RESEARCH ARTICLE OPEN ACCESS

Long-Term Clinical Landscapes of Spinal Hypertrophic Pachymeningitis With Anti-Neutrophil Cytoplasmic Antibody–Associated Vasculitis

Akihiro Nakajima,[1] Mariko Hokari,[1] Fumihiro Yanagimura,[1,2] Etsuji Saji,[1,3] Hiroshi Shimizu,[4] Yasuko Toyoshima,[4,5] Kaori Yanagawa,[1] Musashi Arakawa,[1,6] Akiko Yokoseki,[1,7] Takahiro Wakasugi,[1,8] Kouichirou Okamoto,[9] Kei Watanabe,[10,11] Keitaro Minato,[10] Yutaka Otsu,[1] Yukiko Nozawa,[12] Daisuke Kobayashi,[12] Kazuhiro Sanpei,[13] Hirotoshi Kikuchi,[14] Shunsei Hirohata,[15,16] Kazuaki Awamori,[17] Aya Nawata,[18] Mitsunori Yamada,[19] Hitoshi Takahashi,[4,20] Masatoyo Nishizawa,[1,21] Hironaka Igarashi,[22] Noboru Sato,[23,24] Akiyoshi Kakita,[4] Osamu Onodera,[1] and Izumi Kawachi[1,24]

Correspondence
Dr. Kawachi
ikawachi@bri.niigata-u.ac.jp

Neurology® 2025;104:e213420. doi:10.1212/WNL.0000000000213420

Abstract

Background and Objectives

Spinal hypertrophic pachymeningitis (HP) is an extremely rare disorder characterized by the thickening of the spinal dura mater, which harbors distinct repertoires of immune cells due to the unique partitioning of the arachnoid blood-CSF barrier. The objectives were to identify the pathogenesis and therapeutic strategies for spinal HP.

Methods

This retrospective cohort study analyzed the clinical and pathologic profiles of patients with idiopathic/immune-mediated HP including spinal HP.

Results

Among 61 patients with idiopathic/immune-mediated HP, all 6 Japanese patients with spinal HP, with a median observation period of 88.8 months, were myeloperoxidase (MPO)-anti-neutrophil cytoplasmic antibody (ANCA)–seropositive. The MPO-ANCA$^+$ spinal HP cohort had the following characteristics: (1) a predominance of older women; (2) all patients were classified as having microscopic polyangiitis based on the 2022 American College of Rheumatology/European League Against Rheumatism criteria; (3) 83% of patients developed subacute/chronic myelopathy due to extramedullary spinal cord compression; (4) 50% of patients had lesion extension to the epidural compartment and vertebral column; (5) 50% of patients presented with chronic sinusitis, otitis media, or mastoiditis; (6) 33% of patients had involvement of the lower airways or kidneys; (7) a higher disease activity of the nervous system was noted based on the Birmingham Vasculitis Activity Score (BVAS), in contrast to MPO-ANCA$^+$ cranial HP; (8) granulomatous inflammation with myofibroblasts, immune cells including granulocytes, and B-cell follicle-like structures were observed in the thickened dura mater; (9) immunotherapies (with or without surgical decompression) were effective in reducing the modified Rankin Scale score and reduced BVAS during the first active insults; (10) combined immunotherapies with glucocorticoids and cyclophosphamide/rituximab helped in reducing relapses in the long term; and (11) surgical decompression, including laminectomy and

[1]Department of Neurology, Brain Research Institute, Niigata University, Japan; [2]Department of Neurology, NHO Niigata National Hospital, Kashiwazaki, Japan; [3]Department of Neurology, Niigata City General Hospital, Japan; [4]Department of Pathology, Brain Research Institute, Niigata University, Japan; [5]Department of Neurology, Brain Disease Center, Agano Hospital, Agano, Japan; [6]Musashi Clinic, Niigata, Japan; [7]Department of Neurology, Niigata Medical Center, Japan; [8]Department of Neurology, NHO Nishiniigata Chuo Hospital, Niigata, Japan; [9]Department of Neurosurgery, Brain Research Institute, Niigata University, Japan; [10]Department of Orthopaedic Surgery, Niigata University Medical and Dental Hospital, Japan; [11]Niigata Spine Surgery Center, Kameda Daiichi Hospital, Niigata, Japan; [12]Division of Clinical Nephrology and Rheumatology, Graduate School of Medical and Dental Sciences, Niigata University, Japan; [13]Department of Neurology, Sado General Hospital, Japan; [14]Department of Internal Medicine, Teikyo University School of Medicine, Tokyo, Japan; [15]Department of Rheumatology, Nobuhara Hospital, Tatsuno, Japan; [16]Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Sagamihara, Japan; [17]Department of Neurology, Kaetsu Hospital, Niigata, Japan; [18]Department of Pathology and Oncology, School of Medicine, University of Occupational and Environmental Health, Fukuoka, Japan; [19]Department of Brain Disease Research, Shinshu University School of Medicine, Matsumoto, Japan; [20]Department of Pathology and Laboratory Medicine, Niigata Neurosurgical Hospital, Japan; [21]Niigata University of Health and Welfare, Japan; [22]Center for Integrated Human Brain Science, Brain Research Institute, Niigata University, Japan; [23]Division of Anatomy, Graduate School of Medical and Dental Sciences, Niigata University, Japan; and [24]Medical Education Center, Graduate School of Medical and Dental Sciences, Niigata University, Japan.

The Article Processing Charge was funded by the authors.

Glossary

AAV = ANCA-associated vasculitis; **ABC** = arachnoid barrier cell; **ACE** = arachnoid cuff exit; **ACR** = American College of Rheumatology; **ANCA** = anti-neutrophil cytoplasmic antibody; **BM** = bone marrow; **BVAS** = Birmingham Vasculitis Activity Score; **CHCC** = Chapel Hill Consensus Conference; **CY** = cyclophosphamide; **DBC** = dural border cell; **EMA** = European Medicines Agency; **ENT** = ear, nose, and throat; **EULAR** = European League Against Rheumatism; **GC** = glucocorticoid; **Gd** = gadolinium-enhanced; **GPA** = granulomatosis with polyangiitis; **HP** = hypertrophic pachymeningitis; **IgG4-RDs** = immunoglobulin G4–related disorders; **IQR** = interquartile range; **MPO** = myeloperoxidase; **mRS** = modified Rankin Scale; **PR3** = proteinase 3; **PSL** = prednisolone; **RTX** = rituximab; **SMA** = smooth muscle actin; **WI** = weighted imaging.

duraplasty, was necessary for compressive myelopathy. These data suggest that MPO-ANCA$^+$ spinal HP shares common features with MPO-ANCA$^+$ cranial HP (1, 2, 6, 8, 9, and 10), but also has unique clinical features (3, 4, 5, 7, and 11).

Discussion

Our findings highlight the significant pathogenic role of ANCA in spinal HP. MPO-ANCA$^+$ spinal HP, as an organ-threatening disease, should be positioned as having unique characteristics, whether limited to the CNS or as part of a generalized form in ANCA-associated vasculitis.

Introduction

Hypertrophic pachymeningitis (HP) is a rare disorder that can cause progressive neurologic disabilities[1-3] and is characterized by a diffuse or localized thickening of the dura mater, which harbors a distinct repertoire of immune cells due to the unique partitioning of the arachnoid blood-CSF barrier separating it from the CSF and the parenchyma.[4-9] Based on its pathogenesis, HP is categorized as either (1) idiopathic HP or (2) secondary HP, which can be attributed to (i) autoimmune diseases (e.g., anti-neutrophil cytoplasmic antibody [ANCA]–associated vasculitis [AAV] and immunoglobulin G4–related disorders [IgG4-RDs]) or (ii) infections (e.g., syphilis).[1-3] Based on anatomical localization of lesions, HP is also classified as either (1) cranial HP or (2) spinal HP.[1-3]

Recent epidemiologic advances in the studies on HP have revealed that infections are an extremely rare cause of the disease. However, AAV, including myeloperoxidase (MPO)-specific ANCA (MPO-ANCA)$^+$ AAV and proteinase 3 (PR3)-specific ANCA (PR3-ANCA)$^+$ AAV, is the most frequent cause of HP in Japan.[3,10] In addition, a study on HP, including 33 cases with cranial HP, 2 cases with spinal HP, and 1 case with combined spinal/cranial HP, has shown that MPO-ANCA$^+$ HP often involves lesions limited to the dura mater and upper airways with less severe neurologic deficits as defined by the modified Rankin Scale (mRS) score and lower disease activity as measured by the Birmingham Vasculitis Activity Score (BVAS).[3] This contrasts with PR3-ANCA$^+$ HP, which frequently shows more extensive involvement of the dura mater with leptomeningeal and parenchymal areas and progresses to systemic/generalized disease involving the upper/lower airways and the kidneys, with more severe neurologic deficits and higher disease activity.[3]

Based on a previous epidemiologic study in Japan, the prevalence of HP was 0.949/100,000 population, with the frequencies of spinal HP, cranial HP, and combined spinal/cranial HP reported as 9%, 85%, and 4%, respectively,[10] suggesting that spinal HP is an extremely rare disease. Indeed, there have been few case reports of spinal HP with immune-mediated etiologies including AAV or granulomatosis with polyangiitis (GPA),[11] IgG4-RDs,[12] and idiopathic varieties.[13] Consequently, a comprehensive understanding of the clinical, radiologic, immunologic, and pathologic landscape of spinal HP with immune-mediated etiologies has remained limited. To address these knowledge gaps, we conducted clinical evaluations along with long-term outcome measures in 61 patients with idiopathic or immune-mediated HP including 6 patients with MPO-ANCA$^+$ spinal HP, based on a retrospective cohort strategy (a median observation period of 88.8 months for MPO-ANCA$^+$ spinal HP). Our findings provide evidence that ANCA pathogenicity plays a significant role in spinal HP, and that MPO-ANCA$^+$ spinal HP, as an organ-threatening disease, should be recognized as having unique characteristics, either as a CNS-limited or generalized form of AAV.

Methods

Study Design, Patients, and Diagnostic/Classification Criteria

The research objectives were to define the details of clinical and pathologic characteristics of spinal HP. We retrospectively examined the medical records of 61 Japanese patients with idiopathic or immune-mediated HP between 1993 and 2024 (32 women, 29 men) (Figures 1–5, Tables 1 and 2, eFigures 1–3). The study adhered to the following entry criteria described previously[3]: (1) diagnosis of thickened, abnormally enhanced dura mater on gadolinium MRI before lumbar puncture and (2) exclusion of alternative explanations

such as infection, malignant tumors, meningioma, intracranial hypotension, or the use of drugs known to induce AAV (e.g., propylthiouracil).[14] Immune-mediated HP was categorized as follows: (1) AAV according to (i) the 2012 revised International Chapel Hill Consensus Conference (CHCC) definitions,[15] combined with the 2007 European Medicines Agency (EMA) algorithm (Watts algorithm) (2007/2012 EMA/CHCC Classification Criteria),[16] and (ii) the 2022 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Classification Criteria[17-19]; (2) IgG4-RDs, according to the 2019 ACR/EULAR Classification Criteria[20,21]; (3) rheumatoid arthritis, according to the 2010 ACR/EULAR Classification Criteria[22]; and (4) sarcoidosis, according to the 2018 Consensus Diagnostic Criteria.[23] Idiopathic HP was diagnosed as described previously.[2] We excluded cases with localized dura mater thickening limited to the cavernous sinus and cases of orbital pseudotumor. The cohort in this study (n = 61) included patients with idiopathic or immune-mediated HP investigated from our previous study (n = 35).[3]

Clinical, Immunologic, Radiologic, and Neuropathologic Examination

Clinical status was evaluated by neurologic examination, blood/CSF tests, MRI, and neuropathologic examination. Further details are available in the eMethods.

