**Title:** Monoclonal gammopathy, arthralgias, and recurrent fever syndrome: a new autoinflammatory syndrome?

**Running head:** Monoclonal gammopathy and recurrent fever.

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## Abstract

### Objective

The objective of this work was to describe a new autoinflammatory syndrome with recurrent fever and monoclonal gammopathy that differs from Schnitzler syndrome.

### Methods

We conducted a retrospective study of patients with monoclonal gammopathy and recurrent fever of unknown origin.

### Results

Five patients were included in the description. The median age at onset of symptoms was 44 years old. The median frequency of fever attacks was 6 episodes per year. In the absence of treatment, the median duration of fevers was 3 days.

### Conclusion

This new autoinflammatory syndrome is defined by an association between monoclonal gammopathy, arthralgias, and recurrent fever (MGARF).

**Introduction:**

Autoinflammatory diseases were recently defined by an international consortium of experts of autoinflammatory diseases as: "clinical disorders caused by defect(s) or dysregulation of the innate immune system, characterized by recurrent or continuous inflammation (elevated acute phase reactants-APR) and the lack of a primary pathogenic role for the adaptive immune system." (1). The main symptoms of autoinflammatory diseases are fever, cutaneous rash, arthritis or arthralgia and abdominal pain.

Schnitzler syndrome (SS) is an autoinflammatory disease with recurrent fever (RF), secondary to dysregulation of the interleukin (IL)-1 pathway (2–4). The cornerstones of SS are a chronic urticarial rash and a monoclonal IgM or less frequent IgG gammopathy (3). It remains unclear if the monoclonal gammopathy causes IL-1 pathway dysregulation and leads to symptoms or if chronic dysregulation of the IL-1 pathway leads to development of a monoclonal gammopathy. Despite this lack of understanding, the association between an autoinflammatory syndrome and monoclonal gammopathy is very interesting and could lead to the creation of a new group of autoinflammatory diseases. The aim of this work was to describe a new autoinflammatory syndrome in which RF is associated with a monoclonal gammopathy and does not meet the criteria for SS (3).

**Patients and Methods:**

*Patients:*

We performed a retrospective multi-center study coordinated by the French reference center for autoinflammatory diseases (CEREMAIA, French acronym). Patients from CEREMAIA database with suspected autoinflammatory diseases who presented with RF and a monoclonal gammopathy were selected and their files were reviewed. For describing the new autoinflammatory syndrome, we applied the following inclusion criteria: i) recurrent fever of unknown origin with at least three episodes of fever in more than 6 months and occurring with an elevated C-reactive protein (CRP); ii) the presence of one of the following symptoms during fever attacks: bone pain, arthralgia or arthritis, myalgia, abdominal pain, cutaneous rash; and iii) the presence of a monoclonal gammopathy by blood protein electrophoresis without evidence for multiple myeloma. To confirm the unknown origin of the fever, patients should have had a clinical examination and the following tests should have been performed: blood cultures, HIV, HCV, HBV serology, thoraco-abdominal-pelvic computed tomography for neoplasia, and anti-nuclear and anti-neutrophil cytoplasmic antibody testing to exclude autoimmune disease. Genetic testing for autoinflammatory diseases was not required.

Patients with a definite autoimmune or autoinflammatory disease, especially SS, as well as an infectious or a neoplastic disease were not included in this study.

*Ethics:*

All patients gave they informed consent, and the study followed Helsinki declaration. Ethic board approval was not required in accordance to the French law, and our institutional review board.

**Results:**

*Patients:*

The CEREMAIA database included 751 patients with an autoinflammatory disease. Sixteen patients displayed monoclonal gammopathy and RF but no defined diagnosis. Eleven were excluded from the final description because of genetically confirmed monogenic RF (n=2); hypocomplementemic urticarial vasculitis (n=1); SS fulfilled criteria (n=6); recent kidney neoplasm diagnosis (n=1); lost of follow-up (n=1) (Figure 1, flow chart).

*Syndrome description:*

The 5 remaining patients met all the inclusion criteria; their features are summed up in Table 1. Three patients (60%) were men. The median age at the beginning of symptoms was 44 years old (range: 30 to 71 years old). The median frequency was 6 episodes of fever per year (range: 3 to 12 episodes per year). The median length of the fevers without treatment was 3 days (extreme values: 2 to 12). The most frequently associated symptom was muscle pain, which was found in all patients (100%). Arthralgia was the second most-frequent symptom that was found in four patients (80%) and involved the spine (40%) or multiple peripheric joints (40%). The phenotypes seemed to be stable during follow-up, and no spontaneous remission was mentioned. None of the patients had bone pain, abdominal pain, arthritis or skin involvement. There was no indication of bone remodeling in the plain X-rays. One patient had recurrent episodes of exudative neutrophilic aseptic pleuritis during fever attacks without evidence for malignancy in a pleural biopsy. The most frequent isotype for the monoclonal gammopathy was IgG, which was found in 3 patients (60%), and the amount ranged from “barely detectable” to 19.8 g/L with a median value of 6.6 g/L. For the light chain, lambda was the most frequent and was found in 3 patients (60%). There was no other type than IgG or IgM. All patients had elevated polymorphonuclear values and CRP with a median of 156 mg/L (range: 84 to 250

