Spinal rheumatoid meningitis: Clinicopathological Insights of rheumatoid nodule beyond the joint

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Abstract

Rheumatoid meningitis (RM) is a rare extra-articular manifestation of rheumatoid arthritis (RA), characterized by pachymeningitis and/or leptomeningitis. Cranial RM were more common, while spinal involvement is very rare, particularly in seronegative RA. We described a 56-year-old Thai woman with seronegative RA who presented with acute bilateral leg weakness, gait instability, and urinary retention. MRI revealed circumferential spinal dural thickening and enhancement, consistent with hypertrophic pachymeningitis and leptomeningitis. Histopathology confirmed a rheumatoid nodule with mixed inflammatory patterns. Corticosteroid therapy led to complete clinical and radiological resolution. This case highlights an unusual presentation of spinal pachymeningitis as a neurological manifestation of seronegative RA, which may mimic other meningitides. RM should be considered in RA patients with unexplained myelopathy, regardless of serostatus, as early diagnosis and prompt immunosuppression can result in excellent outcomes.

Keywords: rheumatoid arthritis, rheumatoid nodule, pachymeningitis, granulomatous inflammation

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Introduction

Rheumatoid arthritis (RA) is the most common chronic systemic autoimmune joint inflammatory disease, primarily affecting multiple sites of synovial joints. However, it also exhibits extra-articular manifestations, such as interstitial lung disease, scleritis or episcleritis, peripheral neuropathy, and rheumatoid nodules, which commonly affect the tendons. These presentations are correlated with rheumatoid factor (RF) and/or anti-citrullinated protein antibodies (anti-CCP) positivity, as well as a longer duration of uncontrolled disease activity[1,2]. Central nervous system (CNS) involvement in RA is rare and is often associated with other extra-articular features[3]. Among the neurologic manifestations, rheumatoid meningitis (RM) is exceptionally uncommon and poses a diagnostic challenge. It is defined as inflammation of the dura mater, which may extend to the leptomeninges (arachnoid and pia) and even adjacent brain parenchyma[1]. CNS pathology in RM spans a spectrum including pachymeningitis, rheumatoid nodules, and vasculitis, with mixed patterns sometimes observed[4]. Histopathologic evaluation through biopsy or autopsy remains crucial for diagnosis. Understanding the histologic diversity and the clinical-radio-pathology correlation is essential, particularly in patients presenting with neurologic symptoms in the setting of established RA.

Case presentation

A 56-year-old Thai woman with a 5-year history of chronic symmetric polyarthritis involving the knees, wrists, and ankles had multiple hospital visits for pain relief by using nonsteroidal anti-inflammatory drugs. One year before admission, the joint symptoms had worsened, prompting self-medication with low-dose oral dexamethasone. She presented with acute bilateral lower limb weakness and gait instability of 12 hours duration with acute urinary retention. Neurologic symptoms developed abruptly, following a 2-week history of non-positional dull thoracic back pain. The physical examination revealed synovitis of both knees, left wrist, and both ankles, with no joint deformities or extra-articular features of RA. The neurologic examination demonstrated lower extremity weakness (Iliopsoas), diminished vibration sense in the legs, and urinary retention, but preserved upper limb function, intact cranial nerves, and pinprick sensation. The initial laboratory investigations showed a normal complete blood count but marked elevation of inflammatory markers, with an erythrocyte sedimentation rate (ESR) of 83 mm/hr and a C-reactive protein (CRP) level of 144 mg/L. Despite the negativity of RF and anti-CCP, we observed an increase in RF from 2.5 to 8.9 IU/ml within 5 years. Seronegative RA was diagnosed by a typical radiographic finding of both hands that demonstrated juxta-articular osteopenia, with marginal erosions at the metacarpophalangeal and proximal interphalangeal, and wrist joints bilaterally (Figures 1A and 1B).

