Rheumatoid meningitis

A rare cause of aseptic meningitis with frequently stroke-like episodes

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Abstract

Background

Rheumatoid meningitis (RM) is a rare manifestation of rheumatoid arthritis (RA) and may present with stroke-like episodes. We describe diagnostic findings and the outcome in patients with RM.

Methods

We identified 6 patients with RM in different stages of RA mostly admitted with stroke-like episodes or common features of meningitis. We used MRI, CSF, and histology for in-depth characterization.

Results

We observed RM in 2 patients without history of RA, 1 patient with early seropositive RA, and 3 patients with late-stage RA. Recurrent stroke-like episodes occurred in 5 of 6 patients; headache and partial status epilepticus was in the foreground in 1 patient. Symptoms were accompanied by constitutional symptoms in all patients. MRI showed leptomeningeal or pachymeningeal fluid-attenuated inversion recovery hyperintensities with contrast enhancement. CSF mostly showed mild pleocytosis but can initially be normal. Anticitrullinated peptide antibodies (ACPA) and rheumatoid factor (RF) were positive in all patients. Histopathology revealed granulomatous inflammation in 2 patients. Response to steroids was prompt and further immunosuppressive treatment prevented recurrence.

Conclusions

RM is a rare manifestation of RA and often presents with stroke-like episodes. It is currently not implemented in the workup of aseptic meningitis in national guidelines. Crucial clues for diagnosis included recurrent stroke-like episodes refractory to antiepileptic treatment, headache and constitutional symptoms, meningeal enhancement on MRI, CSF pleocytosis, and positive serology findings for ACPA and RF. Prognosis is favorable with early immunosuppressive treatment.

Rheumatoid meningitis (RM) is a rare and diagnostically challenging manifestation of rheumatoid arthritis (RA).¹⁻³ A few case reports describe stroke-like episodes in RM^{4,5} mimicking transient ischemic attacks besides more common presentations of aseptic meningitis with fever, headache, and altered mental status.^{3,6} RM occurs not only in patients with long-standing RA, but also early in the disease course and even as the sole presentation of

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rheumatoid disease.^{4,6} We reviewed the medical records of 6 patients with RM and describe the diagnostic findings, therapy, and outcome.

Methods

We identified 6 patients either seen on our inpatient neurology wards or outpatient rheumatology clinics of our institution between January 2014 and December 2017. Participating patients provided written consent to use medical information. We did not seek ethics approval for our retrospective study; the diagnostic and therapeutic protocol that we evaluated was according to standards of current practice.

Results

Index case (case 1)

A 48-year-old man without a history of RA had recurrent episodes of acute-onset, 10–15 minute left-sided weakness and numbness. In addition, mild persistent headache and night sweats were present for the last 3 months. No focal neurologic symptoms were present on admission. On the initial cranial CT scan, a small right frontal subdural

hematoma was suspected (figure 1A). There was no history of trauma and no treatment with anticoagulants or antithrombotic drugs. EEG was unremarkable. However, symptoms were classified as most likely being of epileptic origin and levetiracetam was started.

Failure to control symptoms triggered additional investigations. Brain MRI showed fluid-attenuated inversion recovery (FLAIR) hyperintensities of the right frontal and parietal cortex with diffusion restriction accompanied by contrast enhancement of pachymeninges and leptomeninges (figure 1A). CSF analysis revealed 300 mononuclear cells/ μ L, an elevated protein of 137 mg/dL, and intrathecal immunoglobulin synthesis. Empiric treatment for infectious meningitis was initiated and stopped after comprehensive tests for infectious diseases were negative. CSF cytology and flow cytometry were unremarkable. An extensive workup for immunologic disorders showed markedly elevated rheumatoid factor (RF) and anticitrullinated peptide antibodies (ACPA) (298 U/mL and >340 U/mL, respectively); antibody screening for vasculitis was negative. ACPA testing in CSF was also highly elevated (>340 U/mL). C-reactive protein and erythrocyte sedimentation rate were normal. RM was suspected, although articular manifestation was not present clinically or on plain radiograph. Probatory steroid

