Korean J Neurotrauma. 2024 Dec;20(4):296-302
https://doi.org/10.13004/kjnt.2024.20.e39
pISSN 2234-8999·eISSN 2288-2243

KJNT

Case Report

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Myelopathy Due to Hypertrophic Pachymeningitis Associated With ANCA Vasculitis: A 10-Year Follow-up Case Report

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OPEN ACCESS

Received: Oct 14, 2024
Revised: Nov 22, 2024
Accepted: Nov 28, 2024
Published online: Dec 16, 2024

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ABSTRACT

This case report describes a rare presentation of antineutrophil cytoplasmic antibodies-associated hypertrophic pachymeningitis in a 49-year-old woman with cranial and spinal lesions. Initial management comprised decompressive laminectomy and steroid therapy, with the subsequent addition of immunosuppressant therapy following symptom recurrence. After a ten-year follow-up, significant symptom improvement and return of motor function were noted. This case emphasizes the crucial role of early diagnosis, a multidisciplinary approach, and combined medical therapy in managing this rare condition.

Keywords: Myelopathy; Pachymeningitis

INTRODUCTION

Hypertrophic pachymeningitis (HP) is a rare chronic disease characterized by inflammatory and fibrotic thickening of the intracranial and/or spinal dura mater.[6,11] The pathogenesis of HP is unclear in most cases, although several causes have been recognized, including trauma, infection (syphilis, tuberculosis), metabolic diseases, and autoimmune diseases (antineutrophil cytoplasmic antibodies [ANCA]-associated vasculitis [AAV] and rheumatoid arthritis).[2,14]

ANCA-AAVs are rare conditions primarily impacting small blood vessels. They include granulomatosis with polyangiitis (GPA) and microscopic polyangiitis, which make up around 80%–90% of AAV cases.[3,13] HP is observed throughout the clinical course of AAV, particularly among those with GPA. The ear, nose, and throat manifestations such as otitis media, sinusitis, mastoiditis, and mucous membranes/eyes symptoms are strongly linked with HP in AAV.[10,16] Although AAV may lead to HP, instances involving both cranial and spinal lesions are rarely reported. Furthermore, few cases have been documented with a 10-year follow-up.

Funding

No funding was obtained for this study.

Conflict of Interest

The authors have no financial conflicts of interest.

Informed Consent

The author has been obtained informed consent from the involved patient's guardian.

Ethics Approval

The study protocol was approved by the Institutional Review Board of Kyungpook National University Hospital (KNUH 2023-04-043).

We report a case of cranial and spinal pachymeningitis with positive ANCA. In this case, the patient had severe spinal cord compression with myelopathy. A decompressive laminectomy and treatment with steroid and immunosuppressive agents were performed.

CASE REPORT

In May 2012, a 49-year-old woman was admitted to the ENT department for recurrent right ear otalgia, right facial palsy, and severe headache for 2 months. Her brain magnetic resonance imaging (MRI) showed that the dural enhancement of the right temporal area (**FIGURE 1A**). She was diagnosed with chronic otitis media and associated facial nerve palsy and meningitis, and treated with antibiotics with the right myringotomy. However, her symptoms persisted, and after high-dose steroid therapy based on ANCA positivity, her otitis media, and dural thickness improved. She was referred to the rheumatology department for suspected AAV with otitis media and pachymeningitis.

