

An Update on Autoinflammatory Diseases

F. Ciccarelli, M. De Martinis and L. Ginaldi*

Department of Life, Health and Environmental Sciences, University of L'Aquila, Italy

Abstract: Autoinflammatory diseases are a group of clinical conditions other than autoimmune diseases, characterized by recurrent inflammatory episodes. From an aetiological point of view they are determined by a dysregulation of innate immunity, without involvement of specific immunity (auto reactive T cells and auto antibodies). Recently, the increased knowledge in the field of auto inflammation highlighted shared immune mechanisms in the pathogenesis of both classical monogenetic and multifactorial auto inflammatory diseases and a broad spectrum of chronic age-related inflammatory pathologies. The current increase in the prevalence of chronic inflammatory diseases makes this subject of topical interest. In the light of these considerations, we propose an update of auto inflammatory diseases and a new interpretation of auto inflammation with both theoretical and clinical implications.

Keywords: Auto inflammation, chronic inflammatory diseases, innate immunity.

INTRODUCTION

The term “auto inflammatory” appeared on Cell in the spring of 1999 to describe an emerging family of clinical disorders, different from autoimmune syndromes. These were in fact characterized by episodes of apparently unprovoked inflammation, due to dysregulation of the innate immune system, without auto reactive T lymphocytes and auto antibodies and therefore different from classical autoimmune diseases [1].

Although initially auto inflammatory diseases represented a clinical niche sector in the field of medicine, the last decade has witnessed a growing interest in the field of auto inflammation. This interest is related to an increase of the knowledge about the immunopathogenesis of a broad spectrum of diseases not only of immunological and allergic nature, but also of metabolic, chronic degenerative, neoplastic and inflammatory nature. Atherosclerosis, diabetes, neurodegenerative syndrome and osteoporosis [2] are significant examples of common diseases in which the well known inflammatory substrate shares many similarities with the typical auto inflammatory state. From a therapeutic point of view, it is now common experience that shared immunological targets are often used for the treatment of these conditions apparently distant from each other. Also aging, characterized by chronic inflammatory status which supports its progression as well as the onset of age-related diseases, could be considered an auto inflammatory para physiological condition.

In the light of these considerations, a new interpretation of auto inflammation emerges with both theoretical and clinical implications. The current increase in the prevalence of chronic inflammatory diseases makes this subject of topical interest.

*Address correspondence to this author at the Director of Post-graduated School of Allergy and Clinical Immunology, University of L'Aquila Coppito, 67100 L'Aquila, Italy; Tel/Fax: +39 0861 211395; E-mail: lia.ginaldi@univaq.it

EVOLUTION OF THE CONCEPT OF AUTOINFLAMMATORY DISEASE

Historically, auto inflammatory diseases were a group of genetically diverse but clinically similar disorders characterized by recurrent fever associated with rash, serositis, lymphadenopathy and musculoskeletal involvement. The name auto inflammatory disease was referred, originally, to the hereditary recurrent fever syndromes, like familiar Mediterranean fever (FMF) and TNF receptor-associated periodic syndrome (TRAPS). At a later time other four recurrent fever syndromes have been added to the list, including the inherited hyperimmunoglobulinemia D with periodic fever syndrome (HIDS) and a spectrum of three illnesses of varying severity falling within the group cryopyrin associated periodic syndrome (CAPS). Subsequently, the concept of auto inflammation has been extended to a number of clinical entities beyond the confines of the hereditary recurrent fever syndromes, including several Mendelian diseases, such as Blau's syndrome, Majeed syndrome, deficiency of interleukin-1 receptor antagonist (DIRA) and pyogenic arthritis, pyoderma gangrenosum and acne syndrome (PAPA), as well as disorders of uncertain genetic aetiology including periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome (PFAPA), Behcet's disease, Still's disease, Crohn's disease and acquired auto inflammatory syndromes like Schnitzler's syndrome.

Recently, some evidence has shown that the same pathogenetic mechanism responsible for the activation of innate immunity in inherited auto inflammatory diseases may also play a key role in sustaining inflammation in several extremely frequent multifactorial illnesses, such as type II diabetes, gout, pseudogout and atherosclerosis. According to these recent advances, the definition of auto inflammatory syndrome must be revised. Simply put, we can define auto inflammatory diseases as clinical disorders marked by abnormally increased inflammation mediated predominantly by cells and molecules of innate immune system, with a signifi-

cant host predisposition. Such definition still allows to include the mendelian diseases that initially stimulated the concept of auto inflammation, as well as a broader range of common diseases, whose pathogenesis seems linked to innate immune system.