Figure 1 Neuroimaging findings of cases 1, 2, 4, and 5

(A.a) Case 1, cranial CT with isodense right frontal verge initially interpreted as subdural hematoma (red arrow). (A.b) MRI: T2-weighted fluid-attenuated inversion recovery (FLAIR) hyperintensities of the right frontal and parietal cortex with (A.c) diffusion-weighted imaging (DWI) lesions and contrast enhancement of pachymeninges and leptomeninges on (A.d) T1-weighted contrast-enhanced image. (B) Case 4, contrast-enhanced T2-weighted FLAIR sequence shows contrast enhancement of pachymeninges of the left hemisphere. (C) Case 5, contrast enhancement of leptomeninges bifrontal on T1-weighted contrast-enhanced image. (D) Case 2, contrast enhancement of left frontal leptomeninges and pachymeninges on T1-weighted contrast-enhanced imaging.

pulse therapy resulted in rapid clinical improvement. Oral steroids were tapered within 2 months; modifying anti-rheumatic drugs were not administered.

Fifteen months later, the patient presented again with chronic headache. Marked pachymeningeal and leptomeningeal contrast enhancement was seen on MRI; CSF showed 200 mononuclear cells/ μL . Consistently, steroid pulse therapy improved symptoms immediately. The patient was stable with methotrexate treatment over a follow-up period of 20 months. RA with isolated extra-articular manifestation was diagnosed.

We identified further 5 patients (table e-1, links.lww.com/CPJ/A42) with presumed RM. Diagnosis was based on evidence of leptomeningitis or pachymeningitis on MRI in all patients with mostly inflammatory CSF findings (5/6), exclusion of an infectious or malignant cause, positive testing for RF and ACPA, and prompt response to steroid therapy. Two of the 6 identified patients had no history of RA, 1 patient had early seropositive RA, and 3 patients had late-stage RA with articular involvement. Five of 6 patients presented with stroke-like episodes. Headache, altered mental status, and seizures were prominent in one patient. Constitutional symptoms were present in all patients.

Clinically, transient ischemic attacks or focal seizures were initially suspected; differential diagnosis during the workup encompassed infectious and malignant causes of meningitis besides vascular etiologies.

Typical MRI findings were T2 FLAIR hyperintensities with diffusion-weighted imaging restriction and T1 contrast enhancement of pachymeninges or leptomeninges (figure 1). CSF mostly showed elevated mononuclear cells in all but one patient and increased protein in 3/6 patients. CSF glucose was within the normal range in all patients. Extensive workup for infectious and malignant causes was negative. Autoimmune screening indicated increased levels of RF and ACPA in all patients. ACPA testing in CSF was only available for the index patient. Brain biopsy revealed granulomatous inflammation in 2 patients (figure 2). Other granulomatous diseases including tuberculosis, sarcoidosis, and granulomatosis with polyangiitis were thoroughly

Concomitant headache or constitutional symptoms in patients with stroke-like episodes should trigger further investigations for aseptic meningitis.

excluded. None of the patients turned out to have an infectious or neoplastic entity.

Finally, RM was diagnosed and steroid therapy led to prompt clinical and radiologic improvement. Disease-modifying antirheumatoid drugs (DMARD) prevented relapse; in 4 cases, immunosuppressive therapy was stopped or reduced, provoking relapse in all 4 cases. During follow-up, all patients fulfilled the diagnostic criteria for RA; only patient 1 had not yet developed arthritis.

Discussion

Our case series of RM highlights several important clinical findings. Stroke-like episodes as recently described in case reports of rheumatoid meningitis^{4,5} were often seen in our patients with RM. Commonly, recurrent hemisymptoms either assume transient ischemic attacks or focal seizures.⁷ Clinicians should be aware of other etiologies if concomitant headache or constitutional symptoms are present and if there is no satisfactory seizure control. As seizure activity was only evident on EEG in 2 cases (cases 4 and 6), spreading depolarization induced by inflammation of the nearby meninges might be an alternative pathophysiologic concept for stroke-like episodes in our cases. Interestingly, disease activity and duration of rheumatoid arthritis is not a reliable predictor for the appearance of RM. RM was described in patients with long-standing RA¹ with either poorly⁴ or well-controlled⁵ disease, but also emerged in patients with no history of RA or in patients with early rheumatoid disease.^{3,6} In our sample, 2 patients had no evidence of RA at the time of onset of RM.