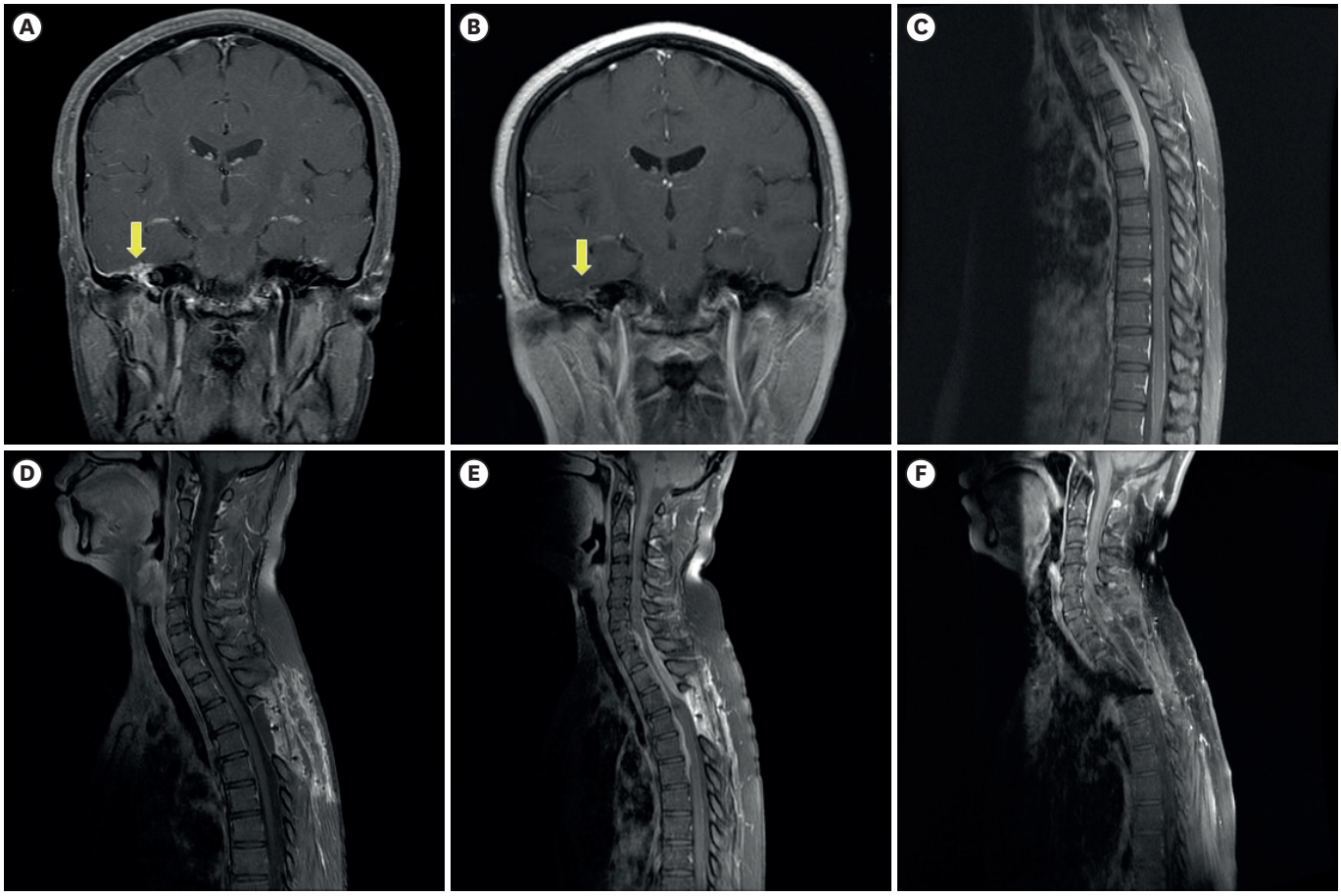

FIGURE 1. Brain and Spine MRI findings of antineutrophil cytoplasmic antibodies-associated hypertrophic pachymeningitis. (A) Brain MRI showed obvious thickened dura mater on right temporal area (yellow arrow). (B) Follow-up brain MRI demonstrated decreased enhancing lesion (yellow arrow). (C) Spine MRI showed thickened dura mater on anterior intradural space from C7 to T6. (D) After 1st operation, follow-up spine MRI demonstrated no distinct enhancing lesion. (E) Spine MRI showed a recurrence of hypertrophic pachymeningitis. (F) Four-year follow-up spine MRI demonstrated no newly visible enhancing focal lesions along the spinal cord and meningeal lining.
MRI: magnetic resonance imaging.

https://doi.org/10.13004/kjnt.2024.20.e39

In August 2012, she was admitted to the Department of Rheumatology due to persistent back pain. Neurological examination at presentation revealed intact motor function. Laboratory examinations showed that a white blood cell count of 16,880/mm^3, hemoglobin of 11.2 g/dL, platelet of 522×10^3/mm^3, erythrocyte sedimentation rate of 84 mm/hr (normal range, 0–30), C-reactive protein of 6.6 mg/dL (normal range ≤0.3), serum creatinine of 0.58mg/dL (estimated glomerular filtration rate, 110 mL/min/bovine serum albumin), and normal urinalysis with no hematuria and proteinuria. Immunologic laboratory findings demonstrated ANCA was positive, and rheumatoid factor and antinuclear antibody were negative. Anti-myeloperoxidase (MPO) and -PR3 antibodies were negative. Serum levels of immunoglobulin G (IgG), IgA, and IgM and the C3 and C4 levels were within normal limits.