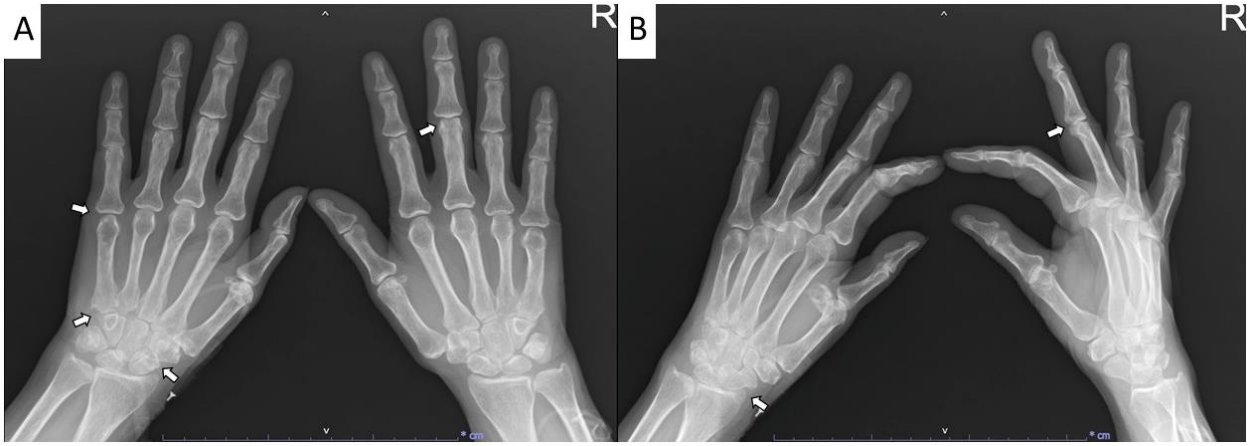

Figure 1 Plain AP and oblique views of both hands showed a juxtaaricular osteopenia, joint space narrowing at the metacarpophalangeal, proximal interphalangeal, and left wrist joints. Marginal erosions were observed at the left 5th carpometacarpal, 5th metacarpophalangeal, right 3rd proximal interphalangeal, and right wrist joints: these findings are compatible with rheumatoid arthritis.

The spinal magnetic resonance imaging (MRI) revealed circumferential, irregular dural thickening and enhancement extending from C3 to T7 levels, consistent with hypertrophic pachymeningitis. The dural thickening was most severe at the T1–T2 level, causing compressive myelopathy (Figure 2A). Additionally, abnormal leptomeningeal enhancement was observed along the conus medullaris and cauda equina roots (Figure 2B). Based on MRI findings, which were consistent with hypertrophic pachymeningitis and leptomeningitis, a comprehensive diagnostic investigated was initiated to identify the underlying etiology, given that pachymeningitis may result from infectious, neoplastic, or autoimmune causes. A lumbar puncture was performed, and it revealed hazy cerebrospinal fluid (CSF) with lymphocytic pleocytosis (148 cells/mm^3; 98% mononuclear), markedly elevated protein (2,270 mg/dL), and low glucose (32 mg/dL, with serum glucose 78 mg/dL). Microbiologic studies, including Acid-Fast Bacilli (AFB) stain, PCR, and cultures for tuberculosis (TB) and fungi, were negative. CSF cytology showed no malignant cells, and CSF adenosine deaminase was mildly elevated at 19 U/L.

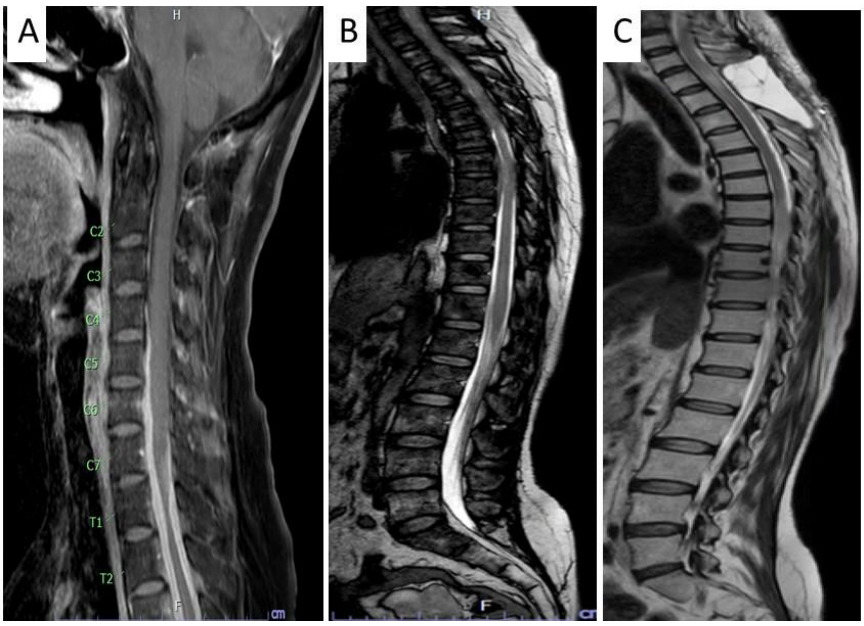

Figure 2A: The sagittal T1-Sagittal T1W showed a marked circumferential irregular dural thickened enhancement, most severe at the T1-T2 level, superior extension up to about the C3 level, resulting in severe mass effect and myelopathy.

