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Association between rheumatoid arthritis and systemic mastocytosis: a case report and literature review

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Abstract

Classically, mast cells (MC) are considered as important actors of the innate immune response playing a pivotal role in IgE-mediated allergic and anti-parasite responses. In the last two decades, many experimental evidences demonstrated that these hematopoietic-derived cells present in both connective and mucosal tissues are also key modulators of the adaptive immune response and could contribute to autoimmune disease notably in rheumatoid arthritis (RA). Recently, Bader-Meunier *et al*., reported a series of 31 patients suffering from inflammatory joint diseases associated with mastocytosis, suggesting that mastocytosis was associated with a higher prevalence in spondyloarthritis. We discuss here the possible link between chronic inflammatory arthritis and mastocytosis through the report of a clinical case describing a patient developing RA after a long history of mastocytosis. Of great interest, antihistamine treatment alone was sufficient to treat RA in this patient.

Key words: mastocytosis - rheumatoid arthritis – osteoporosis – mast cells

Case report

Our patient is a Caucasian male aged 78 years. His past medical history included a chronic obstructive pulmonary disease that led the patient to smoking cessation in 1975 (30 Pack-year). In 1999, patient was admitted to rheumatology department for multiple recurrent bone fractures (vertebral compression fracture, pelvis, acetabulum, ribs, feet, left hip bone, sternum) associated with urticaria pigmentosa. Diagnosis of bone and cutaneous mastocytosis was established after bone and skin biopsies analysis. Furthermore, DEXA analysis of bone mineral density revealed major osteoporosis (T-score at – 4.1 on lumbar spine and -2.6 on hip).

Since establishment of the diagnosis, the patient had received bisphosphonates (injectable pamidronate for two years, then oral alendronate) associated with vitamin D (400UI/d) and calcium (1 g/d) supplementation. He was also prescribed a daily oral intake of selective H1 receptor antagonist (cetirizine 10 mg bid). After two years of anti-osteoporotic treatment, the patient did not present any new fractures and showed an improvement of bone mineral density with stable and normal values leading to bisphophonates discontinuation in 2010. In the meantime, the patient decided to stop antihistamine treatment on his own in 2005.

In june 2012, mastocytosis flared up with severe cutaneous signs and new lumbar spine fracture. High tryptase levels (>20µg/L), indicative of systemic mastocytosis, were found at this time. Patient underwent L5 vertebroplasty and antihistamine treatment was reintroduced (cetirizine 10 mg/d). Six months later, he was admitted to our hospital with joint pain and swelling of hands, and inflammatory pain of the shoulder and pelvic girdles.

Blood tests showed persistent high levels of tryptase (52 µg/L) raising the question of patient good compliance to cetirizine treatment. Elevated C-reactive protein (66 mg/L) and accelerated erythrocyte sedimentation rate (46 mm at 1st hour) were found. ACPA were present at a high titer (> 250 UI/L) whereas HLA-B27 status was negative. At follow-up, X-

rays imaging and ultrasonography showed active inflammatory and erosive polyarthritis. Rheumatoid factors, initially negative, became positive in September 2013 (RF-IgM: 46 UI/L). Clinical presentation was consistent with RA diagnosis according to ACR-EULAR 2010 criteria [1], as others causes of chronic inflammatory arthritis were eliminated. Methotrexate was contraindicated by pulmonary disorders and the presence of non hypermetabolic lung nodules. He was prescribed cortisone 7.5mg/day(0.1mg/Kg), associated with painkillers (tramadol hydrochloride LP 100 mg and acetaminophen 1 g) on demand and received compliance recommendations for regular intake of cetirizine 10 mg/d

Corticosteroids were progressively decreased then stopped after 3 months and mastocytosis and RA remained inactive (DAS28 at 2.3 and Tryptase levels < 20µg/L); during the three following years under antihistamine treatment alone. Last examination, perfomed in june 2016, confirmed none evolutive intracarpal, interphalangeal and metacarpophalangeal radiographic lesions without active synovitis.

Discussion

Mastocytosis and Mast cells

This patient suffered from mastocytosis diagnosed 15 years ago. Mastocytosis is a disorder characterized by mast cell proliferation and accumulation within various organs. Mastocytosis is generally classified into two major types, the cutaneous mastocytosis (CM) corresponding to the accumulation of MC only in skin and the systemic mastocytosis (SM) where the accumulation is occurring in one or more organs, each could be subdivided in a total of seven different categories[2]. Little is known about mastocytosis etiology, however, abnormal mast cell activation/survival or proliferation is most commonly associated with auto-activating mutation on the tyrosine kinase receptor c-KIT[3].

