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## Rheumatoid meningitis sine arthritis.

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**Title:** Rheumatoid meningitis sine arthritis

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## **Abstract**

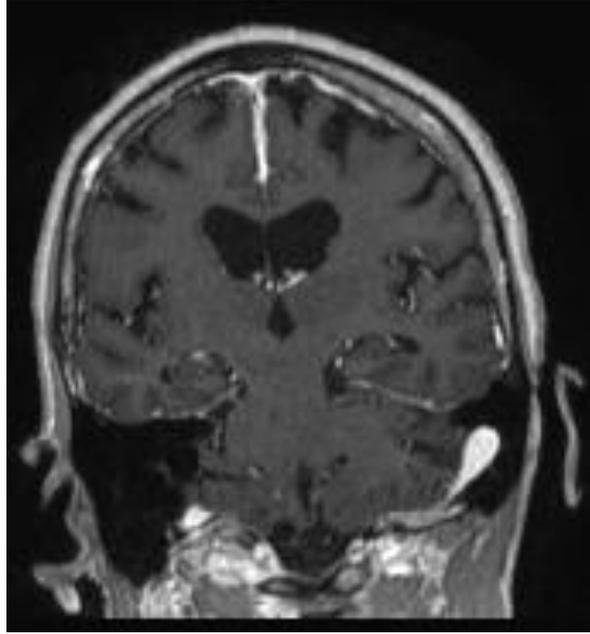
Rheumatoid meningitis is a rare and very serious extra-articular manifestation of rheumatoid arthritis. We present a case of a 72-year-old female with no history of arthritis who developed stroke-like symptoms, seizures, psychosis and compulsive behavior. Serial brain magnetic resonance images (MRI) over four months demonstrated progressive interhemispheric meningeal thickening. She had mild lymphocytic pleocytosis on the cerebrospinal fluid analysis and serum anti-cyclic citrullinated peptide antibodies resulted positive in high titers. She underwent a brain biopsy showing necrotizing granulomas consistent with rheumatoid meningitis. Her symptoms resolved with treatment with glucocorticoids and cyclophosphamide. She has not been diagnosed with rheumatoid arthritis even after 1 year of follow up. Clinicians should be aware of the possibility of rheumatoid meningitis without rheumatoid arthritis and keep it on the differential for patients with aseptic meningitis and otherwise negative work up.

