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Pachymeningitis in Biopsy-Proven Sarcoidosis

Clinical Course, Radiographic Findings, Response to Treatment, and Long-term Outcomes

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Abstract

Background and Objectives

Meningeal inflammation is one of the most common manifestations of neurosarcoidosis, occurring in 16%–69% of affected patients. While the clinical and radiographic features of leptomeningitis in neurosarcoidosis are well known, those of pachymeningitis are far less clear. Our primary aim was to study the clinicoradiographic features of pachymeningeal involvement in neurosarcoidosis and its evolution over time in response to treatment.

Methods

Patients with a diagnosis of neurosarcoidosis seen at Emory University (January 2011–August 2021) were included if pachymeningeal involvement was evident by MRI and the patient's sarcoidosis was pathologically confirmed (from a CNS or non-CNS site).

Results

Twenty-six of 215 (12.1%) patients with neurosarcoidosis qualified for inclusion. Pathologic confirmation came from CNS tissue in 50%. The median age of onset was 43.5 years; most were male (16/26, 61.5%). Symptoms were primarily related to pachymeningitis in 20/26 (76.9%). Headache (19/26, 73.1%), visual dysfunction (12/26, 46.2%), and seizures (7/26, 26.9%) were the most common symptoms. All patients had cranial pachymeningitis; only a single patient undergoing spinal imaging (1/11, 9.1%) had spinal pachymeningitis. The falx cerebri (16/26, 61.5%) was the most commonly affected dural structure, but the anterior and middle cranial fossae and tentorium cerebelli were frequently involved (12/26 each, 46.2%). The pachymeningeal lesions were unifocal (11/26, 42.3%) or multifocal (15/26, 57.7%) in distribution, nodular morphologically (23/25, 92.0%), and homogeneously enhancing (24/25, 96.0%). Symptomatic improvement occurred with steroids initially in 22/25 (88.0%). Ultimately, 23/26 (88.5%) required initiation of steroid-sparing immunosuppressants, including 8/26 (30.8%) eventually undergoing TNF inhibition. Pachymeningeal relapses occurred in 7/26 (26.9%). The median clinical follow-up was 48 months. The median modified Rankin scale score at last follow-up improved to 1.0 from 2.0 at presentation.

Discussion

Pachymeningitis due to sarcoidosis often presents with headaches, visual dysfunction, and seizures; it usually affects the dura of the falx cerebri, anterior and middle cranial fossae, and tentorium cerebelli and tends to require steroid-sparing immunosuppressants. It has the potential to relapse, but the prospect for recovery is good.

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Glossary

ACE = angiotensin converting enzyme; **IgG4** = immunoglobulin G subclass 4; **IgG4-RD** = IgG4-related disease; **mRS** = modified Rankin scale; **TNF** = tumor necrosis factor.

Sarcoidosis is a granulomatous multiorgan disease that affects the nervous system in 3%–5% of patients.[1-3] Despite its discovery a century ago, its etiology remains elusive, but an aberrant immune response to unidentified antigens is believed to occur in genetically susceptible persons.[4] The neurologic manifestations of sarcoidosis are protean and have the potential to affect any subcomponent of the nervous system, but particular clinical scenarios should prompt clinicians to consider neurosarcoidosis in the differential diagnosis, including meningitis (leptomeningitis or pachymeningitis), cranial neuropathies (facial and optic especially), and myelitis.[3,5,6] Meningeal inflammation is one of its most common forms, occurring in 16%–69% of affected patients.[3,7-9] Leptomeningitis (inflammation of the pia and arachnoid mater) occurs much more commonly in neurosarcoidosis than does pachymeningitis (inflammation of the dura mater).[9-11] The features of leptomeningitis secondary to neurosarcoidosis are well-known, including its predilection for the basal meninges and its propensity to spread intra-axially through the perivascular route.[9,12] The clinical features of pachymeningitis, on the contrary, are far less clear.[9,12]

Pachymeningitis due to neurosarcoidosis has been most commonly described through single case reports, but larger cohorts have been embedded within studies broadly examining the general features of neurosarcoidosis.[13,14] Although the pachymeninges may be affected anywhere along its course, both intracranially and within the spinal column, the central skull base in the region of the cavernous sinus, sphenoid wing, and petroclival junction is a favored location.[14] Pachymeningeal inflammation has been noted to respond well to treatment in 1 series except when it encroaches on the orbital apex and compromises optic nerve function with compressive ischemia postulated as the likely mechanism of persistent injury.[13]

In this study, we provide greater clarification of the manner in which pachymeningeal neurosarcoidosis presents, the findings of ancillary testing with particular attention to the location and morphological characteristics of pachymeningeal granulomatous deposits on MRI, how it evolves over time in response to treatment, and what complications may arise because of pachymeningeal compression of adjacent CNS structures.

