Rheumatoid meningitis sine arthritis: an emerging cause of isolated pachymeningitis and leptomeningitis with typical features

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Case Report

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Abstract

Background.

Rheumatoid meningitis (RM) is a meningeal inflammation rarely occurring during the course of rheumatoid arthritis (RA). Anti-citrullinated protein antibodies (ACPA), which are highly specific biomarkers of RA, may allow RM sine arthritis (RMSA) to be diagnosed as an extra-articular early lesion of RA. MRI typically displays pachymeningitis and/or leptomeningitis predating convexity, and CSF diffusivity is focally restricted. Blood ACPA is a strong clue and intrathecal synthesis of ACPA is characteristic.

Case presentation.

We report two cases of RMSA that were confirmed by meningeal biopsy and intrathecal synthesis, and which abated after steroids alone or associated with rituximab.

Conclusions.

We reviewed all published cases of RM and found that RMSA may account for 15% of RM.

Background

Rheumatoid arthritis (RA) is a chronic inflammatory disorder that may involve extra-articular sites. Rheumatoid nodules (RN), which may occur in up to a fifth of RA patients, are granulomas with pseudo-palisading histiocytes and giant multinucleated cells surrounding a fibrinoid core. Apart from the classical involvement of skin and lungs, the meninges are rarely but increasingly involved and feature rheumatoid meningitis (RM).

Although the historical cases of RM described in the early fifties were associated with severe brain lesions leading to death, they also failed to receive efficient treatment for RA and developed vasculitis. However, recent RM cases were mostly resolved by steroids or immunosuppressive drugs with a mostly benign course.

Intriguingly, RM may occur in patients free of RA, i.e. RM sine arthritis (RMSA). The diagnosis is challenging and requires the detection of IgG directed against cyclic citrullinated peptides (ACPA) in blood, which are highly specific biomarkers of RA, or in cerebrospinal fluid (CSF), which is a typical feature of RM. We report two cases of RMSA.

Methods

CSF pattern was analyzed by isoelectric focusing on agarose gel. Intrathecal IgG synthesis was calculated by the Link formula: IgG index = \( Q_{\text{IgG}}/Q_{\text{Alb}} \) (normal values < 0.7), where \( Q_{\text{Alb}} = [\text{Alb}_{\text{CSF}}]/[\text{Alb}_{\text{serum}}] \).
and $Q_{IgG} = [IgG_{CSF}] / [IgG_{serum}]$. The de novo CNS IgG synthesis rate was calculated by Tourtellotte’s formula:

$$IgG_{SYN} = \left( \left[ IgG_{CSF} - \frac{[IgG_{serum}]}{369} \right] - \left[ Alb_{CSF} - \frac{[Alb_{serum}]}{230} \right] \left( \frac{[IgG_{serum}]}{[Alb_{serum}]} \right) 0.43 \right) \times 5;$$

with normal values lower than 3.3 mg/day [1]. The presence of specific antibodies (RF and ACPA) in CSF was used to calculate the specific Antibody Index (AI), which is the ratio of specific antibodies $Q_{Spec} = [Spec_{CSF}] / [Spec_{serum}]$ in the formula: $AI_{spec} = Q_{Spec} / Q_{IgG}$, where AI values > 1.3–1.5 indicate the presence of intrathecal synthesis. IgG and albumin levels were expressed in mg/L and specific antibodies (ACPA, RF) in UI/mL which were normalized by calculating the $Q_{spec}$ ratio. In patient 1, blood ACPA and RF levels exceeded the maximal standard range and were assayed again after a tenfold dilution.

**Cases presentation**

**Patient 1**

A 76-year old man developed permanent headache, bradypsychy, unexplained falls and recurrent stroke-like sensory symptoms over three months. He did not report any medical history. He had taken amoxicillin twice during the preceding months to treat maxillary pain that he considered related with his sinusitis.

Clinical examination was normal except for slightly impaired cognition. For a week, he had suffered from recurring transient episodes of right arm numbness and clumsiness lasting a few minutes. He was admitted to hospital after suffering from a syncopal attack followed by a short confusional state. Temperature was 38.9°C. EEG was slightly slow. CSF was normal, with 4 white blood cells (WBC); C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were high (74mg/L and 80mm/h). Levetiracetam was initiated but the multiple episodes of transient arm numbness recurred.

