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A Fulminant Case of Granulomatosis with Polyangiitis with Meningeal and Parenchymal Involvement

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Key Words
Granulomatosis with polyangiitis · Proteinase 3-anti-neutrophil cytoplasmic antibody · Pachymeningitis · Craniectomy · Venous infarction

Abstract
Central nervous system (CNS) involvement, such as pachymeningitis and/or cerebrovascular events, is rare in patients with granulomatosis with polyangiitis (GPA). Furthermore, the details of pathological examinations of cases have rarely been described. We describe a case of GPA that manifested as an isolated paranasal sinus disease that invaded the subarachnoid space and caused a hemorrhagic venous infarction. We also describe the pathological characteristics of the biopsied brain material from the successful decompressive craniectomy. In particular, granulomatous inflammation with geographic necrosis and multinucleated giant cells were observed in the perivascular area of the thickened dura mater and leptomeninges. Small vessels in the meninges were involved in the granulomatous lesions, and the lumens of the veins were often occluded. In the cerebral cortices and white matter in these areas, hemorrhagic infarction was widely observed. We suggest that our findings represent a novel mechanism of CNS involvement in GPA. Moreover, we believe that the emergency decompressive craniectomy and partial lobectomy for the cerebral infarction in this patient with GPA likely contributed to his survival.

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Case Report

A 75-year-old man with a slightly increased serum creatinine level had developed proteinuria and hypertension in 2000. In 2007, he noticed a gradually progressive hearing loss and repeated bloody nasal discharge resulting from a refractory sinusitis. He was admitted to our hospital for evaluation in June 2008.

Initial laboratory findings revealed elevated serine proteinase 3-anti-neutrophil cytoplasmic antibody (PR3-ANCA; 26.2 EU), blood urea nitrogen (35 mg/dl), and serum creatinine (1.62 mg/dl) levels. Urinalysis indicated proteinuria (0.2 g/day) without hematuria. A head CT revealed maxillary sinusitis. Tissue from a nasal mucosal biopsy showed granulomatous inflammation in the extravascular area. Because of these combined findings, he was diagnosed as having granulomatosis with polyangiitis (GPA) according to the American College of Rheumatology 1990 Criteria for GPA and Watts' algorithm [1, 2]. The Birmingham Vasculitis Activity Score 2003 was 6. Because of the low disease activity, the slow progression and the advanced age, we did not initiate immunosuppressive therapy at this time.

In October 2008, he developed fever lasting for several days. Laboratory data were as follows: C-reactive protein 11.91 mg/dl, PR3-ANCA 49.1 U/ml, fibrinogen 752 mg/dl, D-dimer 1.7 μg/ml, and urinary protein 0.27 g/day. Activated partial thromboplastin time, prothrombin time and fibrin degradation product were within the respective normal range. A chest CT was normal. Although we administered meropenem (2.0 g/day for 1 week), vancomycin (500 mg/day for 17 days) and itraconazole (200 mg/day for 20 days), the fever and C-reactive protein level did not decrease. On day 12 of admission, he showed mild disorientation, severe hearing loss and hoarseness. A brain MRI revealed a mass lesion in the right frontal lobe and hypertrophic mucosa in the paranasal sinuses (fig. 1a) in addition to a thickened and strongly enhanced dura mater surrounding the mass lesion (fig. 1b). He was diagnosed as having GPA with central nervous system (CNS) involvement. The Birmingham Vasculitis Activity Score had increased to 21. We treated him with methylprednisolone 500 mg daily for 3 days. However, he rapidly developed left hemiparesis and deterioration of consciousness [Glasgow Coma Scale (GCS): E1V2M4]. A brain CT revealed that the parenchymal mass lesion had enlarged and the mucous effusion was invading the posterior wall of the right frontal sinus. Due to an impending transtentorial herniation, a decompressive hemicraniectomy and partial right frontal lobectomy were performed, which moderately improved his consciousness (GCS: E2V3M4). After the surgery, he developed bloody sputa, and a chest CT revealed an infiltrative shadow in both lungs. We confirmed alveolar hemorrhage by bronchoscopy.

The biopsied brain material from the surgery revealed a granulomatous inflammation with geographic necrosis and multinucleated giant cells in the perivascular area of the thickened dura mater and leptomeninges (fig. 1c, d). Small vessels in the meninges were involved in the granulomatous lesions, and the lumens of the veins were often occluded. In the cerebral cortices and the white matter in these areas, hemorrhagic infarction was widely observed. After treatment with prednisolone (20 mg/day) and azathioprine (40 mg/day), the disturbance of consciousness substantially improved (GCS: E4V3M5), and the epistaxis stopped. In addition, serum creatinine and PR3-ANCA levels normalized. This study was conducted with the approval of the Ethics Committee of Niigata University Graduate School of Medical and Dental Sciences.