Figure 2 Neuropathologic findings of case 5

(A) Cortex (*) with overlying arachnoid shows marked fibrotic thickening with smudgy necrotic areas (n), scale bar 500 μm . (B) At higher magnification, lymphoplasmacytic infiltrates and scattered multinucleated cells (arrow), scale bar 100 μm .

Brain biopsy might be advisable if sufficient diagnostic accuracy cannot be reached with noninvasive diagnostic tests alone.

MRI was abnormal in all our cases and in most published cases of RM.³ FLAIR hyperintensities, thickening and contrast enhancement of leptomeninges, pachymeninges, or both are characteristic, but not specific for RM. Differential diagnosis includes infectious or carcinomatous meningitis, subdural or subarachnoid hemorrhage, and postictal artefacts.

Aseptic meningitis is commonly defined as an entity with clinical and CSF evidence of meningeal inflammation without evidence of an infectious origin. Rarely, CSF cell count can be normal.⁸ This was also described in RM.^{2,9} Most of our patients had elevated cell counts in the CSF except case 2. In case 4, pleocytosis was only evident after the third lumbar puncture. Hence, CSF pleocytosis is a common finding in aseptic meningitis, but normal cell counts do not completely rule out RM.

Brain biopsy might be advisable if sufficient diagnostic accuracy cannot be reached with noninvasive diagnostic tests alone. Histopathology was described to be nonspecific in RM including pachymeningitis and leptomeningitis or vasculitis with or without rheumatoid nodules.^{1,3,4} In our cases, granulomatous inflammation was present; tuberculosis, sarcoid disease, as well as isolated or systemic granulomatous vasculitis were ruled out thoroughly.

Further differential diagnosis of aseptic meningitis encompasses malignancies, drug-induced, viral, or autoimmune meningitis.¹⁰ Autoimmune processes include systemic lupus erythematosus, sarcoid and Behçet disease, granulomatosis with polyangiitis, primary angiitis of the CNS, giant cell arteritis, Sjögren syndrome, immunoglobulin G4-related meningitis, and RA. In a retrospective cohort study of patients with aseptic meningitis, 7 of 180 patients with aseptic meningitis (4%) had underlying autoimmune diseases¹¹; RM was not identified, most likely due to unavailable analysis of ACPA and RF, which was not part of the autoimmune screening of the study. We emphasize the importance of testing for RF and ACPA in any patient with unexplained meningitis.

Treatment attempt with steroids is justifiable in neurologically impaired patients if a synopsis of clinical, radiologic, and laboratory findings suggests autoimmune meningitis after thorough exclusion of infectious or malignant causes. In patients with RA on DMARD, exclusion of an opportunistic infection or drug-induced meningitis is mandatory. Initial

steroid treatment resulted in significant improvement in our and several published cases of RM.^{3,4,6,12} Monotherapy may not provide recovery or provoke relapse; adding of DMARD such as methotrexate, azathioprine, or cyclophosphamide is recommended.^{2,6,13} Methotrexate, tocilizumab, or cyclophosphamide likewise provided effective treatment in our cases.