Brain MRI disclosed bilateral pachy- and lepto-meningitis with focally restricted diffusivity of CSF (Fig. 1). He was admitted to our neurology department one week later. CSF disclosed 26 WBC, a normal IgG index with oligoclonal pattern 3 (mirror banding, no extrabands) and negative culture. CRP was 21mg/L. Autoantibodies were positive in blood and CSF against ACPA (1180 UI/mL and 29 UI/mL, ratio 1:40) and rheumatoid factor (600 UI/mL and 7.7 UI/mL, ratio 1:78), and specific AI were high: $AI_{ACPA} = 5.2$ and $AI_{RF} = 2.7$ (Table 1). Other biological tests including pANCA, IgG4 and serologies were normal. The Mantoux test was strongly reactive but the quantiferon test was not available.
### Table 1
Intrathecal synthesis

<table>
<thead>
<tr>
<th></th>
<th>Patient #1</th>
<th>Patient #2</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alb$_{CSF}$ (mg/L)</td>
<td>255</td>
<td>158</td>
<td></td>
</tr>
<tr>
<td>Alb$_{blood}$ (mg/L)</td>
<td>31900</td>
<td>34700</td>
<td></td>
</tr>
<tr>
<td>IgG$_{CSF}$ (mg/L)</td>
<td>57.9</td>
<td>102.1</td>
<td></td>
</tr>
<tr>
<td>IgG$_{blood}$ (mg/L)</td>
<td>12140</td>
<td>17270</td>
<td></td>
</tr>
<tr>
<td>Q$_{alb}$ ($x10^{-3}$)</td>
<td>8.0</td>
<td>4.6</td>
<td></td>
</tr>
<tr>
<td>Q$_{IgG}$ ($x10^{-3}$)</td>
<td>4.8</td>
<td>5.9</td>
<td></td>
</tr>
<tr>
<td>IgG index</td>
<td>0.6</td>
<td>1.3</td>
<td>&lt; 0.7</td>
</tr>
<tr>
<td>Daily IgG synthesis rate, Tourtellotte (mg/d)</td>
<td>29.8</td>
<td>268.9</td>
<td>&lt; 3</td>
</tr>
<tr>
<td>ACPA$_{CSF}$</td>
<td>29.0</td>
<td>nd</td>
<td></td>
</tr>
<tr>
<td>ACPA$_{blood}$</td>
<td>1180.0</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Q$_{ACP}$ ($x10^{-3}$)</td>
<td>24.6</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>AI$_{ACP}$</td>
<td>5.2</td>
<td>-</td>
<td>&lt; 1.5</td>
</tr>
<tr>
<td>RF$_{CSF}$ (UI/mL)</td>
<td>7.7</td>
<td>nd</td>
<td></td>
</tr>
<tr>
<td>RF$_{blood}$ (UI/mL)</td>
<td>600.0</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Q$_{RF}$ ($x10^{-3}$)</td>
<td>12.8</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>AI$_{RF}$</td>
<td>2.7</td>
<td>-</td>
<td>&lt; 1.5</td>
</tr>
</tbody>
</table>

nd: not done.

A meningeal biopsy was performed on the right frontal lesion and revealed thickened meninges with a necrotic core surrounded by a few plasma cells (Fig. 2). Headache, transient sensory signs and fever definitively subsided after surgery without any medication. The working diagnosis of RM was confirmed and he received 3 days of high-dose steroids but he refused any further treatment, so treatment against latent tuberculosis was not initiated. His clinical parameters returned to normal within a few days and he remained free of headache and spells. Although all MRI lesions had improved by month 2, slight leptomeningeal lesions persisted with abnormal CSF diffusivity. No treatment was given and no articular sign appeared during two years of follow-up.
Patient 2

A 57-year-old woman was referred to our neurology department for chronic headache. She had a history of hypertension, migraine, stable monoclonal gammapathy of unknown significance (MGUS) IgG kappa, and she had had a gastric bypass 4 years before. She was born in the Francophone West Indies and her family history was non-specific. Fourteen years before, she had suffered from acute lymphocytic meningitis: 26 white blood cells (WBC) with 86% lymphocytes. A transient episode of left-side weakness and paresthesia was observed on day 2 and her headache worsened transiently. During the following years, she complained of chronic daily headache and recurring transient episodes of left-side paresthesia. Cranial MRI (unavailable) performed six years later was reported normal. Her headache had progressively worsened during the previous two years and had become constant and more intense during the night. Medication (paracetamol, NSAID, triptan, propranolol, amitriptyline) did not provide any relief. During this period, transient left-side paresthesia lasting one or two days had occurred at least once a month. CSF was assayed in an emergency ward at year 13 and was normal (3 WBC).