Discussion

CNS involvement such as pachymeningitis and cerebrovascular events is uncommon in GPA, reported in only 2–8% of cases [3, 4]. We previously clarified that leptomeningeal and parenchymal involvement in the brain were significantly more common in PR3-ANCA-positive hypertrophic pachymeningitis compared to myeloperoxidase anti-neutrophil cytoplasmic antibody-positive and idiopathic hypertrophic pachymeningitis in a study of 36 patients (including this case) [5]. Based on the study, MRI findings showed an enhancement of both the pachymeninges and leptomeninges. Moreover, the present case had the extension of the mass lesion with the granulomatous inflammation, and the venous obstruction resulted in severe edema and hemorrhagic infarction. Emergency decompressive craniectomy and partial lobectomy for cerebral infarction with GPA likely contributed to our patient's survival. To our knowledge, this is the first report successfully managed with surgical decompressive craniectomy.

Disclosure Statement

The authors declare no conflicts of interest.

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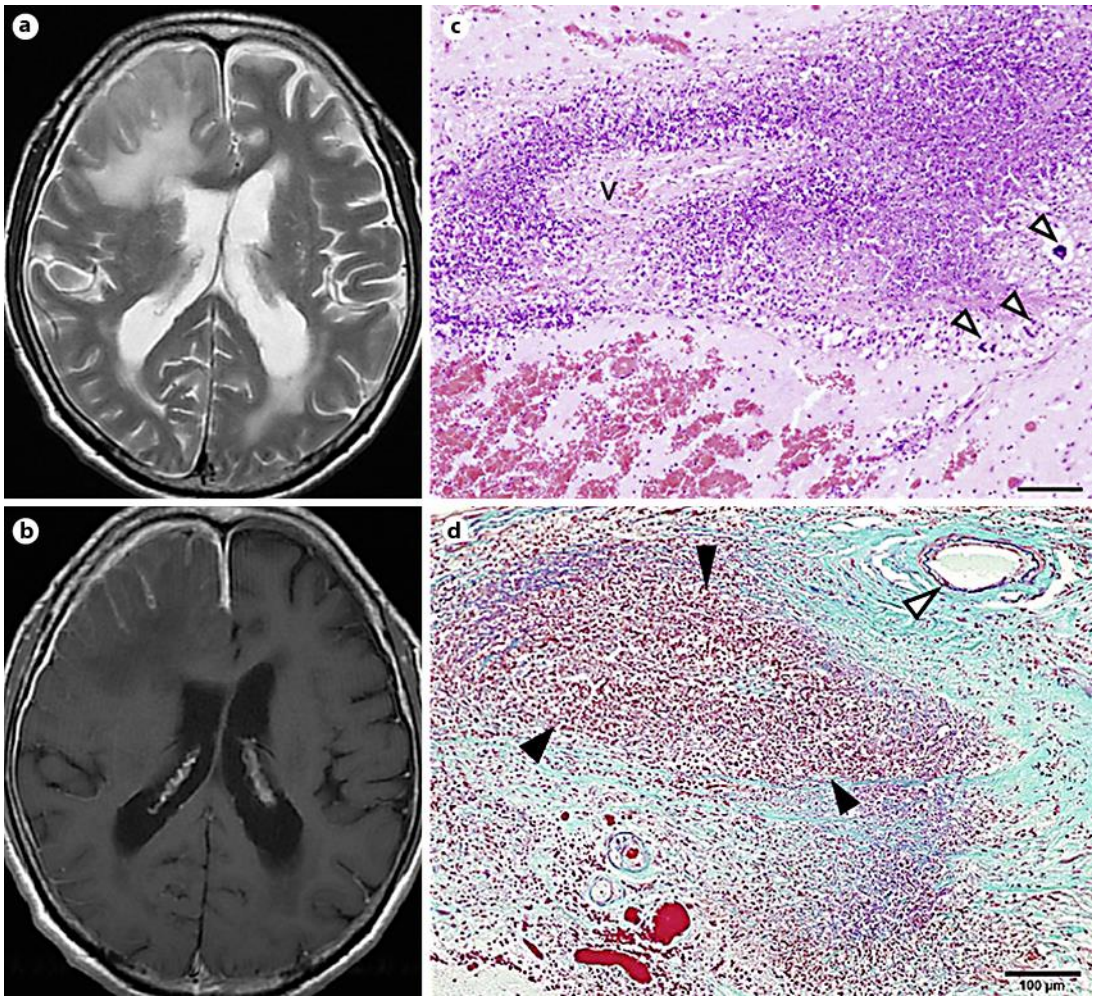

Fig. 1. MRI and microscopic photographs of the patient. **a** T2-weighted MRI revealed a remarkable midline shift caused by a mass lesion with an edema in the right frontal lobe. The lesion was >40 × 60 mm in size. **b** Gadolinium-enhanced T1-weighted MRI revealed a superficial extra-axial enhancement adjacent to the right frontal lobe. The abnormal enhancement was both pia-arachnoid, extending along the pial surface of the brain, and dura-arachnoid, extending along the inner margin of the skull (including the falx cerebri). **c** Hematoxylin-eosin staining of the specimen from the right frontal lobe showed inflammatory cells massively infiltrating the perivascular connective tissues of the subarachnoid space, forming necrotic granuloma with multinucleated giant cells (white arrowheads). A fresh hemorrhagic infarct is observed in the cerebral cortex, which was accompanied by severe congestion and edema. V = vein. **d** Veins (black arrowheads) were severely affected. However, the arteries were less affected in the same area (white arrowheads). Elastica-Goldner stain. Scale bars = 100 μm.