Methods

Patient Identification and Selection

Patients with sarcoidosis who were evaluated by a neurology provider at Emory University were screened for possible inclusion between the dates of January 1, 2011, and August 12, 2021. Patients were included if the presence of pachymeningitis could be substantiated by a review of MRI images and reports. In light of the radiographic differential diagnosis of dural thickening and enhancement, particularly meningioma and immunoglobulin G subclass 4 (IgG4)-related disease, we chose to include only those patients who had biopsy-confirmed sarcoidosis from CNS (meningeal or neural tissue) or non-CNS sites, thus meeting either definite (CNS) or probable (non-CNS) classifications in the 2018 Consensus Diagnostic Criteria from the Neurosarcoidosis Consortium.[15] Patients with a classification of possible (no pathologic confirmation of sarcoidosis) were excluded from this study.[15]

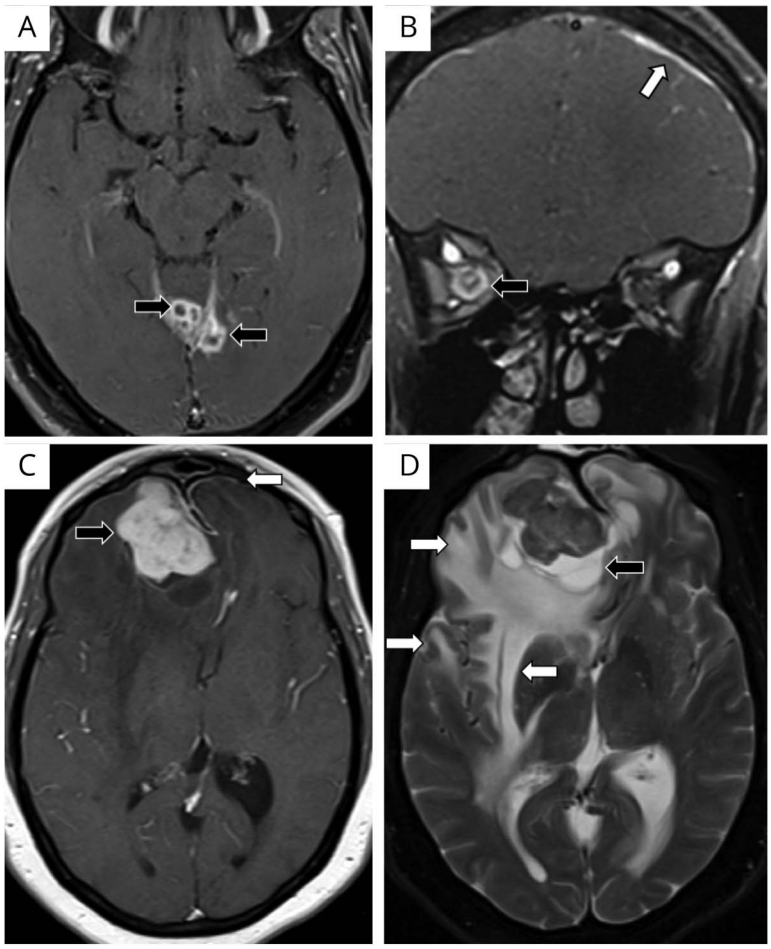
Data Extraction and Analysis

Primary sources of information included clinical notes related to outpatient and inpatient neurology and rheumatology visits, serum and CSF laboratory values, pathology reports, and documentation previously accumulated before the patient seeking care at our health care facilities. Radiographic findings were determined on the basis of patients' MRI. MRI images were personally reviewed by the authors with radiology reports providing supplemental information as necessary. The median values and ranges were used to characterize continuous variables. Fractions and percentages were used to characterize categorical variables. A reduction in the denominator of the total cohort (26 patients) was used to denote missing or incomplete data for a particular patient. Calculations were performed with Microsoft Excel (Microsoft, Redmond, WA).

Definitions

The morphology of pachymeningitis was defined as either: (1) nodular, if any portion of the lesion appeared to be bulky or expansile, or (2) smooth, if dural thickening and enhancement were consistently smooth throughout the entirety of the lesion. These morphological patterns were considered to be mutually exclusive, and examples of both are shown in Figure 1 (white arrow in 1B showing smooth pachymeningitis, black arrow in 1C showing bulky nodular pachymeningitis). The focality of lesions were defined as follows: (1) focal confluent, if a single contiguous lesion was evident, (2) multifocal, if multiple lesions were present and spatially separated by normal-appearing dura, or (3) diffuse, if the entirety of the meninges was involved. A homogeneous pattern of enhancement refers to a consistent level of contrast uptake throughout the entirety of the lesion, while rim enhancement refers to peripheral enhancement surrounding a central region of T1 hypointensity. These enhancement patterns were not considered to be mutually exclusive (some patients had both types present on a single MRI), and examples of both

Figure 1 Radiographic Examples of Pachymeningitis Due to Sarcoidosis (Part 1)



(A) Axial postcontrast fat-saturated T1: peripherally enhancing dural-based mass involving both sides of the tentorium (black arrows). (B) Coronal postcontrast fat-saturated T1: right optic nerve enhancement compatible with optic neuritis. Marked pachymeningeal enhancement of the right optic nerve sheath compatible with perineuritis (black arrow). This patient had additional sites of intracranial pachymeningeal enhancement; note the left convexity pachymeningeal enhancement (white arrow). (C) Axial T1 postcontrast: mixed cystic and solid mass centered in the right anterior cranial fossa with broad dural base along the anterior falx and right frontal convexity. The solid component enhances homogeneously (black arrow). There is associated bifrontal pachymeningeal thickening and enhancement (white arrow). (D) Axial fat-saturated T2: note cystic changes peripherally (black arrow). Extensive parenchymal edema in the right greater than the left frontal lobes, right subinsular region, and right temporal lobe (white arrows). Mass effect results in leftward subfalcine herniation.

are shown in Figure 1 (black arrows in 1A showing rim enhancement, black arrow in 1C showing homogeneous enhancement). Disease remission was principally defined as clinical symptomatic improvement with adjudications supported by improving or stable MRI findings when available.