In the light of this new concept also aging can be seen as an auto inflammatory disease. During aging adaptive immunity significantly declines. This phenomenon is called immunosenescence, wherein innate immunity seems to be activated, inducing a characteristic proinflammatory profile for which the term “inflammaging” has been coined [3].

Interestingly, as previously demonstrated for the “classical” auto inflammatory diseases, recent studies have clarified the role of inflamma some as a key player in the onset of a pro inflammatory state also in the aging process. Inflammasome is a cytoplasmatic multi protein complex assembled after the recognition of “intracellular danger –associated molecular patterns” (DAMPs) by NOD-like receptors (NLR), especially the NLRP3, and it plays a crucial role in the production and secretion of pro-inflammatory cytokines, such as interleukin-1 (IL-1). In general the expression levels of NLRP3 remain low and for its expression the NF- κ B signaling is crucial. Interestingly, the aging process can stimulate NF- κ B system and probably enhances the priming and potential of the inflammasome activity [4].

SYSTEMIC INVOLVEMENT IN AUTOINFLAMMATORY DISEASES

The pathogenetic mechanisms underlying auto inflammation, although still unclear and different from each other from a molecular point of view, are always responsible of an aberrant activation of innate immunity. The result is a systemic involvement of multiple organs and systems, even when the clinical manifestations are predominant in specific organs.

The main clinical feature of both monogenic and multifactorial forms is therefore a marked systemic involvement, also in early stages. Several organs and systems are in fact affected by inflammation and severe clinical manifestations may often occur unpredictably in different tissues and at different times. Almost every organ might be involved, making clinical aspects extremely variable and complex.

These manifestations are often the direct result of the same underlying inflammatory process that variably affects different organs. Other times, such events are complications of the disease or iatrogenic effects of therapies. For example, extra intestinal manifestations of Crohn’s disease have been reported to involve almost every organ system and might represent manifestations of the same pathogenetic mechanisms, such as skin (erythema nodosum, pyoderma gangrenosum), joint (axial and peripheral arthropathy) and eye (episcleritis, uveitis) involvement. However, ocular complications, such as glaucoma and cataract, also may develop as consequences of corticosteroid therapy. Other examples of multifactorial extra intestinal involvement in Crohn’s disease are osteoporosis and pulmonary manifestations. Osteoporosis, whose prevalence in inflammatory bowel diseases ranges from 23% to 59%, recognizes several pathogenetic factors: disease activity and related elevation of inflammatory cyto-

kines, secondary hypogonadism, malabsorption of calcium and/or vitamin D, low body mass index and bone resorbing drug exposure. Pulmonary involvement is particularly complex and multifaceted. Deterioration of lung function appears to parallel underlying disease activity, although sulfasalazine-associated lung disease, including eosinophilic pneumonia, fibro singal veolitis and interstitial pneumonitis, is also observed. Other associated pulmonary disorders include pulmonary vasculitis, apical fibrosis, bronchiectasis, bronchitis, bronchiolitis and granulomatous lung disease which do not typically relate to the severity or activity of the underlying disease. Tuberculosis and other opportunistic infections should also develop in patients taking immunosuppressive medications [5].

MONOGENIC AUTOINFLAMMATORY DISEASES (TABLE 1)

Familial Mediterranean Fever (FMF)

FMF is the most common and well known auto inflammatory syndrome. It is an autosomal recessive inherited condition, prevalent among people of Mediterranean descent, but may affect any ethnic group. Attacks are characterized by brief episodes of fever lasting from few hours to 3 or 4 days and are typically associated with intense serositis. In fact peritonitis and monolateral pleurisy are the cause of two of the most typical symptoms of FMF: severe abdominal pain and chest pain. Serositis and pericarditis can also be present. Also arthritis or arthralgia of large joints, splenomegaly and the erysipelas-like erythema of the lower limbs, which represents the most common skin lesion, can be present. Attacks resolve spontaneously, with no regular periodicity of recurrences. The patient returns to full health during interim periods. Prodromes of FMF attacks may include discomfort of the impending attack site or various constitutional, emotional and physical complaints, including irritability, dizziness, increased appetite and altered taste sensation. Repetitive attacks, without treatment, may result in amyloidosis. However, the advent of daily colchicine therapy, introduced in the early 1970’s, has provided complete protection against the development of amyloidosis. As well, the known effect of this hoary drug abolishes or markedly attenuates the inflammatory episodes [6].

