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Case Report

Pituitary Granulomatosis with Polyangiitis Presenting with Central Diabetes Insipidus

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We report on a case of limited form of granulomatosis with polyangiitis (GPA) with pituitary involvement which presented with central diabetes insipidus. This rare form of GPA has not been reported in Korea. The patient presented with fever, headache, productive cough, nasal symptoms, and polyuria. Laboratory data and imaging studies demonstrated inflammatory lesions in nasal sinus and lungs. Pituitary stalk thickening and enhancement were observed on brain magnetic resonance imaging. The histopathology of the lung lesions showed chronic active granulomatous inflammation. Polyuria, hyperosmolar hypernatremia, and decreased urine osmolality which responded to synthetic vasopressin analog were consistent with central diabetes insipidus. Based on the clinical findings and histopathological results, a diagnosis of GPA with pituitary involvement was established. Treatment with desmopressin as well as concurrent glucocorticoids and immunosuppressant resulted in clinical improvement. **(J Rheum Dis 2015;22:195-199)**

Key Words. Granulomatosis with polyangiitis, Neurogenic diabetes insipidus, Pituitary gland

INTRODUCTION

Granulomatosis with polyangiitis (GPA), previously known as Wegener's granulomatosis causes a systemic granulomatous inflammation and necrotizing vasculitis affecting small to medium sized arteries and veins. Central nervous system (CNS) involvement of GPA is rare and occurs in less than 10% of patients, usually in the form of cranial neuropathies, mass lesions or pachymeningitis. Here, we report the first case of GPA with pituitary involvement which presented as central diabetes insipidus (DI) in Korea. Treatment with desmopressin, glucocorticoids and immunosuppressant resulted in resolution of symptom of GPA as well as central DI.

CASE REPORT

In December 2012, a 64-year-old man was evaluated at the local health clinic for headache, cough and fever which had persisted for several weeks. Clinical diagnosis of meningitis and pneumonia was made and he was treated with empirical antibiotics. His symptoms were not improved however, and he was referred to our hospital for further evaluation. He reported nasal congestion, rhinorrhea, loss of appetite and 10 kg loss of body weight over the preceding 6 months. He also complained of polyuria and increased urinary frequency. He had no notable past medical history other than hypertension diagnosed 8 years ago. On physical examination, there were no abnormal findings except for mucosal hyperemia with discharge in bilateral nasal cavities. The body temperature was 37.5°C. Laboratory studies showed white blood cell count of 25,440 mm^{-3}, hemoglobin of 12.3 g/dL, platelet count of 455,000 mm^{-3}, increased erythrocyte sedimentation rate of 120 mm/h, and C-reactive protein concentration of 20.56 mg/dL. Serum sodium was 155 mmol/L with serum osmolality of 317 mOsm/kg, but the corresponding urine osmolality was inappropriately low

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at 202 mOsm/kg. Serum blood urea nitrogen and creatinine levels were in normal range. Pyuria, hematuria or albuminuria were not detected in urinalysis. Chest radiograph showed bilateral multifocal patchy consolidation (Figure 1A), and there was mucoperiosteal thickening of bilateral maxillary sinus in radiograph. Furthermore, a chest computed tomography demonstrated nodular lesions along the bronchovascular bundles in both lungs (Figure 1B). During the hospitalization, initial daily urine output exceeded 7 liters indicating definitive polyuria. With clinical suspicion of central DI, nasal desmopressin puff was started and the patient responded with improvement of polyuria and hypernatremia supporting the diagnosis of central DI. Water deprivation test was not performed to minimize aggravation of hypernatremia. Magnetic resonance imaging (MRI) of the brain showed thickening and enhancement of pituitary stalk and pachymeninges of left hemisphere (Figure 2A and 2B). A sys-

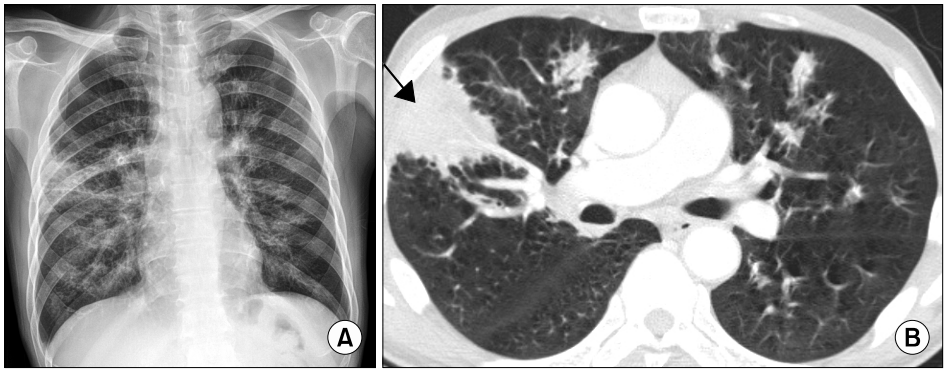

Figure 1. (A) Chest radiograph shows multifocal patchy consolidations in both lungs. (B) Chest computed tomography demonstrated bilateral infiltrations along the bronchovascular bundles (arrow).