Standard Protocol Approvals, Registrations, and Patient Consents

This retrospective cohort analysis was approved by the institutional review board of Emory University, and a complete waiver of consent was granted.

Data Availability

On request, anonymized data will be made available to qualified investigators as subject to ethics board approval.

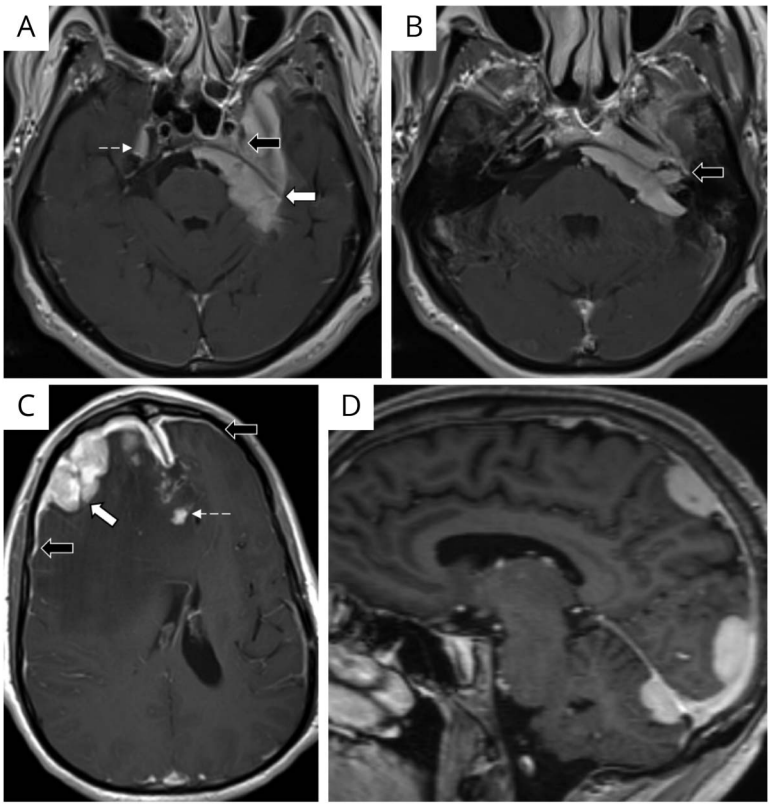
Results

Of the 215 patients with neurosarcoidosis evaluated from January 1, 2011, to August 12, 2021, 37 (37/215, 17.2%) were found to have pachymeningitis as a manifestation of their neurologic disease. Eleven of these patients did not have pathologic confirmation of sarcoidosis and thus were excluded from the study by design, resulting in a final cohort number of 26 patients (26/215, 12.1%) with biopsy-proven sarcoidosis with pachymeningitis. Two patients included were previously reported in a cohort describing the effects of neurosarcoidosis on the cauda equina.[16]

Patient Characteristics

The median age of onset was 43.5 years (range 22.0–70.0 years) with most patients not having a known diagnosis during the neurologic presentation (20/26, 76.9%). Of this group, 12 (46.2%) were diagnosed with neurosarcoidosis before the discovery of systemic sarcoidosis, 7 (26.9%) were diagnosed concurrently with systemic and neurologic sarcoidosis, and 1 (3.8%) was diagnosed with isolated neurosarcoidosis. Most of the patients were African American (20/26, 76.9%) and male (16/26, 61.5%). Half were classified as having "definite" neurosarcoidosis (confirmed by CNS biopsy), and the remainder were "probable" classifications (systemic sarcoidosis confirmed by non-CNS pathology). Of the 13 patients undergoing CNS biopsies, sarcoidosis was pathologically confirmed in 9 meningeal lesions and 4 brain parenchymal lesions. Hilar or mediastinal lymphadenopathy (21/26, 80.8%) and pulmonary disease (15/26, 57.7%) were

Figure 2 Radiographic Examples of Pachymeningitis Due to Sarcoidosis (Part 2)



(A) Axial T1 postcontrast: mass-like pachymeningeal thickening along the medial left middle cranial fossa extends into the left Meckel cave (black arrow) and involves both sides of the tentorium (white arrow). Note pachymeningeal thickening also involving the right Meckel cave (dash white arrow). (B) Axial T1 postcontrast: mass-like pachymeningeal thickening extends inferiorly along the left cerebellopontine angle extending into the left internal auditory canal (black arrow). (C) Axial T1 postcontrast: right frontal convexity dural-based mass with homogeneous enhancement (white arrow). Associated pachymeningeal thickening and enhancement along right frontoparietal convexity and left frontal convexity (black arrows). Note nodular leptomeningeal enhancement at the interhemispheric fissure (dashed white arrow). Right frontal parenchymal edema and mass effect resulting in leftward subfalcine herniation. (D) Sagittal T1 postcontrast: multifocal dural-based masses along the posterior cerebral falx and tentorium. These were initially believed to represent meningiomas.

the most common systemic manifestations. Approximately one-third (9/26, 34.5%) of patients had evidence for sarcoidosis elsewhere in the head and neck (orbits, salivary glands, and sinuses). Most (10/13, 76.9%) of the patients undergoing direct neural biopsies had evidence for extraneural sarcoidosis. Additional patient characteristics are summarized in Table 1.