mg/L) during fever attacks. Molecular investigations of monogenic autoinflammatory diseases were performed for three of them: the *MEFV* (exon 10) and *TNFRSF1A* (exons 2,3 and 4) genes were analyzed by Sanger sequencing for one patient, and for the two others, the *TNFRSF1A, MEFV, NLRP3, MVK* and *NLRC4* genes were analyzed using next-generation sequencing. No deleterious germ line or somatic mutations were identified in these three patients.

*Treatment attempted:*

Two patients were treated with 1 mg of colchicine per day without success. One patient had been treated with 0.7 mg/kg/day prednisolone during fever attacks without success. Two patients had been treated with the IL-1 receptor antagonist anakinra during attacks and had a good response.

**Discussion:**

We report five patients with a new clinical and biological autoinflammatory syndrome. This syndrome should be considered only after careful examination of differential diagnosis, especially SS. This syndrome occurs in adults older than 30 years old who have no prior symptoms. Symptoms included recurrent fevers lasting 3 to 12 days, arthralgia involving the peripheric joints or the spine and myalgia. This condition could also be associated with pleuritis. Biologically, the syndrome is defined by a monoclonal gammopathy of IgG or IgM without specificity for the light chain as well as elevated CRP during fever attacks. Those features are summarized in Figure 2.A.

This syndrome shares common features with SS, including recurrent fever, arthralgia and monoclonal gammopathy. The main difference is the absence of skin involvement in our cases, which is a major criterion for SS. Without chronic urticaria, a diagnosis of SS cannot be confirmed (3). Interestingly, there was no sign of osteosclerosis or bone remodeling in our cases, whereas it is an important finding in SS.

SS is believed to be an autoinflammatory syndrome because of RF, elevated APR, dysregulation of pro-inflammatory cytokines, and the efficiency of anti-IL-1 biotherapies (2,4–6). The new syndrome described in this article is characterized by RF, elevated APR, and the efficacy of anti-IL-1 therapy. Systematic genetic testing or a cytokine profile study has not been done for this new syndrome, but there is no evidence for autoimmunity or infectious disease, so an autoinflammatory disease seems likely. The significance of the monoclonal gammopathy remains unclear. Hypotheses can be formed from what is known about SS. The first hypothesis is that the monoclonal isotype has auto-antibody activity that triggers an IL-1 cascade. This hypothesis is supported in SS by the presence of anti-IL-1α antibodies in some patients, which may increase the half-life of this pro-inflammatory cytokine (7) as well as the efficacy of treatments that reduce the amount of monoclonal gammopathy (8). However, this hypothesis is

currently not supported, and the presence and pathogenic nature of anti-IL-1α antibodies have not been confirmed. The second hypothesis, which is popular in SS research, is that symptoms are secondary to an inflammatory cytokine dysregulation that results in development of a monoclonal gammopathy. This hypothesis is supported by a delayed development of monoclonal gammopathy in some cases (9) and by the discovery of somatic mosaic mutations of the *NLRP3* gene restricted to a myeloid lineage in two patients affected with variant-type SS (10); however, this finding was not confirmed in a recent larger series (11). Next-generation sequencing was performed in two patients, and no deleterious mutations in the *MEFV*, *MVK*, *NLRP3*, *NLRC4* and *TNFRSF1A* genes were identified. Without certainty about the pathogenetic explanation of this syndrome, this disorder seems to be on the border between monoclonal-gammopathies and autoinflammatory disease, which is shown in a scheme (Figure 2.B).

However, the association of a monoclonal gammopathy with autoinflammatory symptoms in Schnitzler syndrome and in our syndrome does not seem to be a coincidence, and a new category of syndrome should be created and could be named Monoclonal Gammopathy of Inflammatory Significance (MGIS) based on other categories, such as what has been done for Monoclonal Gammopathy of Renal Significance (MGRS) and Monoclonal Gammopathy of Cutaneous Significance (MGCS) (12). This group would include SS and the syndrome described in this article.

Another secondary but interesting point in this study is that SS remains underdiagnosed. Among our 16 patients with recurrent fever and a monoclonal gammopathy, 6 (37.5%) fulfilled the diagnostic criteria for SS. All of them had a monoclonal gammopathy with an IgG isotype. Despite inclusion of an IgG monoclonal gammopathy in the diagnostic criteria (3), this variant of SS is not always recognized by clinicians.

