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【 REVIEW ARTICLE 】

The Expanding Spectrum of Autoinflammatory Diseases

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Abstract:
Autoinflammatory diseases are systemic disorders caused by genetic or acquired abnormalities in certain signaling pathways of the innate immune system. Dysregulated activation of the inflammasome, i.e. molecular platforms responsible for the activation of caspase-1 and production of interleukin-1β, causes autoinflammation. Familial Mediterranean fever (FMF), the most common genetic autoinflammatory disease, is characterized by a periodic fever and serositis. The complex and heterogeneous genetic background of Japanese FMF patients, accompanied by potential overlap with other rheumatic diseases, suggests crosstalk between genetic and environmental factors. Recently, FMF has been recognized as being part of a spectrum of autoinflammatory syndromes named pyrin-associated autoinflammatory diseases. The discovery of a new monogenic autoinflammatory disease, A20 haploinsufficiency, may provide novel insights into early-onset Behçet's-like diseases. In contrast, adult-onset Still's disease and Schnitzler's syndrome are acquired autoinflammatory diseases without a monogenic abnormality. Although the concept of autoinflammatory diseases originally applied to monogenic hereditary recurrent fevers, it has been expanded to include non-genetic complex autoinflammatory diseases. Information concerning monogenic autoinflammatory diseases may prove useful for elucidating the molecular mechanisms underlying non-genetic autoinflammatory diseases.

Key words: autoinflammatory diseases, A20 haploinsufficiency Behçet's disease, inflammasome, familial Mediterranean fever, Schnitzler's syndrome

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Introduction

The concept of autoinflammation was driven by the identification of monogenic diseases characterized by unprovoked inflammation in the absence of autoantibodies that were caused by abnormalities of the innate immune system (1). Hence, the elucidation of mechanisms underlying inflammatory cytokine amplification cascades may lead to new therapeutic approaches for autoinflammatory diseases (AIDs) (2), and genetic abnormalities in inflammasome-related molecules have indeed led to a better understanding of the novel mechanisms involved in sensing infectious or noninfectious danger signals by the innate immune system (3).

Inflammasomes are intracellular multicomplex proteins that consist of sensors, adaptor proteins, and caspases (3), and mutations in inflammasome components lead to autoinflammatory diseases (4). Thus, inflammasomes are involved in most well-known autoinflammatory diseases, and the intracellular protein complexes act as cognate innate immune receptors (4). Upon sensing pathogen- or danger-associated molecular patterns, inflammasomes assemble into a molecular platform, resulting in caspase-1 activation and the release of an activated form of interleukin (IL)-1β (5). These processes are attributed to the pyrin inflammasome and mutations in *MEFV*, which codes for the pyrin, causing familial Mediterranean fever (FMF) (6). Furthermore, along with hereditary monogenic autoinflammatory diseases, other symptoms encountered in rheumatic disorders that are presumed to be part of the group of polygenic autoinflammatory diseases (2) include polygenic or multifocal autoinflammatory disease, such as adult-onset Still's disease (AOSD), Behçet's disease (BD), and Schnitzler's syndrome (SchS) (7, 8).

This review focuses on these monogenic disorders, including FMF, and polygenic autoinflammatory diseases and highlights their phenotypic presentation, evaluation, and clinical management.