Finally, enhanced cranial MRI revealed pachymeningitis without any spinal cord involvement. She was admitted to our neurology department 14 years after the initial episode of headache. Her chronic severe headache was holocranial, constant, with accompanying tinnitus and photo-phonophobia. Brain MRI disclosed frontal and sagittal pachymeningitis (Fig. 3). Salivary gland biopsy, whole body computed tomography(CT)-scan and FDG-Pet were normal. Blood parameters were as follows: CRP < 3mg/L, IgG 17.7g/L (including monoclonal 3.4g/L IgG Kappa), IgM 3.4g/L, IgA 3.1g/L, IgG4 0.68 g/L, non-specific low pANCA, ANA 1 :160, anti-native DNA 102 UI (N < 10UI), rheumatoid factor 28 UI/mL, and ACPA 67 UI/mL. CSF contained 3 white blood cells (WBC), 0.34g/L proteins, IgG index 1.3, and oligoclonal pattern 4 (mirror banding with extrabands), but was negative for ACPA (Table 1), Mycobacterium tuberculosis culture and PCR.

Based on high ACPA and typical MRI, the diagnosis of rheumatoid meningitis was evoked and brain biopsy was postponed. She was given high-dose IV corticotherapy for 3 days with oral tapering over the next six months. Her headache and associated signs subsided in three days. However, minimal signs reappeared below a 25mg dose, so her dosage was increased and tapered again. Unfortunately, at month two she developed a steroid-induced cataract so her medication was discontinued. Her headache remained moderate with slight tinnitus. During the next 4 months, she developed left-sided then alternating paroxysmal paresthesia, paroxysmal left leg weakness, and rare hand or foot dystonic episodes. Intercritical examination was normal. Moreover, she suffered rare episodes of typical migraine without aura that responded to NSAID. Brain MRI remained stable.

Owing to the resistance to treatment, a biopsy was planned before initiating immunosuppressive drugs. Meningeal biopsy revealed thickened fibrous meninges infiltrated by CD20, CD138 B-cells, and CD4 T-cells (Fig. 4). No typical rheumatoid nodule was observed. Biology disclosed normal CRP, IgG 14.8g/L, IgM 3.1g/L, IgA 2.9g/L, rheumatoid factor 35 UI/mL, and ACPA 39 UI/mL. She received one dose of rituximab 500mg, followed by lamotrigine 25mg. Her transient sensory episodes abated and thereafter she suffered
only rare episodes of typical migraine. No steroids was given and no articular sign appeared during a six months follow-up.

Discussion

RM is considered a rare complication of RA and is classically revealed by brain autopsy after a severe lethal disease. On the other hand, hypertrophic pachymeningitis is a rare MRI pattern with various etiologies. The discovery of highly RA-specific antibodies directed against citrullinated peptides (ACPA) raises the suspicion of RMSA in patients who do not manifest any articular signs but suffer from pachy/lepto-meningitis. Among the 176 published RM cases, 25 (15%) were RMSA (including ours) [2–24]. Since follow-up was short, rates and times to RA onset are mostly unknown.

Unlike RM complicating longstanding treated RA, the occurrence of RMSA suggests that disease-modifying anti-rheumatic drugs (DMARDs) do not play a role in triggering nodulosis and RM, as was initially thought for steroids, methotrexate, and more recently for TNF inhibitors. Subcutaneous nodules similar to RM have also been observed in several inflammatory and infectious disorders [25], reinforcing the hypothesis that nodules and RM are closely linked with active inflammation rather than being triggered by treatments.

