

Rheumatoid Meningitis: Exploring the Broad Differential of Leptomeningeal and Pachymeningeal Enhancement on Brain MRI

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Abstract

Pachymeningeal and leptomeningeal enhancement on contrast-enhanced brain MRI come with broad differentials, including granulomatous disease of infectious or non-infectious etiology, carcinomatosis, and autoimmune disorders such as vasculitis, giant cell arteritis, and IgG-4 related disease. Among them is rheumatoid meningitis, one of the rare manifestations of central nervous system (CNS) involvement in rheumatoid arthritis (RA). Its clinical presentation is nonspecific and grossly overlaps with that of infectious meningitis. Given its vague neurologic symptoms and broad differential of leptomeningeal and pachymeningeal enhancement, rheumatoid meningitis poses a significant diagnostic challenge. In the absence of tissue sampling, a combination of clinical symptoms, serum markers such as rheumatoid factor and complements, and MRI imaging findings is required to arrive at this diagnosis. Rheumatoid meningitis portends high mortality and morbidity, and appropriate immunosuppressive treatment is often delayed in favor of long-term antibiotics. We present a case report on rheumatoid meningitis and corresponding recent literature review including clinical, laboratory, and imaging findings, as well as an exploration of the differentials of pachymeningeal and leptomeningeal enhancement.

Keywords

Rheumatoid meningitis, Pachymeningitis, Leptomeningitis, Rheumatoid arthritis, Meningitis

Case Report

A 54-year-old woman with past medical history of seropositive rheumatoid arthritis (RA) diagnosed a few years ago, hypertension, and recent hospitalization at outside hospital for meningoencephalitis, presented with altered mental status. Per family, she was recently admitted to an outside hospital for a week where she was treated with antibiotics. Post-discharge, she continued to experience headaches, mild photophobia, nausea and vomiting. Upon admission, she was afebrile at 37.3 C and mildly tachycardic with heart rate of 112 beats per minute. Her white blood cell count was mildly elevated at 11×10^3 u/L. She was also hypokalemic to a potassium level of 2.9 mEq/L, which was subsequently repleted, and was attributed to home Lasix and spironolactone use for hypertension. Her lumbar puncture demonstrated several white blood cells with neutrophilic predominance, with normal glucose and protein. Given her clinical presentation, she was empirically started on broad spectrum antibiotics (vancomycin, ceftriaxone, ampicillin, and metronidazole).

Her MRI brain demonstrated marked leptomeningeal enhancement predominantly at the vertex, also with some degree of pachymeningeal enhancement as well (Figure 1). Additionally, her CT Head demonstrated a 1 cm hypodense lesion in the right basal ganglia, and this lesion on MR Brain was intrinsically T1 hyperintense, T2 hyperintense with restricted diffusion and a peripheral rim of blooming artifact (Figure 2). She was thus diagnosed with meningoencephalitis and treated with ampicillin and metronidazole. Her immunosuppressive therapy (methotrexate and leflunomide) was discontinued in the setting of infection. Her neurocognitive status improved during her hospitalization and she was ultimately discharged one and a half week later with peripherally inserted central catheter and continued home antibiotics. Ultimately, her CSF cultures were negative.

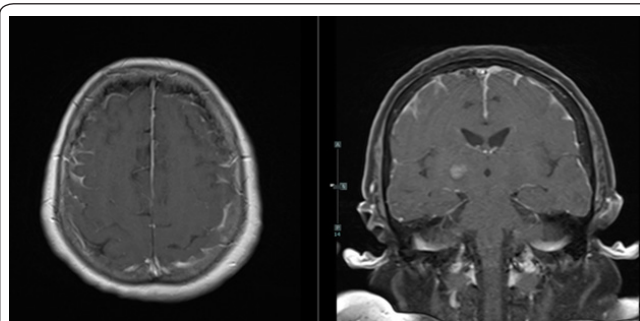


Figure 1: Axial (left) and coronal (right) post-gadolinium T1 images demonstrate leptomeningeal and pachymeningeal enhancement, predominantly at the vertex of the brain.

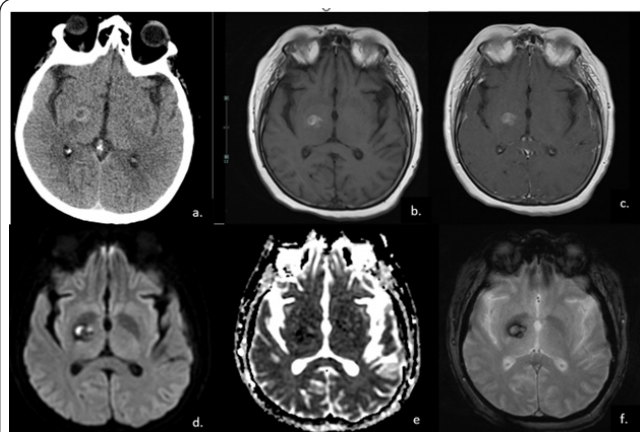


Figure 2: Non-contrast enhanced axial CT (a) demonstrates a 1 cm hypodense lesion in the right basal ganglia. On nonenhanced axial T1 MRI sequence, the lesion is intrinsically T1 hyperintense (b). On enhanced axial T1 sequence it is non-enhancing (c). It demonstrates diffusion restriction on DWI (d) and ADC (e), with peripheral rim blooming artifact on GRE (f) sequences.