Three types of CM are identified, urticaria pigmentosa, diffuse CM and mastocytoma of the skin, usually affecting people in childhood. The most frequently form of CM is urticaria pigmentosa characterized by yellow-brown macules located at the trunk or extremities of the body. Diffuse CM is more severe and it manifests by blisters and bullae.

SM are divided into indolent SM (ISM), SM with an associated hematopoietic non-mast cell lineage disease, aggressive SM and mast cell leukemia (MCL).

Patients affected by ISM present skin lesions, similar to urticaria pigmentosa, and bone marrow infiltration[4]. The aggressive form of mastocytosis is associated with an important infiltration of tissues and MCL is characterized by infiltration with atypic or immature Mast Cells (MCs) in organs and bone marrow.

Organ infiltration by MCs can lead to organomegaly, impairment or loss of organ function.

The different forms of mastocytosis depend on the type of MCs involved and the type and the quantity of mediators released. The evolution of CM into SM, like in our patient, is known and correlates with MCs proliferation in bones and organs[5].

MCs derive from hematopoietic stem cells. They circulate in the blood to migrate to vascularized tissues where they mature under cytokines control, particularly the stem cell factor. They contain several mediators, i.e. histamine, proteases, cytokines, chemokines, growth factors, arachidonic acid metabolites, and reactive oxygen and nitrogen species. All these mediators can be secreted by MCs after degranulation and are involved in different functions of MCs[6].

MCs can be subdivided according to their serine proteases expression (tryptase or chymase only, or both tryptase and chymase[7] or to staining characteristics of their granules and localization (connective tissue MC posseses safranin positive granules whereas mucosal mast cells are safranin-negative)[8].

MCs can be activated by many stimuli, via the high-affinity immunoglobulin E (IgE) receptor (FcεRI) in allergic response, after IgE cross-linking which triggers Lyn and Syk kinase cascade[9]. Pathogens such as bacteria and viruses can result on direct MCs activation through pattern recognition receptor. Other activators are cytokines, chemokines, immunoglobulin G via Fcγ receptor[2].

Once activated, MCs are considered as double-edged sword. In innate and acquired immunity MCs are known to act rapidly via toll-like receptors, complement receptors and Fc receptors and activate neutrophils, dendritic cells and T cells thanks to their mediators. MCs can also phagocyte bacteria and protect against viruses by the recruitment of T cells and natural killers cells [10]. Another function of MCs is their role in host defense against parasites, via IgE response[11].

Although MCs have protective effects, an abnormal activation can promote inflammatory disorders. They are mostly described for their role in anaphylaxis and allergic response by hypersensitivity reactions via IgE binding[12]. Accumulation of MCs mediators in airway smooth muscle are correlated with asthma activity [13]. Moreover, evidence from their overabundant representation/activity in intestine is amply described in inflammatory bowel disease (Crohn's disease or ulcerative colitis) and irritable bowel[14].

More controversially, MCs may also play a role in cancer by promoting growth of tumors via angiogenesis factors[14].

Mastocytosis and osteoporosis

Osteoporosis and vertebral fracture are frequent in patients with systemic mastocytosis with respectively 31% and 17% in a cohort of 75 adult patients[15]. Pathogenesis of mastocytosis-related osteoporosis is not fully understood but relapse of mediators by mast cells within bone marrow is thought to be central. Histamine acts directly on osteoclasts by promoting osteoclast formation directly through paracrine action on the precursors and indirectly through

increased osteoblasts secretion of RANKL[16]. Moreover, heparin and bone resorptive cytokines (IL-1, IL-6 TNFalpha) are known to play a role in osteoclast activation by mast cells[17].

Histomorphometric studies performed in systemic mastocytosis patients have revealed an increased number of osteoclasts due to presence of mast cells, leading to osteoporosis.[18].

Multiple bone fracture associated to high tryptase levels indicated that our patient was suffering from mastocytosis and mastocytosis induced-osteoporosis. Treatment with bisphosphonates and Vitamin D supplementation in association with antihistaminergic drugs leads to absence of bone complication during 10 years with normal BMD values. Such beneficial effects of bisphosphonates treatment in patient suffering from osteoporosis secondary to mastocytosis was already reported [15, 17, 19-22]. Our patient underwent a vertebroplasty after traumatic spinal fracture only 2 years after bisphosphonates cessation but 7 years after patient quit antihistamine treatment.

