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Case Report

# Hypophysitis Secondary to Small Vessel ANCA Vasculitis Treated With Rituximab

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ABSTRACT

*Background/Objective:* Antineutrophil cytoplasmic antibody (ANCA) associated vasculitis is a rare small vessel vasculitis that can cause pituitary hypophysitis. Hypophysitis is difficult to treat, often requiring high doses of glucocorticoids with frequent flaring as glucocorticoids are tapered. We present a case of ANCA vasculitis involving the pituitary gland successfully treated with rituximab.
*Case Report:* Fifty-one-year-old woman developed progressive frontal headaches, congestion, and epistaxis. Sinus computed tomography scan showed pituitary enlargement and chronic mucosal disease. Pituitary magnetic resonance imaging (MRI) confirmed a diffusely enlarged pituitary with a thickened pituitary stalk. Serologic evaluation revealed elevated inflammatory markers, positive perinuclear ANCA (p-ANCA), and an elevated serum anti-proteinase 3 (anti-PR3) antibody. The patient underwent pituitary biopsy, which showed adenohypophysitis with dense lymphoplasmacytic infiltration, some arranged perivascularly, compatible with involvement of the pituitary gland by ANCA vasculitis. The patient began rituximab and reported resolution of daily headaches, congestion, and epistaxis. Pituitary MRI scan 6 months after rituximab showed reduction in pituitary gland size and stalk thickening.
*Discussion:* ANCA vasculitis is a rare etiology of pituitary hypophysitis, which can present a diagnostic and therapeutic challenge. Pituitary involvement of ANCA vasculitis can be identified through p-ANCA or cytoplasmic ANCA (c-ANCA) and biopsy of the involved tissue. Rituximab, a monoclonal antibody against CD20, has been successfully used to treat ANCA vasculitis and in this case, led to clinical improvements and reduction in the size of the pituitary gland.
*Conclusion:* Pituitary biopsy enabled confirmation of ANCA hypophysitis and facilitated treatment with a steroid-sparing agent.


## Introduction

Pituitary involvement in antineutrophil cytoplasmic antibody (ANCA) vasculitis is uncommon, occurring in about 1% to 4% of cases.[1-5] ANCA vasculitis may lead to partial or complete pituitary dysfunction, particularly arginine vasopressin deficiency (AVP-D, previously known as diabetes insipidus) and hypogonadism.[1-6] Typical magnetic resonance imaging (MRI) abnormalities include a diffusely enlarged pituitary gland, thickened pituitary stalk, and

*Abbreviations:* ANCA, antineutrophil cytoplasmic antibody; CT, computed tomography; MRI, magnetic resonance imaging; p-ANCA, perinuclear antineutrophil cytoplasmic antibody; c-ANCA, cytoplasmic antineutrophil cytoplasmic antibody; anti-PR3, anti-proteinase 3; GPA, granulomatosis with polyangiitis.

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absence of posterior pituitary bright spot.[1,3,4,7] Conventional treatment of hypophysitis often relies on high dose glucocorticoids, leading to many side effects; taper is frequently limited by flaring of symptoms.[1-5] Treatment of ANCA vasculitis may also include steroid-sparing agents such as cyclophosphamide or rituximab, which have been used with high rates of remission.[1-5] We present a case of ANCA vasculitis involving the pituitary gland, diagnosed with a pituitary biopsy, that showed clinical response to rituximab.

## Case Report

A 51-year-old woman with a history of Graves' disease post radioiodine therapy and resulting primary hypothyroidism was referred to an endocrine clinic for evaluation of pituitary enlargement. She reported more than one year of worsening fatigue, myalgias, frontal headaches, ear fullness, sinus congestion, and epistaxis. She noted that the symptoms initially improved after a prednisone taper, but subsequently returned. Her otolaryngologist recommended a sinus computed tomography (CT) scan to evaluate these symptoms, which showed pituitary enlargement and chronic mucosal disease. Dedicated pituitary MRI confirmed a diffusely enlarged pituitary (13 mm tall), without differential enhancement and thickened superiorly displaced pituitary stalk (Fig. 1 *A* and *B*). Past medical history was additionally notable for vitamin B-12 deficiency.