Figure 2B: The sagittal T2W showed a leptomeningeal enhancement along the conus medullaris and caudal equina root.

Figure 2C: Demonstrated a complete resolution of previously seen dural thickening and leptomeningeal enhancement after 1 month of corticosteroids

The patient underwent a laminectomy at the T1–T2 level to decompress the spinal cord at the site of maximal pachymeningeal thickening and to obtain tissue for definitive diagnosis. Intraoperatively, there was marked thickening of the ligamentum flavum and dura mater, along with a 2-mm thickened whitish to yellowish subdural tissue. The tissue stain and cultures for aerobic organisms, tuberculosis (TB), and fungi were negative. Histopathological examination revealed a few palisading granulomas, composed of palisading epithelioid histiocytes surrounding necrotic foci that were similar to rheumatoid nodules in the subdural tissue (Figure 3A) and severe chronic inflammation involving epidural tissues without demonstrating features of vasculitis or malignancy (Figure 3B). Despite the immunohistochemical staining demonstrating up to 200 IgG4-positive plasma cells per high-power field (Figures 3D), the staining also showed a large number of IgG-positive plasma cells (Figures 3C), with an IgG4 to IgG ratio of approximately 10%, which is below the threshold for IgG4-related disease. There was no evidence of light chain restriction.

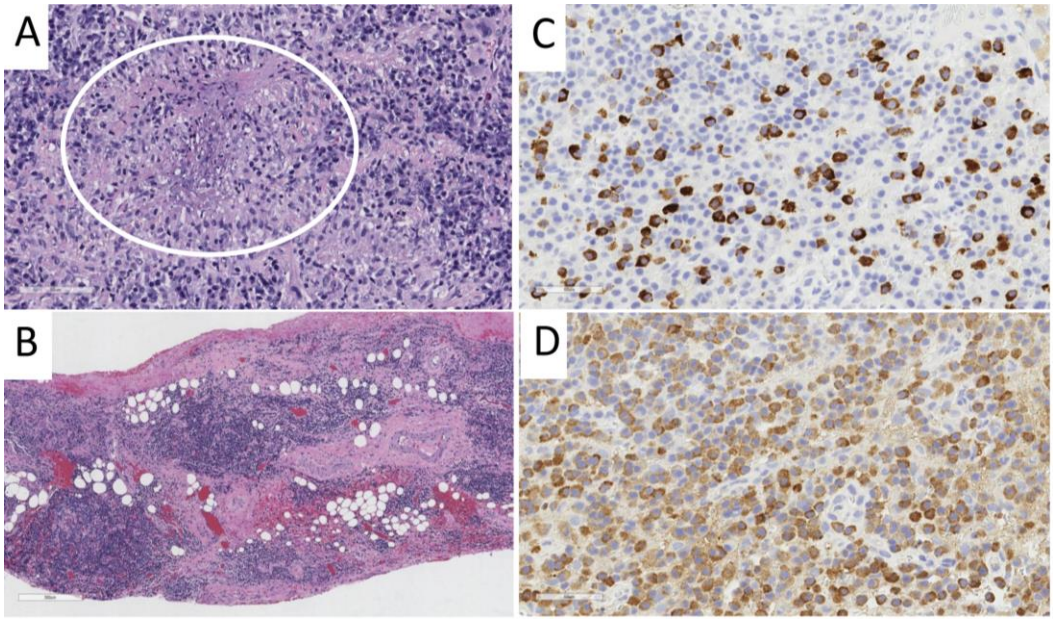

Figure 3 The tissue histopathology from a laminectomy

3A: Subdural tissue (x200) showed severe chronic inflammation with palisading epithelioid histiocytes surrounding necrosis (white circle).

3B: Epidural tissue (x100) showed severe chronic inflammation.

3C: Immunohistochemistry showed an abundance of IgG plasma cells

3D: Showed IgG4 plasma cell up to 200/HPF with IgG4/IgG ratio <10%

The final diagnosis was seronegative RA with spinal RM. The patient was treated initially with intravenous methylprednisolone 1 g/day for three consecutive days, followed by oral prednisolone 30 mg/day with subsequent tapering. Methotrexate was initiated at 7.5 mg/week and titrated to 15 mg/week. Within one month of treatment, the patient showed significant clinical improvement: resolution of sensory ataxia, recovery from acute urinary retention, and independence from assistive devices, as well as the normalization of the inflammatory markers. The follow-up MRI was performed six weeks later, which demonstrated complete resolution of previously noted cervicothoracic pachymeningitis. Mild residual myelopathy was observed at T1–T2 and T7–T8 levels and improved leptomeningeal enhancement along the conus medullaris and caudal equina root (Figure 2C).