Statistical Analyses

Data were analyzed using the Prism 9 software package (GraphPad Software, San Diego, CA). Statistical comparisons between the 2 groups, MPO-ANCA$^+$ spinal HP and MPO-ANCA$^+$ cranial HP, were performed using the Fisher exact test or the Mann-Whitney *U* test, as appropriate. Cumulative probabilities of relapse-free survival were estimated using the Kaplan-Meier method, followed by the log-rank test. Changes in mRS scores and BVASs before and after treatments were analyzed by the Wilcoxon signed-rank test. A p value of <0.05 was considered statistically significant.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the Institutional Review Board of the Niigata University School of Medicine (2015-1622/2015-2280). Informed consent was waived because of the retrospective study design, with an informed opt-out procedure, but it was obtained from patients who could be reached.

Data Availability

Data that support results of this study are available from the corresponding author on reasonable request.

Results

Demographics

This study included 61 Japanese patients with immune-mediated or idiopathic HP, comprising the following categories: (1) MPO-ANCA$^+$ HP (22 patients [36%]), (2) PR3-ANCA$^+$ HP (7 patients [11%]), (3) HP associated with IgG4-RDs (4 patients [7%]), (4) HP associated with other immune-mediated disorders (8 patients [13%]), and (5) idiopathic HP (20 patients [33%]) (Table 1 and Figure 1). Among these, 4 patients (7%), 2 patients (3%), and 55 patients (90%) had spinal HP without cranial HP, spinal HP with cranial HP, and cranial HP without spinal HP, respectively. Henceforth, we defined "spinal HP (n = 6)" as including both "spinal HP with cranial HP (n = 2)" and "spinal HP without cranial HP (n = 4)." Similarly, "cranial HP (n = 16)" referred to "cranial HP without spinal HP (n = 16)" in MPO-ANCA$^+$ patients, to delineate the rare disease "spinal HP" in this study, unless otherwise specified.

All 6 patients with spinal HP (100%) were seropositive for MPO-ANCA (Figure 1), indicating that MPO-ANCA pathogenicity plays a significant role in spinal HP. Female predominance was present in both MPO-ANCA$^+$ spinal HP and MPO-ANCA$^+$ cranial HP (Table 2). The median ages at onset were 66.0 years and 66.5 years for MPO-ANCA$^+$ spinal HP and MPO-ANCA$^+$ cranial HP, respectively (Table 2). The median (interquartile range [IQR]) observation periods were 88.8 months (39.7–136.7) for MPO-ANCA$^+$ spinal HP and 106.6 months (26.7–177.1) for MPO-ANCA$^+$ cranial HP, indicating comparatively long-term follow-up in this study (Table 2).

Clinical Profiles of MPO-ANCA$^+$ Spinal HP

Progressive myelopathy with subacute/chronic onset (83%, 5/6), back pain (67%, 4/6), radicular pain (67%, 4/6), and fever (50%, 3/6) were common in patients with MPO-ANCA$^+$ spinal HP (Figure 1). These findings were consistent with previously published case reports (eFigure 4 and eTable 1).

33% (2/6) and 19% (3/16) of patients with MPO-ANCA$^+$ spinal HP and MPO-ANCA$^+$ cranial HP had renal or pulmonary involvements, respectively (Table 2). Among "surrogate markers for GPA" in the 2007 EMA algorithm,[16] the frequency of "chronic sinusitis, otitis media, or mastoiditis for 3 months" was lower in patients with MPO-ANCA$^+$ spinal HP compared with patients with MPO-ANCA$^+$ cranial HP (Table 2).

Nonspecific serum markers of inflammation, such as C-reactive protein, were elevated in most patients with MPO-ANCA$^+$ spinal and cranial HP (Table 2). Drastic increase in protein with xanthochromia and marked coagulation in the CSF, corresponding to Froin syndrome,[24,25] were observed in patients with MPO-ANCA$^+$ spinal HP (80%, 4/5), suggesting spinal CSF flow obstruction caused by HP lesions.

Radiologic Profiles of MPO-ANCA$^+$ Spinal HP

MRI findings of MPO-ANCA$^+$ spinal HP revealed hypointense thickened dura mater on T2-weighted imaging (WI) with abnormal enhancement on gadolinium-enhanced (Gd) T1WI (Figure 2).[26] In all patients with MPO-ANCA$^+$ spinal HP, the thickened dura mater extended into the epidural space with abnormal enhancement on GdT1WI (83%, 5/6).

Table 1 Demographic Characteristics of Patients With Immune-Mediated or Idiopathic Hypertrophic Pachymeningitis in the Study

Clinical characteristics	Summary
Patients, n	61
Male/female, n (%)	29 (48)/32 (52)
Age at onset, y[a]	66.0 (58.0–72.0)
Age at final evaluation, y[a]	73.2 (66.0–78.5)
Disease duration, mo[a]	47.0 (24.9–123.0)

[a] Median (interquartile range).

In 50% (3/6) of patients, the lesions extended into the epidural space and spinal column without destructive bone involvement. These findings are consistent with previous case reports of AAV involving vertebral lesions,[27-30] but in contrast to neoplasms that metastasize to the dura and cause bone destruction.[31] In addition, 83% (5/6) of patients with MPO-ANCA$^+$ spinal HP had extramedullary spinal cord compression, with hyperintense signals in the spinal cord parenchyma on the T2WI at the same levels as in the spinal HP lesions.

We identified 3 radiologic patterns of thickened dura in MPO-ANCA$^+$ spinal HP (Figure 2): (1) a circumferential/longitudinal pattern (67%, 4/6), (2) a circumscribed mass pattern (17%, 1/6), and (3) a consecutive cranial and spinal pattern (17%, 1/6).

Regarding the longitudinal distribution of lesions in patients with MPO-ANCA$^+$ spinal HP, abnormally enhanced HP lesions were predominantly located on the thoracic spine, with T9 being the most affected spinal level in patients with MPO-ANCA$^+$ spinal HP (Figure 1). All patients with MPO-ANCA$^+$ spinal HP (100%, 6/6) had longitudinally extensive lesions that spanned 2 or more vertebral segments (Figure 2). This finding is consistent with previous case reports indicating that T3 or T4 is the most affected spinal level in patients with spinal HP associated with AAV (eFigure 4).

Macroscopic and Microscopic/Pathologic Profiles of MPO-ANCA$^+$ Spinal HP

Pathologic studies were conducted on 5 biopsied samples from patients with MPO-ANCA$^+$ spinal HP. All samples showed severe dural thickening, characterized by severe fibrosis and mild-to-severe infiltration of inflammatory cells (Figure 3).

All patients with MPO-ANCA$^+$ spinal HP (100%, 5/5) exhibited moderate-to-severe fibrosis in the dura mater. A middle fibrous meningeal layer, composed of SMA^{neg} fibroblasts, was sandwiched by thick layers of SMA$^+$ myofibroblasts and inflammatory foci: one at the outer dural border layer and the other at the inner dural border cell (DBC) layer of the dura mater (Figure 3). These 3 layers, that is, the middle fibrous meningeal layer and the 2 outer and inner inflammatory layers (the outer dural border layer and the inner DBC layer), formed the thickened dura mater characteristic of pachymeningitis. Pathologically, MPO-ANCA$^+$ spinal HP lesions extended outward into the epidural space (60%, 3/5) and inward toward the arachnoid membrane (60%, 3/5). However, no direct infiltration of inflammatory foci into the pia mater or spinal cord parenchyma was observed.

Granulomatous inflammation (60%, 3/5), necrosis (40%, 2/5), and vasculitis (40%, 2/5), all of which are characteristic pathologic features of GPA,[15,17,18,32,33] were present in biopsied materials collected from patients with MPO-ANCA$^+$ spinal HP (Figure 3).

Sixty percent (3/5) of MPO-ANCA$^+$ spinal HP samples had B-cell follicle-like structures within the thickened dura, which contained CD21$^+$CD35$^+$ follicular dendritic cells corresponding to B-cell areas.