On presentation to the endocrine clinic, she additionally noted a 20-pound weight gain over the preceding year, dyspnea on exertion, and fatigue. She reported increased thirst and nocturia (woke to urinate once per night). She denied constipation, cold intolerance, nausea or vomiting, abdominal discomfort, breast discomfort, or galactorrhea. She was post-menopausal since the age of 46. She reported adherence to all prescribed medications, which included levothyroxine 125 μg daily, cyanocobalamin 1000 μg daily, cholecalciferol 50 μg daily, azelastine 0.15% nasal solution, and fluticasone propionate nasal spray.

Her family history was notable for significant rheumatologic disease. Her mother had systemic lupus erythematosus and Sjogren's syndrome. Her sister had dermatomyositis, and her cousin had Sjogren's syndrome.

Her personal and family history of rheumatologic disease and symptoms of epistaxis, nasal congestion, and ear fullness, along with the above findings, led to a clinical suspicion for infiltrative etiology of pituitary enlargement. Assessment of pituitary function showed hyperprolactinemia and lower gonadotropin levels than expected for post-menopausal status, most consistent with stalk effect hyperprolactinemia and resulting gonadotroph suppression (Table). Pituitary corticotroph, thyrotroph, and somatotroph axes were intact (Table). She did not have polyuria, and urine osmolarity and sodium levels were normal, confirming the absence of AVP-D (Table).

Rheumatologic conditions were assessed and were unremarkable, except for positive perinuclear ANCA (p-ANCA), elevated serum anti-proteinase 3 (anti-PR3) antibody, normal myeloperoxidase (MPO) level, and elevated erythrocyte sedimentation rate and c-reactive protein (Table).

Given concern for ANCA-associated vasculitis, rheumatology repeated ANCA testing and performed additional screening for hepatitis, tuberculosis, and sarcoidosis. Repeat ANCA testing corroborated original results. Hepatitis and tuberculosis testing was unremarkable. Chest CT showed a nonspecific right lower lobe nodular opacity and right upper lobe peribronchial fibrosis, both without overt evidence of active vasculitis. Neither chest abnormality was amenable to biopsy, so a pituitary biopsy was performed without complications. Post-operatively, the patient did not develop either AVP-D or syndrome of inappropriate antidiuretic hormone secretion. Anterior pituitary function remained unchanged. Pathology showed adenohypophysitis with dense lymphoplasmacytic infiltrate, some arranged perivascularly (Fig. 2 and 3). In the setting of anti-PR3 serum autoantibodies, this finding was consistent with the granulomatosis with polyangiitis (GPA) subtype of ANCA vasculitis. Treatment with rituximab was initiated to improve symptoms of headache, epistaxis, and sinus congestion. The treatment regimen was 375 mg/m$^2$ weekly for 4 weeks and then 500 mg every 6 months.

Approximately 2 months after beginning rituximab, she reported resolution of daily headaches, epistaxis, and congestion. She continued to experience fatigue and myalgias. MRI 6 months after the initiation of rituximab showed decreased size of the pituitary gland and stalk thickening (Fig. 1 *C* and *D*). Follow up chest CT showed decreased size of the right lower lobe opacity and persistence of the right upper lobe nodule, possibly representing peribronchial fibrosis. At her most recent visit, 10 months after starting rituximab, she continued to report clinical improvements.

After discussing the data on rituximab treatment and potential side effects of prolonged B cell depletion, the patient agreed to a treatment course of 18 to 24 months and close monitoring by clinical evaluation, laboratory tests, and imaging following the conclusion of treatment.

