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Association of mastocytosis with inflammatory joint diseases: A series of 31 patients

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ABSTRACT

Objectives: We studied the clinical phenotypes and tolerance to treatments in a series of patients affected by both inflammatory joint diseases and mastocytosis.
Methods: This retrospective multicenter study was conducted on behalf of 3 networks focused on mastocytosis, pediatric, and adults' inflammatory joint diseases. Patients who displayed both mastocytosis and inflammatory joint diseases were included.
Results: A total of 31 patients were included. They had spondyloarthritis (SpA) (16 patients), rheumatoid arthritis (6 patients), juvenile idiopathic arthritis (2 patients), and undifferentiated arthritis (7 patients). The median ages at diagnosis of *arthritis* and mastocytosis were 44 and 40.5 years, respectively. Disease-modifying anti-rheumatic drugs (DMARDs) were required in 22 patients, comprising mostly

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methotrexate (13 patients), salazopyrin (8 patients), anti-tumor-necrosis-factor agents (7 patients), and corticosteroids (9 patients). They were well tolerated. Adverse events occurred in 2/24 patients receiving non-steroidal anti-inflammatory drugs. The prevalence of SpA among the 600 patients included in the mastocytosis cohort was 2.33%, which is significantly higher than the prevalence of SpA in the French population ($p < 0.001$).

Conclusions: This study suggests that mastocytosis is associated with a higher prevalence of SpA than expected, and that DMARDs, notably anti-TNFα agents, are well tolerated in patients with mastocytosis. Mast cells might be involved in the development of SpA.

Introduction

Mast cells (MCs) were initially described as central effector cells of IgE-mediated immediate-type immune responses. There is now increasing evidence that these cells also play a critical role in the pathogenesis of some chronic inflammatory disorders, including inflammatory joint diseases [1–3]. However, the association of mastocytosis and inflammatory joint diseases has not been investigated.

Herein, we undertook a retrospective study to identify patients who display both inflammatory joint diseases and mastocytosis through 3 networks: the French referral center for mastocytosis (Centre National de reference des mastocytoses—CEREMAST), the French collaborative work group of rheumatologists (Club Rhumatismes et Inflammation—CRI), and the French Society for Pediatric Rheumatology (Société Francophone pour la rhumatologie et les maladies inflammatoires en pédiatrie—SOFREMIP). We assessed the clinical phenotypes of inflammatory joint diseases in these patients and determined the tolerance to treatment. Finally, we tried to clarify the relationship between inflammatory joint diseases and mastocytosis.

Patients and methods

This retrospective, multicenter study was conducted on the behalf of CEREMAST, CRI, and SOFREMIP. We retrospectively collected the medical records from patients who were followed up between September 2012 and September 2013 in rheumatology, internal medicine, hematology, or pediatric departments in French hospitals. Patients were included if they displayed both mastocytosis and inflammatory joint diseases. Diagnosis of mastocytosis was based on the WHO criteria [4] classifying mastocytosis as cutaneous mastocytosis (CM), indolent systemic mastocytosis (ISM), aggressive systemic mastocytosis (ASM), and mast cell activation syndrome (MCAS). Inflammatory joint diseases comprised (1) rheumatoid arthritis (RA), according to the 2010 ACR/EULAR classification criteria for RA [5]; (2) non-psoriatic or psoriatic spondyloarthritis, (SpA) according to the Assessment of SpondyloArthritis International Society (ASAS) classification criteria for axial and peripheral SpA [6,7]; (3) juvenile idiopathic arthritis (JIA), according to the ILAR classification [8]; and (4) undifferentiated arthritis. The referring physicians were invited by mail to participate in this survey by completing a questionnaire sent online. We recorded demographic data, subtype of mastocytosis and of arthritis, treatments and their tolerance, and clinical and biological autoimmune features. The diagnosis of RA, SpA, or JIA was always carried out by a qualified rheumatologist and we checked that the diagnosis fulfilled the criteria of the set standards listed above. Results of synovial biopsy were also compiled. An exact binomial test was used to compare the prevalence of SpA and RA in the French national CEREMAST database to the estimated prevalence of SpA and RA in the French general population (R software version 2.15.0). A $p < 0.05$ was considered statistically significant. In accordance with French regulations, no ethical committee agreement was needed for this retrospective study.

Results

We identified 31 patients with inflammatory joint diseases and mastocytosis referred through CEREMAST (26 patients), CRI (3 patients), and SOFREMIP (2 patients). Demographic and clinical features of the patients are shown in the Table. Arthritis comprised psoriatic and non-psoriatic SpA (16 patients), RA (6 patients), JIA (2 patients), and undifferentiated arthritis, either non-destructive (6 patients) or destructive (1 patient) without serological markers. SpA was mostly axial (14 patients), Eleven patients were positive for HLA B27 and 11 had sacroiliitis on imaging. CM, ISM, and MCAS were diagnosed in 10, 19, and 2 patients, respectively. The median ages at diagnosis of inflammatory arthritis and that of mastocytosis were 44 years (range: 17–65) and 40.5 years (range: day 1–65) respectively. In 23 (74%) patients, the diagnosis of mastocytosis preceded that of *arthritis* with a median interval of 4 years (range: 1.3–16 years). In 3 (10.2%) patients, mastocytosis and arthritis were simultaneously discovered. In 5 (17.3%) patients, the diagnosis of arthritis preceded that of mastocytosis with a median interval of 8 years (range: 2–17 years). Unfortunately, the age at which manifestations of each condition first started to appear, especially mastocytosis, was missing in most patients. Autoimmune disease was associated with arthritis in 6 patients (Table). A synovial biopsy showed a non-specific inflammatory infiltrate without excess of mast cells in 1 patient with JIA.

Disease-modifying-anti-rheumatic drugs (DMARDs) were required in 22/31 (71%) patients and were well tolerated. They comprised mostly methotrexate (13 patients), salazopyrin (8 patients), corticosteroids (9 patients), and anti-tumor-necrosis-factor (TNF) agents (7 patients). Of the 24 patients who received non-steroidal anti-inflammatory drugs (NSAIDs), 2 developed labial edema and anaphylactic shock. None of these treatments resulted in changes to the course of mastocytosis.

The estimated prevalence of RA in the French population is 0.31% and that of SpA is 0.30–0.43% [9–11]. It is unknown in JIA. CEREMAST was used to identify 14 of the 16 SpA patients and 4 of the 6 RA patients. Considering that 600 patients were followed up in this mastocytosis network during the year of the study, the prevalences of SpA and of RA in this cohort were 2.33% and 0.66%, respectively. There was no significant difference between the expected and observed prevalence of RA in our mastocytosis cohort ($p = 0.12$). Conversely, the observed prevalence of SpA in this cohort was significantly higher than the expected minimal and maximal of this disease ($p < 0.001$).

Discussion

In this French retrospective study, we report for the first time a series of patients displaying both various types of inflammatory joint diseases and mastocytosis. Arthritis was often severe because