## **Introduction**

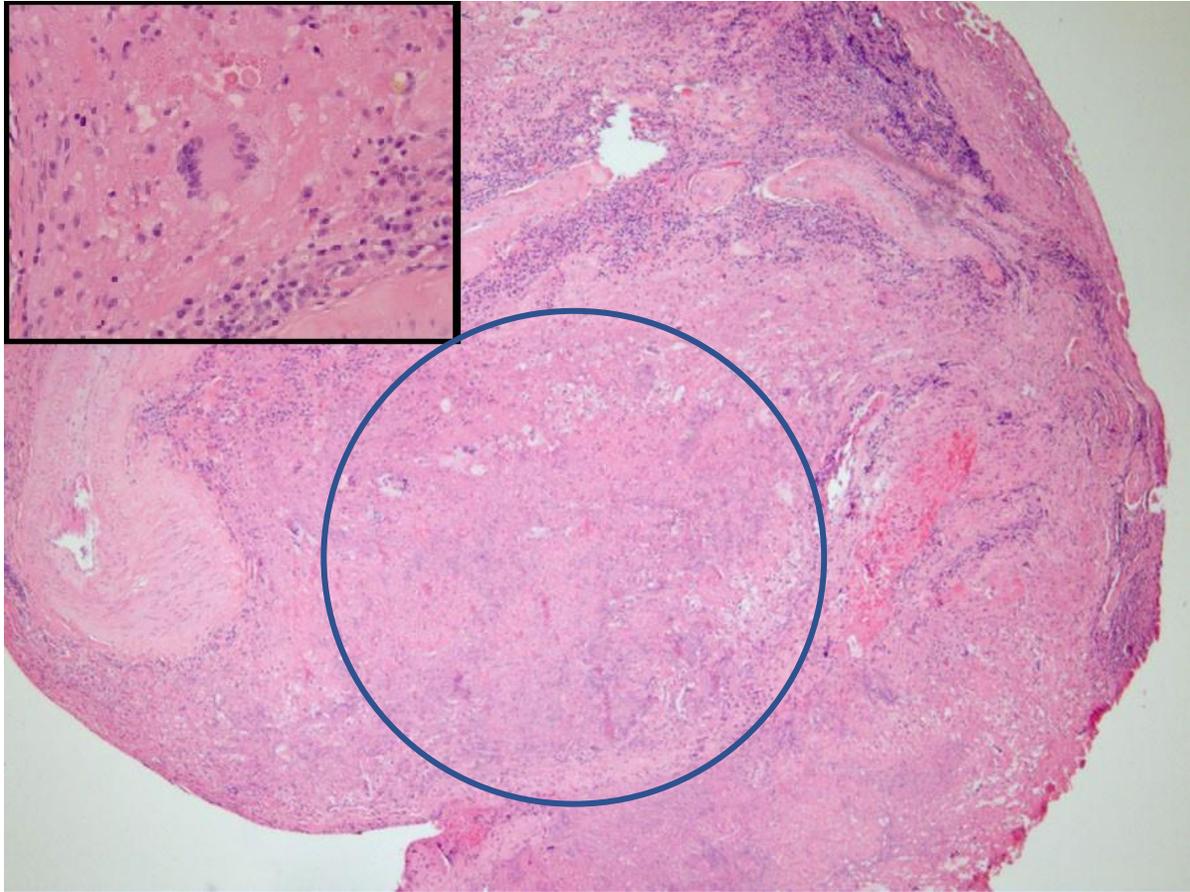
Rheumatoid meningitis is a rare, but very serious extra-articular manifestation of rheumatoid arthritis (R.A)<sup>1</sup>. The prevalence is unknown, as it has only been described in case reports. Since 1954, around fifty-four histopathologically proven cases of rheumatoid meningitis have been published, most of them in patients with a longstanding history of seropositive R.A. In only five reported cases, the diagnosis of rheumatoid meningitis preceded the diagnosis of R.A within the first 3 months of initial presentation or were diagnosed simultaneously <sup>2-21</sup>. Here, we present the first case of biopsy proven rheumatoid meningitis in a patient without any prior history or new development of clinical arthritis after one year of follow up, and we highlight the value of testing for rheumatoid factor (R.F) and anti-cyclic citrullinated peptide (CCP) antibodies in aseptic meningitis of unclear etiology, even in the absence of arthritis.