Six months later, our patient presented signs of inflammatory joint disease; blood tests and medical imaging led to the diagnosis of rheumatoid arthritis according to ACR/EULAR 2010 rheumatoid arthritis criteria[23].

Mast Cells and Rheumatoid Arthritis

Clinical implication of MCs in inflammatory arthritis is not yet well defined but has been established in several studies. Increased density of MCs in synovial tissues is found in patients with RA when compared to osteoarthritis (OA) and normal joints patients, density of mast cells correlated positively with disease severity index and swollen joint counts[24]. RA-associated mast cell hyperplasia is associated with changes in mast cells subset regarding their protease expression. In normal synovium, tryptase and chimase double positive mast cells (MC_{TC}) are mainly found. In early inflammatory rheumatoid arthritis, specific expansion of

tryptase only positive mast cells (MC_T) is observed followed by increases of MC_{TC} in established or chronic disease[25, 26].

Mast cells specific mediators such as histamine and tryptase are elevated in synovial fluid from RA patients[27]. Mast cells are also the main IL-17 producing cells in synovium of established RA and spondyloarthritic patient[28] contributing to synovial inflammation[29].

Several MCs activation pathways have been described in RA. In addition to toll-like receptors (TLR2, 4 and endosomal TLRs) or cytokines (IL-3, IL4 and the more recently studied IL-33[30]) mediated activation, Suurmond *et al.* recently demonstrated that MCs could be activated by ACPA immune complex in a citrulline-dependent manner through crosslinking FcγRIIA [31]. Mast cells can also interact directly with T cell, contributing to T cell subset expansion[32] or activation[33] but also changing their own phenotype [34].

It is plausible that MCs response in RA results from integrated signals of multiple activation pathways contributing to the chronicity of disease.

Consequences of MCs activation could easily be linked to pathogenesis of RA. Indeed, once activated (by ACPA for instance), MCs produce large amount of IL-8, a potent activator of neutrophil chemotaxis[31]. MCs can also produce IL-1, TNF and IL-17, all responsible for synovial fibroblast activation and deleterious consequences on cartilage. Finally, MCs are thought to be partly responsible for drastic tissue remodeling occurring in RA. MCs are often found in the vicinity of blood synovial vessels and MC-mediators (VEGF, tryptase, chymase) are known to be potent angiogenic factors[35]. Matrix metalloproteinases (MMPs) secretion and osteoclasts activation responsible for cartilage breakdown and bone erosion, two hallmarks of RA, could be considered as consequence of MCs mediators' release. As mentioned above, MCs could activate synovial fibroblasts but also induce MMPs release by chondrocyte. Moreover, tryptase is recognized as a potent activator of MMPs[36].

Mechanisms explaining systemic mastocytosis-associated osteoporosis are supposed to be identical in RA, possibly though a direct effect of histamine on osteoclasts[37].

Association between MCs and inflammatory arthritis can lead to new considerations in inflammatory arthritis therapy. Recently, Bader-Meunier *et al*. reported the association between mastocytosis and spondyloarthritis in a series of 31 patients. They conclude that mastocytosis was associated with a higher prevalence of SpA and that TNF inhibitors were well tolerated in these patients[38]. On the other hand, inhibiting the c-kit receptor by imatinib, decreased MCs numbers in rheumatoid synovium extracted from patients[39], whereas sulfasalazine, a drug used to treat peripheral SpA, was proven to have an effect on MCs[29]. In our case, antihistamine and symptomatic treatment were sufficient at a first time to manage arthritis progression while controlling MCs activity.

Conclusion

Patients with mastocytosis should be closely monitored for rheumatoid arthritis or other autoimmune diseases. One should also consider that case of mastocytosis-associated autoimmune disease are underestimated since signs and symptoms of mastocytosis are unspecific and overlap with many other diseases, correct diagnosis may be difficult and is often made later than first symptoms[4].

This case report and the literature provide data in favor of a possible development of autoimmune disease secondary to mastocytosis. Therapeutic management of these patients should take into account both mastocytosis and inflammatory arthritis.

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Approving final version of manuscript: IL, MK, JH, DL, PN, JYJ, ICV, DM. ICV takes responsibility for the integrity of the data analysis.

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