Diagnosis of RM is challenging due to misleading presentation with stroke-like episodes and can present early in the disease course even in the absence of other clinical features suggesting RA. Accompanying constitutional symptoms and refractory stroke-like episodes should trigger further investigations. With cranial MRI and CSF alone, RM is indistinguishable from other entities causing aseptic meningitis. Therefore, ACPA and RF testing should be part of the autoimmune workup of aseptic meningitis. They are reliable and specific markers for rheumatoid disease¹⁴ and were detectable in most of the published cases of RM.^{1,3} National guidelines do not provide a diagnostic approach to autoimmune causes of aseptic meningitis, probably accounting for unrecognized cases of autoimmune-mediated aseptic meningitis. We strongly recommend testing for ACPA and RF in patients with refractory aseptic meningitis and in patients with clinical and radiologic evidence of meningitis despite normal CSF findings. Treatment is justified even without histopathology if diagnostic findings suggest RM after thorough exclusion of other infectious or malignant diseases. Steroids are an appropriate first-line therapy; DMARDs should be administered in order to prevent relapse.

Author contributions

S. Schuster: study concept and design, acquisition of data, analysis and interpretation of data, drafting the manuscript. H. Braass: study concept and design, acquisition of data, analysis and interpretation of data, drafting the manuscript. C. Iking-Konert: acquisition of data, analysis and interpretation of data, critical revision of manuscript. U. Schnoor: acquisition of data, analysis and interpretation of data. J. Matschke: acquisition of data, analysis and interpretation of data. C. Gerloff: analysis and interpretation of data, critical revision of manuscript. G. Thomalla: analysis and interpretation of data, critical revision of manuscript. T. Magnus: analysis and interpretation of data, critical revision of manuscript.

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References

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

TAKE-HOME POINTS

- Recurrent stroke-like episodes with headache or constitutional symptoms should prompt further investigation for aseptic meningitis.
- Rheumatoid meningitis should be considered in the differential diagnosis of aseptic meningitis even without history of rheumatoid disease.
- Routine ACPA and RF testing in serum is useful in the diagnostic workup of patients with aseptic meningitis.
- Steroids are an appropriate first-line therapy after exclusion of an infectious or malignant cause in aseptic meningitis.

2. Kato T, Hoshi KI, Sekijima Y, et al. Rheumatoid meningitis: an autopsy report and review of the literature. *Clin Rheumatol* 2003;22:475–480.
3. Magaki S, Chang E, Hammond RR, et al. Two cases of rheumatoid meningitis. *Neuropathology* 2016;36:93–102.
4. Bourgeois P, Rivest J, Bocti C. Rheumatoid meningitis presenting with stroke-like episodes. *Neurology* 2014;82:1564–1565.
5. Roy B, Uphoff DF, Silverman IE. Rheumatoid meningitis presenting with multiple stroke-like episodes. *JAMA Neurol* 2015;72:1073–1076.
6. Starosta MA, Brandwein SR. Clinical manifestation and treatment of rheumatoid pachymeningitis. *Neurology* 2007;68:1079–1080.
7. Nadarajan V, Perry RJ, Johnson J, Werring DJ. Transient ischaemic attacks: mimics and chameleons. *Pract Neurol* 2014;14:23–31.
8. Dawood N, Desjobert E, Lumley J, Webster D, Jacobs M. Confirmed viral meningitis with normal CSF findings. *BMJ Case Rep* 2014;2014:bcr2014203733.
9. Ramos M, Mandybur TL. Cerebral vasculitis in rheumatoid arthritis. *Arch Neurol* 1975;32:271–275.
10. Kupersmith M, Martin V, Heller G, Shah A, Mitnick H. Idiopathic hypertrophic pachymeningitis. *Neurology* 2004;62:686–694.
11. Jarrin I, Sellier P, Lopes A, et al. Etiologies and management of aseptic meningitis in patients admitted to an internal medicine department. *Medicine* 2016;95:1–9.
12. Chowdhry V, Kumar N, Lachance DH, Salomao DR, Luthra HS. An unusual presentation of rheumatoid meningitis. *J Neuroimaging* 2005;15:286–288.
13. Hasiloglu ZI, Asik M, Ezer B, Dikici AS, Altintas A, Albayram S. Magnetic resonance imaging of rheumatoid meningitis: a case report and literature review. *Rheumatol Int* 2012;32:3679–3681.
14. Nishimura K, Sugiyama D, Kogata Y, et al. Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. *Ann Intern Med* 2007;146:797–808.

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