### Highlights

- Hypophysitis is rare and can present a diagnostic challenge
- Serologic evaluation for etiology may include antineutrophil cytoplasmic antibodies
- Biopsy at a Pituitary Center of Excellence can provide definitive diagnosis
- Identification of the etiology can facilitate use of steroid sparing agents

### Clinical Relevance

Selective pituitary biopsy can aid in identifying the subtype of pituitary hypophysitis and enable the use of steroid-sparing anti-inflammatory agents. Rituximab may be an effective initial treatment for antineutrophil cytoplasmic antibody vasculitis involving the pituitary.

## Discussion

ANCA vasculitis is a rare etiology of pituitary hypophysitis, which can present a diagnostic and therapeutic challenge. ANCA vasculitis most commonly affects the upper and lower respiratory tract and kidneys. Initial presentation often involves constitutional symptoms, such as fatigue, malaise, myalgias, and arthralgias. The lack of specific localizing symptoms can contribute to a delay in diagnosis. Pituitary involvement of ANCA vasculitis may lead to anterior pituitary dysfunction or AVP-D when the posterior pituitary is affected.[1-6] MRI of the pituitary may exhibit a diffusely enlarged pituitary gland with thickened pituitary stalk and loss of the posterior pituitary bright spot.[1,3,4,7] ANCA vasculitis may be identified through positive p-ANCA or c-ANCA levels and biopsy of the involved tissue.

Our case demonstrates that, when infiltrative lesions of the pituitary are suspected, collaboration with rheumatology and neurosurgical colleagues and biochemical evaluation for these etiologies are essential for accurate diagnosis and treatment.