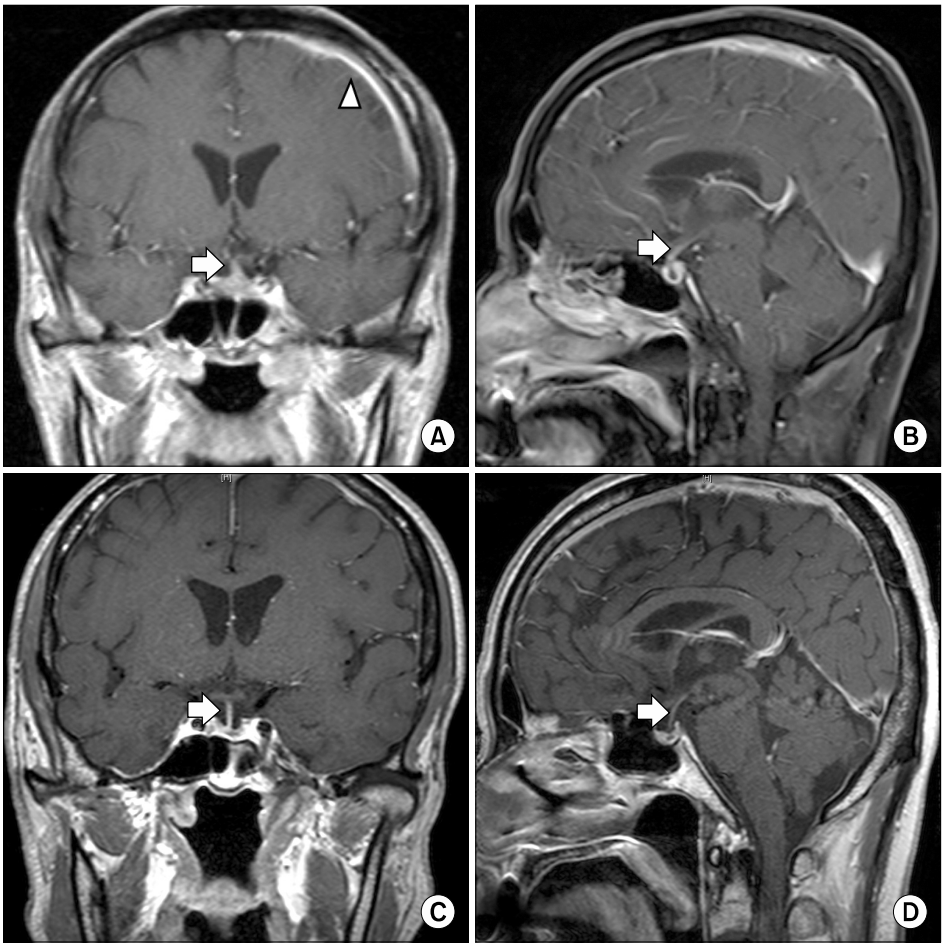

Figure 2. (A, B) Baseline brain magnetic resonance imaging (MRI) of T1 weighted image with contrast showing thickening and enhancement of pituitary stalk (arrows). Leptomeningeal and pachymeningeal involvement of left hemisphere are also seen (arrow head). (C, D) Follow-up MRI shows resolustion of pituitary stalk thickening and enhancement (arrows), as well as pachymeningeal enhancement.

tematic inflammatory process with CNS involvement was suspected and further investigation was carried out. Anti-nuclear antibody was positive and serum anti-neutrophil cytoplasmic antibody (ANCA) was negative. Bronchoscopy with bronchoalveolar lavage (BAL) was performed. BAL fluid analysis demonstrated a marked increase in neutrophils and biopsy of endobronchial nodules revealed chronic active inflammation with focal necrosis. Transthoracic core needle lung biopsy showed chronic active inflammation with microscopic necrosis and ill-defined granuloma (Figure 3). Microbiological tests for bacteria, fungus, and mycobacteria were negative in the blood, sputum, and lung tissue. Based upon the clinical features, laboratory data and histopathological findings, a diagnosis of GPA with pituitary involvement was established.

