) HE with blood eosinophilia, (ii) HE-related organ damage, and (iii) the absence of an alternative explanation for the observed organ damage.⁸ HE in the present case appears to be secondary (reactive) to allergic rhinitis and parasinusitis as possible underlying conditions. Several factors, including elevated IgE and allergic rhinitis, are associated with higher blood eosinophil counts.⁹ However, the total number of peripheral blood

Table 1 Primary antibodies used for immunohistochemistry

Antibodies	Clone	Source	Dilution	Pretreatment
Amyloid- β protein	4G8	Signet, Dedham, MA, USA	1:20000	FA, Heat/SCB/pH6
CD1a	MTB1	Leica Biosystems, Newcastle Upon Tyne, UK	RTU	Heat/SCB/pH6
CD3	LN10	Leica Biosystems, Newcastle Upon Tyne, UK	RTU	Heat/T-EDTA/pH9
CD8	C8-144B	Dako, Glostrup, Denmark	1:100	Heat/T-EDTA/pH9
CD20	L26	Dako, Glostrup, Denmark	1:2000	Heat/SCB/pH6
CD68	PG-M1	Dako, Glostrup, Denmark	1:200	Heat/T-EDTA/pH9
CD138	MI15	Leica Biosystems, Newcastle Upon Tyne, UK	RTU	Heat/SCB/pH6
GFAP	GA5	Leica Biosystems, Newcastle Upon Tyne, UK	RTU	None
Ki-67	MIB-1	Dako, Glostrup, Denmark	1:300	Heat/T-EDTA/pH9
S-100 protein	polyclonal	Dako, Glostrup, Denmark	1:600	Heat/SCB/pH6
IDH1 R132H	H09	Dianova, Hamburg, Germany	1:800	Heat/T-EDTA/pH9

GFAP, glial fibrillary acidic protein; Heat/SCB/pH6, heat-induced antigen retrieval in 15 mM sodium citrate buffer at pH6; Heat/T-EDTA/pH9, heat-induced antigen retrieval in 10 mM Tris buffer solution containing 1 mM disodium ethylenediaminetetraacetate at pH9; IDH1 R132H, isocitrate dehydrogenase 1 with an arginine to histidine substitution at codon 132; RTU, ready to use.

eosinophils does not exceed $1.5 \times 10^9/L$ in patients with asthma, regardless of the clinical severity,¹⁰ even with comorbid allergic rhinitis.¹¹ Based on these previous observations, allergic rhinitis and parasinusitis may not necessarily be considered direct causes of blood hyper-eosinophilia in the present case. Although detailed genetic analyses were unavailable, there was no specific underlying disease accounting for blood hyper-eosinophilia, including leukemia, parasitic infection, and connective tissue diseases. Accordingly, the present case appears to be clinicopathologically consistent with idiopathic rather than primary (neoplastic) or secondary (reactive) HES.¹² Cutaneous manifestations in HES are characterized by erythematous lesions rather than palpable purpura commonly occurring in EGPA. Serum CRP level is generally low or within the normal range in HES, which also appears to support the diagnosis of HES in the present case, while it is high in patients with EGPA.¹³ Neurological manifestations in HES are relatively uncommon compared to those in EGPA, and cerebral vasculitis is rare; it is reported in only 1% of patients with HES.¹³ Recently, the term “idiopathic eosinophilic vasculitis (EoV) or HES-associated vasculitis” was proposed as an additional manifestation of HES, characterized clinicopathologically by an eosinophil-rich, non-granulomatous necrotizing, systemic form of vasculitis that affects vessels of various sizes in ANCA-negative, asthma-free patients.¹⁴ Although it is difficult to interpret such cases, including our case, according to the CHCC2012 definitions² because of the ambiguous distinctions between the categories, particularly “variable vessel vasculitis (VVV),” “vasculitis associated with systemic disease,” and “vasculitis associated with probable etiology,” this disease concept, in agreement with the previous report,¹⁴ would better be added to the VVV list according to these definitions. CNS involvement seems rare in HES-associated vasculitis, as there was no case of histopathologically proven CNS EoV among the 10 original cases in the publication,¹⁴ and its extensive English literature review,¹⁴ together with our own PubMed search, identified only two reported cases similar to EoV or HES-associated vasculitis affecting particularly the small vessels in the CNS in an ANCA-negative, asthma-free patient who showed rapid improvement in symptoms with high-dose intravenous steroid administration.^{5,15} However, one of these cases lacks eosinophil infiltration in the vasculitis lesion despite persistent marked peripheral blood hyper-eosinophilia,⁵ which argues against the histopathological feature of EoV¹⁴; at the same time, the other does not seem clinically consistent with “HES”-associated vasculitis because of the raised CRP and lack of peripheral blood hyper-eosinophilia.¹⁵ Furthermore, some patients meeting neither the definition and classification criteria of EGPA nor criteria of HES-associated vasculitis may still

be considered EGPA based mainly on biopsy findings.¹⁶ Therefore, the possibility that patients with HES-associated vasculitis, similar to our case, are interpreted as “ANCA-negative, asthma-free, and biopsy-false negative EGPA” cannot be ruled out.

In conclusion, we described a patient who initially presented with a tumor-like cerebral lesion on MRI, histologically showing eosinophil-rich non-granulomatous small vessel vasculitis, followed by other systemic manifestations, requiring clinicopathological differential diagnosis from EGPA and others. This patient appears to be the first reported case consistent with idiopathic EoV or idiopathic HES-associated vasculitis in the CNS. Further clinicopathological studies enrolling similar cases are necessary to unravel the underlying pathogenesis, which would help establish the disease concept for a reliable clinicopathological classification and diagnostic criteria for vasculitis in the future.

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DISCLOSURE

The authors declare no conflict of interest.

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