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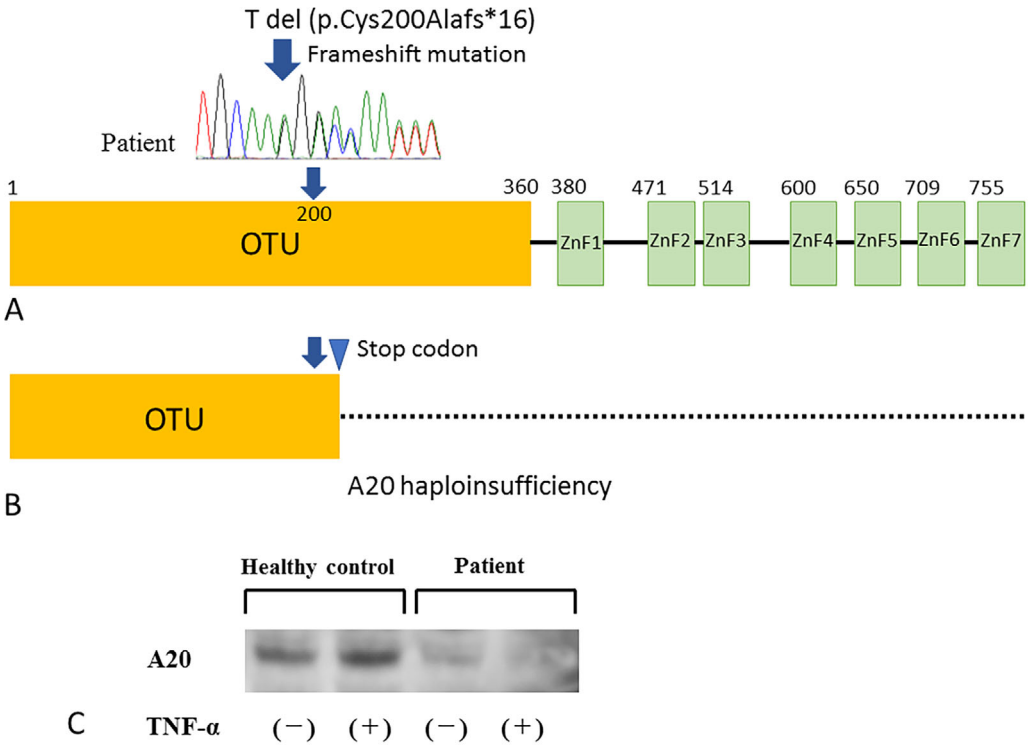

Figure 1. **The A20/TNFAIP3 mutation observed in our case. Schematic illustration of the A20 protein and A20/TNFAIP3 mutation (arrows) (p.Cys200Alafs*16) (original figure). A: The c597-598 T deletion (arrow) variant induced a frameshift and premature stop codon in the ovarian tumor (OTU) domain in our patient. B: A20 disruption of both OTU and zinc finger (ZnF) functional domains, resulting in A20 haploinsufficiency. C: Reduced A20 protein levels in the patient's peripheral blood mononuclear cells were observed compared to healthy controls, despite stimulation with tumor necrosis factor (TNF)-α (10 ng/mL for 24 h), on immunoblotting. The protein A20 consists of an OTU and seven ZnF domains. Mutations are indicated with arrows, including the mutation observed in our case (circled). This figure is modified from reference 31. Modification/reproduction of this figure is permitted from the publisher.**

FMF

Pathogenesis and genetic abnormalities

FMF is a common monogenic autoinflammatory disease that is characterized by a periodic fever, serositis, and synovitis (9). This disease is prevalent among Mediterranean populations; however, cases have also been reported in non-related countries, including Japan (10). FMF is caused by mutations in *MEFV*, which encodes pyrin, and the disease is caused by gain-of-function mutations that lead to the formation of an additional protein complex, the pyrin inflammasome. Pyrin is regulated by phosphorylation of two serine residues in its domain, and is kept in the inactive state by binding with the 14-3-3 protein (11). Various bacterial toxins trigger the inactivation of Rho GTPase, resulting in the dephosphorylation of these serine residues and consequent pyrin inflammasome activation (Fig. 1) (12).

Most of the known pathogenic mutations in *MEFV* are in exon 10; however, exon 2 or exon 3 variants with low penetrance are frequently seen in the Japanese population (10) and are thought to be benign polymorphisms. Furthermore, as the carrier status of these benign *MEFV* polymorphisms may confer a lower activation threshold for pyrin inflammasome activation (13), it is necessary to better understand relevant gene-environment interactions and their potential implications on susceptibility to FMF. Mutations in *MEFV* cause multiple diseases, such as pyrin-associated autoinflammatory disease with neutrophilic dermatosis, among others (14); therefore, it has been proposed that FMF be classified as a pyrin-associated autoinflammatory disease (11).