Periodic Fever Associated With Mevalonate Kinase Deficiency (Hyperimmunoglobulin D Syndrome)

It is another autosomal recessive auto inflammatory syndrome caused by mutations in the mevalonate kinase (*MVK*) gene [7]. It was identified in 1984 in six patients of Dutch ancestry with a long history of recurrent attacks of fever of unknown cause and a high serum IgD level. For this reason this disorder has also been named hyper IgD syndrome or Dutch fever. In addition to fever severe abdominal pain, often accompanied by vomiting and/or diarrhea, is the most frequent manifestation. Splenomegaly and cervical lymphadenopathy are common features too. Axillary, inguinal and intra-abdominal lymph node enlargement may also be present. Mucocutaneous manifestations are frequent and include erythematous macules, urticarial-like lesions and oral aphthoses. Also, articular involvement occurs frequently. The mevalonic kinase deficiency is believed to predispose to in-

Table 1. Monogenic Auto Inflammatory Diseases

Monogenic Auto Inflammatory Diseases	Mode of Inheritance	Gene (Protein)	Prevalence
Familial Mediterranean Fever (FMF)	Recessive	MEFV (Pyrin)	1-5 / 10 000 (www.orpha.net)
TNF receptor-associated periodic syndrome (TRAPS)	Dominant	TNFRSF1A (TNFR1)	Unknown (www.orpha.net)
Hyperimmuno globulinemia W with periodic fever syndrome (HIDS)	Recessive	MVK (Mevalonate kinase)	Unknown (www.orpha.net)
Cryopyrin associated periodic syndrome (CAPS) -Familial cold auto inflammatory syndrome (FCAS) -Muckle-Wells syndrome (MWS) -Neonatal onset multisystemic inflammatory disorder (NOMID)	Dominant	NLRP3 (cryopyrin)	<1 / 1 000 000 (www.orpha.net)
NALP12-associated periodic fever	Dominant	NALP12 (NALP12)	Unknown (www.orpha.net)
Deficit of IL-1 receptor antagonist (DIRA)	Recessive	IL1RN (IL1 receptor antagonist)	<1 / 1 000 000 (www.orpha.net)
Majeed's syndrome	Recessive	LPIN2 (LPIN2)	<1 / 1 000 000 (www.orpha.net)
Pyogenic arthritis pyoderma gangrenosum and acne syndrome (PAPA)	Dominant	PSTPIP1 (PSTPIP1)	<1 / 1 000 000 (www.orpha.net)
Blau's syndrome	Dominant	NOD2/CARD15 (CARD15)	<1 / 1 000 000 (www.orpha.net)

inflammatory attacks due to diminished amounts of downstream anti-inflammatory isoprenylated proteins such as farnesyl pyrophosphate [8]. Fever attacks usually respond dramatically to the administration of steroids. Colchicine has proven to be ineffective. Anti-TNF therapy has been found to reduce the frequency and intensity of fever attacks in some patients but not in others. Recently, the use of the IL-1 receptor antagonist (anakinra) was found to be effective in a patient [9].

TNF Receptor Associated Periodic Syndrome (TRAPS)

A dominant mode of inheritance and long-lasting fever episodes identify another periodic fever syndrome, defined by the acronym TRAPS, caused by mutations in the p55 TNF receptor (TNFR1A). TRAPS attacks last generally more than five days and up to three weeks. Abdominal pain and a wide spectrum of skin rashes with a migratory course from the root to the extremity of the limbs can be observed. Also thoracic pain, painful myalgia, arthritis, orbital oedema and conjunctivitis may be present during fever attacks. In TRAPS, glucocorticoids are usually efficacious. Colchicine is ineffective. Based on the mutation of TNFRSF1A, etanercept, a TNFRSF1B receptor-immunoglobulin fusion molecule, has been tried with mixed results [10, 11]. Interestingly, a paradoxical reaction with exacerbation of the inflammatory signs has been observed after administration of anti-TNF monoclonal antibody (infliximab) in some TRAPS patients. Thus this drug should not be used in this indication. Recently, it has become clearer that the use of the anti-IL-1 inhibitors can have a better and longer-lasting effect on control of the clinical manifestations [12].