Classification of MPO-ANCA$^+$ Spinal HP

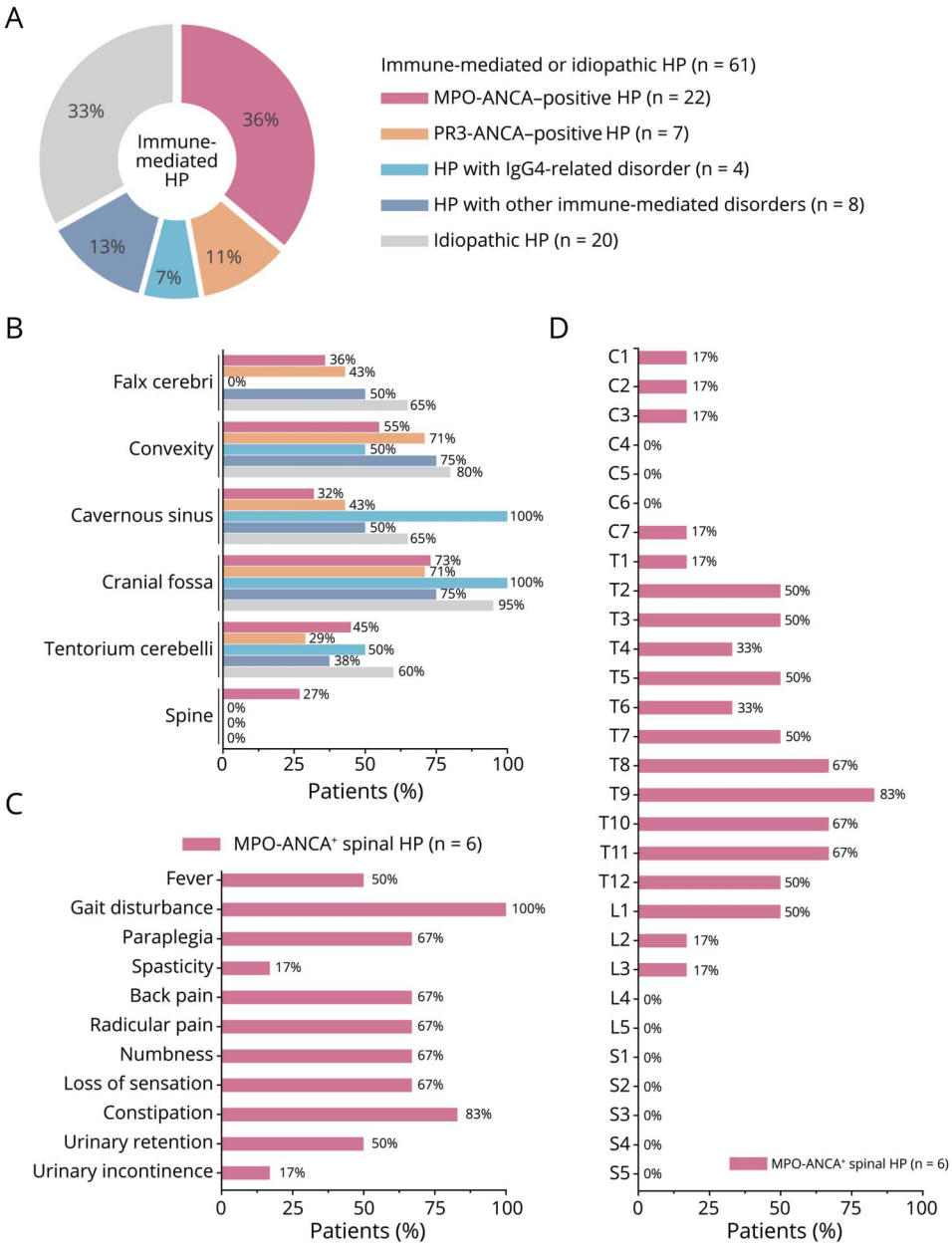
The 2007/2012 EMA/CHCC Classification Criteria classified as MPA, GPA, or eosinophilic granulomatosis with polyangiitis based on a stepwise algorithm with the inclusion of ANCA positivity but not ANCA specificity in the criteria (eFigure 2).[15,16] The classification of GPA was prioritized over that of MPA in the 2007/2012 EMA/CHCC Classification Criteria.[16] The 2022 ACR/EULAR Classification Criteria[17-19] were recently proposed, incorporating ANCA specificity (MPO-ANCA or PR3-ANCA) and using a novel weighted scoring system based on organ system manifestations, serology, and histopathologic characteristics. In particular, ANCA specificity is assigned the highest weight, in addition to clinical, histologic, and imaging characteristics, for the classification of MPA or GPA.[17-19]

In this study, we classified 83% (5/6) of patients and 17% (1/6) of patients with MPO-ANCA$^+$ spinal HP as having GPA or as being unclassifiable, respectively, based on the 2007/2012 EMA/CHCC Classification Criteria (eFigure 2). However, when using the 2022 ACR/EULAR Classification Criteria, all patients with MPO-ANCA$^+$ spinal HP (100%, 6/6) were reclassified as having MPA, although 50% (3/6) had granulomatous inflammation, a key feature of GPA under the 2012 CHCC definition (eFigure 3). This reclassification of MPO-ANCA$^+$ spinal HP was consistent with the classification of MPO-ANCA$^+$ cranial HP using both the 2007/2012 EMA/CHCC Classification Criteria and the 2022 ACR/EULAR Classification Criteria (eFigures 2 and 3).

Disease Activity of MPO-ANCA$^+$ Spinal HP

The annual relapse rates for MPO-ANCA$^+$ spinal HP and MPO-ANCA$^+$ cranial HP were 0.12 ± 0.18 and 0.26 ± 0.40 relapses/year (mean ± SD), respectively. Kaplan-Meier estimates for the percentages of relapse-free patients at 1,000 days were 62% and 45% for MPO-ANCA$^+$ spinal HP and MPO-ANCA$^+$ cranial HP, respectively.

Figure 1 Demographics and Clinical Profiles of 61 Patients With Immune-Mediated or Idiopathic HP Including 6 Patients With MPO-ANCA$^+$ Spinal HP



(A) Demographic characteristics of 61 patients with immune-mediated or idiopathic HP. Thirty-six percent (22 patients) of patients had MPO-ANCA$^+$ HP, 11% (7 patients) had PR3-ANCA$^+$ HP, 7% (4 patients) had HP associated with IgG4-RD, 13% (8 patients) had HP associated with other immune-mediated disorders, and 33% (20 patients) had idiopathic HP. (B) Lesion distribution among the 61 patients with immune-mediated or idiopathic HP. All patients with spinal HP (6 patients) were MPO-ANCA seropositive. (C) Cumulative symptoms (%) at the first active insult in each of the 6 patients with spinal HP, all of whom were seropositive for MPO-ANCA, based on clinical profiles. Symptoms related to myelopathy, along with fever and back/radicular pain, were prominent in MPO-ANCA$^+$ spinal HP. (D) Cumulative distribution (%) of the first active insult in each of the 6 patients with spinal HP, all of whom were seropositive for MPO-ANCA, based on radiologic profiles. HP was defined as thickening of the dura mater with abnormal enhancement on MRI findings. ANCA = anti-neutrophil cytoplasmic antibody; HP = hypertrophic pachymeningitis; IgG4-RD = IgG4-related disorder; MPO = myeloperoxidase; PR3 = proteinase 3.

Disease activity in patients with MPO-ANCA$^+$ spinal HP was assessed using the BVAS, which is a clinical checklist organized into the 9 organ-based systems.[34] These scores were compared with those obtained for patients with MPO-ANCA$^+$ cranial HP (Figure 4, A and B). The median BVAS for the nervous systems (9) in patients with MPO-ANCA$^+$ spinal HP was significantly higher than that in patients with MPO-ANCA$^+$ cranial HP. By contrast, the median BVAS for the ear, nose, and throat (ENT) system (4) was significantly lower in patients with MPO-ANCA$^+$ spinal HP than that in patients with MPO-ANCA$^+$ cranial HP. These data indicate that patients with MPO-ANCA$^+$ spinal HP had higher disease activity in the nervous system, but lower disease activity in the ENT system.

Neurologic damage in patients with MPO-ANCA$^+$ spinal HP was assessed using the mRS. The median mRS score at nadir was similar between patients with MPO-ANCA$^+$ spinal HP and patients with MPO-ANCA$^+$ cranial HP (Figure 4A).

Treatments and Long-Term Outcomes of MPO-ANCA$^+$ Spinal HP

Patients with MPO-ANCA$^+$ spinal HP received the following treatments: (1) long-term immunotherapies and (2) surgical decompression as appropriate.

1. Long-term immunotherapies consisted of (a) high-dose glucocorticoids (GCs) in combination with either

Table 2 Clinical and Demographic Characteristics of Patients With MPO-ANCA–Positive HP

	Spinal HP[a] (n = 6)	Cranial HP[a] (n = 16)
Demographics		
Age at onset, y[b,c]	66.0 (61.0–67.5)	66.5 (60.5–71.8)
Male/female, n (%)	2 (33)/4 (67)	4 (25)/12 (75)
Observation periods, mo[b,c]	88.8 (39.7–136.7)	106.6 (26.7–177.1)
Serum findings		
Seropositivity for rheumatoid factor, n (%)	5/6 (83)	12/16 (75)
CRP (≥0.3 mg/dL), n (%)	6/6 (100)	10/14 (71)
CRP, mg/dL[b,d]	7.52 (5.00–12.55)**	1.42 (0.10–3.96)**
ESR (≥20 mm/h), n (%)	6/6 (100)	10/13 (77)
CSF findings		
CSF nucleated cells (/mm^3)[b,e]	57 (17–205)*	8 (2–26)*
Marked pleocytosis (≥50/mm^3), n (%)	3/5 (60)	2/16 (13)
Protein, mg/dL[b,e]	1,223 (473–2,844)**	57 (37–87)**
Protein (≥50 mg/dL), n (%)	5/5 (100)	9/16 (56)
IgG index[b,f]	1.949 (1.780–3.122)	1.505 (0.735–1.872)
IgG index (≥0.658), n (%)	3/3 (100)	12/14 (86)
Otologic findings		
Otologic symptoms, n (%)	3/6 (50)	14/16 (88)
Sinusitis, otitis media, or mastoiditis by MRI or CT findings, n (%)	3/6 (50)*	14/14 (100)*
Surrogate markers for GPA[g]		
X-ray evidence of fixed pulmonary infiltrates, nodules, or cavitations present for >1 mo, n (%)	1/6 (17)	3/16 (19)
Bronchial stenosis, n (%)	0/6 (0)	0/16 (0)
Bloody nasal discharge and crusting for >1 mo, or nasal ulceration, n (%)	0/6 (0)	0/16 (0)
Chronic sinusitis, otitis media, or mastoiditis for 3 mo, n (%)	3/6 (50)*	16/16 (100)*
Retro-orbital mass or inflammation (pseudotumor), n (%)	0/6 (0)	2/16 (13)
Subglottic stenosis, n (%)	0/6 (0)	0/16 (0)
Saddle nose deformity/destructive sinonasal disease, n (%)	0/6 (0)	0/16 (0)
Surrogate markers for renal vasculitis[g]		
Hematuria associated with red cell casts or >10% dysmorphic erythrocytes, n (%)	1/6 (17)	0/16 (0)
2+ hematuria and 2+ proteinuria on urinalysis, n (%)	1/6 (17)	0/16 (0)
Treatments		
Surgical decompression/laminectomy, n (%)	5/6 (83)	0/16 (0)
Glucocorticoids, n (%)	6/6 (100)	16/16 (100)
Immunosuppressants (AZA, MTX, CY, TAC), n (%)	5/6 (83)	9/16 (56)
Rituximab, n (%)	1/6 (17)	0/16 (0)

Abbreviations: ANCA = anti-neutrophil cytoplasmic antibody; AZA = azathioprine; CRP = C-reactive protein; CY = cyclophosphamide; ESR = erythrocyte sedimentation rate; GPA = granulomatosis with polyangiitis; HP = hypertrophic pachymeningitis; MPO = myeloperoxidase; MTX = methotrexate; PR3 = proteinase 3; TAC = tacrolimus.
Statistically significant in comparison between MPO-ANCA–positive spinal HP and MPO-ANCA–positive cranial HP (*$p < 0.05$; **$p < 0.01$).
[a] "Spinal HP" was defined as including both "spinal HP with cranial HP (n = 2)" and "spinal HP without cranial HP (n = 4)." "Cranial HP (n = 16)" referred to "cranial HP without spinal HP (n = 16)."
[b] Median (interquartile range).
[c] MPO-ANCA–positive spinal HP (n = 6) and MPO-ANCA–positive cranial HP (n = 16) were analyzed.
[d] MPO-ANCA–positive spinal HP (n = 6) and MPO-ANCA–positive cranial HP (n = 14) were analyzed.
[e] MPO-ANCA–positive spinal HP (n = 5) and MPO-ANCA–positive cranial HP (n = 16) were analyzed.
[f] MPO-ANCA–positive spinal HP (n = 3) and MPO-ANCA–positive cranial HP (n = 14) were analyzed.
[g] Surrogate markers for GPA or for renal vasculitis were based on Watts algorithm.[16]

cyclophosphamide (CY) or rituximab (RTX) and (b) high-dose GCs alone. High-dose GCs were initiated as methylprednisolone pulse therapy (500 mg/d or 1,000 mg/d for 3 days), followed by oral GCs at a starting dose of 1 mg/kg/d prednisolone (PSL), with a gradual stepwise reduction, aiming to achieve a dose of 5 mg/d or less over months or years.
2. Surgical decompression included (i) laminectomy and (ii) duraplasty, which was performed if patients had progressive myelopathy.