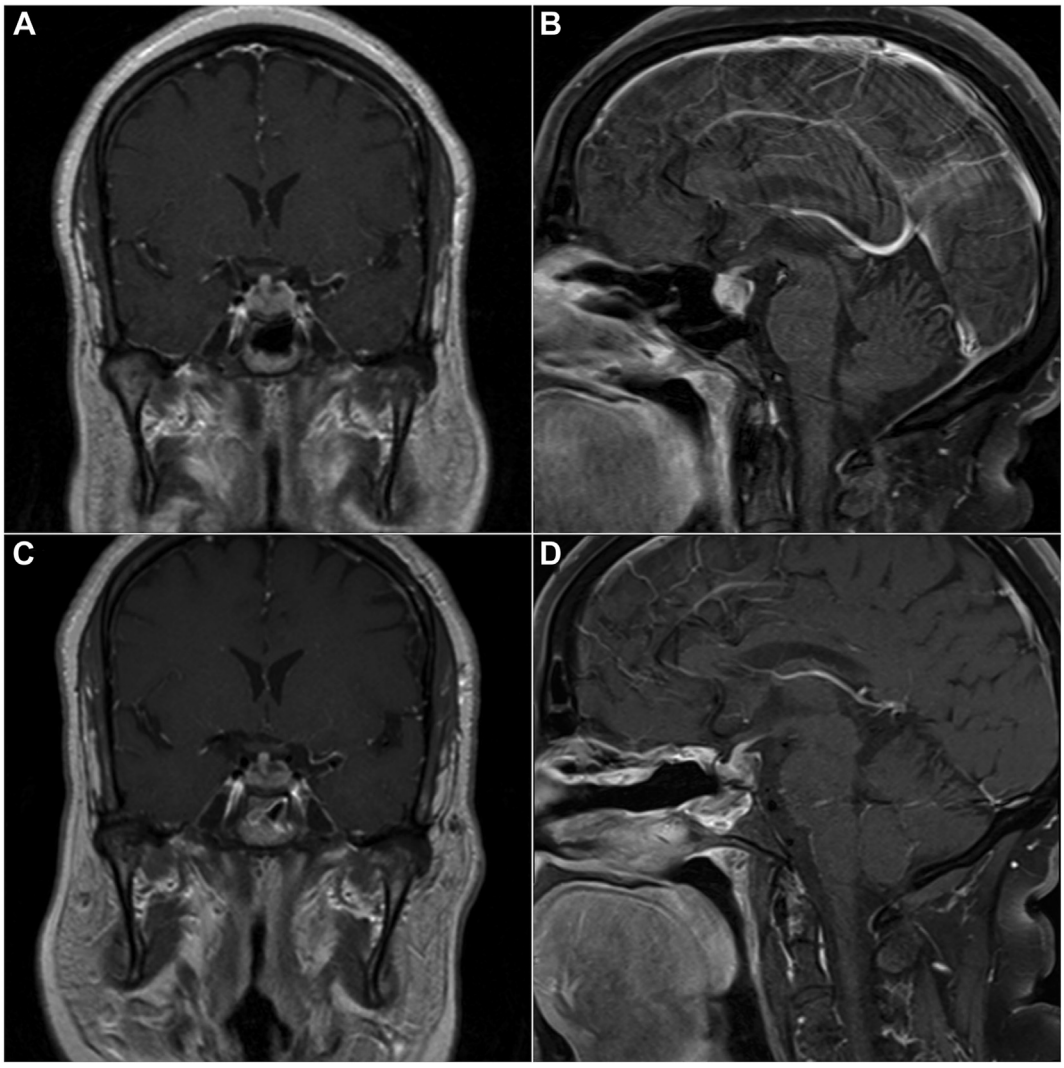


**Fig. 1.** Coronal (A) and sagittal (B) T1, post gadolinium magnetic resonance imaging (MRI) of the pituitary pre-treatment demonstrating enlarged pituitary gland and superiorly displaced and thickened pituitary stalk. Coronal (C) and sagittal (D) T1, post gadolinium MRI of the pituitary 6 months after rituximab initiation, demonstrating decreased size of the pituitary gland, decreased suprasellar protrusion, and improved thickening of the pituitary stalk compared to prior.

Surgical biopsy can provide definitive diagnosis for the use of steroid-sparing agents, while leaving pituitary function intact.

The patient in our case notably had intact pituitary function aside from hyperprolactinemia, attributed to loss of dopaminergic inhibition of prolactin release in the context of pituitary gland and stalk involvement by GPA. She also had lower gonadotropin levels than expected for her post-menopausal status, likely gonadotroph suppression from hyperprolactinemia versus direct injury of the pituitary gonadotrophs from GPA.

She was treated with rituximab, a monoclonal antibody directed against the CD20 antigen on the surface of B-lymphocytes, on the basis of her definitive biopsy. In hypophysitis due to ANCA vasculitis, rituximab has historically been reserved for refractory cases or cases in which patients cannot tolerate first-line agents, such as high-dose corticosteroids and cyclophosphamide, or are concerned about fertility.[1,5,8] While patients reliably achieved remission with rituximab, it has not been well researched as a first-line agent for hypophysitis secondary to ANCA vasculitis specifically.

We used rituximab first-line, as opposed to glucocorticoids and cyclophosphamide, because rituximab has demonstrated similar efficacy to cyclophosphamide and may be a safer option.[9-11] Two large multicenter randomized controlled trials (RAVE and RITUXVAS) demonstrated non-inferiority of rituximab over cyclophosphamide for induction of remission in ANCA vasculitis.[9,10] Another randomized control trial found that rituximab achieved complete remission at 6 months more frequently than cyclophosphamide in patients with GPA.[11] Multiple trials (MAINRITSAN trials and RITAZAREM) demonstrated the superiority of rituximab over azathioprine for maintenance of remission and lower incidence of relapse.[12,13] Additionally, rituximab is not associated with the significant, potentially life-threatening side effects of cyclophosphamide such as hemorrhagic cystitis, bladder cancer, bone marrow suppression, and cardiotoxicity.