Clinical features and treatments

FMF is typically diagnosed based on clinical findings of a recurrent self-limiting fever (>38°C) accompanied by serositis and synovitis (15), with each episode lasting about 1-3 days. The prevalence of febrile symptoms (95.5%), chest pain (pleuritis 35%), and arthritis (31.3%) among Japanese patients is comparable to that seen in Mediterranean FMF patients (10); in contrast, abdominal pain (peritonitis, 62.7%) and amyloid A (AA) amyloidosis association (3.7%) are less prevalent (10). Furthermore, patients with a typical FMF phenotype have a shorter fever duration, along with

pleuritis or peritonitis, and are likely to carry *MEFV* exon 10 mutations. Conversely, patients with atypical FMF phenotypes have a longer period of disease without characteristic serositis (pleuritic or peritonitis) and have *MEFV* exon 2 or exon 3 variants (10). Approximately 10% of all Japanese patients with FMF do not respond to colchicine (10), and although there is no consensus on the definition of colchicine resistance, The European Alliance of Associations for Rheumatology (EULAR) recommendations define resistant patients as those with ≥1 attack per month despite adherence to the sufficient dose of colchicine (2.5 mg/day) for at least 6 months (16). In addition, as IL-1β is the major cytokine in FMF, blockade therapy is recommended for patients resistant to colchicine, based on the pathogenesis of FMF (17).

Behçet's disease (BD) and BD-like syndromes

BD is a systemic inflammatory disease of unknown etiology that is characterized by recurrent oral and genital ulcers, uveitis, enterocolitis, skin manifestations, and inflammation in other organs (18). This disease frequently affects young adults and typically exhibits a geographic distribution throughout the ancient "Silk Road," with a substantially high prevalence in Turkey, Iran, South Korea, and Japan (19, 20). The pathogenesis of BD is thought to involve both autoimmune and autoinflammatory processes, suggesting that both innate and adaptive immune responses are associated with this disease (21). BD is a polygenic disease, and the penetration of individual loci is low (22); specifically, while the human leukocyte antigen (HLA)-B*51 displays the strongest genetic predisposition to BD, about 15% of healthy Japanese people possess this mutation, and 30% of patients with BD do not have it. Recently, genome-wide association analyses have revealed many BD susceptibility loci in inflammatory cytokines and related molecules, such as HLA-class 1, IL-1β, IL-12A, IL-23 receptor, and endoplasmic reticulum aminopeptidase 1 (22, 23). Enhanced neutrophil activity and elevated levels of IL-1β have been observed in both BD and autoinflammatory diseases, implying the presence of certain autoinflammatory aspects in the pathogenesis of BD, and congruently, treatment regimens, such as colchicine and antitumor necrosis factor (TNF) inhibitor, also show partial overlap between BD and autoinflammatory diseases.

Early-onset BD or BD-like disease

As BD often occurs at a young age, with 15-20% of all patients with BD developing the condition in childhood (24), it is essential to understand the genetic background of each patient for the differential diagnosis, as certain inflammatory diseases mimic BD symptoms. For example, it was recently reported that symptoms due to A20 haploinsufficiency syndrome (HA20), an important but emerging disorder, resemble those of BD (25) and that younger patients with BD with intestinal involvement may show concurrent trisomy 8-positive myelodysplastic syndromes (MDS), which can render BD symptoms refractory to immunosuppressive therapy (26). Thus, we next discuss these two important conditions and relevant recent case reports from our research group.

a. HA20

HA20 is a newly discovered monogenic disease that is caused by heterozygous mutations in the TNFAIP3 gene, which encodes the A20 protein (25). A20 contains an N-terminal ovarian tumor (OTU) and seven zinc finger (ZnF) domains in its C-terminus (27). A20 is a critical negative regulator of inflammation, as it inhibits NF-κB signaling, and it has recently been shown to restrict both autophagy and the interferon (IFN) regulatory factor pathway (30). Many HA20 patients suffer from BD-like symptoms at a relatively young age, such as oral aphthous ulcers, genital ulceration, and gastrointestinal symptoms, along with clinical symptoms of autoinflammatory and/or autoimmune diseases (25, 29). Multiple mutations have been reported in HA 20 patients with complicated manifestations and individual variation, but recent reports suggest that disruption of each part of an A20 domain is associated with corresponding clinical manifestations (27, 28). For example, Chen et al. reported that, compared with patients exhibiting mutations in the ZnF domains, HA20 patients with a mutation in the OTU and ZnF domains were more likely to have musculoskeletal disorders, whereas those with mutations in OTU or OTU and ZnF were more likely to be initially diagnosed with BD due to symptom similarity (27). Furthermore, some missense TNFAIP3 variants (lle310Thr and Gln709Arg) may not be pathogenic upon *in vitro* functional assays in Japanese patients (30). We previously described a 17-year-old Japanese boy with a TNFAIP3 mutation (Cys200Alafs*16) in the OTU domain of A20 (Fig. 1) who suffered from recurrent painful oral ulcers, epigastralgia, and a low-grade fever. His mother and sister also had oral and genital ulcers, and his sister was suspected of presenting with BD symptoms (31). Treatment with prednisolone relieved the clinical symptoms and improved the inflammation in this patient, and an investigation of the effects of this mutation in peripheral blood mononuclear cells (PBMCs) from this patient showed that the expression of A20 and IκB-α was suppressed, regardless of TNF-α administration (Fig. 1). These findings imply that haploinsufficiency of TNFAIP3, which leads to an impaired A20 expression, may be responsible for the exacerbated TNF-α mediated inflammation with BD-like symptoms (31). Nevertheless, data from a larger number of HA20 patients will be needed to catalog the clinical features and outcomes of this condition.