All 11 first-onset or relapsing active diseases (6 cumulative first-onset active insults of spinal HP and 5 cumulative relapses, in 6 patients) of MPO-ANCA$^+$ spinal HP were included in this study. During the induction phase for the first active insults of spinal HP, treatments (6 active insults of spinal HP, excluding relapses, in 6 patients) included the following: (1) 3 active insults (3 patients) were treated with surgical decompression followed by combined immunotherapy with high-dose GCs and either CY or RTX; (2) 2 active insults (2 patients) were treated with surgical decompression followed by high-dose GCs alone; and (3) 1 active insult (1 patient) was treated with high-dose GCs and CY without surgical decompression.

Eighty-three percent (5/6) of patients with MPO-ANCA$^+$ spinal HP, who had rapidly progressive, mild-to-severe myelopathy with subacute/chronic onset, underwent urgent surgical decompression. Only 17% (1/6) of patients with MPO-ANCA$^+$ "spinal HP with cranial HP," who exhibited no signs of myelopathy (i.e., latent spinal HP with manifest cranial HP), received long-term immunotherapy without surgical intervention. For surgical decompression, laminectomy was performed in 100% (5/5) of cases and duraplasty in 80% (4/5) of cases. The median time from disease onset to surgical decompression was 95 days (IQR 68–265). None of the patients with MPO-ANCA$^+$ spinal HP required surgical stabilization of the spine because all patients with MPO-ANCA$^+$ spinal HP maintained spinal stability with no destructive changes in the vertebral column, although 50% (3/6) of patients had spinal involvement based on MRI findings. No patients underwent surgical procedures more than twice.

During the initial induction of the remission phase for the first insult, immunotherapies, with or without surgical decompression as appropriate, significantly reduced mRS scores and BVASs compared with pretreatment levels for all 6 active insults of HP (Figure 4C). Among patients receiving combined immunotherapy with high-dose GCs and CY/RTX as induction treatment for first active insults of spinal HP, remission (BVAS = 0) was achieved in 100% (4/4) of patients and sustained remission for 3 years was achieved in 100% (4/4) of patients. By contrast, among those receiving high-dose GCs alone, remission (BVAS = 0) was achieved in 100% (2/2) of patients but sustained remission for 3 years was achieved in 0% (0/2) of patients. After induction therapy for first active insults of spinal HP, 33% (2/6) of patients had 5 relapses (1 relapse of spinal HP, 2 relapses of cranial HP, 1 relapse of rapidly progressive glomerulonephritis, and 1 relapse of fever with increased MPO-ANCA titer). Kaplan-Meier estimates and log-rank statistical analyses revealed that the percentage of relapse-free patients receiving combined immunotherapy with GCs and CY/RTX was significantly higher than of those receiving high-dose GCs alone for MPO-ANCA$^+$ spinal HP (Figure 4D). We were unable to identify whether RTX was superior to CY for induction or maintenance of remission in patients with MPO-ANCA$^+$ HP because of the limited number of patients.

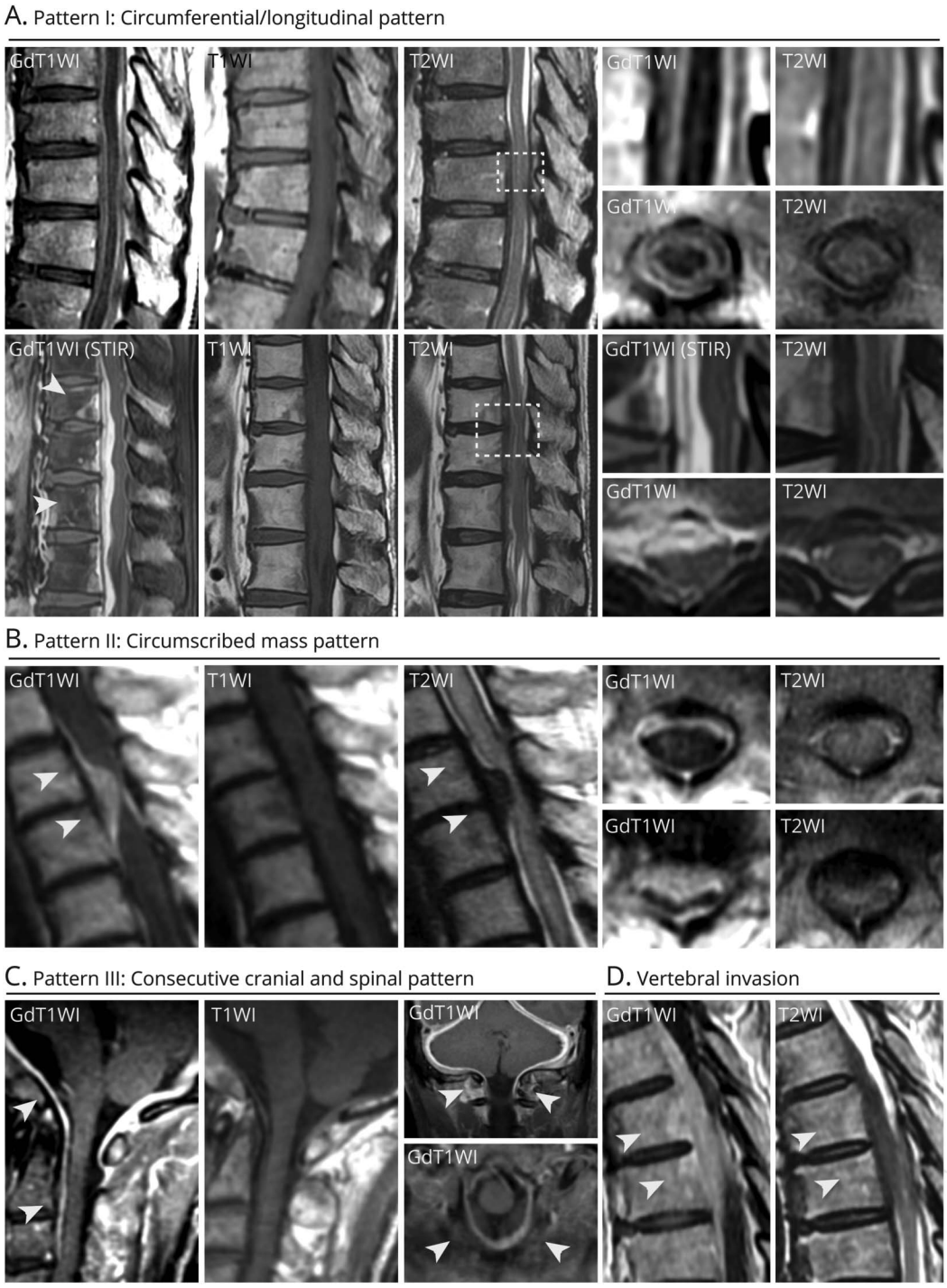
We identified several adverse events in patients with MPO-ANCA$^+$ spinal HP: 1 patient developed diabetes mellitus, 1 developed liver dysfunction, 2 developed severe infections, and 3 developed hypercholesterolemia among patients receiving combined immunotherapy with high-dose GCs and CY/RTX and 1 patient developed deep vein thrombosis and 1 developed severe infection among patients receiving high-dose GCs alone. Three deaths due to infections were reported: 2 patients (a woman older than 80 years with a 14.2-year clinical course and a man older than 75 years with a 10.5-year clinical course, at the time of death) receiving combined immunotherapy with high-dose GCs and CY/RTX and 1 patient (a woman older than 65 years with a 5.8-year clinical course, at the time of death) receiving high-dose GCs alone. They took no trimethoprim-sulfamethoxazole prophylaxis in the year before their deaths, because of reduced dosages of PSL (5 mg/d). These data are consistent with those of a previous article indicating that patients with AAV aged 75 years or older have a higher incidence of death.[35]

Discussion

We analyzed 61 patients with idiopathic or immune-mediated HP including 6 patients with spinal HP, all of whom had MPO-ANCA seropositivity (median observation period: 88.8 months). MPO-ANCA$^+$ spinal HP shared common clinical features with MPO-ANCA$^+$ cranial HP: (1) an older female predominance; (2) 100% (6/6) of patients classified as having MPA based on the 2022 ACR/EULAR Classification Criteria, although 83% (5/6) and 17% (1/6) of patients were classified as having GPA and unclassifiable AAV based on 2007/2012 EMA criteria, respectively; (3) a low frequency (33%, 2/6) of patients with involvement of the lower airways or kidneys; (4) a moderate frequency of patients (60%, 3/5) exhibiting granulomatous inflammation with T cells, B cells, granulocytes, and macrophages in biopsied materials; (5) efficacy of immunotherapy (with or without surgical decompression as appropriate) in reducing the mRS and BVAS during the first active insults; and (6) efficacy of combined immunotherapy with GCs and CY/RTX in reducing relapses over the long term.

