Hypertrophic Pachymeningitis as a Delayed Complication of Granulomatosis with Polyangiitis

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Abstract

A 69-year-old man presented with upper airway symptoms, multiple lung nodules and masses, proteinuria and hematuria, and an increased level of proteinase 3 anti-neutrophil cytoplasmic antibody (PR3-ANCA). Granulomatosis with polyangiitis (GPA) was diagnosed by a transbronchial lung biopsy. All of these symptoms were ameliorated and the level of PR3-ANCA declined following treatment with prednisolone and cyclophosphamide. The patient developed a headache 16 months after the onset of symptoms, and contrast-enhanced magnetic resonance imaging showed the thickening of the dura mater, which suggested that hypertrophic pachymeningitis (HP) had developed as a complication of GPA. HP can be a unique complication of GPA at recurrence, and can occur without the relapse of other lesions or an increase in PR3-ANCA level.

Key words: granulomatosis with polyangiitis, hypertrophic pachymeningitis, PR3-ANCA, relapse

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Introduction

Granulomatosis with polyangiitis (GPA) complicated with hypertrophic pachymeningitis (HP) is not as rare as previously thought (1, 2). GPA can relapse through HP without the recurrence of other lesions (3) or a re-increase in the level of proteinase 3 anti-neutrophil cytoplasmic antibody (PR3-ANCA) (4). In the present case, the patient’s remission was maintained, despite the symptoms at the onset of GPA (such as runny nose, nasal congestion, multiple lung nodules, proteinuria and hematuria) and the level of PR3-ANCA did not re-increase after the administration of prednisolone and cyclophosphamide. The patient’s GPA relapse was associated with HP. This report may be useful for drawing attention to the possibility of HP during the follow-up of GPA patients. The thickening of the dura mater is often detected only by contrast-enhanced magnetic resonance imaging (MRI), rather than by brain computed tomography (CT) or non-contrast MRI. Therefore, contrast-enhanced MRI should be performed when there is a possibility of GPA relapse associated with HP.

Case Report

A 69-year-old man presented 2 years before his current admission with a runny nose, nasal congestion, and cough. His chest X-ray showed multiple nodules and tumors in the bilateral lungs (Fig. 1a). A laboratory analysis revealed proteinuria (30 mg/dL), hematuria (dipstick test 3+, and 10-19 erythrocytes per high power field), and an increased PR3-ANCA level of 77 U/mL. The levels of creatinine (0.61 mg/dL) and creatinine clearance (93.0 mL/min) were within the normal range (Table). A transbronchial biopsy showed necrotic granulomas with multi-nucleated giant cells, and a renal biopsy showed crescentic glomerulonephritis. GPA was diagnosed. After the initiation of high-dose corticosteroid treatment [prednisolone (PSL) 50 mg/day] and the intravenous administration of cyclophosphamide (500 mg/body once per month), all of the patient’s symptoms and chest X-ray findings rapidly improved and the PR3-ANCA level promptly decreased to the normal range. The PSL dosage was tapered to 17.5 mg/day for 7 months and cyclophosphamide was given once a month for 6 months. Although the symptoms and laboratory data showed no signs of recur-

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The level of PR3-ANCA, which had been markedly elevated at the onset of GPA, was within the normal range, and there was no proteinuria or hematuria, both of which were detected at the onset of GPA. The other representative data are shown in Table. The recurrence of abnormal shadows, which occurred at the onset of GPA, was not detected on a chest X-ray or CT (Fig. 1b). Contrast-enhanced brain MRI showed the enhanced thickening of the dura mater at the right frontal, temporal and parietal lobes (Fig. 2a). The patient’s cerebral spinal fluid showed slightly elevated levels of protein (61 mg/dL), but no evidence of infectious meningitis (Table). HP, as a complication of GPA, was diagnosed based on these findings and the patient’s past history of GPA.