Rituximab treatment regimens for ANCA vasculitis are an area of active research. Based on the 2021 American College of Rheumatology/Vasculitis Foundation guidelines, the optimal duration of remission-maintenance therapy is not well established.[14] Clinical trials have typically administered remission-maintenance therapy for $\geq$18 months.[14] However, at least one randomized controlled trial demonstrated benefit with longer durations of maintenance therapy, up to 48 months.[15] The duration of maintenance therapy

**Table**
Biochemical Evaluation

| Biochemical evaluation | Before biopsy | Two months after rituximab | Normal value(s) |
|---|---|---|---|
| **Pituitary hormones** | | | |
| Adrenocorticotropin hormone | 26.7 | 20.4 | 7.2-63.3 pg/mL |
| Cortisol | 13.4 | 9.7 | 4.8 to 19.5 μg/dL |
| Thyroid stimulating hormone | 1.07 | 1.13 | 0.45-5.33 μIU/mL |
| Total thyroxine | 9.7 | 9.3 | 4.50-11.70 μg/dL |
| T3 uptake | 0.93 | 0.94 | 0.76-1.25 |
| Free Thyroxine Index | 9.06 | 8.7 | 4.4-11.4 μg/mL |
| Prolactin | 53.6 | 38.37 | 2.74-19.64 ng/mL |
| Estradiol | <20 | <20 | ≤25.1 pg/mL |
| Luteinizing hormone | 4.6 | 6.27 | 10.87-58.64 mIU/mL |
| Follicle stimulating hormone | 23.03 | 24.99 | 16.74-113.6 mIU/mL |
| Insulin-like growth factor 1 | 130 | – | 53-234 ng/mL |
| Sodium | 140 | 143 | 136-144 mmol/L |
| Urine osmolality | 488 | 727 | 50-1200 mosmol |
| 24 hour urine volume | 2.4 | | <3 liters |
| **Rheumatologic workup** | | | |
| ANCA | p-ANCA | – | Negative |
| Anti-PR3 antibody | 74 | – | 0-20 unit(s) |
| Myeloperoxidase | 6 | 3 | 0-20 unit(s) |
| ESR | 73 | 26 | 0-30 mm/h |
| CRP | 7.9 | 0.40 | ≤7.4 mg/l |
| Anti-Jo-1 antibody | 2 | – | 0-19 unit(s) |
| Anti-SCL-70 antibody | 0.1 | – | 0.0-0.9 unit(s) |
| ANA | Negative | – | Negative |
| Anti-SSA/SSB antibody | 0.1 | – | 0.0-0.9 unit(s) |
| Anti-Sm antibody | 3 | – | ≤19 unit(s) |
| Anti-RNP antibody | 3 | – | ≤19 unit(s) |
| CCP | 7 | – | ≤19 unit(s) |
| RF | <7 | – | ≤12.4 IU/ml |
| Anti-dsDNA | <10 | – | 0-99 IU/ml |
| IgG subclass 1 | 1211 | – | 240-1118 mg/dl |
| IgG subclass 2 | 441 | – | 124-549 mg/dl |
| IgG subclass 3 | 104 | – | 21-134 mg/dl |
| IgG subclass 4 | 31 | – | 1-123 mg/dl |

Abbreviations: ANA = antinuclear antibody; ANCA = antineutrophil cytoplasmic antibody; anti-dsDNA = anti-double-stranded DNA; anti-PR3 = anti-proteinase 3; anti-RNP = anti-ribonucleoprotein; ESR = erythrocyte sedimentation rate; CCP= cyclic citrullinated peptide; CRP = c-reactive protein; IgG = immunoglobulin G; p-ANCA = perinuclear antineutrophil cytoplasmic antibody; RF = rheumatoid factor; anti-SSA/SSB = anti-Sjögren's syndrome type A/B.

should be decided on a case-by-case basis. Important factors include previous relapse history, extent of organ involvement, and disease characteristics such as ANCA status.[14] Our patient is anti-PR3 positive, which carries a higher risk of relapse. On the other hand, this episode of vasculitis is her first, and she has no history of relapse. As such, we decided to continue the treatment for 18 to 24 months.