Treatment was initiated with intravenous methylprednisolone at a dosage of 40 mg per day, and 7 days after initiation it was changed to 40 mg of oral prednisolone. Fifty milligram of oral cyclophosphamide was subsequently added in the treatment regimen. The patient was discharged 3 weeks after hospitalization with prednisolone 40 mg, cyclophosphamide 50 mg, and 0.1 mg of oral desmopressin. In the outpatient clinic, prednisolone was further tapered down to 15 mg. After 6 weeks of the cyclophosphamide therapy, cyclophosphamide was discontinued due to newly developed neutropenia; absolute neutrophil count of 240/ μL. Neutropenia was resolved after discontinuation. Instead, 50 mg of azathioprine was initiated for maintenance. Desmopressin was discontinued after 3 months of treatment with complete resolution of signs and symptoms of DI. Additional sellar MRI was carried out after 4 months, which showed a resolution of thickening and enhancement of pituitary stalk and meninges (Figure 2C and 2D). The current medical regimen includes 2.5 mg of prednisolone and azathioprine 75 mg, without relapse of symptoms.

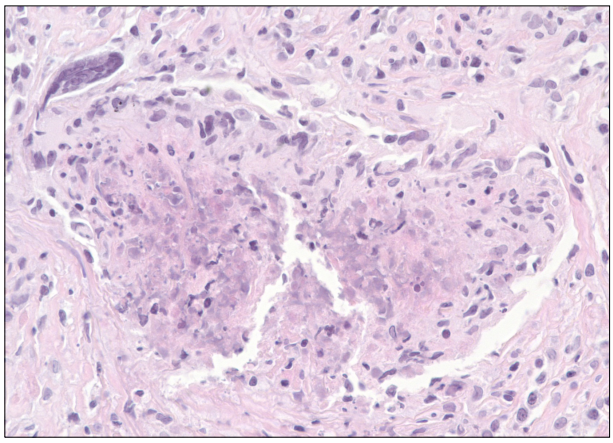

Figure 3. Histopathological finding of the lung biopsy. Microscopic necrosis and ill-defined granuloma formations are demonstrated (H&E, ×400).

DISCUSSION

GPA is a systemic necrotizing granulomatous vasculitis of small to medium vessels. Pathophysiology is not fully understood, but it is considered as an autoimmune-mediated process associated to ANCA. The classic GPA involves a triad of upper respiratory tract, lung, and kidney. But any organs may be involved. Neurological involvement occurs in approximately 30% of patients with peripheral neuropathy being predominant [1]. CNS involvement is uncommon and previously reported frequency is no more than 10% of patients. CNS manifestations include cranial neuropathies, cerebrovascular events, cerebritis, meningitis, seizures, and hemorrhage [1,2]. Pituitary gland involvement is extremely rare complication of GPA. Only a few case reports have been published worldwide [3-9], and there has been no report in Korea so far. According to the prior study, less than 1% of patients with GPA have pituitary involvements [10]. Central DI is the most common presentation in patients who have pituitary involvement, frequently with combined anterior hypopituitarism, which usually develops after pulmonary or kidney involvement [4,11]. Meanwhile, Düzgün et al. [5] reported a case of a patient with GPA who presented with central DI early in the disease course before renal and pulmonary involvement. In addition, a case with isolated pituitary involvement in the absence of lung or renal complication was also reported previously [6]. In this case, polyuria with daily urine volume exceeding 7 liters appeared as one of the major initial presentations with hyperosmolar hypernatremia and inappropriately low urine osmolality. Central DI was diagnosed based upon the clinical manifestations and response to desmopressin, a vasopressin analog. Although serum ANCA test was negative, histopathological examination of lung tissues showed typical granulomatous inflammation. Differential diagnosis included infections including tuberculosis, malignancies, and other noninfectious granulomatous disease such as sarcoidosis or Churg-Strauss syndrome. Ill-defined granuloma accompanying necrosis were more compatible with GPA rather than sarcoidosis which is characterized by discrete, well-formed, non-ne-

crotizing granuloma [12]. Furthermore, increased neutrophils in the BAL analysis and the absence of lymphadenopathies also favored the diagnosis of GPA [13]. It is reported that BAL fluid in sarcoidosis have increased lymphocytes and normal or decreased neutrophils [14]. Although vasculitic changes were not seen in the pathologic specimen, both vasculitic and necrotizing granulomatous inflammations may not always coexist in GPA [15,16]. Moreover, diagnostic yield of core needle biopsy may not have been sensitive enough to detect the vasculitic changes. Churg-Strauss syndrome was unlikely considering the absence of bronchial asthma history and eosinophilia in the blood test and tissues. Overall, this patient met the 1990 American College of Rheumatology classification criteria for GPA [17]. Sinusitis, bilateral lung nodules, and central DI with pituitary stalk enhancement seen in brain MRI, increased inflammatory markers could be explained in the context of GPA. Notably, the patient had no evidence of renal involvement which indicates that the disease was a limited form [18].