Clinical Manifestations

Detailed data regarding clinical manifestations are summarized in Table 2. Symptoms related to pachymeningitis were the primary reason for presentation in 20/26 (76.9%) patients but were secondary to other forms of neurosarcoidosis in 6 (23.1%) cases, including myelitis (2), optic neuritis (2), hypophysitis (1), and widespread leptomeningitis (1). Pachymeningitis was symptomatic, however, in 23/26 (88.5%). The median modified Rankin scale (mRS) score at presentation was 2.0 (SD 1.0, range 1–4). In those with a known acuity of presentation (24 patients), symptoms were chronic (>28 days) for most of the patients (17/24, 70.8%) with a median estimated delay of presentation of 90 days (range 1–720 days). Of the 3 patients presenting hyperacutely, all were secondary to seizures. Headache was the most common symptom, being present in 19/26 (73.1%). In those 19, the location of headache was specified in 12 patients and was found to be in an anatomic distribution referable to the pachymeningitis in 9/12 (75.0%). At least 1 feature potentially suggestive of raised intracranial pressure (nausea, emesis, awakening from sleep, positional changes) was present in 6/26 (23.1%) patients. Intracranial hypertension was confirmed by opening pressure on lumbar puncture in only 1 of these 6 patients, and radiographic features suggestive of intracranial hypertension (herniation and hydrocephalus) was found in another 2 of these 6 patients. Specifics regarding responsiveness of headache to analgesics and steroids were limited for this portion of the cohort, but 5/8 (62.5%) were reported as responding to analgesics and 11/13 (84.6%) reported as responding to steroids.

Seizures occurred in 7/26 (26.9%) with most (6/7, 85.7%) occurring in the setting of either convexal (4/7, 57.1%) and/or falcine (5/7, 71.4%) pachymeningitis. The 1 exception was pachymeningitis in the middle cranial fossa. Evidence of edema in the brain cortex subjacent to the pachymeningitis was seen in 6/7 (85.7%) cases. Seizures were present in 6 of the 13 (46.2%) patients with brain edema underlying areas of pachymeningitis. Only 1/13 patients without radiographic evidence of brain edema had seizures (7.7%). Almost all seizures were controlled with a single antiepileptic drug (6/7, 85.7%).

Compressive cranial neuropathies were present in 12 patients (12/26, 46.2%) with the following nerves affected: optic (9), vestibulocochlear (2), oculomotor (1), trigeminal (1), and

Table 1 Patient Characteristics

Age, y, median	43.5
Sex (n = 26), n (%)	
Male	16 (61.5)
Female	10 (38.5)
Race/ethnicity (n = 26), n (%)	
African American	20 (76.9)
White	5 (19.2)
Asian Indian	1 (3.8)
Diagnosis of neurosarcoidosis (n = 26), n (%)	
Presystemic disease	12 (46.2)
Concurrent with systemic disease	7 (26.9)
Postsystemic disease	6 (23.1)
Isolated neurosarcoidosis	1 (3.8)
Systemic organ involvement (n = 26), n (%)	
Hilar/mediastinal lymph nodes	21 (80.8)
Pulmonary	15 (57.7)
Other lymph nodes	9 (34.6)
Sinuses	7 (26.9)
Skin	6 (23.1)
Cardiac	5 (19.2)
Bone	4 (15.4)
Liver	3 (11.5)
Salivary glands	3 (11.5)
Spleen	3 (11.5)
Orbits	2 (7.7)

Table 2 Clinical Manifestations of Pachymeningitis Due to Sarcoidosis

Acuity of presentation (n = 24), n (%)	
Hyperacute (<1 d)	3 (12.5)
Acute (1–7 d)	2 (8.3)
Subacute (8–28 d)	2 (8.3)
Chronic (>28 d)	17 (70.8)
mRS score, median (range)	2.0 (1–4)
Cranial symptoms/signs (n = 26), n (%)	
Headache	19 (73.1)
Seizures	7 (26.9)
Cranial neuropathies	12 (46.2)
Cognitive dysfunction	6 (23.1)
Weakness	5 (19.2)
Numbness	5 (19.2)
Anosmia	3 (11.5)
HPA dysfunction	3 (11.5)
Ataxia	1 (3.8)
Bladder dysfunction	1 (3.8)

Abbreviations: HPA = hypothalamic pituitary adrenal axis; mRS = modified Rankin scale.
The denominator is reduced from 26 when data for a particular variable were missing or unclear. The clinical manifestations of spinal pachymeningitis and the breakdown of cranial neuropathy types are discussed in the main text.

abducens (1). Additional symptoms and signs of cranial pachymeningitis included cognitive dysfunction (confusion, disorientation, and personality changes) in 6 (6/26, 23.1%), weakness and numbness (5/26 each, 19.2%), anosmia (3/26, 11.5%), hypopituitarism (3/26, 11.5%), and altered level of consciousness (1/26, 3.8%). Visual dysfunction not attributable to coexisting optic nerve disease was present in 3 (3/26, 11.5%) patients. Aphasia and neglect were not observed in the cohort. Spinal pachymeningitis was observed only in 1 patient (1/26, 3.8%) who presented with symptoms typical of myelopathy (weakness with spasticity, gait impairment, and bowel and bladder dysfunction).