b. BD-like disorders and trisomy-8

A previous report has indicated that trisomy 8 is a frequent cytogenetic abnormality that may be involved in the onset of MDS by Fas-mediated apoptosis (32). In addition, the association between BD-like disorders and trisomy-8-positive MDS has been reported, albeit mainly from Asian countries (33), wherein intestinal symptoms in these patients became largely intractable (34). It is not entirely clear why

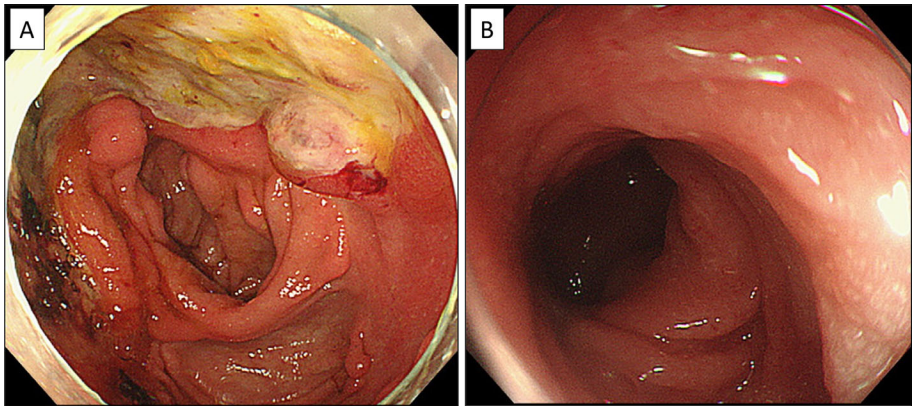

Figure 2. Colonoscopy findings of ileocecal ulcers before and after ileocecal resection. A: A huge ulcer that occupies three-quarters of the ileocecal region is shown. B: No new ulcers appeared after ileocecal resection followed by hematopoietic stem cell transplantation (HSCT) (original figure).

patients with trisomy 8-positive and BD-like disorders develop intractable symptoms, especially upon involvement of the digestive tract. Interestingly, Hamzaoui et al. and Hasegawa et al. have reported high serum levels of proinflammatory cytokines, such as TNF-α, IFN-α, IL-1β, IL-6, IL-8, and IL-17, in patients with BD-like disorders who were trisomy-8-positive (35, 36). Similarly, Chen et al. reported gene upregulation of proinflammatory cytokines, such as INF-β2, IL-6, IL-7 receptor, transforming growth factor (TGF)-β, and monocyte chemotactic protein (MCP)-1, in CD 34^+ hematopoietic progenitor cells from patients with MDS who were trisomy-8-positive (37), suggesting that the overexpression of these proinflammatory cytokines may be involved in BD-like disorders complicated by MDS and the presence of trisomy-8. Trisomy-8-positive MDS can be complicated with a lung disorder, secondary pulmonary alveolar proteinosis (SPAP) in addition to BD-like symptoms (38). Recently, we experienced a rare case of intestinal BD with SPAP showing several chromosomal abnormalities, including trisomy 8, trisomy 9, and X chromosome (38). These genetic abnormalities may induce both gastrointestinal and lung symptoms through aberrant inflammatory cytokine expression. Therefore, we should pay attention to not only gastrointestinal manifestations but also lung complications in cases of trisomy-8-positive MDS with chromosomal abnormalities.