Cryopyrin-Associated Periodic Syndromes (CAPS)

Familial cold auto inflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and chronic infantile neurological cutaneous and articular syndrome (CINCA) represent autosomal dominant disorders caused by different mutations in a single gene, *NLRP3* (NOD-like receptor 3)[13]. CAPS present with episodes of fever, urticarial rash and elevations in acute phase reactants, but differ in the spectrum of multiorgan disease manifestations and in long-term morbidity and mortality. In patients with MWS and NOMID, typically the first attack appears at birth, while for FCAS it may present itself later in life. In FCAS, episodes of urticarial eruption and fever are induced by cold exposition, while in MWS the attacks are not strictly triggered by cold exposure. NOMID is the most severe of the three syndromes. It occurs mostly in the neonatal period or in early childhood, with an urticarial rash. One third of children have a typical "facies" including frontal prominence, saddle nose and facial hypoplasia; other skeletal features are abnormal bone and cartilage growth in the distal extremities of hands, feet, knees and particularly of the patella. This syndrome also includes the possible involvement of the central nervous system (aseptic chronic meningitis, hearing loss, chronic headache, mental retard, epilepsy) and of eyes (anterior uveitis, papillitis and optic nerve atrophy)[14]. Interleukin-1 blockade has shown very good therapeutic efficacy with rapid resolution of clinical symptoms and complete normalization of inflammatory markers such as C-reactive protein (CRP). Anakinra is currently the most used medication for the treatment of CAPS. Canakinumab (a recombinant, fully human, monoclonal, anti-IL-1 β antibody) and rilonacept (a dimeric fusion protein

consisting of the extracellular domains of IL-1R1 and IL-1RAP, joined to Fc domain of human IgG1) are effective alternative IL-1 inhibitors for this indication.

NLRP12-Associated Autoinflammatory Disorders

A subset of patients with clinical manifestations attributable to CAPS (recurrent fever and cold sensitivity associated with additional symptoms such as neuronal hearing loss, aphthous ulcers, lymphadenopathy, abdominal pain and acute phase response), but without mutations at the NLRP3 locus, have mutations at the *NLRP12* gene [15].

Deficiency of Interleukin-1 Receptor Antagonist (DIRA)

The recently reported deficiency of interleukin-1 receptor antagonist (DIRA) is an autosomal recessive inherited disease leading to absence of IL-1RA and subsequent IL-1 over activity. DIRA manifests itself clinically with perinatal-onset pustular dermatitis, joint swelling, painful multifocal osteolytic lesions and periosteitis [16]. Persistent elevation of acute phase reactants are also observed. Treatment with anakinra, substituting the missing protein in patients with its recombinant form, results in rapid clinical improvement.

Pyogenic Arthritis-Pyoderma Gangrenosum-Acne (PAPA) Syndrome

PAPA syndrome is a monogenic auto inflammatory disease characterized by sterile erosive arthritis usually starts in early childhood. Severe cystic acne, which can persist well into adulthood, develops with puberty, while arthritic symptoms tend to regress. Pyoderma gangrenosum develops on the distal limbs but also, in a multifocal fashion, on the entire skin. Less common features include adult-onset insulin-dependent diabetes mellitus and proteinuria. The treatment of PAPA syndrome largely depends on the dominant clinical manifestation. Anakinra has been shown to be effective in controlling inflammatory lesions in PAPA syndrome patients [17]. Infliximab has been reported to be successful. Arthritis episodes are usually successfully treated with corticosteroids. Pyoderma gangrenosum often responds poorly to systemic corticosteroids and is therefore usually treated with immunosuppressants.

Majeed Syndrome

In 1989 three related Arab children presenting an association of chronic recurrent multifocal osteomyelitis (CRMO), fever, neutrophilic dermatosis, (ranging from palmoplantar-pustulosis to psoriasis), growth failure, and congenital dyserythropoietic anemia were described by Majeed and co-workers [18]. Unlike isolated and sporadic CRMO (see below under multifactorial auto inflammatory diseases), the CRMO associated with this syndrome has an onset at an earlier age (in infancy), more frequent episodes, shorter and less frequent remissions, leading to retarded growth and/or joint contractures.