Radiographic Findings

Illustrative examples of typical radiographic findings in pachymeningitis due to sarcoidosis are shown in Figures 1 and 2. All patients (26/26, 100.0%) had radiographic evidence of cranial pachymeningitis. Lesions were single and confluent in 11/26 (42.3%) and multifocal in a spatially separate fashion in 15/26 (57.7%). No diffuse holocephalic lesions were seen. Edema in the subjacent brain was present in 13/26 (50.0%). Two lesions (2/26, 7.7%) were large enough to cause subfalcine cerebral herniation. Information regarding lesion morphology and contrast enhancement patterns was available in 25 patients. A nodular morphology was found in 23/25 (92.0%); the remainder (2/25, 8.0%) demonstrated a smooth focal expansion of the dura. Contrast enhancement was homogeneous in 24/25 (96.0%), while an additional 4 patients (4/25, 16.0%) exhibited a rim-enhancing pattern. A dural tail was present in at least 1 pachymeningeal lesion in 4/26 (15.4%) patients.

The dura of the falx cerebri was the most common structure affected (16/26, 61.5%), with its anterior portion affected in 10/26 (38.5%) and its posterior portion in 7/26 (26.9%). Other dural structures commonly affected included those of the anterior cranial fossa (12/26, 46.2%), middle cranial fossa (12/26, 46.2%), and the tentorium cerebelli (12/26, 46.2%). Pachymeningitis overlying the cerebral convexities was present in 11/26 (42.3%) with the frontal region being most commonly affected (10/26, 38.5%). Additional details regarding the radiographic features of cranial pachymeningitis are summarized in Table 3. Coexisting cranial leptomeningitis

Table 3 Radiographic Findings of Cranial Pachymeningitis

Locations of dural involvement (n = 26), n (%)	
Falx cerebri	16 (61.5)
Anterior fossa	12 (46.2)
Middle fossa	12 (46.2)
Tentorium cerebelli	12 (46.2)
Cerebral convexities	11 (42.3)
Frontal	10 (38.5)
Parietal	4 (15.4)
Temporal	2 (7.7)
Occipital	0 (0.0)
Cavernous sinus	6 (23.1)
Optic canal	6 (23.1)
Clivus	4 (15.4)
Cerebellar convexity	4 (15.4)
Internal auditory canal	3 (11.5)
Meckel cave	3 (11.5)
Foramen magnum	2 (7.7)
Distribution of pachymeningeal lesions (n = 26), n (%)	
Multifocal	15 (57.7)
Unifocal	11 (42.3)
Diffuse	0 (0.0)
Lesion morphology (n = 25), n (%)	
Nodular	23 (92.0)
Smooth	2 (8.0)
Lesion enhancement patterns (n = 25), n (%)	
Homogeneous	24 (96.0)
Rim-enhancing	4 (16.0)
Associated features (n = 26), n (%)	
Subjacent parenchymal edema	13 (50.0)
Herniation (subfalcine)	2 (7.7)
Hydrocephalus	2 (7.7)
Nondural structures involved (n = 26), n (%)	
Leptomeninges	12 (46.2)
Cranial nerves	9 (34.6)
Cerebral parenchyma	6 (23.1)
Pituitary/stalk	6 (23.1)
Hypothalamus	5 (19.2)
Brainstem parenchyma	3 (11.5)
Cerebellar parenchyma	3 (11.5)

Details related to the 1 case of spinal pachymeningitis are presented in the main text. The denominator is reduced from 26 when data for a particular variable were missing or unclear. Patterns of enhancement were not mutually exclusive, and both types of enhancement patterns could be seen in the same patient.

was present in less than half (12/26, 46.2%). Cerebral hemispheric (6/26, 23.1%), brainstem (3/26, 11.5%), and cerebellar (3/26, 11.5%) parenchymal disease were relatively uncommon. Parasellar structures (optic canal, cavernous sinus, pituitary and its stalk, and the hypothalamus) were commonly involved (11/26, 42.3%, see Table 3 for individualized details).

A total of 11 patients underwent some form of spinal cord imaging: cervical 10/26 (38.5%), thoracic 6/26 (23.1%), and lumbosacral 7/26 (26.9%). Only 1 patient was found to have spinal pachymeningitis (1/11, 9.1%). This single lesion was located in the thoracic segment of the intradural extramedullary compartment, less than the length of 1 vertebral body in its longitudinal axis, and associated with compression and edema of the adjacent spinal cord. Additional neuroinflammatory findings included spinal leptomeningitis in 4/11 (36.4%), cervical cord parenchymal disease in 4/10 (40.0%), thoracic cord parenchymal disease in 2/6 (33.3%), and lesions of the conus medullaris in 1/7 (14.3%) and cauda equina in 2/7 (28.6%).

