

[ CASE REPORT ]

## Central Diabetes Insipidus in Refractory Antineutrophil Cytoplasmic Antibody-associated Vasculitis

Keiji Ohashi, Michiko Morishita, Haruki Watanabe, Ken-Ei Sada, Takayuki Katsuyama, Yoshia Miyawaki, Eri Katsuyama, Mariko Narazaki, Noriko Tatebe, Katsue Watanabe, Tomoko Kawabata and Jun Wada

### Abstract:

We herein describe two cases of refractory antineutrophil cytoplasmic antibody-associated vasculitis (AAV) complicated with diabetes insipidus (DI) possibly related to hypertrophic pachymeningitis (HP). One patient had microscopic polyangiitis and HP, which were refractory to cyclophosphamide, azathioprine, rituximab, mycophenolate mofetil (MMF), and mizoribine. Remission was finally achieved with the use of etanercept, but DI occurred 5 years later. The other patient had granulomatosis with polyangiitis, which that was refractory to cyclophosphamide, methotrexate, MMF, and rituximab. DI subsequently developed, but was successfully treated with etanercept. Dura mater hypertrophy was macroscopically observed in the latter case.

**Key words:** antineutrophil cytoplasmic antibody-associated vasculitis, diabetes insipidus, etanercept, hypertrophic pachymeningitis, rituximab

(Intern Med 56: 2943-2948, 2017)

(DOI: 10.2169/internalmedicine.8683-16)

### Introduction

Diabetes insipidus (DI) is a rare complication in patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). In these patients, it is assumed to be caused by hypothalamic vasculitis or direct granulomatous involvement (1). Hypertrophic pachymeningitis (HP) is another rare complication of AAV (2, 3), and some studies have described a possible link between HP and DI (4, 5). Previous reports suggest that central nervous involvement, including DI, in patients with AAV is a refractory condition (6, 7) and that HP frequently relapses and adversely affects the prognosis of these patients (2, 3). A combination of glucocorticoid (GC) and cyclophosphamide (CYC) or rituximab (RTX) is widely accepted as standard remission induction treatment for AAV (8); however some cases are refractory to standard immunosuppressive treatment. We herein present two cases of refractory AAV complicated with DI.

### Case Reports

#### Case 1

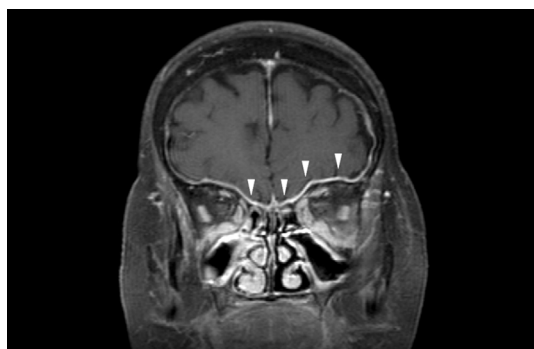
In June 2006, a 72-year-old woman was diagnosed with microscopic polyangiitis (MPA) based on the identification of necrotizing crescentic glomerulonephritis in a renal biopsy specimen and myeloperoxidase (MPO)-ANCA positivity. Remission was achieved with a combination of GC and intravenous CYC. Azathioprine (AZA) was administered to maintain remission but was discontinued due to abnormal liver test results. Subsequently, AZA was switched to mizoribine.

In December 2007, the patient developed left oculomotor nerve paralysis with negative to positive conversion of MPO-ANCA. Magnetic resonance imaging (MRI) showed thickening and contrast enhancement of the basilar dura mater and extraocular muscle, and the patient was diagnosed with AAV relapse associated with HP (Fig. 1). After GC

Department of Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Japan

Received: December 9, 2016; Accepted: February 24, 2017; Advance Publication by J-STAGE: September 25, 2017

Correspondence to Dr. Ken-Ei Sada, sadakenn@md.okayama-u.ac.jp



**Figure 1.** Magnetic resonance imaging of the head (Case 1). The white arrowheads show gadolinium enhancement of the hypertrophic dura mater.

pulse therapy, the patient's symptoms and MRI findings improved. Mycophenolate mofetil (MMF) or RTX were administered concomitantly with high-dose GC and methylprednisolone pulse; it was not possible to reduce the dose of GC. Finally, etanercept (ETN) was initiated, and the dose of the prednisolone (PSL) could be reduced to 1 mg/day (Fig. 2).