Based on the co-occurrence of Alzheimer/amyloid angiopathy and RMSA, some authors proposed that brain citrullination initiated by neurodegenerative processes may trigger leptomeningeal inflammation and local ACPA synthesis [2]. Among the many post-translational modification enzymes, the peptidyl deaminases (PADs) are able to citrullinate (de-iminate) protein arginine residues. Citrullination modifies the electric charge, which in turn changes the spatial conformation and function of the modified proteins. The expression of PAD isoforms is tissue-dependent, PAD2 is expressed in rat brain as poorly active enzyme, and citrullinated proteins are usually absent from normal brain. However, PAD2 is activated when the human brain undergoes neurodegeneration, and citrullination involves GFAP and vimentin, which are the most susceptible proteins [26]. Further evidence in favor of the hypothesis of an associated degenerative trigger is the difference in the age of onset between RM and RA: median age at onset of RM was 63 years [27 to 89] in RA patients and 66 years [37 to 93] in RMSA, which is a more than a difference of 10 years for RM onset (with arthritis or not) than the median age of RA onset.

Lastly, RM could be compared to lung disease associated with ACPA in RA-free patients [27]. Protein citrullination is also known to occur in the lungs, but its relationship with ACPA and RA remains uncertain. These rare lung disorders also occur in older patients (median 67 years, [27]), and overt RA occurs in only 9% of them within 1.5 years after diagnosis.

MRI provides major clues in the diagnosis of RM, although minute lesions are easily missed [28]. The meninges of the skull base and white matter are usually spared. Pachymeningitis is often located on the frontal convexity and falx. Leptomeningitis, which is often congruent with pachymeningitis, appears like a 'sugar-coated' leptomeningeal enhancement [29]. Lesions are commonly lateralized or asymmetric. Moreover, due to local high protein content, CSF in the sulci may show a high signal on FLAIR sequences
and diffusion is focally restricted [29], erroneously evoking pseudo-cortical stroke. Cranial CT scan is usually normal, but whole-body CT scan may disclose disseminated rheumatoid nodules. FDG-PET scan is usually normal (Fig. 5).

In historical cases, massive pachymeningitis has been associated with non-obstructive hydrocephalus, sinus thrombosis or cranial nerve involvement (hearing loss). Authors suggested that headache and cranial neuropathies might be related to pachymeningitis, whereas leptomeningitis could be more associated with spells, seizures, paresis, a change in mental status and gait imbalance [30], and probably to intrathecal IgG synthesis.

Onset after presumed viral meningitis is common ([31]; patient #2). Headache, which is almost always reported, may fluctuate, and is sometimes associated with transient neurological signs. Transient symptoms (spells) may mimic stroke emergencies, seizure or migraine: unilateral paresthesia, weakness or aphasia commonly last 5 to 15 minutes. They may recur stereotypically many times a day, suggesting cortical spreading depolarization, although apparently real seizures are rarely reported. The spinal cord and cranial nerves are usually spared except in severe historical cases. Death used to be the classical outcome but this is no longer the case since improvement is easily obtained with steroids and/or immunosuppressive drugs.

ACPA and rheumatoid factor levels are high, which is a major clue evoking RMSA. CRP and sedimentation rate are usually abnormal. CSF may variably reveal a normal WBC count, a slight increase or frank lymphocytic meningitis up to 200/mm³. Proteins may be normal or high, and glucose is usually normal, unlike pleural rheumatoid effusion. Although rarely investigated, intrathecal IgG synthesis is common, especially local synthesis of ACPA.

Biopsy results may be deceptive. Typical lesions are rheumatoid nodules inside hyalinized and inflammatory dura mater: a central core of fibrinoid necrosis surrounded by palisading histiocytes with giant cells is also inconstant in rheumatoid synovitis, and non-specific inflammatory infiltrates rich in plasma cells generally predominate. However, given the small size of samples, it is common to observe plasma cell-rich inflammation inside a thickened dura, whereas fibrinoid necrosis or hyaline fibrosis may predominate in older lesions. Minute lesions may therefore be deceptive, as in patient #1. The leptomeninges may also be involved, and inflammation may penetrate the outer cortex along the Virchow-Robin spaces.

RA vasculitis, which was a severe complication occurring before the era of DMARDs, is not a pathologic feature observed in association with RM. Angiography is normal and no stroke occurs in RM. Therefore, stroke-like symptoms, or the so-called 'rheumatoid spells', are more likely reactive cortical depolarization events than ischemic events.