Ancillary Investigations

Testing of the CSF was conducted in 16 patients, of which results were known in 14. A leukocytosis (>5 cells/mm^3, range 8–1,000 cells/mm^3) was present in 9/14 (64.3%), all of which were lymphocyte predominant. Protein was elevated in 10/14 (71.4%, range 49–254 mg/dL). Hypoglycorrhachia was present in 2/12 (16.7%). CSF-restricted oligoclonal bands were present in 1/3 (33.3%) tested, while IgG index was normal in all 5 patients tested. CSF angiotensin converting enzyme (ACE) was normal in 5 patients undergoing testing.

CSF was analyzed according to the presence or absence of concurrent leptomeningitis. In those without leptomeningitis (6 patients), CSF findings included a pleocytosis in 3/6 (50.0%, range 8–13 cells/mm^3), elevated protein in 3/6 (50.0%, range 49–57 mg/dL), and hypoglycorrhachia in 0/6 (0.0%). In those with concurrent leptomeningitis (8 patients), CSF findings included a pleocytosis in 6/8 (75.0%, range 8–1,000 cells/mm^3), elevated protein in 7/8 (87.5%, range 65–254 mg/dL), and hypoglycorrhachia in 2/8 (25.0%).

Serum angiotensin converting enzyme levels were elevated in 4/20 (25%) tested, all of whom had extraneural sarcoidosis

Table 4 Response to Treatment

Regimen	Treatment courses	Improved	Failed	Success rate, %
Adalimumab	1	1	0	100.0
Infliximab	7	6	1	85.7
Methotrexate	12	6	6	50.0
Rituximab	5	2	3	40.0
Mycophenolate mofetil	7	2	5	28.6
Azathioprine	6	1	5	16.7
Cyclophosphamide	1	0	1	0.0

involving the hilar and mediastinal lymph nodes and lungs. Serum calcium levels were normal in all tested (23/23). Erythrocyte sedimentation rate and C-reactive protein were elevated in 13/16 (81.3%) and 7/15 (46.7%), respectively. Serum IgG4 levels were tested in 5 patients, only one of which had a value exceeding 135 mg/dL (1/5, 20%).

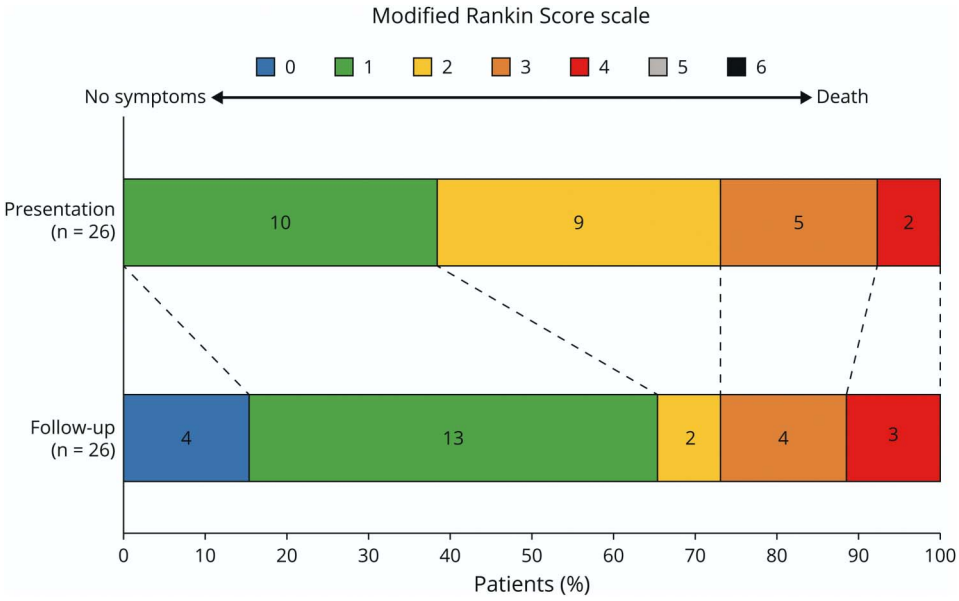
Treatment

Twenty-five (25/26, 96.2%) patients received steroid treatment, including 11 initially with IV methylprednisolone (typically 1,000 mg daily for 3–5 days). All 25 were treated with prednisone, most commonly at an initial starting dose of 60 mg daily with tapering over several months depending on clinical response. Twenty-two (22/25, 88.0%) had symptomatic improvement. Of the remaining 3 patients, 2 did not adhere to the prescribed prednisone taper. The details of the third case were insufficient to judge response to treatment.

Twenty-three (23/26, 88.5%) patients were treated with a first line of steroid-sparing immunosuppression, including 18 (18/26, 69.2%) with standard nonbiologic immunosuppressants (methotrexate, azathioprine, and mycophenolate mofetil). Ten (10/26, 38.5%) subsequently required treatment with a second line of immunosuppression, and 5 (5/26, 19.2%) required a third line of immunosuppression. One patient (1/26, 3.8%) required 5 lines of immunosuppression to achieve disease remission.

Tumor necrosis factor alpha inhibitors (TNF inhibitors, to include infliximab and adalimumab) were the most successful forms of treatment observed; 7/8 (87.5%) treatment courses resulted in disease remission despite these agents being used as second line or later in 6/8 (75%) instances. Disease remission occurred in 6/12 (50%) cases on methotrexate monotherapy. Additional treatment details regarding other agents are summarized in Table 4.