MPO-ANCA$^+$ spinal HP presented unique clinical features: (1) 83% (5/6) of patients developed subacute/chronic

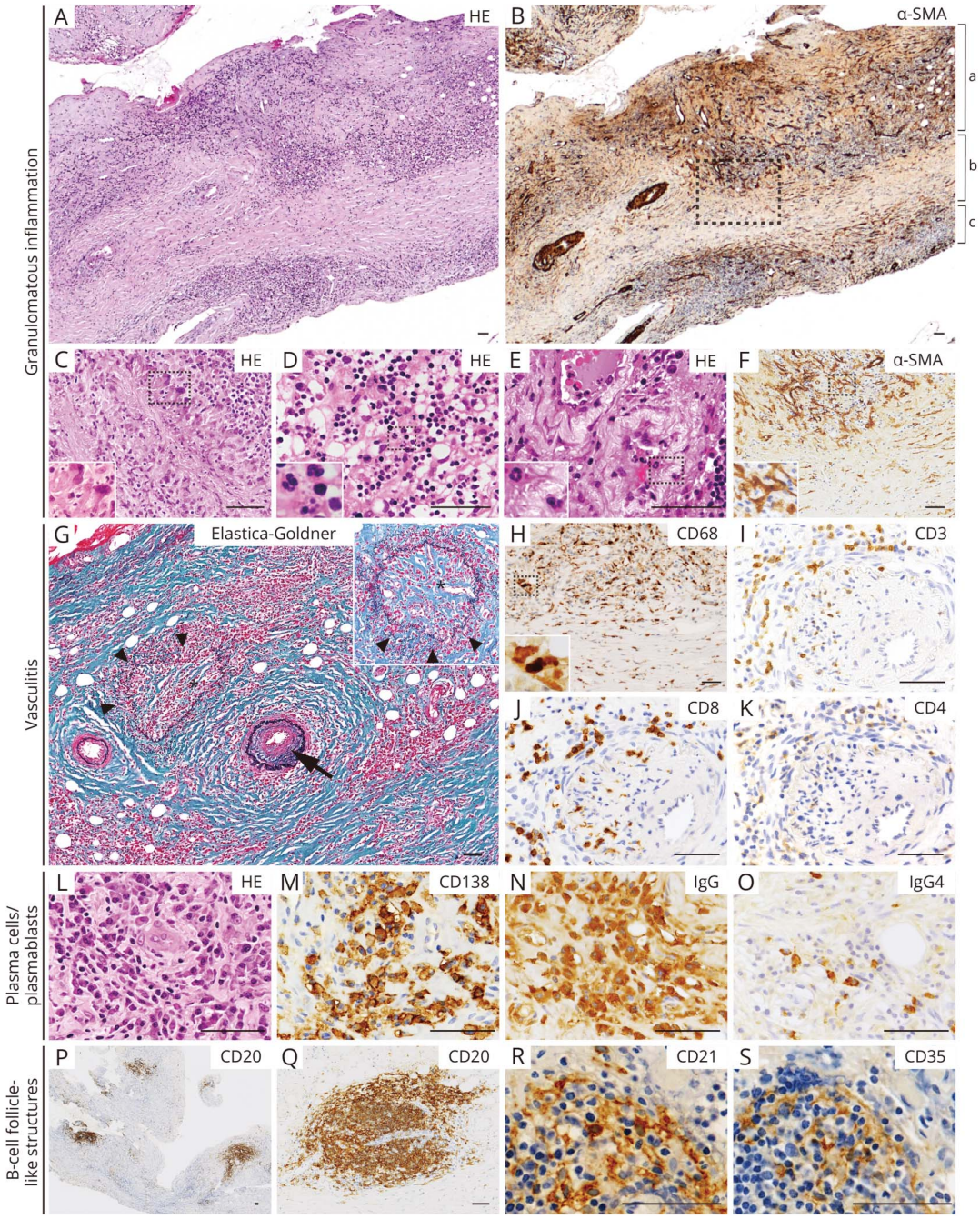
Figure 2 Radiologic Profiles of MPO-ANCA$^+$ Spinal HP



Representative MRI patterns of MPO-ANCA$^+$ spinal HP. Abnormal hypointense thickening of the dura mater was observed on T2WI with abnormal enhancement on GdT1WI (arrowheads, A–C). Three distinct radiologic patterns of thickened dura were identified in patients with MPO-ANCA$^+$ spinal HP: (1) a circumferential/longitudinal pattern (A), (2) a circumscribed mass pattern (B), and (3) a consecutive cranial and spinal pattern (C). Fifty percent (3/6) of patients exhibited epidural extension with spinal bone involvement (A and D). Spinal bone involvement appeared as hyperintense lesions on T2WI with abnormal enhancement on GdT1W1 (A and D, arrowheads) and typically presented with persistent spinal stability without destructive features on MRI. ANCA = anti-neutrophil cytoplasmic antibody; GdT1WI = T1-weighted postgadolinium imaging; HP = hypertrophic pachymeningitis; MPO = myeloperoxidase; T2WI = T2-weighted imaging.

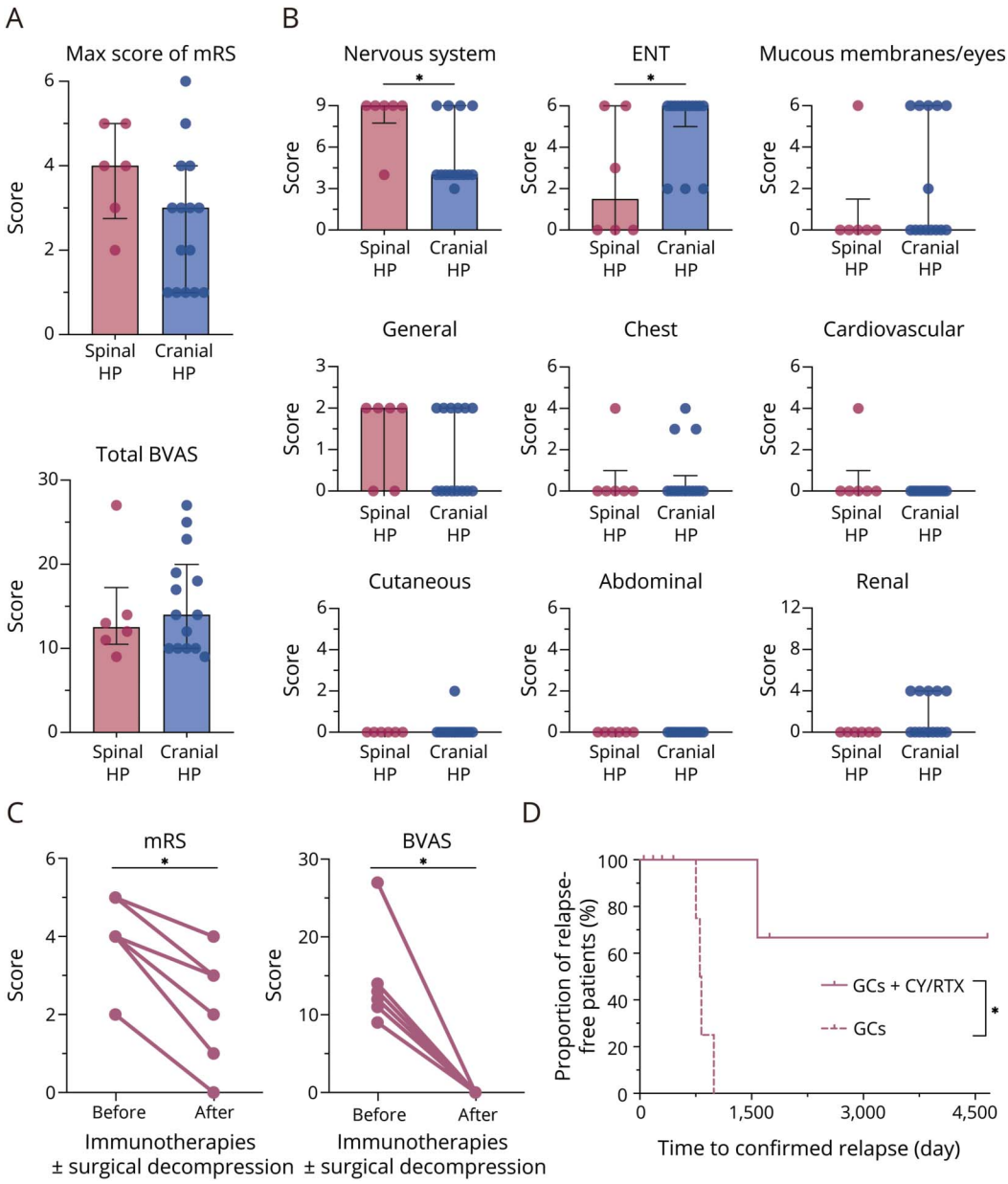
myelopathy due to extramedullary compression of the spinal cord; (2) 50% (3/6) of patients had lesion extension to the epidural compartment and vertebral column, but 100% (6/6) of patients had no direct involvement of the pia mater and the spinal cord parenchyma; (3) a lower frequency (50%, 3/6) of patients had chronic sinusitis, otitis media, or mastoiditis, compared with those with MPO-ANCA$^+$ cranial HP (100%, 16/16); (4) higher disease activity was observed in the

Figure 3 Pathologic Profiles of MPO-ANCA$^+$ Spinal HP



Representative pathologic patterns of MPO-ANCA$^+$ spinal HP from microscopic findings in 5 biopsied materials. All samples showed severe thickening of the dura mater with severe fibrosis and mild-to-severe infiltration of inflammatory cells (A–S). The thickened dura mater (A and B) consisted of 3 layers: a middle fibrous meningeal layer with SMA^{neg} fibroblasts (B, b) and 2 thick inflammatory layers with abundant SMA$^+$ myofibroblasts and inflammatory foci located at both the outer dural border layer (B, a) and the inner DBC layer (B, c). Sixty percent (3/5) of MPO-ANCA$^+$ spinal HP samples showed granulomatous inflammation (A–F). Forty percent (2/5) of MPO-ANCA$^+$ spinal HP samples showed necrotizing granulomatous inflammation surrounded by palisading epithelioid histiocytes (C) but without multinucleated giant cells or geographic necrosis. Forty percent (2/5) also showed vasculitis (G–K). Vascular changes included mild-to-severe inflammation (G–K), breakdown of the internal elastic layer (G, arrowheads), occlusive arteries (G, *), and vessels with intimal hyperplasia (G, arrow), but no vessels with fibrinoid necrosis. The thickened dura mater exhibited severe infiltration of CD68$^+$ macrophages (H); moderate infiltration of granulocytes (D and E); and moderate infiltration of CD3$^+$ T cells (I), CD8$^+$ T cells (J), CD4$^+$ T cells (K), CD20$^+$ B cells (P and Q), and CD138$^+$ or IgG$^+$ plasma cells (L–N). Sixty percent (3/5) of MPO-ANCA$^+$ spinal HP samples showed mild-to-moderate infiltration of IgG4$^+$ plasma cells (O). According to the 2019 ACR/EULAR IgG4-RD Classification Criteria,[20,21] all samples (100%, 5/5) met the serologic domain/item in step 2 (exclusion criteria) indicating seropositivity of ANCA and none were classified as having IgG4-RDs. However, 20% (1/5) of samples met the immunostaining domain/item in step 3 (inclusion criteria), with an assigned weight score ≥7 (IgG4$^+$:IgG$^+$ ratio ≥41%, and ≥10 IgG4$^+$ cells per high-power field). Sixty percent (3/5) of the MPO-ANCA$^+$ spinal HP materials contained B-cell follicle-like structures (P–S) in the thickened dura, which included CD21$^+$ and CD35$^+$ follicular dendritic cells (R and S) corresponding to B-cell areas. Only 20% (1/5) of samples had PNAd$^+$ HEV-like structures, corresponding to T-cell areas (data not shown). All scale bars represent 50 μm. ACR = American College of Rheumatology; ANCA = anti-neutrophil cytoplasmic antibody; DBC = dural border cell; EULAR = European League Against Rheumatism; HE = hematoxylin and eosin; HEV = high endothelial venule; HP = hypertrophic pachymeningitis; MPO = myeloperoxidase; PNAd = peripheral lymph node addressin; SMA = smooth muscle actin.