## Case report

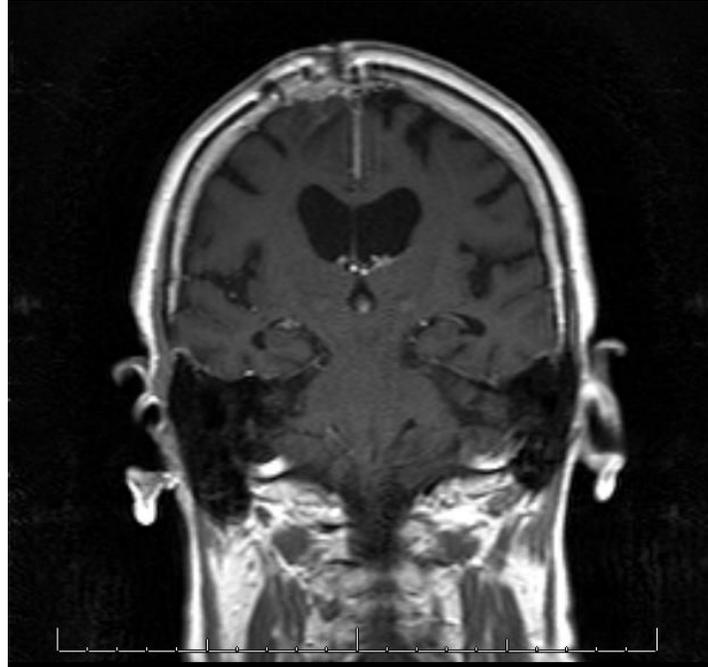
A 72-year-old African American female with a history of hypertension and peripheral vascular disease developed sudden onset left sided weakness and dysphasia in October 2017. Based on clinical history and abnormal MR imaging, she was diagnosed with a stroke at an outside institution and placed on antiplatelet therapy. During the following six months, she had several hospital admissions due to changes in mental status and seizure episodes. She also developed vivid hallucinations (visual and auditory), paranoid delusions, insomnia, and compulsive behavior. She was evaluated by Neurology and Psychiatry and was placed on different combinations of anti-epileptic drugs (divalproex, levetiracetam, lacosamide, gabapentin, clonazepam, lorazepam) and quetiapine for delirium without noticeable improvement, thus prompting transfer to a tertiary care center for evaluation and treatment. Her 12-point review of systems was otherwise negative. Her physical exam was remarkable for cachexia, scarring alopecia, and minimal hyperextension of the interphalangeal and proximal interphalangeal joints. Her neurologic exam demonstrated intact alertness, orientation, explicit memory, and language, though notable for inattentiveness, poor concentration, emotional lability, paranoid delusions, and response to internal stimuli. She had mild weakness of her left lower extremity. Review of the patient's previous MR brain images and repeated brain MRI obtained at our institution demonstrated changes not consistent with ischemia but rather progressive interhemispheric meningeal disease. *See Fig 1.* MRA and MRV of the head and neck were normal. The patient underwent a lumbar puncture and the cerebrospinal fluid (CSF) analysis was remarkable for mild lymphocytic pleocytosis [12 white blood cells (normal 0-5/uL), 94% lymphocytes, 5% monocytes/macrophages, 1% neutrophils, 6 red blood cells (normal  $\leq 0$ /uL), protein 25 mg/dl (normal 15-45 mg/dl), glucose 58 mg/dl (normal 40-70 mg/dl), serum glucose 88 mg/dl]. Extensive infectious and neoplastic work up was negative, including, but not limited to syphilis, cryptococcus, HIV, meningitis/encephalitis panel, CJ prion testing, aerobic/anaerobic, fungal and acid-fast bacilli (AFB) cultures of blood and CSF; cytology and flow cytometry of the CSF. Her interferon gamma release assay (QuantiFERON) testing was initially borderline positive, but repeat testing was negative. Autoimmune work up revealed mildly elevated inflammatory markers (Erythrocyte sedimentation rate 39 mm/hr and C-reactive protein 0.9 mg/dl) and high levels of CCP IgG (197.5 units, ref 0-19). Serum antinuclear antibody, rheumatoid factor and anti-neutrophil cytoplasmic antibodies were negative. Hand x-rays were not obtained due to patient's refusal. Bilateral foot x-rays were normal. The patient underwent a right frontal lobe biopsy, which showed necrotizing granulomas in the leptomeninges and dura mater consistent with rheumatoid meningitis. *See Fig 2.* Special stains for bacteria, mycobacteria and fungi were negative. An IgG4 immunohistochemistry stain was also non-diagnostic. The patient was treated with IV methylprednisolone 1 g daily for 5 days and cyclophosphamide 500 mg/m<sup>2</sup> for four monthly doses with resolution of meningeal enhancement on follow up brain MRI (*see Fig 3*) and resolution of the patient's hallucinations and emotional lability. The initial borderline QuantiFERON test was interpreted as a false positive result given the negative AFB stains and cultures, absence of risk factors in the patient's history and, in retrospect analysis, her clinical improvement with immunosuppressive therapy.



**Figure 1.** MRI Brain with and without contrast. Coronal view T1 sequence showing diffuse post-contrast leptomeningeal enhancement. No parenchymal disease.



**Figure 2.** Biopsy of the right frontal lobe cortex and meninges (40x) with predominantly leptomeningeal inflammatory process with extensive necrosis (circle) and multinucleated giant cells (inset). Special stains for bacteria (Brown-Brenn), fungi (Grocott), and mycobacteria (Kinyoun auramine-rhodamine) are negative for organisms.



**Figure 3.** Post-Cyclophosphamide MRI Brain with and without contrast. Coronal view T1 sequence showing resolution of previous leptomeningeal enhancement

## Discussion

Rheumatoid arthritis can cause pachymeningitis, leptomeningitis or a combination of both. The inflammation can be localized or diffuse and involve the meninges surrounding the brain or the spinal cord. It usually causes asymmetric meningeal involvement. Rheumatoid meningitis has been seen almost exclusively in patients with a longstanding history of seropositive rheumatoid arthritis, even if their disease has been in remission.<sup>1,3</sup>