Figure 3 Trend in Modified Rankin Scale Score From Disease Nadir to the Time of Last Follow-up



A Long-term Follow-up

Patients were followed up clinically for a median period of 48 months (range 9–225). The median modified Rankin scale score at the last follow-up was 1 (range 0–4, SD 1.3). Overall, only 4 patients (4/26, 15.4%) completely improved to a fully asymptomatic state with no residual deficits. Most of the patients (15/26, 57.7%) partially improved with a median mRS score of this group of 1.0 (range 1–4). Two patients (2/26, 7.7%) stabilized at their disease nadir, and 5 patients (5/26, 19.2%) worsened by the time of the last follow-up. No patients died. Residual symptoms included symptoms referable to the cranial nerves (11/26, 42.3%), gait impairment (9/26, 34.6%), headache (5/26, 19.2%), cognitive impairment (4/26, 15.4%), weakness (4/26, 15.4%), urinary dysfunction (3/26, 11.5%), dizziness (2/26, 7.7%), and sensory loss (2/26, 7.7%). Persistent visual dysfunction from optic neuropathy (7/26, 26.9%) was the most common residual symptom from the involvement of the cranial nerves.

The median period of radiographic surveillance with MRI was 54 months (range 3–222 months). Imaging abnormalities (pachymeningeal thickening and enhancement) completely resolved in only 4 patients (4/26, 15.4%), but features of inflammation (degree of contrast enhancement, and size of the pachymeningeal lesion) were improved in another 12 patients (12/26, 46.2%). Imaging abnormalities were stable on follow-up imaging compared with those taken at disease nadir in 3/26 patients (11.5%). Imaging from the remaining 7 patients (7/26, 26.9%) had worsened by the time of last imaging.

Seven patients (7/26, 26.9%) experienced relapses in the form of pachymeningitis with a median time to the first relapse of 15 months (range 3–60 months). Three patients experienced a single relapse, whereas the remainder had 2 or more relapses (2 with 2 relapses and the third with 4 relapses).

Discussion

Pachymeningitis carries an impressive differential diagnosis of neoplastic, infectious, and inflammatory etiologies, and among inflammatory agents, sarcoidosis should always be considered as a likely suspect.[17] In this report, we detailed the clinical and radiographic features of 26 patients with pachymeningitis due to sarcoidosis and outlined their response to treatment and last outcomes after a long-term follow-up. Key findings of the study include the following: (1) frequent coinvolvement of other head structures by sarcoidosis (salivary glands, sinuses, and orbits), (2) headaches, cranial neuropathies, and seizures being the primary clinical manifestations, (3) a predilection for lesions to affect the dura of the falx cerebri, anterior and middle cranial fossae, and tentorium cerebelli, (4) refractoriness to standard immunosuppressants with TNF inhibitors not uncommonly needed, and (5) good long-term prognosis for recovery with potential for relapse in one-fourth of patients.

Pachymeningeal thickening and enhancement can be a challenging diagnosis to make because the potential causes are myriad and their treatments highly divergent.[17] The experience of our cohort emphasizes that difficulty because half of the included patients required direct CNS biopsies to achieve a confident diagnosis, which is an unusually high percentage for the neurosarcoidosis literature, even despite all but one of these patients having evidence for systemic sarcoidosis.[8,18,19] We suspect that the elevated risk for neoplasia in the differential diagnosis of dural-based lesions played a primary role in efforts to achieve a higher degree of diagnostic certainty in this particular clinicoradiographic phenotype of neurosarcoidosis. Potential clues, however, that neurosarcoidosis could be the cause included accompanying evidence of leptomeningitis, brain and brainstem parenchymal disease, and involvement of the hypothalamus and pituitary stalk.

The leptomeningitis of neurosarcoidosis is commonly held to have a predilection for the basal cisterns.[9,14] We did not find pachymeningitis to behave similarly in our cohort. Although this study clearly demonstrates the capacity for granulomatous inflammation to affect all dural structures, supratentorial pachymeningitis was most common, particularly of the falx cerebri with or without extension into the anterior cranial fossa or along the tentorium cerebelli. Pachymeningitis of the middle cranial fossa was also a common feature. Although the reason behind the propensity for pachymeningitis to affect free-floating dural structures (falx cerebri and tentorium cerebelli) remains to be clarified, sarcoidosis tends to invade cranial structures along perivascular routes.[12,20] The falx and tentorium are highly vascular structures and are situated in close approximation to 3 major venous sinuses, the superior and inferior sagittal sinuses and the straight sinus, which may increase their susceptibility to form pachymeningeal granulomatous deposits. In addition, the CNS has been shown recently to harbor a lymphatic system in the dural meninges, including in regions proximate to the dural venous sinuses.[21-23] The pachymeningitis of sarcoidosis may essentially represent the CNS equivalent of lymphadenopathy seen elsewhere in the body in sarcoidosis because the disease is highly lymphotropic.

Seizures occurred in 26.9% of the cohort, all in patients with supratentorial pachymeningitis, particularly of the falx and dura overlying the cerebral convexities. By contrast, seizures are less commonly observed to be a manifestation of neurosarcoidosis in general cohorts where their frequency is reported between 4% and 17%.[18,19,24] We suspect the likely mechanisms of epileptogenesis in pachymeningitis due to sarcoidosis are compression and deformation of the adjacent cerebral cortex. Edema of the subjacent brain, likely signifying more significant distortion to the underlying cortical architecture, was a major marker of seizure risk because roughly half of these patients went on to develop seizures requiring treatment with antiepileptic drugs. Conversely, seizures were only rarely observed in those without associated brain edema.