She re-presented a day after admission for diffuse joint pain. Her pain was controlled with bilateral knee steroid injections and low-dose prednisone 5 mg, and the rest of her immunosuppressive therapy (methotrexate, Arava, Rituxan) was still not re-initiated as she still needed to complete her antibiotic course. She completed her intravenous course of antibiotics with discontinuation of PICC line and transitioned to oral regimen with augmentin. Her follow-up MRI Brain

demonstrated mildly decreased but persistent dural and leptomeningeal enhancement (Figure 3). The right basal ganglia lesion remained largely unchanged, with no significant adjacent edema or local mass effect.

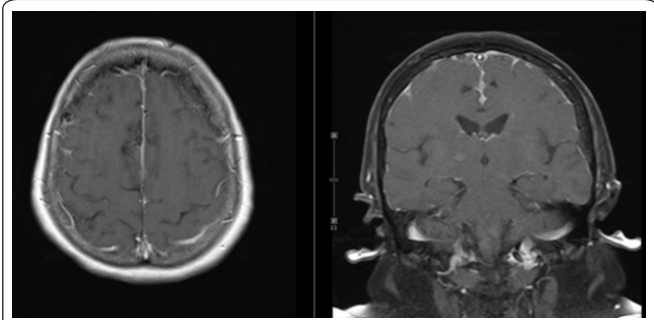


Figure 3: T1 post-gadolinium axial (left) and coronal (right) images demonstrate persistent leptomeningeal and pachymeningeal enhancement.

During subsequent outpatient follow-up her leflunomide was re-started and prednisone up-titrated. She re-presented several weeks later with diffuse joint pain, headache, and fever concerning for acute rheumatoid arthritis flare and recurrent meningoencephalitis. Her C3 serum levels were 167 mg/dL (normal 90-180) and her C4 serum levels were 25.7 mg/dL (normal 10.0-40.0). Her ANA titers were elevated at 1:160, while her IgG serum was normal at 774 (normal range 600 – 1640 mg/dL). Additional rheumatologic workup was negative, including antibody assays for DNase B, Myeloperoxidase, Proteinase-3, Immunoglobulin E and M, and Sjogren SSA and SSB.

CT brain demonstrated a ring enhancing right basal ganglia lesion. MRI brain again demonstrated a stable right basal ganglia lesion with diffusion restriction, T1 hyperintensity, and no significant enhancement or surrounding mass effect. Given the stability of the appearance of the right basal ganglia lesion despite prolonged course of antibiotics, the lesion was deemed to be an intraparenchymal hematoma, likely secondary to hypertension or to underlying cavernous malformation. Importantly, there was persistent pachymeningeal and leptomeningeal enhancement (Figure 4). Additionally, the patient exhibited new findings of left temporomandibular joint synovial enhancement (Figure 5), likely indicating an active rheumatoid arthritis flare. Given setting of active rheumatoid

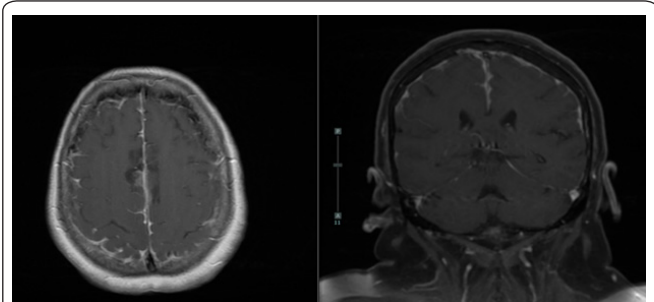


Figure 4: T1 post-gadolinium axial (left) and coronal (right) images again show persistent and significant leptomeningeal and pachymeningeal enhancement.

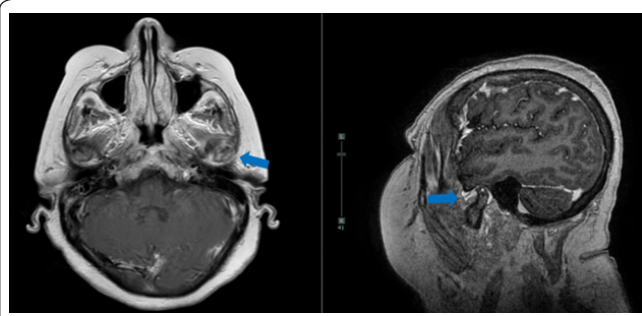


Figure 5: T1 post-gadolinium axial (left) and coronal (right) images demonstrate swelling and abnormal enhancement of the left temporomandibular joint synovium (blue arrows).