**Conclusion:**

We report the first series of a new gammopathy-related autoinflammatory syndrome that is different from Schnitzler syndrome due to the absence of skin involvement. This new syndrome could be named monoclonal gammopathy, arthralgias, and recurrent fever syndrome (MGARF), which includes the three main features of the syndrome.

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## Figure legends

**Figure 1:** Flow chart of the study

Abbreviations: MG = monoclonal gammopathy; RF = recurrent fever; FMF = familial Mediterranean fever; CAPS = cryopyrin-associated periodic syndromes; HUV = hypocomplementemic urticarial vasculitis; SS = Schnitzler syndrome.

**Figure 2:**

Panel A: Main clinical features of the patients.

Panel B: Proposition of a nosological classification of this entity in the spectrum of autoinflammatory diseases and monoclonal gammopathies.

Abbreviations: MGUS = monoclonal gammopathy of undetermined significance; MGRS = monoclonal gammopathy of renal significance; MGCS = monoclonal gammopathy of cutaneous significance; MGIS = monoclonal-gammopathy of inflammatory significance; SS = Schnitzler syndrome.

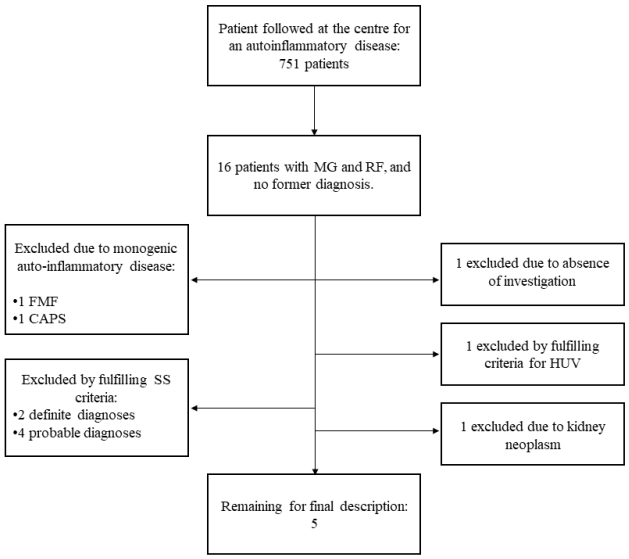


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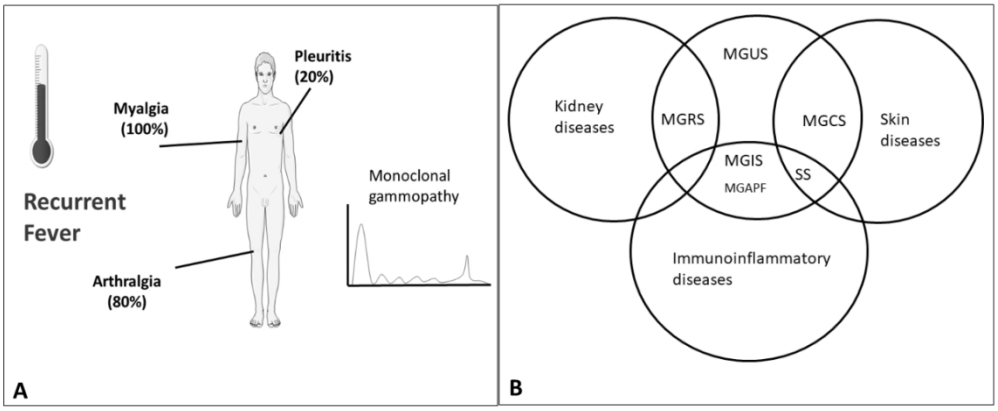
**Table:**

Table 1: Main clinical and biological features of the patients.

| Patient | Sex | Ethnicity | Family history | Age at onset of symptoms (years) | Frequency of fever attacks (per year) | Length of the fever (days) | Joint pain (location) | Muscle pain | Type of monoclonal gammopathy |
|---|---|---|---|---|---|---|---|---|---|
| **1** | M | Caucasian | 1 sister SLE* | 44 | 6 | 3 | Yes (spine) | Yes | IgM lambda |
| **2** | W | Caucasian | Mother: psoriasis | 30 | 12 | 4 | Yes (spine) | Yes | IgG lambda |
| **3** | W | Caucasian | None | 71 | 3 | 2 | No | Yes | IgG kappa and IgM kappa |
| **4** | M | Caucasian | None | 39 | 12 | 3 | Yes (PA‡) | Yes | IgG lambda |
| **5** | M | Caucasian | None | 71 | 4 | 12 | Yes (PA‡) | Yes | IgM kappa |

Legends: *systemic lupus erythematosus; ‡ polyarthralgia.

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