Figure 4 Disease Activity, Course, and Treatment Outcomes in MPO-ANCA$^+$ Spinal HP

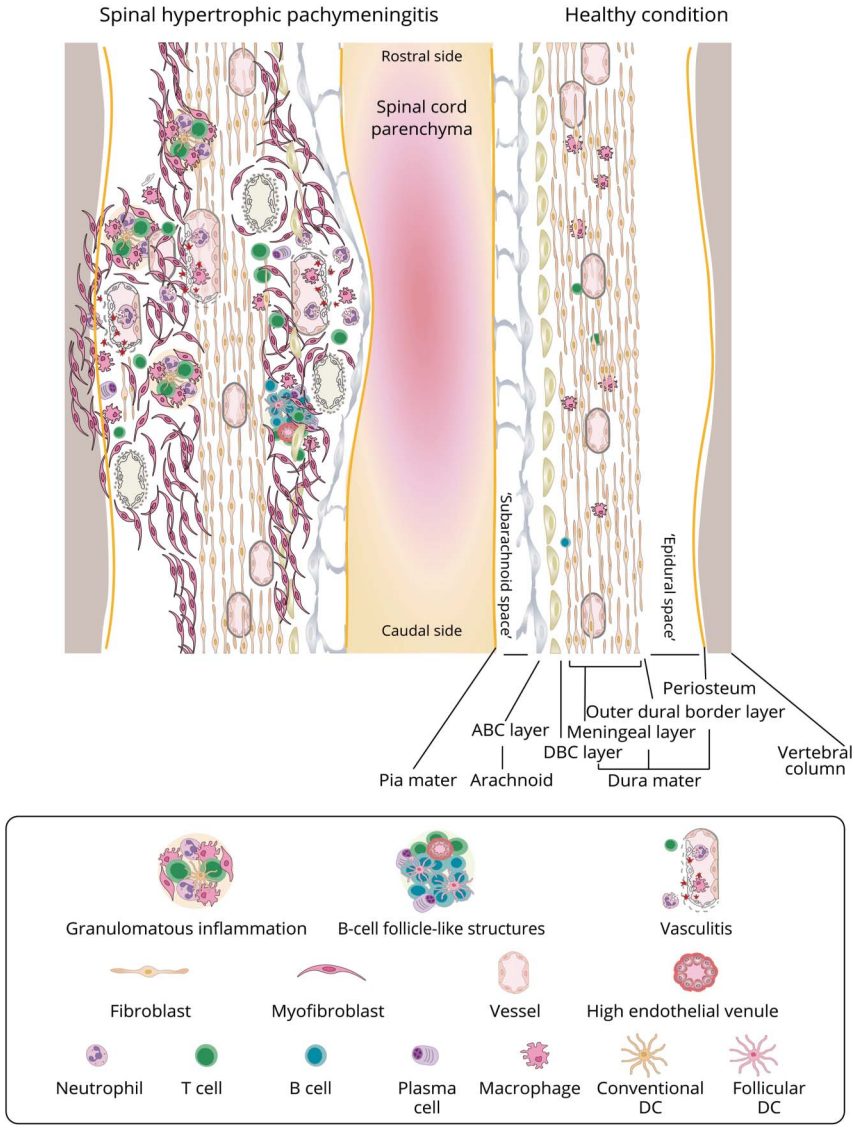


Neurologic damage in MPO-ANCA$^+$ spinal HP was assessed using the mRS (A). The median mRS score at nadir was similar between MPO-ANCA$^+$ spinal HP (6 first active insults) and MPO-ANCA$^+$ cranial HP (15 first active insults) (A). Disease activity in MPO-ANCA$^+$ spinal HP (6 first active insults) was evaluated using the BVAS, which assesses 9 organ-based systems: (1) general, (2) cutaneous, (3) mucous membranes/eyes, (4) ENT, (5) chest, (6) cardiovascular, (7) abdominal, (8) renal, and (9) nervous systems,[34] compared with that of MPO-ANCA$^+$ cranial HP (14 first active insults) (A and B). The median BVAS for the nervous systems (9) was significantly higher in MPO-ANCA$^+$ spinal HP compared with MPO-ANCA$^+$ cranial HP (B). By contrast, the median BVAS for the ENT system (4) was significantly lower in MPO-ANCA$^+$ spinal HP compared with MPO-ANCA$^+$ cranial HP (B). Statistical significance (B) was analyzed using the Mann-Whitney *U* test between spinal HP and cranial HP (*$p < 0.05$). Immunotherapies, with or without surgical decompression as appropriate, significantly reduced mRS scores and BVASs compared with pretreatment levels for all 6 first active insults (6 patients) (C). Statistical significance (C) was analyzed using the Wilcoxon signed-rank test before and after treatments (*$p < 0.05$). Kaplan-Meier estimates and log-rank analysis showed that relapse-free survival rates were significantly higher in patients with active insults of MPO-ANCA$^+$ spinal HP receiving combined treatments of GCs and CY/RTX (5 active insults) compared with those receiving high-dose GCs alone (6 active insults) for all 11 active insults of MPO-ANCA$^+$ spinal HP (*$p < 0.05$) (D). Each symbol represents individual data from each image in the region of interest, and bars show the median and interquartile range. ANCA = anti-neutrophil cytoplasmic antibody; BVAS = Birmingham Vasculitis Activity Score; CY = cyclophosphamide; ENT = ear, nose and throat; GCs = glucocorticoids; HP = hypertrophic pachymeningitis; MPO = myeloperoxidase; mRS = modified Rankin Scale; RTX = rituximab.

nervous system, as assessed using BVAS, compared with MPO-ANCA$^+$ cranial HP; and (5) there was the necessity of emergency of surgical decompression, including laminectomy and duraplasty, for compressive myelopathy.

Spinal HP forms thickened lesions on the dura mater, which is composed of 3 layers: the outermost thin dural border layer, the middle thickest meningeal layer, and the innermost DBC layer with few cell junctions (Figure 5).[36] The arachnoid,

Figure 5 Graphic Summary of Immunopathology in MPO-ANCA$^+$ Spinal HP



The human "dura" (meaning "tough" or "hard" in Latin) in the spine is composed of 3 distinctive dural layers, from outside to inside: (1) the outermost thin dural border layer consists of loosely arranged collagen fibers and is less than 2-μm thick; (2) the middle thickest meningeal layer consists of approximately 80 layers of collagen fibers arranged in different directions with numerous elastic fibers and infrequent fibroblasts; and (3) the innermost DBC layer consists of one to several layers of DBCs together with amorphous nonfibrillar materials, but no collagen or elastic fibers, and is less than 8-μm thick.[36] The spinal dura mater contains dural fibroblasts, immune cells, blood vasculature, and lymphatic vessels.[7,36] The dura mater has a different immune milieu compared with the arachnoid, for example, (1) the dura mater includes DALT, which consists of lymphatic vasculature, blood vasculature, and resident immune cells,[4] whereas the arachnoid contains very few short-lived myeloid cells (e.g., Ly-6C^{high} monocytes, neutrophils, and dendritic cells) and lower numbers of adaptive immune cells (CD4$^+$ and CD8$^+$ T cells and B cells)[4] and (2) BAMs in the dura mater are substantially replaced by peripheral monocytes and may be locally produced in hematopoietic niches within the dura and adjacent bone, whereas BAMs in the leptomeninges are not.[7] The arachnoid, located inside the innermost DBC layer with few cell junctions, is composed of the outermost ABC layer, which contains numerous tight junctions. This ABC layer functions as a morphological and physiologic "blood-CSF barrier" between the CSF in the subarachnoid space and the blood circulation in the dura mater. However, the ABC layer is sometimes interrupted by ACE points, which allow for exchange between the dura mater and the subarachnoid space.[4] These findings suggest that the dura mater and systemic blood circulation are strictly separated from the CNS and the CSF by the arachnoid blood-CSF barrier (i.e., ABC layer), except for communication through ACE points. The spinal epidural space, located between the dura mater and the osteofibrous wall (periosteum) of the vertebral column, contains the epidural fat pad and the IVVP and is considered to facilitate the spread of infection, tumor metastasis, and emboli through systemic circulation.[36] In vivo cell labeling in rodent studies revealed the migration of myeloid cells and B cells between the skull/vertebral BM and the dura through microvascular channels (BM-dura channels).[37,38] MPO-ANCA$^+$ spinal HP is characterized by granulomatous inflammation with fibrosis in/around the dura mater. A middle fibrous meningeal layer containing SMA^{neg} fibroblasts is sandwiched between thick layers of SMA$^+$ myofibroblasts and inflammatory foci located at both the outer dural border layer and the inner DBC layer of the dura mater. This inflammation extends into the epidural space and vertebrae while maintaining spinal stability; however, it does not expand into the spinal cord parenchyma beyond the arachnoid blood-CSF barrier. These data of human MPO-ANCA$^+$ spinal HP support the concept that the dura mater and systemic blood circulation are strictly separated from the CNS and the CSF by the arachnoid blood-CSF barrier, except for communication through ACE points, and that immune foci migrate between the vertebral BM and dura through BM-dura channels, based on recent meningeal biology by rodent models.[37,38] On the contrary, PR3-ANCA$^+$ cranial HP sometimes shows more extensive involvement of the dura matter with leptomeningeal and parenchymal areas.[3] This may be caused by ACE points that sometimes interrupt the ABC layer and allow for exchange between the dura mater and the subarachnoid space.[4] ABC = arachnoid barrier cell; ACE = arachnoid cuff exit; ANCA = anti-neutrophil cytoplasmic antibody; BAM = border-associated macrophage; BM = bone marrow; DALT = dura-associated lymphoid tissue; DBC = dural border cell; HP = hypertrophic pachymeningitis; IVVP = internal vertebral venous plexus; MPO = myeloperoxidase; SMA = smooth muscle actin.

located inside the innermost DBC layer, consists of an outermost arachnoid barrier cell (ABC) layer that contains numerous tight junctions,[36] suggesting that the ABC layer serves as an important morphological and physiologic blood-CSF barrier between the CSF in the subarachnoid space and the blood circulation in the dura mater.[4,36] However, the ABC layer is sometimes interrupted by arachnoid cuff exit (ACE) points, which allow for exchange between the dura mater and the subarachnoid space.[4] Moreover, recent rodent studies have revealed that the dura mater has a different immune milieu compared with the arachnoid (e.g., dura-associated lymphoid tissue in the dura mater).[4] These findings suggest that the dura mater and systemic blood circulation are strictly separated from the CNS and the CSF by the arachnoid blood-CSF barrier (i.e., ABC layer), except for communication through ACE points. This may explain that most lesions in MPO-ANCA$^+$ spinal HP are confined to the dura mater and areas outside the dura mater, without spreading into the pia mater or the spinal cord parenchyma beyond the arachnoid blood-CSF barrier.

In vivo cell labeling in rodent studies revealed the migration of myeloid cells and B cells between the skull/vertebral bone marrow (BM) and the dura through microvascular channels.[37,38] In the radiologic findings of our study, we observed that 50% (3/6) of lesions in MPO-ANCA$^+$ spinal HP extended into the epidural space and the vertebral column, with no evidence of spinal instability (Figure 2). These data suggested the migration of immune foci between the vertebral BM and the dura mater through BM-dura channels.[37,38] These vertebral lesions are consistent with findings of previous case reports on MPO-ANCA$^+$ or PR3-ANCA$^+$ AAV.[27-30] Overall, we demonstrated that the lesions of MPO-ANCA$^+$ spinal HP were primarily centered on the dura mater. The inner portion of the lesions was blocked by the arachnoid blood-CSF barrier, with no direct involvement of the spinal cord parenchyma, while the outer portion extended into the epidural space or vertebral column.