An MRI showed diffuse soft tissue thickening with a long diameter of 13 mm in the anterior intradural space from C7 to T6 (**FIGURE 1C**). Differential diagnoses included neoplasm (lymphoma, meningioma en plaque) and inflammatory conditions. ANCA-associated HP was suspected, but a definitive diagnosis required histopathological confirmation through a biopsy. At the request of the rheumatology department, a biopsy was planned. She underwent laminectomy on T3, T4 and a tissue biopsy was performed. Intraoperatively, after cutting the dentate ligament of the left T3–4 region, a slightly reddish and gray-colored soft mass was confirmed in the ventral portion of the spinal cord. On microscopic examination, the lesion consisted of granulation tissue with lymphoplasmacytic and histiocytic infiltration, which suggested HP (**FIGURE 2A**).

Considering the findings from these investigations, the patient was diagnosed with ANCA-associated HP. Treatment with steroid pulse therapy (glucocorticoid, 1 g/day for 3 days) was started and then gradually tapered to high-dose steroid (1 mg/kg). At that time, *Staphylococcus aureus* was cultured in the auditory canal, antibiotics for *S. aureus* were also given and immunosuppressive therapy was withheld. Immediately after initiating steroid treatment, her headache and back pain was dramatically relieved. The patient was discharged one month after the steroid treatment, and follow-up brain and spine MRI findings showed marked improvement (**FIGURE 1B & D**).

In November 2012, she was readmitted due to acute onset motor weakness and hypoesthesia below the T4 level. Her neurological examination revealed myelopathy with paraparesis and decreased anal tone. A follow-up MRI showed enhancing lesions in both anterior and posterior thickened dura mater from C7 to T6, severely compressing the spinal cord (**FIGURE 1E**). A second operation was planned, and decompressive laminectomy on C7, T1, and T2, excision of thickened dura, and duroplasty were performed. Microscopic examination of the surgically resected specimen showed granuloma with dense fibrosis with lymphoplasmacytic infiltration and several foci of neutrophil and some histiocytes infiltration (**FIGURE 2B & C**). Due to the suspected recurrence of ANCA-associated HP, immunosuppressant therapy was added to conventional steroid therapy after the second operation. The patient was given prednisolone 1 mg/kg and cyclophosphamide (CTX) 100 mg. The patient's neurological deficits gradually improved following rehabilitation treatment, so he visited the neurosurgery outpatient clinic once every two years from 2012. Following the second surgery, the rheumatology department provided regular follow-up care every four months, during which immunosuppressant therapy was prescribed and monitored.

In August 2016, the 4-year follow-up MRI showed no new enhancing focal lesions compared to the MRI of her spine four years earlier (**FIGURE 1F**). In August 2016, Laboratory