The clinical manifestations of rheumatoid meningitis are diverse, including: headaches, meningismus, stroke like symptoms, cranial neuropathies, seizures, impairment of vigilance and consciousness, hydrocephalus, sinus thrombosis, dementia, parkinsonism and behavioral modifications.<sup>1,8,21</sup>

Rheumatoid meningitis is a diagnosis of exclusion and requires a combination of lumbar puncture, brain MRI and brain biopsy to establish the diagnosis. The CSF analysis can be normal or show modest lymphocytic pleocytosis, mildly elevated protein and/or slightly decreased glucose levels. R.F and interleukin-6 levels have also been found to be elevated in the CSF of patients with rheumatoid meningitis. Brain MRI findings include meningeal thickening and contrast enhancement on fluid-attenuation inversion recovery images (FLAIR) or diffusion-weighted sequences. Biopsy of the lesions identified by MRI reveal a characteristic, but nonspecific, mononuclear cell infiltration of the meninges with T and B cell lymphocytes and abundant plasma cells. Rheumatoid nodules within the meninges are specific for rheumatoid meningitis but are not always seen. They are composed of focal areas of necrosis surrounded by palisaded epithelioid giant cells. Granulomatous inflammation and vasculitis can be present.<sup>1,3,4,6,8</sup>

It is important to exclude other inflammatory or infiltrative diseases, such as infections (HSV, VZV, enteroviruses, tuberculous meningitis, atypical mycobacteria, neuroborreliosis, fungal infections, meningovascular syphilis, etc.), lymphoma, meningeal metastasis, drug induced (non-steroidal anti-

inflammatory drugs, tumor necrosis factor alpha inhibitors), neurosarcoidosis, antineutrophil cytoplasmic autoantibody-associated vasculitis (mainly granulomatosis with polyangiitis), immunoglobulin G4-related disease, giant cell arteritis and neuro-Behcet's<sup>1,3-5, 17, 21</sup>

A thorough investigation to rule out infectious and malignant etiologies is necessary before starting immunosuppressive therapy. There are no guidelines or clinical trials that have studied the optimal agent or treatment duration in rheumatoid meningitis patients, but there are anecdotal experiences with steroids (usually intravenous pulses of methylprednisolone) and steroid sparing agents, such as methotrexate, azathioprine, cyclosporine, cyclophosphamide and rituximab. Limited data available suggest that tumor necrosis factor alpha inhibitors (TNFi) are not effective. We preferred to use cyclophosphamide in our patient in order to improve medication adherence, central nervous system penetration and quicker onset of action. In terms of prognosis, in the largest case series reported by Bathon et al, 3 out of 19 patients died from systemic necrotizing vasculitis associated with R.A and 14 died of other causes (sepsis, cardiac disease).<sup>1, 3, 5, 6, 17, 18, 23</sup>

Our case is unique in that this is the first description of a patient with biopsy proven rheumatoid meningitis who has not developed symptoms or signs of arthritis after 1 year of follow up from her initial presentation. This emphasizes the importance of keeping rheumatoid meningitis in the differential diagnosis of aseptic meningitis (pachy- or lepto- meningitis), when alternative etiologies have been ruled out and testing for rheumatoid factor and CCP antibodies even in the absence of arthritis. We should contemplate the possibility that the prevalence of rheumatoid meningitis may have been underestimated over the years because of underdiagnosis. Our patient did have minimal hyperextension of few interphalangeal joints of her hands, but in the absence of radiological evaluation, this is difficult to interpret as a sign of early arthropathy versus a benign finding.

Additionally, to our knowledge, this is the first reported case of rheumatoid meningitis presenting with psychotic features with visual and auditory hallucinations, which completely resolved after immunosuppressive therapy.

As a final thought, one could argue that there are no pathognomonic histopathologic features of rheumatoid meningitis and that the possibility of neurosarcoidosis remains, however neurosarcoidosis usually causes non caseating granulomas and affects the meninges at the skull base, rather than at the brain convexity.<sup>13</sup> Furthermore, CCP antibody is highly specific for R.A (more than 90% specificity).<sup>22</sup> Our patient was worked up for possible sarcoidosis with computed tomography scan of her chest, abdomen and pelvis to look for lymphadenopathy and with angiotensin converting enzyme levels in the CSF, all of which were unremarkable.