Although remission was maintained for about 5 years after the initiation of ETN, the patient visited a community hospital in February 2014 for dry cough, apnea, anorexia, vomiting, and dry mouth that had persisted 2 weeks. The patient was diagnosed with a relapse of AAV with organized pneumonia accompanied by elevated MPO-ANCA levels. After admission, polyuria (4,000-12,000 mL/day) was detected with a decreased urinary sodium level (65 mmol/L), while the serum antidiuretic hormone (ADH) level was normal (0.9 pg/mL), despite the hyperosmolarity of the plasma (295.4 mOsm/kg H<sub>2</sub>O). The levels of thyroid-stimulating hormone were slightly low (0.24 μU/mL; normal range, 0.33-4.05) because of the GC treatment (PSL 30 mg/day), although the levels of other pituitary hormones (follicle-stimulating hormone, luteinizing hormone, growth hormone, adrenocorticotrophic hormone, and prolactin) were within the normal limits. T1-weighted MRI showed disappearance of the high-intensity signal in the posterior lobe of the pituitary. Based on these findings, central DI was diagnosed and intranasal desmopressin (DDAVP) was initiated in addition to GC pulse therapy. Subsequently, the patient's general and respiratory symptoms improved, and her urine volume decreased to a normal level (Fig. 3). The daily dose of PSL was tapered to 20 mg and continued as maintenance therapy. She was thereafter transferred to another hospital in April 2014.

## Case 2

In June 2011, a 72-year-old woman was diagnosed with granulomatosis with polyangiitis (GPA), sensorineural hearing loss, and otitis media, along with MPO-ANCA positivity. Although 50 mg/day of PSL was initiated at a community hospital and her symptoms improved temporarily, facial nerve paralysis developed 2 months later. Intravenous CYC was administered concomitantly, but oculomotor nerve pa-

ralysis occurred, without any abnormalities detected on head MRI. After the dose of PSL was increased, the patient's symptoms improved, but despite the concomitant use of methotrexate, CYC (per os), and MMF, the dose of PSL had to remain high.