We found that 100% (16/16) of patients with MPO-ANCA$^+$ cranial HP had coexisting upper airway involvement, including chronic sinusitis, otitis media, or mastoiditis lasting for >3 months, while upper airway involvement in patients with MPO-ANCA$^+$ spinal HP was less frequent, occurring in only 50% (3/6) of patients (Table 2). In MPO-ANCA$^+$ cranial HP, inflammatory mediators from otitis media in the middle ear may spread to the cranial dura mater through emissary veins, such as the pterygoid plexus or petrosquamosal sinus, which connect the intracranial to extracranial drainage system. This could potentially form or exacerbate cranial HP.[3,39-41] The spine is located farther away from the upper airway (e.g., otitis media), while the cranium is situated close to it. These findings may explain why patients with MPO-ANCA$^+$ spinal HP are extremely rare compared with patients with MPO-ANCA$^+$ cranial HP. In this study and previous case reports, lesions in MPO-ANCA$^+$ spinal HP were predominantly located in the dura mater of the thoracic spine (Figure 1, eFigure 4), although the reason for this distribution remains unclear.

We observed a discrepancy in the classification of MPO-ANCA$^+$ spinal or cranial HP between the 2007/2012 EMA/CHCC Classification Criteria and the 2022 ACR/EULAR Classification Criteria (eFigures 2 and 3). Recent validation studies of the 2022 ACR/EULAR Classification Criteria revealed that 16 of 374 patients in population-based cohorts from Sweden[42] and 35 of 477 patients in population-based cohorts from Japan,[43] who were previously classified as having GPA based on the 2007/2012 EMA/CHCC Classification Criteria, were reclassified as having MPA under the 2022 ACR/EULAR Classification Criteria. It is important to note that all these patients were MPO-ANCA$^+$. Moreover, in both the Swedish and Japanese cohorts, 4 patients in each group, classified as having MPA according to the 2022 ACR/EULAR Classification Criteria, exhibited granulomatous inflammation on histologic examination, and all those patients were MPO-ANCA$^+$.[42,43] Overall, a case with clear evidence of granulomatous inflammation and MPO-ANCA seropositivity could be classified as MPA based on the 2022 ACR/EULAR Classification Criteria, despite granulomatous inflammation being a defining feature of GPA based on the 2012 CHCC definition.[42,43] This may explain why MPO-ANCA$^+$ spinal HP was reclassified as having MPA under the 2022 ACR/EULAR Classification Criteria, even if MPO-ANCA$^+$ spinal HP had granulomatous inflammation in the thickened dura mater. Moreover, recent clinical studies have indicated that ANCA specificities (MPO-ANCA vs PR3-ANCA) are more relevant to pathogenicity, clinical course, and disease severity, than traditional disease types (MPA vs GPA). For example, genome-wide association studies have shown that the strongest genetic associations are linked to ANCA specificities rather than traditional disease types.[44] Furthermore, ANCA specificities independently predict relapse, contrasting with traditional disease types in clinical data from 502 patients with biopsy-proven AAV.[45] Given these findings and those of our study, a new classification system for AAV that would not only label the disease but also serve as a tool for predicting disease recognition, treatment responses, and prognosis should be undertaken in the future. Such a classification system could potentially be based on ANCA specificities.[42] To accurately describe the disease, we used terms based on ANCA specificities (e.g., MPO-ANCA$^+$ spinal HP) rather than traditional disease types (e.g., GPA or MPA) in this study.

We observed that immunotherapies, with or without surgical decompression as appropriate, significantly reduced mRS scores and BVASs compared with pretreatment levels for all first active insults (Figure 4C). Kaplan-Meier estimates and log-rank statistical analyses revealed that the percentage of relapse-free patients receiving combined immunotherapy with GCs and CY/RTX was significantly higher than of those receiving high-dose GCs alone for MPO-ANCA$^+$ spinal HP during long-term follow-up (Figure 4D). These findings reinforce the use of the EULAR recommendations for the management of AAV,[46] suggesting that a combination of high-dose GCs with either RTX or CY is recommended for inducing remission in life-threatening or organ-threatening

AAV, and that a continued combination of tapered GCs and RTX is recommended for maintaining remission in AAV. Future studies on other immunotherapies, including the oral C5aR inhibitor avacopan, are warranted for inducing or maintaining remission, particularly to reduce GC exposure in patients with MPO-ANCA$^+$ spinal HP. This recommendation is supported by recent clinical trials, including the ADVOCATE study for AAV.[47]

This study has several limitations. First, the cohort was extremely small (immune-mediated HP, n = 61; spinal HP, n = 6), because of the rarity of the disease. Second, the median observation period for patients with MPO-ANCA$^+$ spinal HP was 88.8 months, and longer-term follow-up data are needed. Third, all materials from patients with MPO-ANCA$^+$ spinal HP were obtained from biopsies, which are typically small. Based on pathologic studies of the head and neck, only 16% of biopsied samples from patients with GPA provided evidence of necrotizing granulomatous inflammation.[32] Fourth, all patients with spinal HP in this cohort were diagnosed with MPO-ANCA$^+$ spinal HP, with no cases of PR3-ANCA$^+$ spinal HP. This skewed distribution likely reflects geographic differences because MPO-ANCA$^+$ AAV is the predominant form of AAV in Asia, including Japan, while PR3-ANCA$^+$ AAV is more common in Europe and the United States according to global epidemiologic data.[48,49] Compared with reports of MPO-ANCA$^+$ or p-ANCA$^+$ AAV, previous case reports of PR3-ANCA$^+$ or c-ANCA$^+$ spinal HP are scarce and most have been from Europe and the United States (eTable 1).

Our findings provide evidence that ANCA pathogenicity plays a significant role in spinal HP, based on the distinct clinical characteristics of MPO-ANCA$^+$ spinal HP observed in this retrospective cohort study. MPO-ANCA$^+$ spinal HP, which presents with fibrosis and granulomatosis with formation of tertiary lymphoid structures in the thickened dura mater, should be recognized as either a CNS-limited or generalized form of AAV, representing an organ-threatening disease. Future studies involving larger cohorts and longer follow-up periods are necessary to further elucidate the pathogenicity of ANCA and other immune elements, refine the classification of AAV, and explore effective treatments aimed at mitigating tissue fibrosis and damage and potentially achieving a cure.

Acknowledgment

The authors thank S. Kawaguchi, T. Yahata, and M. Kaneko (Department of Neurology, Brain Research Institute, Niigata University, Japan) for technical assistance with neuropathological and immunological investigations.

Author Contributions

A. Nakajima: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. M. Hokari: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. F. Yanagimura: major role in the acquisition of data; analysis or interpretation of data. E. Saji: major role in the acquisition of data; analysis or interpretation of data. H. Shimizu: major role in the acquisition of data; analysis or interpretation of data. Y. Toyoshima: major role in the acquisition of data; analysis or interpretation of data. K. Yanagawa: major role in the acquisition of data; analysis or interpretation of data. M. Arakawa: major role in the acquisition of data; analysis or interpretation of data. A. Yokoseki: major role in the acquisition of data; analysis or interpretation of data. T. Wakasugi: major role in the acquisition of data; analysis or interpretation of data. K. Okamoto: major role in the acquisition of data; analysis or interpretation of data. K. Watanabe: major role in the acquisition of data; analysis or interpretation of data. K. Minato: major role in the acquisition of data; analysis or interpretation of data. Y. Otsu: major role in the acquisition of data; analysis or interpretation of data. Y. Nozawa: major role in the acquisition of data; analysis or interpretation of data. D. Kobayashi: major role in the acquisition of data; analysis or interpretation of data. K. Sanpei: major role in the acquisition of data; analysis or interpretation of data. H. Kikuchi: major role in the acquisition of data; analysis or interpretation of data. S. Hirohata: major role in the acquisition of data; analysis or interpretation of data. K. Awamori: major role in the acquisition of data; analysis or interpretation of data. A. Nawata: analysis or interpretation of data. M. Yamada: analysis or interpretation of data. H. Takahashi: major role in the acquisition of data; analysis or interpretation of data. M. Nishizawa: major role in the acquisition of data; study concept or design; analysis or interpretation of data. H. Igarashi: analysis or interpretation of data. N. Sato: analysis or interpretation of data. A. Kakita: major role in the acquisition of data; analysis or interpretation of data. O. Onodera: major role in the acquisition of data; analysis or interpretation of data. I. Kawachi: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

Study Funding

This work was supported in part by JSPS KAKENHI Grant Numbers JP20K07899 (I.K.) and JP23K06923 (I.K.), and by the MHLW Research Program on Rare and Intractable Diseases, Grant/Award (JPMH 20FC1030, JPMH 23FC1009, and JPMH 23FC1015) (I.K.).

Disclosure

I. Kawachi reports receiving funding for research, travel, and/or speaker's honoraria from Chugai Pharmaceuticals, Novartis Pharma, Biogen, Alexion Pharmaceuticals, Mitsubishi Tanabe Pharma, Takeda Pharmaceutical Company, Teijin Pharma, Argenx, UCB, and Daiichi-Sankyo; and is a scientific advisory board member for UCB, Mitsubishi Tanabe Pharma, and Chugai Pharmaceuticals. The other authors report no disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* November 12, 2024. Accepted in final form January 7, 2025. Submitted and externally peer reviewed. The handling editors were Assistant Editor Marcello Moccia, MD, PhD, and Deputy Editor Bradford Worrall, MD, MSc, FAAN.