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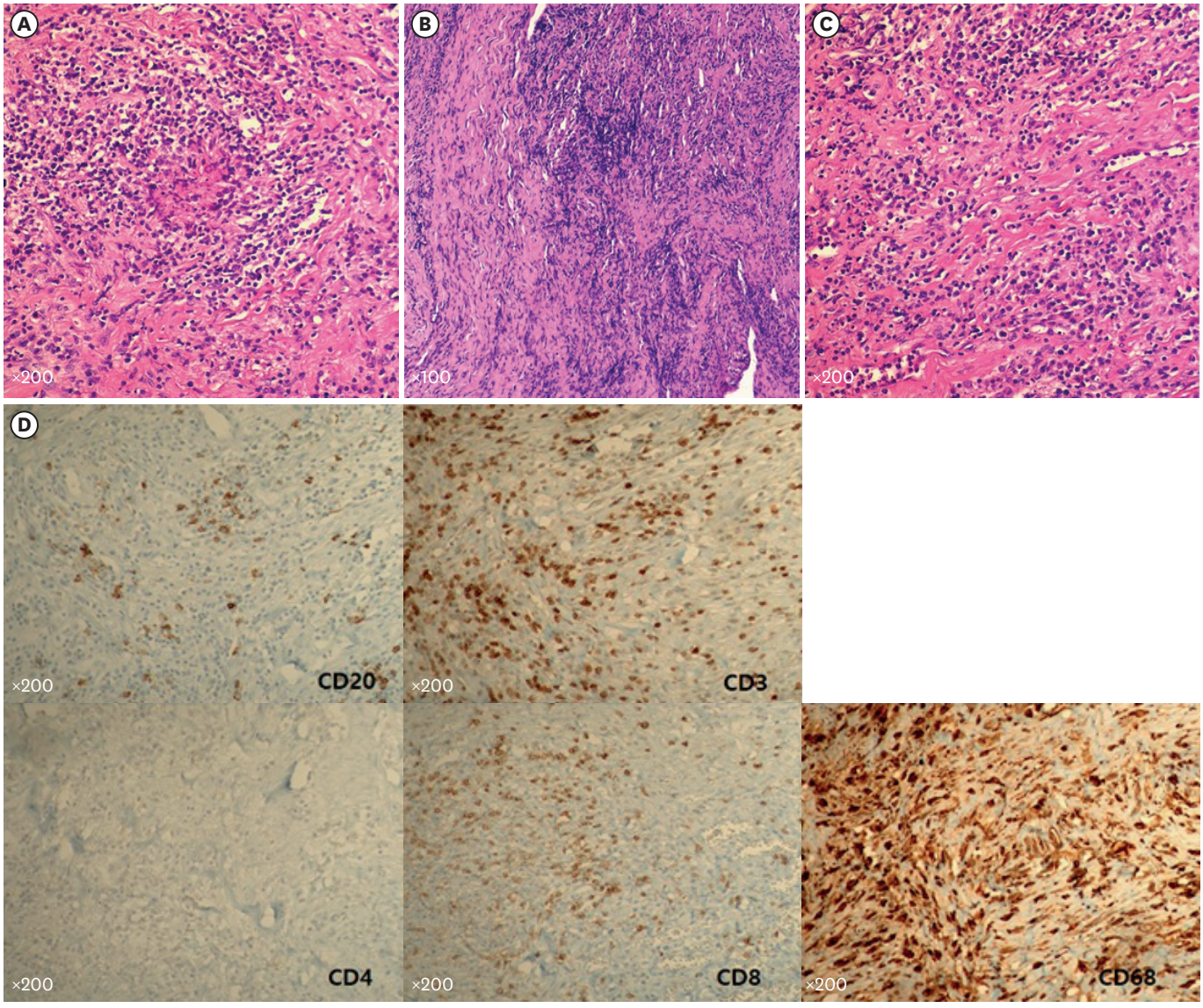

FIGURE 2. Histopathological and immunohistochemical findings of hypertrophic pachymeningitis. (A) H&E staining ×200: granuloma with lymphoplasmacytic and histiocytic infiltration. (B) H&E staining ×100: inflammatory cell infiltrates with dense fibrotic stroma. (C) H&E staining ×200: mixed inflammatory cells with lymphocytes, histiocytes, and plasma cells. (D) In immunohistochemistry, CD3(T cell marker) was stained more dominantly than CD20 (B cell marker), most of the T cells were CD8 positive T cells, CD4 showed negative findings, CD 68 was diffusely stained as a histiocytic marker.
H&E: hematoxylin and eosin stain.

examinations showed that a white blood cell count, hemoglobin, platelet, erythrocyte sedimentation rate and C-reactive protein were within normal limits. Immunologic laboratory findings demonstrated ANCA, rheumatoid factor, and antinuclear antibody were negative. Anti-MPO and -PR3 antibodies were also negative. ANCA titration has been consistently negative since February 18, 2013. In March 2023, ten years after discharge, she is still taking tacrolimus as an immunosuppressant and has demonstrated full improvement in her motor function. She experiences no problems in her daily life.