This series shows that sarcoidosis-associated pachymeningitis requires treatment beyond an initial round of prolonged steroid therapy. Almost all (23/26, 88.5%) required an initiation of steroid-sparing immunosuppression in an effort to achieve disease remission, which we defined as clinical symptomatic improvement (supported by improving or stable MRI findings when available). Furthermore, this form of meningitis proved difficult to eliminate because many of the patients went on to a second line of immunosuppression and 11/26 (42.3%) were treated with agents usually reserved for more severe disease (TNF inhibitors, cyclophosphamide, and rituximab). As has been shown for other forms of neurosarcoidosis, TNF inhibitors (infliximab and adalimumab) were particularly successful in the treatment of medically refractory pachymeningitis (remission achieved in 7/8 treatment courses in this cohort).[25-27]

The cohort ultimately fared well over 4 years of clinical observation with the median mRS score at the last follow-up being 1.0. Figure 3 shows the trend in mRS score from disease nadir to the time of last follow-up with most of them (17/26, 65.4%) reaching an mRS score of 1 or better by the end of the study period, consistent with no persistent disability in the long-term. This correlates well with most of them (16/26, 61.5%) also experiencing radiographic improvement of their pachymeningitis. The factors allowing for such significant improvement over disease nadir are likely rooted in this form of neurosarcoidosis being predominantly extra-axial with lower rates of associated intraparenchymal disease and therefore lower attendant risks for permanent damage to eloquent brain tissue. As has been observed in one other study, residual symptoms from cranial neuropathy, particularly optic neuropathy, were still common and likely reflect their vulnerabilities to meningeal inflammation because they traverse the dura en route to their end organs.[13]

This study, in combination with others covering the spectrum of rheumatologic effects on the pachymeninges, highlights dural inflammation potentially occurring more commonly in men. Most of the individuals in our cohort (61.5%) were men despite sarcoidosis occurring twice as commonly in women.[28] Rheumatoid arthritis also occurs twice more commonly in women on a systemic scale but is male predominant (57%) in its pachymeningeal form.[29,30] Granulomatosis with polyangiitis occurs in equal portions in men and women, but, interestingly, the frequency shifts heavily to men (80%) when the pachymeninges are involved.[30,31] IgG4-related disease (IgG4-RD) does generally occur more commonly in men, and its primary neurologic manifestation is hypertrophic pachymeningitis.[32,33] Why the meninges may be more susceptible to inflammation in men is unclear but notable, given systemic and neurologic autoimmune diseases are generally more common in women.

IgG4-related pachymeningitis is a topic of increasing interest because it seems that pachymeningitis is the principal CNS manifestation of IgG4-RD.[34] Of importance, available data suggest that serum ACE concentrations and serum IgG4 levels are insensitive for the diagnoses of the neurologic forms of sarcoidosis and IgG4-RD, respectively and, moreover, that elevated serum IgG4 levels are insufficient in isolation to establish a diagnosis of IgG4-RD.[11,34-36] Both sarcoidosis and IgG4-RD are clinical diagnoses supported by nonspecific findings of ancillary tests, and clinicians must carefully ensure that diagnoses are rendered only in the proper clinical context. As an example, in our cohort, 5 patients were screened for serum IgG4 levels, including one of which (1/5, 20%) who had a value exceeding twice the upper limit of normal.[35] This patient had biopsies confirmatory of noncaseating granulomas from 2 different nonneural organs and responded successfully to combination methotrexate and infliximab treatment. In the future, studies on neurosarcoidosis-related pachymeningitis should include more comprehensive testing for serum IgG4 to improve our understanding in how useful this test is in differentiating the 2 diseases, especially because one-third of our patients also exhibited sarcoidosis of the head and neck in a manner that mimics one of the typical distributions of IgG-related disease.[37]

We included only patients with pathologic confirmation of sarcoidosis in this series to maximize diagnostic certainty in the pachymeningeal lesions being granulomatous in origin. Excluding patients who may belong in the cohort does have the potential to affect the direction and magnitude of the study findings, but we deemed it a necessary trade-off, given the vast differential diagnosis of pachymeningitis. As a retrospective cohort study, the approach to evaluation and management was nonstandard, which reduces our ability to understand the full scope of the disease (especially regarding the extent of neuraxis MRI coverage) and precise response to its treatment (given no uniform approach to initial agent selection and subsequent treatment escalation).

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Pressley A. Chakales, MD	Emory University School of Medicine, Atlanta, GA	Major role in the acquisition of data; analyzed the data; drafted the article for intellectual content; and revised the article for intellectual content

Continued

Appendix *(continued)*

Name	Location	Contribution
Max C. Herman, MD	Emory University School of Medicine, Atlanta, GA	Major role in the acquisition of data; revised the article for intellectual content; creation of figure
Ling Chen Chien, MD	Emory University School of Medicine, Atlanta, GA	Creation of figures; revised the article for intellectual content
Spencer K. Hutto, MD	Emory University School of Medicine, Atlanta, GA	Designed and conceptualized study; major role in the acquisition of data; analyzed the data; drafted the article for intellectual content; study supervision; creation of tables

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