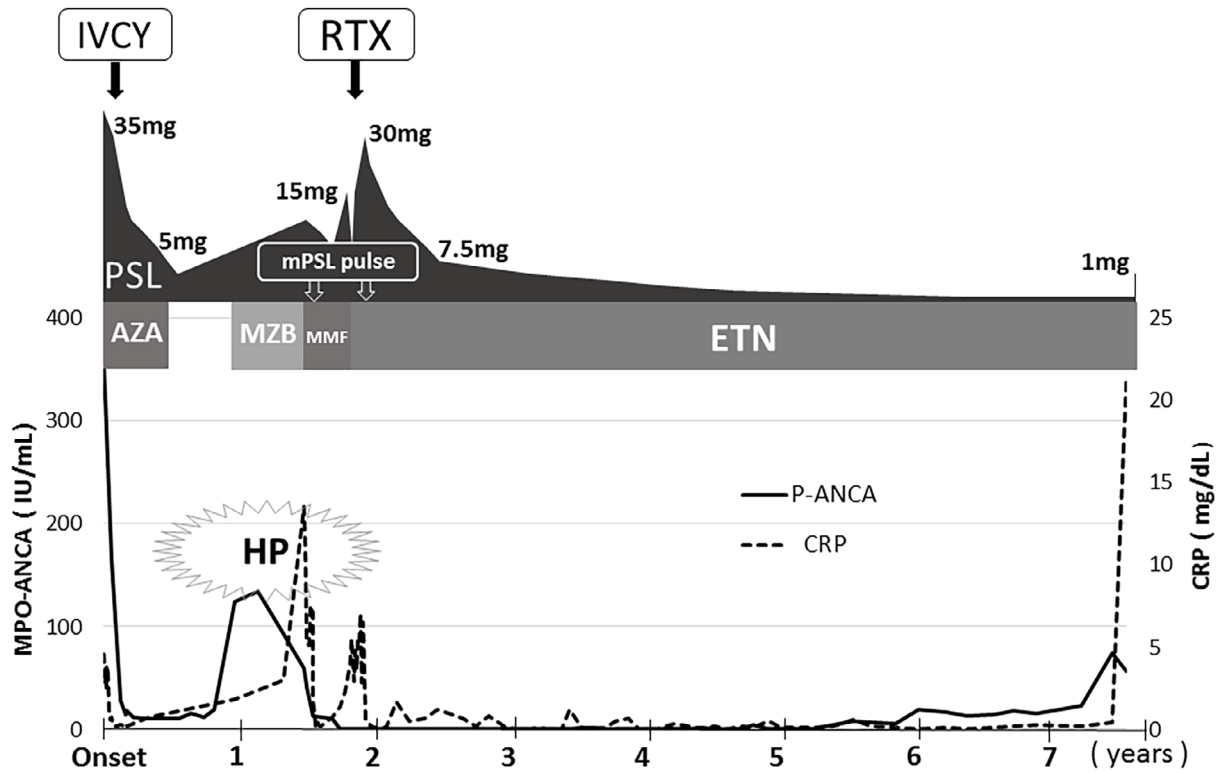
In July 2012, the patient was admitted to our hospital for headache. Laboratory data showed elevated C-reactive protein (CRP) levels, while MRI showed an enlarged pituitary gland. A relapse was diagnosed based on these findings (Fig. 4). RTX was administered but polydipsia and polyuria occurred just after the fourth administration of the agent. Additionally, the patient's urine volume increased to 6,000 mL/day. A water deprivation test revealed hyposthenuria, hypernatremia (148 mmol/L), and a marked decrease in the patient's serum ADH level (<1.2 pg/mL). Since DDAVP administration decreased urine volume and increased urine osmolality, the patient was diagnosed with central DI. The levels of other pituitary hormones were normal. To determine the cause of DI, a biopsy of the dura and pituitary was performed. During the surgical biopsy, dural hypertrophy was observed macroscopically, but a microscopic examination of the specimen showed no abnormal findings. The patient's symptoms improved with nasal DDAVP treatment; however, her CRP levels remained elevated. After the initiation of ETN, the pituitary gland returned to normal size and the dose of PSL could be reduced to 5 mg/day (Fig. 5).

## Discussion

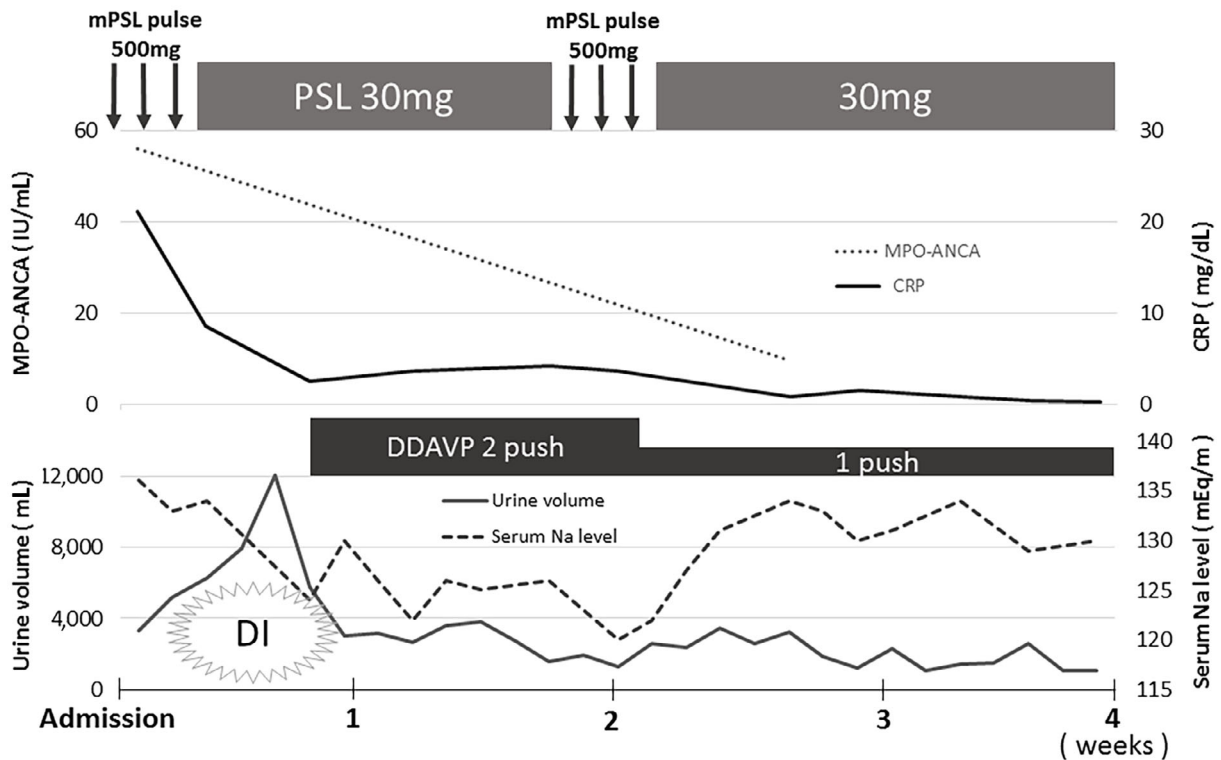
We presented two cases of refractory AAV that were complicated by DI. In one case, DI developed during ETN treatment; in the other, DI was successfully treated using ETN.