There are no established treatments for refractory intestinal BD, and anti-inflammatory agents, such as TNF-α inhibitors, which are used against inflammatory bowel disease, have been used for primary treatment (39). Despite the report by Kimura et al. that adalimumab, an anti-TNF-α inhibitor, was effective in intestinal BD among patients with trisomy 8 (40), we often encounter cases refractory to these treatment regimens. Nevertheless, hematopoietic stem cell transplantation (HSCT) has been reported to be highly effective in patients with BD-like disorders complicated by MDS and trisomy 8 (41, 42). We previously described an 18-year-old girl who underwent HSCT after ileocecal resection due to perforation with no response to therapy with biological agents (26). HSCT with her mother as a donor led to complete remission without relapse of intestinal BD in this patient (Fig. 2), suggesting that aberrant proinflammatory cytokine production from hematopoietic cells in bone marrow adds to the pathogenicity of BD-like disorders, rendering them intractable.

Adult-onset Still's disease

Pathogenesis

Bywaters, in the early 1970s, was the first to describe AOSD as a condition that was similar to juvenile rheumatoid arthritis in adults (43). AOSD is a rare systemic autoinflammatory disease that is accompanied by multiple symptoms, including inflammation due to a cytokine storm (44) (Fig. 3), and both the genetic background and environmental factors are associated with its pathogenesis (44). In contrast to monogenic, hereditary, periodic syndromes, its underlying genetic background is mostly unknown, even though HLA-DRB1*15:01, DQB1*06:02, DR5 alleles, and *MEFV* exon 10 variants have been reported to be associated with AOSD susceptibility in Japanese subjects (45-47). Furthermore, the DRB1*09:01 allele is associated with protection against AOSD in the Japanese (45).

Damage-associated molecular patterns (DAMPs), pathogen-associated molecular patterns, and infectious triggers are known environmental factors associated with AOSD (44), and the proinflammatory cascade induced by these molecules activates specific inflammasomes and the overproduction of active forms of IL-1β and IL-18 as well as consequent intense innate immune cell activation (48). Indeed, serum levels of activated IL-18 are significantly higher in AOSD patients than in healthy controls (49), and our recent research identified extracellular cold-inducible binding protein, which belongs to a family of cold-shock proteins that respond to cellular stress, as a DAMP that is elevated in AOSD patients (46). Thus, various danger signals seem to be involved in the pathogenesis of AOSD.