Discussion

Our case underscores two atypical features of RA. Firstly, an extra-articular disease affecting an unusual organ in seronegative RA is uncommon when compared to seropositive RA. Secondly, a very rare extra-articular manifestation of spinal cord involvement, particularly when associated with RM. The histopathology revealed patterns consistent with typical rheumatoid nodules and mixed patterns, reflecting focal macrophage, inflammatory cytokines, and B-cell activation—hallmark processes in RA pathogenesis.

RM is rare but increasingly recognized. Although approximately 100 cases have been reported, a systematic review found preceding articular manifestations in only 27.4% of cases[2], with the majority classified as rheumatoid meningitis sine arthritis (RMSA)—characterized by pachymeningitis on imaging and anti-CCP positivity without prior joint symptoms[5]. For relevance to our case, we focus on typical RM with preceding arthritis. Nonetheless, RMSA supports the theory that RM may arise from active inflammation, local protein citrullination, and anti-CCP synthesis, rather than from disease-modifying antirheumatic drugs (DMARDs) exposure. From the review literature, the clinical manifestations of RM vary

with lesion location; cranial involvement is most common, presenting with focal neurological deficits (64.6%), and approximately half of patients experience systemic symptoms, episodic headache, or neuropsychiatric features[2]. Motor and sensory deficits or gait instability due to spinal involvement are rarely reported. A literature review identified three such cases, all RF-seropositive, summarized in Table 2[6-8]. Our patient's presentation—progressive lower limb weakness and gait instability due to isolated spinal RM following a long history of peripheral arthritis—was comparable to the case described by Duray et al[6].

Table 2: The reported cases of spinal rheumatoid meningitis from a review of the literature

Source	Presentation	Serology	MRI finding	Histology	Treatment
Duray et al.[6]	Paraplegia, cranial symptoms	RF+	Spinal meningeal enhancement	granulomatous meningitis with palisading histiocytes and focal necrosis	GCs and immunosuppressants
Hauge et al.[7]	Cord compression, sensory deficit at T6	RF+	Spinal pachymeningitis from T2 to T11	granulomatous: lymphocytes, plasma cells, epithelioid cells, fibrinoid material	Surgical decompression
Ishii et al.[8]	Gait disturbance, sensory loss	RF+	Subdural mass from T1 to T6	hypertrophic pachymeningitis without granuloma	Laminectomy high-dose GCs

GCs; glucocorticosteroids, RF; rheumatoid factor,T; thoracic level

While RM is most commonly associated with seropositive RA, with RF and/or anti-CCP antibodies present in nearly 90% of cases and often linked to poorly controlled, long-standing disease[1,2], several reports have described seronegative presentations similar to our patient[9-11]. We hypothesize that the underlying mechanism involves cellular immune activation—particularly macrophage-driven cytokine production—and focal autoantibody synthesis, as evidenced by abundant IgG plasma cell infiltration. In our case, despite negative serology, alternative inflammatory arthritis, such as psoriatic arthritis or spondyloarthritis, was excluded based on history and imaging. Definite peripheral joint erosions were present, and prior undocumented glucocorticoids (GCs) use may have contributed to persistent seronegativity.

Establishing an RM diagnosis requires exclusion of mimicking conditions and histopathological confirmation using a combination of typical imaging and histopathological findings of RM. Contrast-enhanced MRI is instrumental, revealing pachymeningeal involvement in 60% and leptomeningeal involvement in 82.7%[2]. Pachymeningitis most often affects the frontal convexity and falx, with "sugar-coated" leptomeningeal enhancement frequently congruent with these areas[12]. Elevated CSF protein may cause focal hyperintensity on FLAIR and restricted diffusion in the sulci, mimicking cortical stroke[12]. As RM can be disseminated, comprehensive imaging of both the brain and spinal cord is recommended. Clinically, pachymeningitis has been associated with headache and cranial neuropathies, whereas leptomeningitis—likely reflecting intrathecal IgG synthesis—has been linked to seizures, paresis, altered mental status, and gait disturbance[13].