## References

- 1.- DeQuattro K and Imboden JB 2017. Neurologic Manifestations of Rheumatoid Arthritis. *Rheum Dis Clin N Am* 43: 561-571.
- 2.- Starosta MA and Brandwein SR 2007. Clinical manifestations and treatment of rheumatoid pachymeningitis. *Neurology* 68: 1079-1080.
- 3.- Choi SJ, Park YH, et al 2017. Pearls & Oy-sters: Asymmetric meningeal involvement is a common feature of rheumatoid meningitis. *Neurology* 88: 108-110.

- 4.- Duray MC, Marchand E, et al 2012. Granulomatous meningitis due to rheumatoid arthritis. *Acta Neurol Belg* 112: 193-197.
- 5.- Alexander SK, Di Cicco M, et al 2018. Rheumatoid disease: an unusual cause of relapsing meningoencephalitis. *BMJ Case Rep* doi:10.1136/bcr-2017-222587.
- 6.- Matsushima M, et al 2010. MRI and pathological findings of rheumatoid meningitis. *Case Reports / Journal of Clinical Neuroscience* 17: 129-132.
- 7.- Kim HY, Park JH, et al 2011. A case of rheumatoid meningitis: pathologic and magnetic resonance imaging findings. *Neurol Sci* 32: 1191-1194.
- 8.- Cianfoni A, Falcone C, et al 2010. Rheumatoid Leptomeningitis: Magnetic Resonance Imaging and pathologic Findings—A Case Report. *J Neuroimaging* 20: 192-194.
- 9.- Magaki S, Chang E, et al 2016. Two cases of rheumatoid meningitis. *Neuropathology* 36: 93-102.
- 10.- Shibahara T, et al 2016. Anti-Cyclic Citrullinated Peptide Antibody-Positive Meningoencephalitis in the Preclinical Period of Rheumatoid Arthritis. *Case Rep Neurol* 8: 156-160.
- 11.- Li Y and Kuzuhara S 2009. Rheumatoid cranial pachymeningitis successfully treated with long-term corticosteroid. *Rheumatol Int* 29: 583-585.
- 12.- Nihat A, et al 2016. Rheumatoid meningitis. *Pract Neurol* 16: 312-314.
- 13.- Lu L, Chwalisz B, et al 2015. Rheumatoid meningitis: a rare complication of rheumatoid arthritis. *BMJ Case Rep*. doi:10.1136/bcr-2014-208745.
- 14.- Finkelshtein V, Lampl Y, et al 2018. Self-limited Rheumatoid Meningitis as a Presenting Symptom of Rheumatoid Arthritis. *IMAJ* 20: 262-264.
- 15.- Lubomski M, Sy J, et al 2018. Rheumatoid leptomeningitis presenting with an acute neuropsychiatric disorder. *Pract Neurol* 0: 1-4.
- 16.- Padjen I, Mayer M, et al 2015. Redefining a diagnosis: from meningeal plasma cell granuloma to rheumatoid meningitis. Report of a patient follow-up. *Neurol Sci* 36: 1047-1048.
- 17.- Schmid L, Müller M, et al 2009. Induction of Complete and Sustained Remission of Rheumatoid Pachymeningitis by Rituximab. *Arthritis & Rheumatism* 60(6): 1632-1634.
- 18.- Luessi F, Sollors J, et al 2009. Infliximab in the treatment of rheumatoid meningoencephalitis. *J Neurol* 256: 2094-2096.
- 19.- Parsons A, Zuniga L, et al 2018. Rheumatoid meningitis a case review. *The Neurologist* 23(3): 83-85.
- 20.- Koide R, Isoo A, et al 2009. Rheumatoid leptomeningitis: rare complication of rheumatoid arthritis. *Clin Rheumatol* 28: 1117-1119.
- 21.- Chowdhry V, Kumar N, et al 2005. An Unusual Presentation of Rheumatoid Meningitis. *J Neuroimaging* 15: 286-288.

22.- Mathsson Alm L, Fountain DL, et al 2018. The performance of anti-cyclic citrullinated peptide assays in diagnosing rheumatoid arthritis: a systematic review and meta-analysis. *Clin Exp Rheumatol* 36(1): 144-152

23.- Bathon JM, Moreland LW, DiBartolomeo AG 1989. Inflammatory central nervous system involvement in rheumatoid arthritis. *Semin Arthritis Rheum* 18: 258-266.