It is likely that HP was related to the pathophysiology in these cases. Recent reports have shown the relationship between HP and AAV, especially in its localized GPA stage but frequency of HP in whole AAV patients was not elucidated yet (9). A nationwide survey conducted in Japan showed that 34% of patients with HP were diagnosed with AAV (10), while approximately 30% of AAV patients had otitis media complicated with HP (3). Furthermore, MPO-ANCA was detected more frequently than proteinase 3 (PR3)-ANCA among the patients with AAV and HP in these two studies (approximately 30-50% vs. 15%). In another report, half of the cohort of Japanese patients with GPA tested positive for MPO-ANCA (11). Thus, granulomatous inflammation manifesting as GPA may also affect the dura mater, as was found in our cases.

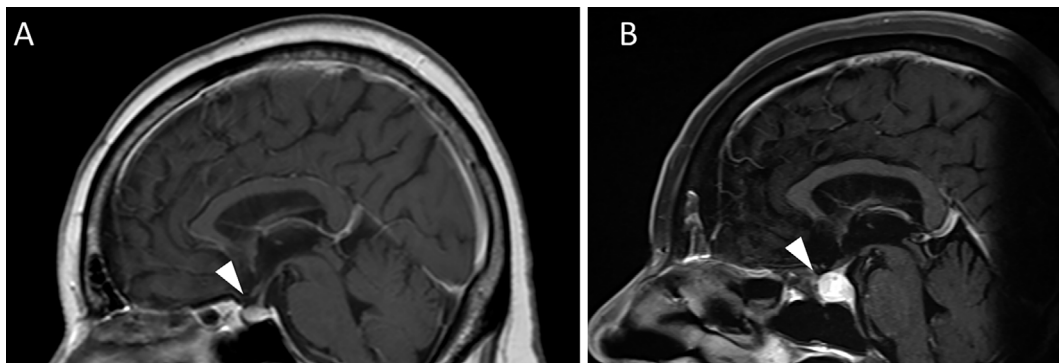
Several case series on AAV with central DI have been reported, and most patients were classified as having GPA with PR3-ANCA positivity (12-23). Thus far, three mechanisms have been suggested to explain the occurrence of DI in patients with AAV: vasculitis affecting the pituitary vessels; involvement of the adjacent pituitary by granulomatous masses originating in the ear, nose, and throat tract; and granulomatous inflammation originating *in situ* (24). However HP has not been considered a cause of DI in AAV,