arthritis flare, and stability of pachy- and leptomeningeal enhancement despite prolonged course of intravenous and oral antibiotics, these findings were most consistent with rheumatoid arthritis related pachymeningitis. Accordingly, the patient reported significant clinical improvement of her headache as well as fevers and joint pain after high-dose intravenous methylprednisolone. Since her imaging findings were most consistent with non-infectious meningitis and right basal ganglia hemorrhage as opposed to infectious meningitis with abscess, she was able to initiate rituximab treatments after completion of antibiotic course. She continued to do well clinically on her home immunosuppression regimen of leflunomide and oral prednisone.

Discussion

Pachymeningitis, inflammation of the dura mater, is caused by numerous etiologies, including intracranial hypotension, granulomatous disease of infectious (tuberculosis, coccidiomycosis) or non-infectious (sarcoidosis) pathology, and dural carcinomatosis, with lymphoma, breast or prostate cancer being some of the most common instigating primary cancers. Other causes of pachymeningitis include IgG-4 related disease and autoimmune disorders such as vasculitis, giant cell arteritis, and rheumatoid arthritis. On the other hand, leptomeningitis, inflammation of the arachnoid and pia mater, may also be caused by infection but is predominantly due to bacterial and viral agents. Additionally, both primary (for example, medulloblastoma, ependymoma, glioblastoma) and secondary (lymphoma, breast) cancers may exhibit leptomeningeal carcinomatosis [1]. As seen in this case, pachymeningitis with concomitant leptomeningitis further narrows the differential and brings autoimmune diseases such as sarcoidosis and rheumatoid arthritis, as well as dural and leptomeningeal carcinomatosis, to the top of the list. Given the patient's clinical and imaging presentation of acute rheumatoid arthritis flare and absence of known primary malignancy, this case of concomitant pachy- and lepto-meningeal enhancement was most consistent with rheumatoid meningitis.

Central nervous system (CNS) involvement in RA is rare, and it is less extensively characterized than in those with Sjogren's syndrome or systemic lupus erythematosus [2]. CNS manifestations in RA include CNS vasculitis, development of CNS rheumatoid nodules, and aseptic meningitis as seen in

our patient. Mortality and morbidity of rheumatoid meningitis is high: in a literature review of 23 described cases, Kato et al. found that 70% of them died of the meningitis itself or of associated complications including infections such as pneumonia. Surprisingly, several of these patients presented with rheumatoid meningitis even in the inactive disease state. Clinical presentation is broad and nonspecific and may include headache, seizures, cranial neuropathies [3], hydrocephalus [4], sinus thrombosis [4], and transient ischemic attack-like spells [5].

Without definite tissue sampling, the diagnosis of rheumatoid meningitis may be extremely challenging, especially since clinical presentation substantially overlaps with infectious meningitis. Though there are no specific markers for definitive proof of the disease, rheumatoid factor in the CSF, hypocomplementemia, and elevated serum cytokines including IL-6 have all been reported to help obtain the diagnosis. Additionally, as discussed above, contrast enhanced brain MRI demonstrates leptomeningeal and/or pachymeningeal thickening and enhancement. If concomitant CNS vasculitis is present, CT or MR angiography and conventional angiography shows decreased caliber and contour irregularity of involved vessels [6].

Rheumatoid meningitis is histopathologically characterized by the formation of rheumatoid nodules and infiltration of mononuclear white blood cells around small vessels in the leptomeninges [7]. This is in contrast to other etiologies which may also present with meningeal enhancement. IgG4-related pachymeningitis demonstrates dense lymphoplasmacytic infiltrate, fibrosis with storiform pattern, obliterative phlebitis, and > 10 IgG4+ plasma cells per high power field (HPF) [8]. Granulomatosis with polyangiitis reveals numerous multinucleated giant cells and arteritis, and sarcoidosis reveals noncaseating granulomas surrounded by lymphocytes, plasma cells, and mast cells [9]. Treatment for rheumatoid meningitis is based on aggressive immunosuppression, and favorable outcomes have been reported with regimens such as intravenous methylprednisolone with transition to oral prednisolone [10], rituximab, or a combination of corticosteroids with azathioprine and cyclophosphamide [2].

In summary, rheumatoid meningitis is a diagnostic challenge given its nonspecific clinical presentation grossly overlapping with infectious meningitis, broad differential of meningeal enhancement on MRI, and lack of specific serum marker. It can manifest even in the inactive state of rheumatoid arthritis. Though it is rare, rheumatoid meningitis should be kept in mind especially since it portends a high mortality and morbidity, notably when initiation of immunosuppressive therapy is delayed in favor of long-term antibiotics. Rheumatoid meningitis remains an important entity on the differential for leptomeningeal and/or pachymeningeal enhancement on contrast-enhanced brain MRI.

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