https://doi.org/10.13004/kjnt.2024.20.e39

DISCUSSION

The pathogenesis of HP remains unclear, but it has been associated with various conditions such as infection, metabolic diseases, and autoimmune diseases.[8,9,18] HP is observed throughout the clinical course of AAV, and AAV is known to affect the ear, nose, throat as well as the central nervous system, it has rarely been reported that HP, involving both cranial and spinal lesions, presents with ENT symptoms.[16] Li et al.[12] described a 67-year-old male patient with ANCA-associated cranial and spinal pachymeningitis. Unlike the present case, the patient was treated with methylprednisolone and immunosuppressant without surgical intervention. Additionally, the J-CANVAS study, a multicenter study conducted in Japan, reported HP in 4.5% of patients with AAV. This study emphasizes the relative rarity of HP within the spectrum of AAV and underscores the importance of recognizing specific clinical features for predicting HP development in AAV.[15] In this case, the patient initially presented with right ear otalgia, right facial palsy, and headache and later developed severe back pain. The diagnosis was made through a combination of clinical symptoms, radiological findings, and histopathological examination of dural biopsy specimens. The patient was treated with decompressive laminectomy, steroid therapy, and immunosuppressive agents, which led to a marked improvement in her symptoms.

In contemplating the pathological characteristics of AAV, it is common to observe granulomatosis along with infiltration of inflammatory cells.[12,15] But granulomatous inflammation, multinuclear giant cell infiltration, and necrotizing vasculitis are not always demonstrated in all patients with ANCA-associated HP.[5,16,17] In the case presented here, the lesion demonstrated dense fibrosis and granulation tissue populated with lymphoplasmacytic and histiocytic infiltration (**FIGURE 2**). Notably, in the immunohistochemical examination, the staining revealed a marked dominance of CD3 (a marker of T cells) compared to CD20 (a marker for B cells), indicating a predominance of T cells within the lesion. Interestingly, the majority of these T cells were CD8 positive, while CD4 staining was notably absent, suggesting a specific subset of T cells in this inflammatory process. Furthermore, there was diffuse staining for CD68, a histiocytic marker, signifying a substantial histiocytic component in the inflammatory infiltrate. These findings give insights into the cellular composition of the inflammatory process in ANCA-associated HP (**FIGURE 2D**).

Treatment for HP is tailored to the underlying cause if identified. Corticosteroids are the primary treatment for ANCA-associated HP, often combined with immunosuppressive agents including CTX, methotrexate, and mycophenolate mofetil for remission. Rituximab is beneficial for treatment-resistant ANCA-associated HP.[16] In this case, the patient initially responded well to corticosteroid therapy, which significantly improved her symptoms. However, the patient experienced a recurrence of symptoms, warranting a second surgical intervention and the addition of immunosuppressive therapy with CTX. This combination of treatments proved successful in managing her condition.

Following steroid pulse therapy and tapering, oral CTX was selected as the primary immunosuppressive agent due to its efficacy in managing severe conditions such as central nervous system involvement.[19] CTX is known to be effective for induction therapy in serious case, and in this case, a total dose of 5,000 mg was administered orally at a dose of 100 mg per day. However, due to its long-term risks including an increased risk of malignancy, CTX was eventually discontinued and alternative immunosuppressive agents were introduced.[1,4] The patient was transitioned to a combination of cyclosporine and azathioprine for five years.

https://doi.org/10.13004/kjnt.2024.20.e39

This combination therapy was employed to maximize immunosuppression while minimizing adverse effects. From 2018 to the present, the patient has been taking tacrolimus alone. Since cyclosporine is a large drug and inconvenient for patients to take, tacrolimus was chosen to have a similar mechanism of action to cyclosporine while improving patient compliance.[7]

One noteworthy aspect of this case is the long-term follow-up of the patient, which spanned over ten years. The long-term follow-up demonstrates the importance of continuous monitoring and appropriate adjustments in treatment, as the patient's condition and response to therapy evolved. This case also emphasizes the need for a multidisciplinary approach, involving radiology, neurosurgery, rheumatology, and pathology, to ensure accurate diagnosis and optimal management of HP. Neurosurgeon played a central role in surgical intervention and biopsy, while pathologist provided histopathological confirmation of the diagnosis. Radiologist contributed through detailed imaging analysis, enabling precise localization of lesions, and the rheumatologist determined and managed immunosuppressive treatment. This multidisciplinary approach was instrumental in the significant improvement of the patient's symptoms and long-term outcomes.

CONCLUSION

This case highlights the importance of considering ANCA-associated HP in the differential diagnosis of patients presenting with neurological symptoms and dural thickening on imaging. Early diagnosis, surgical intervention when necessary, and appropriate medical therapy with steroids and immunosuppressive agents are crucial for managing this rare and potentially debilitating condition. Further research is needed to better understand the pathophysiology of HP and to develop more effective treatment strategies.

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