Histopathological examination played a crucial role in excluding mimicking conditions and confirming RM. The lesions span a spectrum of inflammatory changes involving the dura, leptomeninges, and occasionally adjacent parenchyma. Across published case reports and series, histological confirmation was achieved in approximately 70–75% of cases[2]. Four principal patterns have been described: *chronic inflammation and fibrosis* – the most common finding in biopsy specimens, typically

characterized by lymphoplasmacytic infiltrates and fibrotic thickening of the dura. *Classic rheumatoid nodules* – featuring central fibrinoid necrosis with palisading histiocytes, these lesions are less frequently seen in biopsy but occasionally observed in autopsy or large excision samples. However, rheumatoid nodules were presented in less than half of those with histologic confirmation[4]. *Non-necrotising granulomatous inflammation* – lacking central necrosis, this pattern may mimic sarcoidosis or granulomatosis with polyangiitis (GPA) and may include scattered neutrophilic infiltrates. *Hypertrophic pachymeningitis (non-granulomatous)* – characterized by diffuse dural thickening with chronic inflammation, but without nodule or granuloma formation. Looking back at the histopathology reported in our patient, which revealed a combination of chronic inflammation and hypertrophic pachymeningitis, the gross tissue showed thickening of the dura mater, and the histology showed severe chronic inflammation in the epidural tissue and lymphoplasmacytic infiltrates of the dura. In addition, we highlight a less common pathology finding: classic rheumatoid nodules, characterized by palisading histiocytes and granulomatous inflammation. These findings support the hypothesis that multiple inflammatory mechanisms may underlie this condition.

In comparing RM to other inflammatory conditions involving the CNS, a few key features assist in differentiation: *IgG4-related disease (IgG4-RD)* – typically shows storiform fibrosis, obliterative phlebitis, a high IgG4/IgG-plasma cell ratio (>40%), and eosinophils can also be seen, none of which are characteristic of RM. *GPA* often features necrotizing granulomas and prominent vasculitis. In contrast, vasculitis is either absent or only focal in RM. Notably, the histological comparison further emphasizes the importance of distinguishing RM from its mimics, particularly when histological patterns are non-specific or overlap. Table 3 shows a comparison of histological features in RM and mimicking diseases.

Table 3: A comparison of histological features in rheumatoid meningitis and mimicking diseases.

Feature	Rheumatoid meningitis	IgG4-RD	Granulomatosis with polyangiitis
Lymphoplasmacytic infiltrate	*Present*	*Prominent*	Variable
Storiform fibrosis	Rare/minimal	*Characteristic*	Absent
Obliterative phlebitis	Absent	*Typical finding*	Absent
IgG4+/IgG+ ratio >40%	Low ratio (<10%)	*Yes (>40%)*	May be present (not diagnostic)
Eosinophilic infiltration	Absent	*Mild to moderate*	Rare
Necrotising granuloma	Occasionally (non-classic)	Absent	*Characteristic*
Vasculitis	Rare or focal	Absent	*Prominent*
Palisading histiocytes	*Present in nodules*	Absent	May be seen
Multinucleated giant cells	Rare	Absent	*Common*
Neutrophilic infiltrates	Occasional	Minimal	*Marked*

Elevated anti-CCP levels in CSF have been proposed as a potential diagnostic marker, particularly in patients unsuitable for biopsy[14,15]. The previous studies also found a marked evaluation of TNF-α, IL-1, and IL-6, which are the inflammatory cytokines that are crucial to the pathophysiology of RA[16,17]. Using these biomarkers in combination with MRI findings—typically demonstrating dural or leptomeningeal enhancement—in the context of chronic arthritis, especially seropositive RA, these results should prompt consideration of RM in the differential diagnosis. However, further studies are required to validate the diagnostic utility of this approach.

Although no standardized treatment regimen for RM exists, GCs remain the mainstay of initial therapy, typically administered as high-dose oral or intravenous pulse regimens. Adjunctive

immunosuppressants, such as methotrexate, cyclophosphamide, azathioprine, and biologic agents, have also been reported[5,18,19]. Most patients improve with treatment, and over half achieve complete recovery; however, relapse occurs in approximately one-third of cases[2]. Further research is needed to establish optimal regimens, evaluate targeted therapies, and identify prognostic factors to improve long-term outcomes.

Conclusion

RM is a rare extra-articular manifestation of RA that can present with diverse neurologic symptoms, involving both the cranial and spinal cord. Diagnosis relies on a combination of imaging and histopathological evaluation, with CSF biomarkers emerging as potential adjuncts. Histopathologic patterns range from chronic inflammation to classic nodules and granulomatous lesions. Careful differentiation from mimicking conditions, especially IgG4-RD and GPA, is essential. Despite its rarity, early recognition and timely corticosteroid-based treatment can result in favourable outcomes, with prognosis generally improved when intervention is prompt.

Patient consent for publication

The informed consent had been obtained from the patient

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