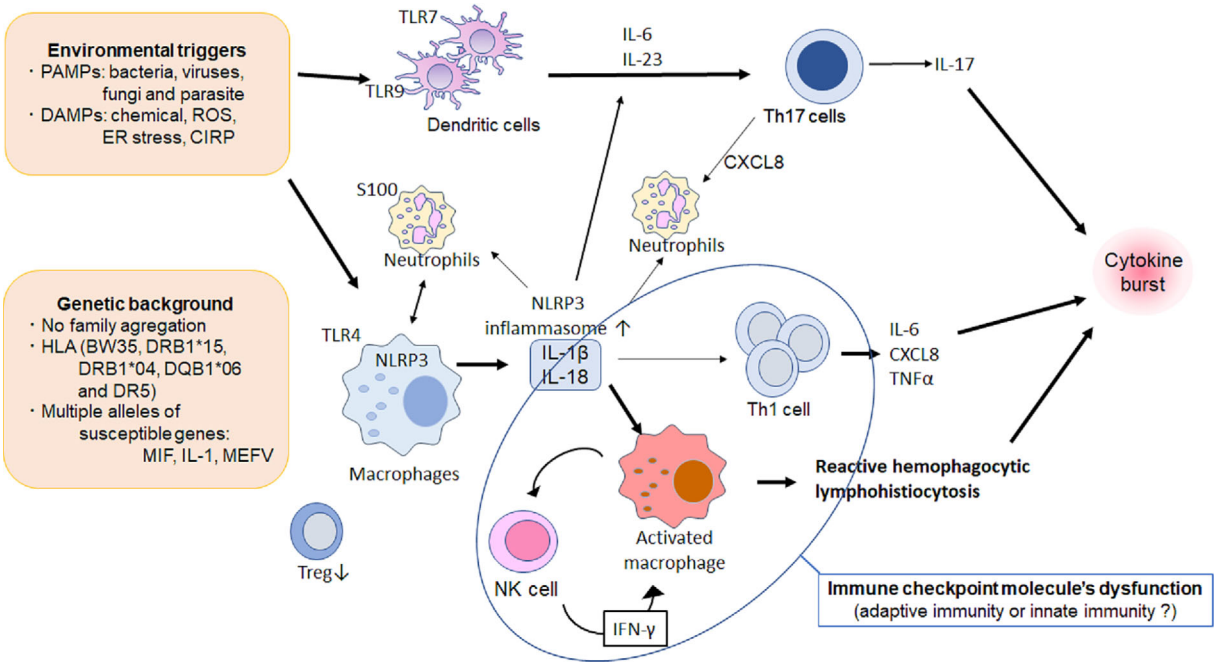

Figure 3. **Pathological model for adult-onset Still's disease (AOSD). Danger signals [pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs), infections, and environmental chemical factors] activate macrophages and neutrophils through Toll-like receptors, triggering the activation of the NACHT, LRR, and PYD domain-containing protein 3 (NLRP3) inflammasome in patients with a predisposing genetic background. The activation of the NLRP3 inflammasome results in the production of proinflammatory cytokines, such as interleukin (IL)-1β and IL-18, and Th1-polarization of CD4-lymphocytes. Similarly, dendritic cells are activated through Toll-like receptor (TLR)-7 and promote the production of IL-6 and IL-23, which induce Th17 response. Th17 increases neutrophil recruitment. Furthermore, IL-1β can itself confer retrograde activation of macrophages and neutrophils. Activated macrophages lead to reactive hemophagocytic lymphohistiocytosis. Immune checkpoint molecules, such as T cell immunoglobulin and mucin-containing-molecule-3 (TIM-3), in innate and adaptive immune cells become dysfunctional in active phase of AOSD. Amplification of inflammation results in cytokine bursts (original figure).**

T cell immunoglobulin and mucin-containing-molecule-3 (TIM-3), an immune checkpoint molecule, was recently shown to control not only adaptive immunity but also innate immunity (50), and we reported that TIM-3 is significantly elevated in patients with AOSD (51). Nonetheless, due to the diversity of this immune checkpoint molecule's functions, further research is necessary to elucidate its role in AOSD.

Clinical characteristics and treatment

The typical clinical manifestations of AOSD are spike fever, arthralgia or arthritis, skin rash, sore throat, and serositis (52). The rash in AOSD is characterized as salmon pink and is mainly visible during fever spikes. However, atypical rashes, such as urticaria and pruritis, are also often observed. Laboratory data are remarkable for elevated leukocyte (>10,000/μL) and neutrophil counts (>80%), liver abnormality, hyperferritinemia, and elevated C-reactive protein (52). Serum levels of IL-1β, IL-18, IL-6, and TNF-α are also elevated depending on the disease activity (53). The course of AOSD can be classified into three types as polycyclic systemic, monocyclic systemic, and chronic arthritis type (54). The polycyclic systemic type is characterized by a relapse after a few months or years of treatment or after discontinuation of therapy, the monocyclic systemic type is self-limiting or may achieve drug-free remission over time, and the chronic arthritis type is involved in continuous inflammation that results in joint erosion. Nonsteroidal anti-inflammatory drugs, glucocorticoids, and conventional synthetic disease-modifying antirheumatic drugs have been used to treat AOSD (44), but at least 30-40% of patients show poor control (44). Recently, the therapeutic effects of biologics that target IL-1, IL-6, IL-18, and TNF-α have been reported (44). Macrophage activation syndrome is a life-threatening complication (55) that is related to cytokine storm and involves many proinflammatory cytokines (55). Strong treatment using high-dose corticosteroids should be started immediately if this condition develops (54).