Our case suggests that rituximab may be used as an effective initial treatment for ANCA vasculitis involving the pituitary, eliminating the need for steroids that often cause undesired and wide-ranging side effects.

## Conclusion

Infiltrative lesions of the pituitary gland are rare and present a diagnostic challenge. On MRI, they can be confused with pituitary adenomas, leading to resection and inadvertent hypophysectomy with post-operative hypopituitarism. When an infiltrative or inflammatory lesion is suspected based on clinical or radiographic features, collaboration with rheumatology and neurosurgical colleagues and biochemical evaluation is essential. Serologic evaluation is driven by the clinical context and may include heme profile, inflammatory markers, and ANCA. While pituitary resection is discouraged in hypophysitis, our case demonstrates that judicial use of surgical biopsy can leave pituitary function intact and provide definitive diagnosis for the use of steroid-sparing agents. Our case also adds to the growing literature showing the effectiveness of rituximab, a well-tolerated monoclonal antibody in the treatment of hypophysitis.

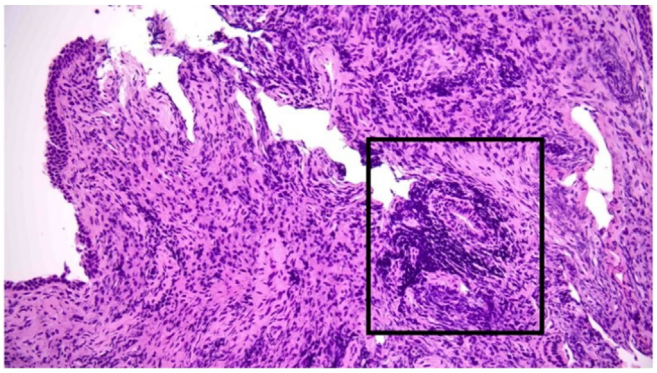

**Fig. 2.** Histopathology of pituitary biopsy; the black box indicates entrapped gland with significant chronic inflammation; the background is busy with significant mixed lymphoplasmacytic inflammation.

## Disclosure

The authors have no conflicts of interest to disclose.

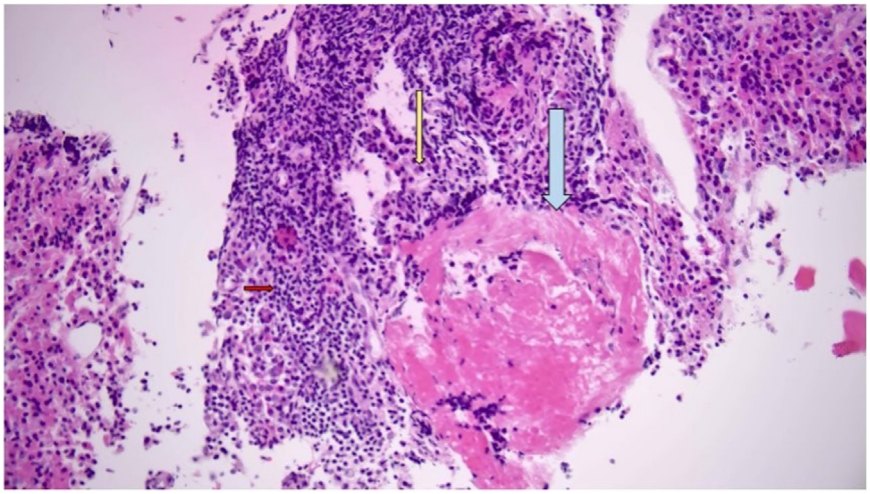

**Fig. 3.** Histopathology of pituitary biopsy showing dense lymphoplasmacytic inflammation. The yellow arrow indicates plasma cells, and the blue arrow indicates the focus of necrosis.

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The patient provided informed consent.

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