There is no gold standard treatment owing to insufficient knowledge of RMSA. More than a half of RM cases subsided with tapered steroids and symptoms dramatically improved within days [27, 32]. Others may require immunosuppressive drugs alone or in association (rituximab, methotrexate,
cyclophosphamide). CSF IL-6 may sometimes be high, which suggests that tocilizumab might be efficient on RM [33]. However, there is still no therapeutic consensus, and in many cases, strong immunosuppressive treatments were given early in anticipation of the severity of the pathology. None of the more recent cases display the same degree of severity.

Conclusion

Rheumatoid meningitis sine arthritis may account for 15% of RM and displays typical MRI features allowing an early diagnosis.

Declarations

Ethics approval and consent to participate

Informed consent was obtained from the patients before treatments.

Consent for publication

Informed consent was obtained from the patients for the publication of the case report. All the authors have read the manuscript and have approved this submission.

Availability of data and materials

All the available and relevant data were given as text or figures in the main and supplemental files. All data reported within the article are available as an anonymized set by request from qualified investigators.

Competing interests

The authors declare no competing interests.

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None.

Authors’ contributions

M.B. designed the study and drafted the manuscript; M.B., M.F., A.O., N.D., J.R., G.D., C.H. collected the data; D.C.H., F.B. provided histological analysis; F.F. provided biological tests; all authors read and approved the final manuscript.

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References


Figures
Patient #1. Non-enhanced CT scan was apparently normal (a), although Hounsfield CSF values were slightly higher in frontal convexity area (HU +30 ±7) than in ventricles or occipital areas (HU +7 ±5). No enhancement was observed on CT (not shown). MRI FLAIR sequence displayed diffuse high signal of CSF bathing frontal cortex (b), possibly due to a high protein concentration. Slices were taken 1cm left from sagittal axis, besides sagittal vein (inset, black line). Slight asymmetric frontal pachymeningitis is
associated with typical ‘sugar-coated’ leptomeningeal enhancement (c). CSF appears diffusely abnormal on FLAIR (d) and diffusion sequences (e). At onset, the patient displayed both an abnormal CSF signal and pachy- and leptomeningeal lesions (f, g, h). Although he received only 3 days of high-dose steroids and refused further treatment, his clinical features rapidly returned to normal. Although all lesions had improved by month 2, slight lesions persisted (i, j, k). At follow-up in month 12, minor lesions (enhanced FLAIR and diffusion) were still present on the left frontal pole and a lesion was visible on the right frontal base (not shown).
Figure 2

**Patient #1, meningeal biopsy (H&E).** (A) Meninges were thick and fibrotic with (B) central fibrinoid necrosis surrounded by a few histiocytes without typical rheumatoid nodule. (C) Plasma cells were numerous in hyaline fibrosis (arrow).

Figure 3
**Patient #2.** Pachymeningitis predominates on falx cerebri and left frontal convexity (a). No leptomeningitis was visible but FLAIR-enhanced sequences were not performed. CSF close to the falx displayed high signal on FLAIR sequence (b) and restricted diffusivity (c). At month 3 following steroid initiation, pachymeningitis was dramatically improved (d), and abnormal CSF signal had completely disappeared (e, f). Two months after steroid tapering, a minor clinical relapse (slight headache and recurring paroxysmal signs) was associated with an MRI relapse (g,h,i), so rituximab was initiated. Month 0 is the day of diagnosis, 14 years after clinical onset of headache. Rows: MRI sequences T1-enhanced, FLAIR and diffusion. Lines: timepoints at months 0, 3 and 8.
Figure 4

Patient #2, meningeal biopsy (H&E, and immunostains). (A) Meninges were fibrotic and covered by a dense lymphoplasmocytic infiltrate without necrosis. (B) Lymphocytic infiltrate was predominantly composed of T cells stained by CD4 antibody. (C) Plasma cells were also numerous stained by CD138 antibody.
Figure 5

(A) Probable rheumatoid nodule in right lung (at least three others were observed; Patient #1). (B, C) Whole-body FDG-PET was negative on lung, meninges and articulations. (B: Patients #1; C: #2).