References

1. Naffziger HC, Stern WE. Chronic pachymeningitis; report of a case and review of the literature. *Arch Neurol Psychiatry*. 1949;62(4):383-411.
2. Kupersmith MJ, Martin V, Heller G, Shah A, Mitnick HJ. Idiopathic hypertrophic pachymeningitis. *Neurology*. 2004;62(5):686-694. doi:10.1212/01.wnl.0000113748.53023.b7
3. Yokoseki A, Saji E, Arakawa M, et al. Hypertrophic pachymeningitis: significance of myeloperoxidase anti-neutrophil cytoplasmic antibody. *Brain*. 2014;137(pt 2):520-536. doi:10.1093/brain/awt314
4. Smyth LCD, Xu D, Okar SV, et al. Identification of direct connections between the dura and the brain. *Nature*. 2024;627(8002):165-173. doi:10.1038/s41586-023-06993-7
5. Park JH, Alexander JF, Smyth LCD, Kipnis J. DALT: the brain's border patrol. *Cell Res*. 2024;34(9):603-604. doi:10.1038/s41422-024-00976-7
6. Rustenhoven J, Drieu A, Mamuladze T, et al. Functional characterization of the dural sinuses as a neuroimmune interface. *Cell*. 2021;184(4):1000-1016.e27. doi:10.1016/j.cell.2020.12.040
7. Como CN, Kim S, Siegenthaler J. Stuck on you: meninges cellular crosstalk in development. *Curr Opin Neurobiol*. 2023;79:102676. doi:10.1016/j.conb.2023.102676
8. Niu C, Yu J, Zou T, et al. Identification of hematopoietic stem cells residing in the meninges of adult mice at steady state. *Cell Rep*. 2022;41(6):111592. doi:10.1016/j.celrep.2022.111592
9. Schain AJ, Melo-Carrillo A, Borsook D, Grutzendler J, Strassman AM, Burstein R. Activation of pial and dural macrophages and dendritic cells by cortical spreading depression. *Ann Neurol*. 2018;83(3):508-521. doi:10.1002/ana.25169
10. Yonekawa T, Murai H, Utsuki S, et al. A nationwide survey of hypertrophic pachymeningitis in Japan. *J Neurol Neurosurg Psychiatry*. 2014;85(7):732-739. doi:10.1136/jnnp-2013-306410
11. Li X, Zhao J, Wang Q, Fei Y, Zhao Y. ANCA-associated systemic vasculitis presenting with hypertrophic spinal pachymeningitis: a report of 2 cases and review of literature. *Medicine (Baltimore)*. 2015;94(46):e2053. doi:10.1097/MD.0000000000002053
12. Yang F, Liu Z, Zhang Y, et al. Case report: clinical highlights and radiological classification of IgG4-related spinal pachymeningitis: a rare case series and updated review of the literature. *Front Oncol*. 2022;12:1035056. doi:10.3389/fonc.2022.1035056
13. Ito Z, Osawa Y, Matsuyama Y, Aoki T, Harada A, Ishiguro N. Recurrence of hypertrophic spinal pachymeningitis. Report of two cases and review of the literature. *J Neurosurg Spine*. 2006;4(6):509-513. doi:10.3171/spi.2006.4.6.509
14. Arnold S, Kitching AR, Witko-Sarsat V, et al. Myeloperoxidase-specific antineutrophil cytoplasmic antibody-associated vasculitis. *Lancet Rheumatol*. 2024;6(5):e300-e313. doi:10.1016/S2665-9913(24)00025-0
15. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference nomenclature of vasculitides. *Arthritis Rheum*. 2013;65(1):1-11. doi:10.1002/art.37715
16. Watts R, Lane S, Hanslik T, et al. Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. *Ann Rheum Dis*. 2007;66(2):222-227. doi:10.1136/ard.2006.054593
17. Suppiah R, Robson JC, Grayson PC, et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for microscopic polyangiitis. *Arthritis Rheumatol*. 2022;74(3):400-406. doi:10.1002/art.41983
18. Robson JC, Grayson PC, Ponte C, et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for granulomatosis with polyangiitis. *Ann Rheum Dis*. 2022;81(3):315-320. doi:10.1136/annrheumdis-2021-221795
19. Grayson PC, Ponte C, Suppiah R, et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for eosinophilic granulomatosis with polyangiitis. *Ann Rheum Dis*. 2022;81(3):309-314. doi:10.1136/annrheumdis-2021-221794
20. Wallace ZS, Naden RP, Chari S, et al. The 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-related disease. *Arthritis Rheumatol*. 2020;72(1):7-19. doi:10.1002/art.41120
21. Wallace ZS, Naden RP, Chari S, et al. The 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-related disease. *Ann Rheum Dis*. 2020;79(1):77-87. doi:10.1136/annrheumdis-2019-216561
22. Neogi T, Aletaha D, Silman AJ, et al. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis: phase 2 methodological report. *Arthritis Rheum*. 2010;62(9):2582-2591. doi:10.1002/art.27580
23. Stern BJ, Royal W III, Gelfand JM, et al. Definition and consensus diagnostic criteria for neurosarcoidosis: from the Neurosarcoidosis Consortium Consensus Group. *JAMA Neurol*. 2018;75(12):1546-1553. doi:10.1001/jamaneurol.2018.2295
24. Mirza S, Adams WM, Corkhill RA. Froin's syndrome revisited, 100 years on. Pseudo-Froin's syndrome on MRI. *Clin Radiol*. 2008;63(5):600-604. doi:10.1016/j.crad.2007.07.027
25. Fries FL, Kleiser B, Schwarz P, et al. Diagnosis of Froin's syndrome by parallel analysis of ventriculoperitoneal shunt and lumbar cerebrospinal fluid in a patient with cervical spinal stenosis. *J Clin Med*. 2023;12(15):5012. doi:10.3390/jcm12155012
26. Friedman DP, Flanders AE. Enhanced MR imaging of hypertrophic pachymeningitis. *AJR Am J Roentgenol*. 1997;169(5):1425-1428. doi:10.2214/ajr.169.5.9353473
27. Wang DC, Wei JW, Liu JH, Hu YG. The upper thoracic spinal cord compression as the initial manifestation of Wegener's granulomatosis: a case report. *Eur Spine J*. 2007;16(suppl 3):296-300. doi:10.1007/s00586-007-0318-x
28. Kawanishi K, Nishiwaki H, Kawata N, Omiya S, Inoue Y, Koiwa F. Granulomatosis with polyangiitis in a patient with a thoracic vertebral lesion: a case report. *Mod Rheumatol Case Rep*. 2021;5(2):347-353. doi:10.1080/24725625.2021.1911426
29. Yoshida Y, Kaieda S, Furuta T, Ida H. Juxta-vertebral lesions associated with granulomatosis with polyangiitis. *Intern Med*. 2019;58(17):2587-2588. doi:10.2169/internalmedicine.2903-19
30. Durant C, Martin J, Godmer P, Moreau A, Masseau A, Hamidou M. Exceptional osseous and meningeal spinal localization of ANCA-associated granulomatous vasculitis with hypertrophic spinal pachymeningitis. *J Neurol*. 2011;258(6):1172-1173. doi:10.1007/s00415-010-5886-8
31. Smith AB, Horkanyne-Szakaly I, Schroeder JW, Rushing EJ. From the radiologic pathology archives: mass lesions of the dura: beyond meningioma-radiologic-pathologic correlation. *Radiographics*. 2014;34(2):295-312. doi:10.1148/rg.342130075
32. Devaney KO, Travis WD, Hoffman G, Leavitt R, Lebovics R, Fauci AS. Interpretation of head and neck biopsies in Wegener's granulomatosis. A pathologic study of 126 biopsies in 70 patients. *Am J Surg Pathol*. 1990;14(6):555-564. doi:10.1097/00000478-199006000-00006
33. Jennette JC, Falk RJ, Andrassy K, et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum*. 1994;37(2):187-192. doi:10.1002/art.1780370206
34. Luqmani RA, Exley AR, Kitas GD, Bacon PA. Disease assessment and management of the vasculitides. *Baillieres Clin Rheumatol*. 1997;11(2):423-446. doi:10.1016/s0950-3579(97)80052-0
35. Sattui SE, Jiang B, Fu X, et al. The effects of age and frailty on the risks of end-stage renal disease, death, and severe infection in older adults with antineutrophil cytoplasmic antibody-associated vasculitis: a retrospective cohort study. *Lancet Rheumatol*. 2024;6(11):e771-e779. doi:10.1016/S2665-9913(24)00193-0
36. Vandenabeele F, Creemers J, Lambrichts I. Ultrastructure of the human spinal arachnoid mater and dura mater. *J Anat*. 1996;189(pt 2):417-430.
37. Brioschi S, Wang WL, Peng V, et al. Heterogeneity of meningeal B cells reveals a lymphopoietic niche at the CNS borders. *Science*. 2021;373(6553):eabf9277. doi:10.1126/science.abf9277
38. Cugurra A, Mamuladze T, Rustenhoven J, et al. Skull and vertebral bone marrow are myeloid cell reservoirs for the meninges and CNS parenchyma. *Science*. 2021;373(6553):eabf7844. doi:10.1126/science.abf7844
39. Iwasaki S, Ito K, Sugasawa M. Hypertrophic cranial pachymeningitis associated with middle ear inflammation. *Otol Neurotol*. 2006;27(7):928-933. doi:10.1097/01.mao.0000231498.61781.ec
40. Marsot-Dupuch K, Gayet-Delacroix M, Elmaleh-Berges M, Bonneville F, Lasjaunias P. The petrosquamosal sinus: CT and MR findings of a rare emissary vein. *AJNR Am J Neuroradiol*. 2001;22(6):1186-1193.
41. Inokuchi G, Tsutsumi N, Komatsu H, Fujita T, Sawada N, Kumoi K. Persistent petrosquamosal sinus: underlying cause of otitic hydrocephalus with lateral sinus thrombosis. *Int J Pediatr Otorhinolaryngol*. 2013;77(11):1908-1911. doi:10.1016/j.ijporl.2013.08.034
42. Rathmann J, Segelmark M, Mohammad AJ. Evaluation of the ACR/EULAR 2022 criteria for classification of ANCA-associated vasculitis in a population-based cohort from Sweden. *Rheumatology (Oxford)*. 2024;63(7):1965-1972. doi:10.1093/rheumatology/kead516
43. Sada KE, Kaname S, Higuchi T, et al. Validation of new ACR/EULAR 2022 classification criteria for anti-neutrophil cytoplasmic antibody-associated vasculitis. *Mod Rheumatol*. 2023;34(1):144-150. doi:10.1093/mr/road017
44. Lyons PA, Rayner TF, Trivedi S, et al. Genetically distinct subsets within ANCA-associated vasculitis. *N Engl J Med*. 2012;367(3):214-223. doi:10.1056/NEJMoa1108735
45. Lionaki S, Blyth ER, Hogan SL, et al. Classification of antineutrophil cytoplasmic autoantibody vasculitides: the role of antineutrophil cytoplasmic autoantibody specificity for myeloperoxidase or proteinase 3 in disease recognition and prognosis. *Arthritis Rheum*. 2012;64(10):3452-3462. doi:10.1002/art.34562
46. Hellmich B, Sanchez-Alamo B, Schirmer JH, et al. EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update. *Ann Rheum Dis*. 2024;83(1):30-47. doi:10.1136/ard-2022-223764
47. Jayne DRW, Merkel PA, Schall TJ, Bekker P; ADVOCATE Study Group. Avacopan for the treatment of ANCA-associated vasculitis. *N Engl J Med*. 2021;384(7):599-609. doi:10.1056/NEJMoa2023386
48. Fujimoto S, Watts RA, Kobayashi S, et al. Comparison of the epidemiology of anti-neutrophil cytoplasmic antibody-associated vasculitis between Japan and the U.K. *Rheumatology (Oxford)*. 2011;50(10):1916-1920. doi:10.1093/rheumatology/ker205
49. Kitching AR, Anders HJ, Basu N, et al. ANCA-associated vasculitis. *Nat Rev Dis Primers*. 2020;6(1):71. doi:10.1038/s41572-020-0204-y