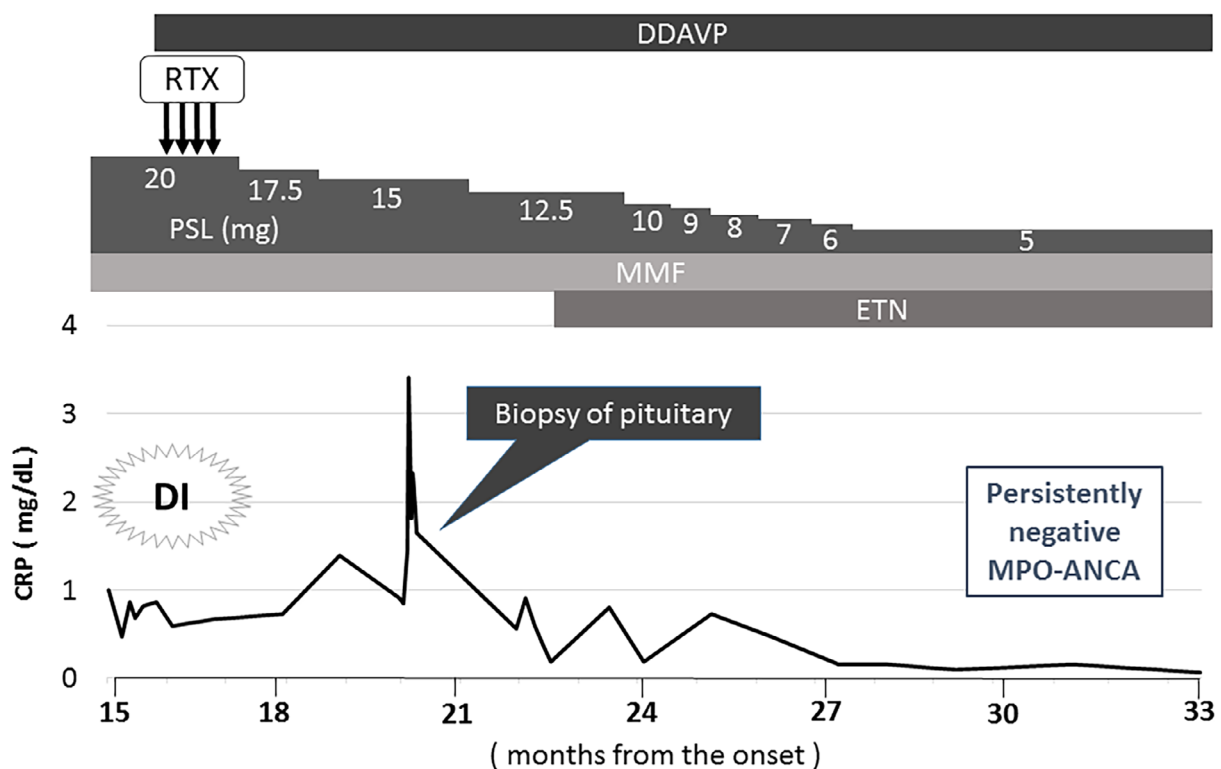
**Figure 2.** The clinical course in Case 1. IVCY: intravenous cyclophosphamide, RTX: rituximab, PSL: prednisolone, mPSL: methylprednisolone, AZA: azathioprine, MZB: mizoribine, MMF: mycophenolate mofetil, ETN: etanercept, HP: hypertrophic pachymeningitis



**Figure 3.** The clinical course in Case 1 during the development of diabetes insipidus. PSL: prednisolone, mPSL: methylprednisolone, DDAVP: 1-desamino-8-D-arginine vasopressin, DI: diabetes insipidus



**Figure 4.** Magnetic resonance imaging of the pituitary gland (Case 2). A: Before relapse. B: At relapse. The white arrowheads show the excessively enlarged pituitary gland.



**Figure 5.** The clinical course in Case 2. RTX: rituximab, PSL: prednisolone, MMF: mycophenolate mofetil, ETN: etanercept, DDAVP: 1-desamino-8-D-arginine vasopressin, DI: diabetes insipidus

since dural abnormalities on MRI were not mentioned in previous reports (25). However, HP was detected in both of the cases of AAV complicated by DI that we encountered. DI developed after HP in one patient, while the other showed focal dural hypertrophy at the onset of DI. Thus, HP may in fact be strongly linked to DI.

In the Wegener's Granulomatosis Etanercept Trial (WGET), which evaluated the effects of add-on treatment with ETN in patients with GPA who received standard therapy, ETN was not found to be of benefit to AAV therapy (26). However, the WGET study only included patients with limited AAV disease or those who had been newly diagnosed with the condition. Thus, the effectiveness of ETN

in refractory cases has not been investigated, and this TNF inhibitor may in fact be a treatment option for refractory AAV. Some case reports or series have mentioned the use of infliximab for DI in GPA with or without dural enhancement (7, 22, 25) (Table). In the present cases, DI developed after the initiation of ETN in one patient but remained in remission for a while; the second patient was successfully treated with ETN.