The patient received 1 g/day of intravenous methylprednisolone (mPSL) for 3 days, followed by oral PSL (20 mg/day). After the start of these treatments, his inflammatory reactions improved and his headaches resolved. Furthermore, one month after the start of treatment, brain MRI showed an improvement of the thickening of the dura mater. However, the patient’s headache was exacerbated in July. After the dose of PSL was increased to 30 mg/day, the patient’s headache improved and PSL was then tapered to 10 mg/day over 7 months without a relapse (Fig. 3). Subsequent contrast-enhanced brain MRI showed further improvement of the thickening of the dura mater (Fig. 2b).

**Discussion**

HP is characterized by inflammatory or fibrotic thickening of the dura mater. The multiple neurological manifestations of HP include chronic headaches, cranial neuropathy and seizures. HP was first described by Charcot and Joffroy in 1869 as a cryptogenic thickening of the dura mater (5). Since then, various diseases, including syphilis, tuberculosis and fungi, connective tissue diseases such as rheumatoid arthritis and Sjögren syndrome and various malignant diseases (6). Contrast-enhanced brain MRI shows strong contrast enhancement of the thickened dura mater and is the most useful diagnostic technique for the detection of HP; non-contrast brain MRI shows lower sensitivity (1).

Two pathogenic mechanisms of HP as a complication of GPA have been proposed (7): i) the direct extension of granulomatous inflammation or vasculitis from the contiguous affected structures, such as the sinus, orbit, pharynx and mastoid antrum; ii) granulomas or vasculitis remote from the involved nasal or paranasal structures. The majority of case reports including autopsy reports have indicated the former mechanism, suggesting direct extension (8). In the present case, however, HP occurred without the recurrence of upper airway symptoms and the thickening of the dura mater was remote from the upper airways, indicating the latter mechanism. Furthermore, several cases which are considered to have developed via the latter mechanism have been previously reported. In these patients, HP was not preceded by the other signs of GPA (9, 10) and the HP seemed to affect...
no other organs (11). Therefore, it seems that a considerable number of cases develop via the latter mechanism.

HP as a complication of GPA has been considered to be a rare clinical disorder. Nishino et al. reported that only 2 of their 324 GPA patients showed HP (12). On the other hand, Murphy et al. reported that 11 of 19 GPA patients with neurologic symptoms showed meningeal thickening on brain MRI (1) and Provenzale et al. reported that 3 of 15 GPA patients who underwent brain imaging study showed meningeal thickening (2). These findings suggest that the complication of HP is not as rare in GPA as previously thought. However it is difficult to recognize HP when it is a complication of GPA, especially in our case, for the three reasons mentioned below.

The first reason is that headache, which is the most common symptom associated with HP, is also a common symptom of GPA, due to the chronic inflammation of the paranasal sinus and/or orbit. Thus, not all complaints of headache are investigated by contrast-enhanced brain MRI. For this reason, the number of GPA cases in which HP was not diagnosed may be considerable.

The second reason is that GPA may relapse through HP without the recurrence of the symptoms of upper airway, lungs and kidneys. Similar cases have been reported previously (3). More than 80% of patients experience one or more relapses during tapering or within 10 years after the cessation of treatment (13). It is therefore important to be mindful of the possible relapse of GPA through HP without the recurrence of other lesions.

The third reason is that PR3-ANCA, which was elevated in the present patient at the onset of GPA did not show a similar elevation when GPA relapsed through HP. Generally it is considered that the level of PR3-ANCA is correlated with GPA activity and that it can be a marker of recurrence and therapeutic effect. More than 80% of generalized GPA patients are positive for PR3-ANCA, while 50-60% of patients in the limited GPA subgroup are positive (14). In GPA complicated with HP, only 37% patients are positive (15).
Boomsma et al. reported that 15-48% of GPA patients showed no elevation of PR3-ANCA at recurrence (4). Therefore the measurement of PR3-ANCA is not always useful for the prediction of relapses in patients with GPA. In our case, the PR3-ANCA titer might not have been elevated because the relapse was localized only in the dura mater.

In conclusion, when a patient with GPA complains of a headache or other neurological abnormalities, it is important to consider the possibility of HP and to carry out appropriate investigations, such as contrast-enhanced MRI, even if other common symptoms of GPA do not appear, or when the PR3-ANCA titer is not elevated.

The authors state that they have no Conflict of Interest (COI).

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