There are a few suggested mechanisms of pituitary involvement of GPA. One explanation is that vasculitis of CNS vessels might cause secondary granulomatous hypophysitis or consequent infarction. Secondly, spreading of granulomas from adjacent anatomical areas such as sinus or orbit is another possibility. Lastly, in-situ new granuloma formation in pituitary gland tissue is also suggested [1,7,9]. The extent of pituitary involvement might be variable. In general, it is assumed that the pathologic process involves the posterior pituitary with manifestation of central DI first, than anterior pituitary later in the disease course. According to previous literature review, 52% of patients had isolated central DI and 13% of patients had only anterior pituitary dysfunction while 35% had both anterior and posterior pituitary involvement including panhypopituitarism [6].

GPA has been largely associated with ANCA, and reported ANCA positivity is up to 95% of patients, with especially anti-proteinase 3 antibody present in 70% to 80% of those who are ANCA-positive [19]. However this patient had no circulating ANCA. Since immunofluorescence assay was negative, additional enzyme immunoassays were not performed. Even though ANCA has substantial diagnostic value, it is important to note that negative ANCA assays do not exclude ANCA-associated vasculitis because between 10% and 50% of patients with ANCA associated vasculitis may be ANCA negative. Earlier studies indicated that about 10% of patients with active, untreated GPA are ANCA negative. Furthermore, 30% or more lack ANCA in limited GPA initially. The proportion of ANCA positivity, however, might change with disease duration, as more patients become ANCA positive with the time [20,21]. ANCA assay was not repeated in the patient.

In most cases of pituitary involvement, MRI reveals pituitary gland enlargement, enhancement, cystic change, and infundibular thickening. Pituitary enlargement is the most common finding, but is not pathognomic of GPA. But rare cases with normal appearance of gland on imaging study were also reported [3,6,7]. Meanwhile, other granulomatous disease, for example, tuberculosis, sarcoidosis and histiocytosis may exhibit similar findings on MRI without clear differential criteria compared to GPA [7]. For the final diagnosis of GPA, a tissue confirmation is required considering the potential risk of subsequent treatment.

The treatment choice of GPA depends on the extent of disease. Limited GPA is also referred to as "non-renal" GPA. Although several criteria have been established by experts, limited GPA is considered when there is an absence of an immediate threat to either the function of a vital organ or the patient's life within a short time. And this decision is mainly based on the individual clinical judgment. Although central nervous system was involved in this case, we regarded this case as limited form since the patient had no renal involvement and the central DI was adequately controlled with desmopressin. Currently it is recommended that severe GPA is to be treated with cyclophosphamide based regimen combined with glucocorticoids while limited disease might be well controlled with milder therapy such as methotrexate and glucocorticoids alone. As for GPA with pituitary involvement, Yong et al. [6] reported that 65% of patients underwent induction therapy with conventional combination of high-dose glucocorticoids and cyclophosphamide, which led to successful remission in all patients although relapse occurred in 27% after a median of 10.5 months. Meanwhile, 50% of patients treated with nonconventional regimen such as methotrexate, azathioprine, infliximab relapsed after a median of 4.5 months. Thus, the authors recommended induction treatment with cyclophosphamide regimen for GPA with pituitary involvement. The usual regimen consists of daily oral cyclophosphamide of 2 mg/kg, or intermittent intravenous pulse. However, as there were no life threatening manifestations, 50 mg of cyclophosphamide was initiated at first, with plans to titrate up the dose de-

pending on the clinical course. However, cyclophosphamide was discontinued after 6 weeks due to neutropenia. Irrespective of immunosuppression, in most cases of hypopituitarism due to GPA, specific endocrine replacement therapy was required simultaneously [6]. Cases which showed improvement with pituitary MRI findings of variable degrees after immunosuppressive therapy have been reported. It is uncertain that the resolution of MRI findings is correlated with clinical improvement of pituitary dysfunction [6]. Pituitary dysfunction may persist even after achievement of remission of GPA. And the long term prognosis and natural course of pituitary involvement in GPA require further investigations.

SUMMARY

We present a rare case of GPA with central DI due to pituitary gland involvement, which showed a dramatic response to treatment with glucocorticoids, immunosuppressant and concurrent vasopressin analog replacement. Clinicians should consider GPA with pituitary involvement when any patient presents with pituitary dysfunction in conjunction with nasal, respiratory, or renal symptoms. Tissue diagnosis is mandatory and cyclophosphamide-based treatment is currently the preferred regimen.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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