In conclusion, DI in patients with AAV may be partially related to HP and be refractory to the usually administered immunosuppressants.

We did not obtain written consent from the patients because

**Table. Use of Infliximab for Granulomatosis with Polyangiitis and Diabetes Insipidus.**

Patient	Organ involved	ANCA	Anterior pituitary dysfunction	Magnetic resonance imaging findings	Immunosuppressants administered before IFX	Response to IFX	Reference
1	ENT	N/A	+	Enlarged pituitary, heterogeneous enhancement of anterior pituitary, loss of posterior signal	MTX, GC	No	(25)
2	ENT, lung	N/A	+	Heterogeneous enhancement of pituitary	MTX, GC	No	(25)
3	ENT, eye	N/A	+	Enlargement and infiltration of pituitary with heterogeneous enhancement, contact with optic chiasm	None	Yes	(25)
4	ENT	PR3-ANCA	-	Inflammation involving the sphenoid sinus and left cavernous sinus, dural enhancement	CYC, GC, MTX	No <sup>a</sup>	(22)
5	ENT, eye	PR3-ANCA	+	Pituitary gland enlargement and enhancement	MTX, GC→CYC	Yes	(7)
6	None	PR3-ANCA	+	Nodular enlargement and enhancement	CYC, GC	Yes	(7)

<sup>a</sup>DI occurred after IFX administration.

ANCA: antineutrophil cytoplasmic antibody, ENT: ear, nose, and throat, N/D: not available, IFX: infliximab, MTX: methotrexate, GC: glucocorticoid, CYC: cyclophosphamide, PR3: peroxidase-3

any personally identifiable information was removed. This report of two cases was approved by the ethics committee of Okayama University Hospital and Graduate School of Medicine, Dentistry and Pharmaceutical Sciences <ken1610-020>.

#### Author's disclosure of potential Conflicts of Interest (COI).

Jun Wada: Honoraria, Astellas, Boehringer Ingelheim, Novartis and Tanabe Mitsubishi; Research funding, Astellas, Bayer, Chugai, Daiichi Sankyo, Kissei, Kyowa Hakko Kirin, MSD, Otsuka, Teijin, Torii, Pfizer, Takeda and Taisho Toyama.

#### Financial Support

This work was supported by the Research Committee of Intractable Vasculitis Syndrome of the Ministry of Health, Labour, and Welfare of Japan under Grant <nannti-ippann-044>.

#### Acknowledgement

We are grateful to all of the medical staff members at our department.