Schnitzler's syndrome

SchS is a rare autoinflammatory disease that was first described by Schnitzler et al. in 1972 (56). The main symptoms are urticarial rash (Fig. 4A), a fever, and joint and

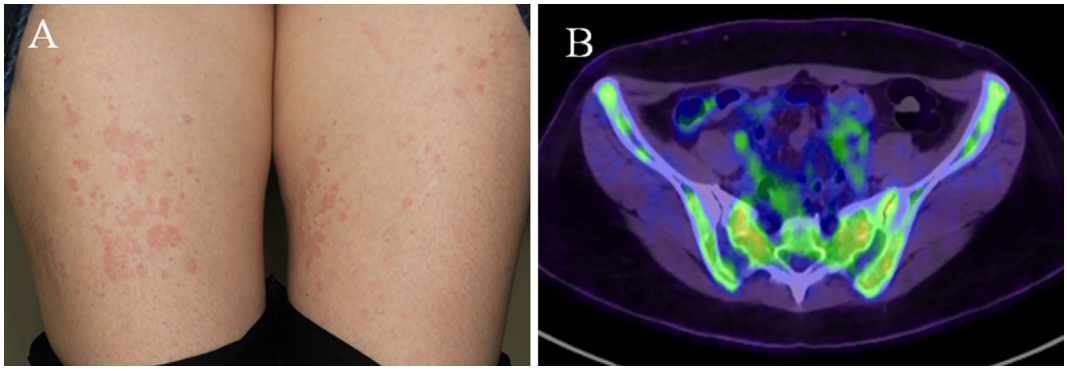

Figure 4. **A: Cutaneous manifestation in Schnitzler syndrome - a urticarial rash on the femur. B: Fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) shows an increased ^{18}FDG uptake in the pelvic bone marrow. This figure is modified from reference 64. Modification/reproduction of this figure is permitted from the publisher.**

bone pain. Monoclonal gammopathy of immunoglobulin (Ig) M, or rarely IgG, is usually present, along with systemic inflammation reflected as an elevated erythrocyte sedimentation rate and C-reactive protein levels (57). A bone evaluation by magnetic resonance imaging and positron emission tomography/computed tomography (PET/CT) is helpful for the diagnosis of SchS (58) (Fig. 4B). Unlike other autoinflammatory diseases, a family history is not usually present. Although a diagnosis of SchS is based on Lipsker's criteria (59) or the Strasbourg criteria (60), establishing the diagnosis is challenging because of its rarity and the challenges associated with ruling out other inflammatory diseases due to allergic, genetic, infectious, or neoplastic causes.

SchS can progress to Waldenström macroglobulinemia or other lymphoproliferative disorders (59-61) at a frequency comparable to that seen among patients with IgM monoclonal gammopathy of undetermined significance. Furthermore, even though systemic AA amyloidosis due to chronic inflammation may develop (62), clinicians should be aware that monoclonal gammopathy of IgM or IgG may not be observed in the early stages of the disease (63). In fact, we recently described Japanese SchS patients without IgM monoclonal gammopathy (64).

The pathogenesis of SchS is controversial, and inflammation and proinflammatory cytokines, particularly IL-1β, are thought to play a crucial role (65). Multiple treatments have been proposed for SchS, including colchicine, dapsone, steroids, nonsteroidal anti-inflammatory drugs, antihistamines, pefloxacin, and tocilizumab (60), and recent reports indicate that IL-1 blockade is remarkably effective in SchS (66). However, these treatments are not curative and probably do not prevent the development of lymphoproliferative disorders (66).

Summary

Monogenic autoinflammatory diseases are caused by mutations of causative genes of the innate immune system. FMF is the most common monogenic autoinflammatory disease. However, there is accumulating evidence suggesting that environmental factors contribute to the development of FMF. Although FMF is caused by gain-of-function mutations of the MEFV gene in most cases, pyrin inflammasome activation in response to sensing the bacterial products contributes to the pathophysiology of FMF. Furthermore, in addition to monogenic autoinflammatory diseases, such as FMF or A20 haploinsufficiency, genetically complex autoinflammatory diseases also present with rheumatic manifestations. These diseases include AOSD, BD, and Schnitzler's syndrome. We have begun learning about these expanding autoinflammatory diseases in which genetic or acquired abnormalities of the innate immune system contribute to the occurrence of various rheumatic disorders. Further investigations to identify the environmental or genetic factors that trigger autoinflammation will help clarify the molecular mechanisms of these autoinflammatory diseases.

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