#### References

- Dutta P, Hayatbhat M, Bhansali A, Bambery P, Kakar N. Wegener's granulomatosis presenting as diabetes insipidus. *Exp Clin Endocrinol Diabetes* **114**: 533-536, 2006.
- Yokoseki A, Saji E, Arakawa M, et al. Hypertrophic pachymeningitis: significance of myeloperoxidase anti-neutrophil cytoplasmic antibody. *Brain* **137**: 520-536, 2014.
- Harabuchi Y, Kishibe K, Tateyama K, et al. Clinical features and treatment outcomes of otitis media with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (OMAAV): a retrospective analysis of 235 patients from a nationwide survey in Japan. *Mod Rheumatol* **27**: 87-94, 2017.
- Li JY, Lai PH, Lam HC, et al. Hypertrophic cranial pachymeningitis and lymphocytic hypophysitis in Sjögren's syndrome. *Neurology* **52**: 420-423, 1999.
- Hatano N, Behari S, Nagatani T, et al. Idiopathic hypertrophic cranial pachymeningitis: clinicoradiological spectrum and therapeutic options. *Neurosurgery* **45**: 1336-1342; discussion 1342-1334, 1999.
- De Luna G, Terrier B, Kaminsky P, et al. Central nervous system involvement of granulomatosis with polyangiitis: clinical-radiological presentation distinguishes different outcomes. *Rheumatology (Oxford)* **54**: 424-432, 2015.
- Seror R, Mahr A, Ramanoelina J, Pagnoux C, Cohen P, Guillevin L. Central nervous system involvement in Wegener granulomatosis. *Medicine (Baltimore)* **85**: 54-65, 2006.
- Yates M, Watts RA, Bajema IM, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. *Ann Rheum Dis* **75**: 1583-1594, 2016.
- Di Comite G, Bozzolo EP, Praderio L, Tresoldi M, Sabbadini MG. Meningeal involvement in Wegener's granulomatosis is associated with localized disease. *Clin Exp Rheumatol* **24**: S60-S64, 2006.
- Yonekawa T, Murai H, Utsuki S, et al. A nationwide survey of hypertrophic pachymeningitis in Japan. *J Neurol Neurosurg Psychiatry* **85**: 732-739, 2014.
- Sada KE, Yamamura M, Harigai M, et al. Classification and characteristics of Japanese patients with antineutrophil cytoplasmic antibody-associated vasculitis in a nationwide, prospective, inception cohort study. *Arthritis Res Ther* **16**: R101, 2014.
- Tappouni R, Burns A. Pituitary involvement in Wegener's granulomatosis. *Nephrol Dial Transplant* **15**: 2057-2058, 2000.
- Garovic VD, Clarke BL, Chilson TS, Specks U. Diabetes insipidus and anterior pituitary insufficiency as presenting features of Wegener's granulomatosis. *Am J Kidney Dis* **37**: E5, 2001.
- Barlas NB, Hassan HH, Al Badr FB, Bilal A. Structural and functional involvement of pituitary gland in Wegener's granulomatosis. *Clin Neuroradiol* **21**: 31-33, 2011.
- Xue J, Wang H, Wu H, Jin Q. Wegener's granulomatosis complicated by central diabetes insipidus and peripheral neutrophily with normal pituitary in a patient. *Rheumatol Int* **29**: 1213-1217, 2009.
- Yong TY, Li JY, Amato L, et al. Pituitary involvement in Wegener's granulomatosis. *Pituitary* **11**: 77-84, 2008.
- Thiryayi W, Donaldson MH, Border D, Tyagi A. An enhancing pituitary lesion in a young woman: a diagnostic dilemma. *J Clin Neurosci* **14**: 286-288, 2007.
- Duzgun N, Morris Y, Gullu S, et al. Diabetes insipidus presentation before renal and pulmonary features in a patient with

- Wegener's granulomatosis. *Rheumatol Int* **26**: 80-82, 2005.
19. Goyal M, Kucharczyk W, Keystone E. Granulomatous hypophysitis due to Wegener's granulomatosis. *AJNR Am J Neuroradiol* **21**: 1466-1469, 2000.
  20. Katzman GL, Langford CA, Sneller MC, Koby M, Patronas NJ. Pituitary involvement by Wegener's granulomatosis: a report of two cases. *AJNR Am J Neuroradiol* **20**: 519-523, 1999.
  21. Santoro SG, Guida AH, Furioso AE, Glikman P, Rogozinski AS. Panhypopituitarism due to Wegener's granulomatosis. *Arq Bras Endocrinol Metabol* **55**: 481-485, 2011.
  22. Cunnington JR, Jois R, Zammit I, Scott D, Isaacs J. Diabetes insipidus as a complication of Wegener's granulomatosis and its treatment with biologic agents. *Int J Rheumatol* **2009**: 346136, 2009.
  23. McIntyre EA, Perros P. Fatal inflammatory hypophysitis. *Pituitary* **10**: 107-111, 2007.
  24. Kapoor E, Cartin-Ceba R, Specks U, Leavitt J, Erickson B, Erickson D. Pituitary dysfunction in granulomatosis with polyangiitis: the Mayo Clinic experience. *J Clin Endocrinol Metab* **99**: 3988-3994, 2014.
  25. De Parisot A, Puéchal X, Langrand C, et al. Pituitary involvement in granulomatosis with polyangiitis: report of 9 patients and review of the literature. *Medicine (Baltimore)* **94**: e748, 2015.
  26. Etanercept plus standard therapy for Wegener's granulomatosis. *N Engl J Med* **352**: 351-361, 2005.

The Internal Medicine is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).