Blau's Syndrome

Blau's syndrome, or familial juvenile systemic granulomatosis, is an autosomal-dominant, auto inflammatory disease characterised by a non caseating granulomatous in-

flammation affecting the joint, the skin, and the eyes. Disease onset is usually observed during the first years of life. Asymmetrical polyarticular arthritis with "boggy" appearance is the typical joint manifestation. Eye involvement is characterised by uveitis or panuveitis, complicated by glaucoma and cataract. The typical skin manifestation is a tan-coloured, scaly, ichthyosiform rash. It is conceivable that in Blau's syndrome the mutation of NOD2 causes a gain of the protein's function resulting in a sustained pro-inflammatory state. Patients are treated with oral steroids and immunosuppressive drugs (methotrexate, cyclosporin) with variable outcomes. Recent anecdotal reports suggest a beneficial effect of anti-TNF and anti-IL-1 treatment [19]. *NOD2* has been linked also to Crohn's disease (see below under multifactorial auto inflammatory disease) [20].

MULTIFACTORIAL AUTOINFLAMMATORY DISEASES (TABLE 2)

Periodic Fever, Aphthous Stomatitis, Pharyngitis and Adenopathy Syndrome (PFAPA)

The PFAPA syndrome is characterized by periodic fever attacks, lasting 3-6 days, similar to those observed in monogenic periodic fevers in children negative for mutations of *MEFV*, *MVK* and *TNFRSF1A* genes. In fact, no single genetic mutation has been identified. The diagnosis is based on clinical criteria that require the presence of a disease onset before the age of 5 years and at least one of the three associated constitutive symptoms (aphthosis, cervical adenitis, pharyngitis) in the absence of upper respiratory tract infection or cyclic neutropenia. Recent studies have demonstrated that T-cell-regulated complement activation and IL-1 production are altered in PFAPA patients, thus supporting the hypothesis that PFAPA is an auto inflammatory disease [21].

Behcet's Disease

Behcet's disease is a chronic systemic inflammatory disorder characterized by recurrent oral aphthous ulcers, genital ulcers cutaneous lesions (pseudo folliculitis and erythema nodosum-like lesion), eye manifestations (eg anterior uveitis, cataract, glaucoma, posterior segment involvement with vasculitis, vitritis, retinitis, panuveitis, retinal edema, cystoid macular degeneration, venous and arterial occlusion, disc edema and retinal detachment), venous thrombosis, arterial involvement (thrombosis and/or aneurysms), arthralgia and/or arthritis, neurological manifestations (headache, meningitis, meningoencephalitis, seizure, hemiplegia, and cranial nerve palsies), lymph or splenic enlargement, cardiopulmonary involvement, gastrointestinal symptoms and genitourinary complications [22]. The etiology of Behcet's disease is still unknown, but over the past years substantial advances have been done in the understanding of the genetic and immunology of the disease. Behcet's disease is at the crossroad between autoimmune and auto inflammatory syndromes. Originally Behcet's disease has long been regarded as a TH1 type autoimmune disease, because of the association with HLA-B51 and hyper reactivity against streptococcal antigens. However, it was recently found that Behcet's disease and auto inflammatory diseases share several features. As FMF, Behcet's disease is prevalent in the Mediterranean basin and it is treated with colchicine. Furthermore

Table 2. Multifactorial Autoinflammatory Diseases

Multifactorial Auto inflammatory Syndromes	Prevalenza	Main Clinical Features
Periodic fever, aphthous stomatitis, pharyngitis and adenopathy syndrome (PFAPA)	<1 / 1 000 000 (www.orpha.net)	Recurrent episodes of fever lasting 3-6 days, aphthosis, cervical adenitis, pharyngitis
Behcet's Disease	7.1 per 100,000 adults	Recurrent oral aphthous ulcers, genital ulcers, eye manifestations, venous thrombosis, arterial involvement, arthralgia/arthritis, neurological manifestations, cardio-pulmonary involvement, lymph and splenic enlargement, gastrointestinal symptoms, genitourinary complications
Chron's Disease	10–200 per 100,000 people in North America and Europe	Abdominal pain, diarrhea, rectal bleeding, weight loss, reduced appetite, fever, fatigue, arthritis, uveitis, mouth sores, skin rash, osteopenia/osteoporosis delay growth or sexual development in children, hematological disorders, neurological involvement, cardio-pulmonary manifestations, pancreatitis, genitourinary involvement
Still's Disease	16 to 150 cases per 100,000 children worldwide	Remitting fever, erythematous skin rash, serositis, arthritis, lymphadenopathy, hepatosplenomegaly, anemia
Adult-onset Still Disease	1.5 cases per 100,000-1000,000 people	High spiking fever, arthralgia or arthritis, sore throat, transit maculopapular rash, lymphadenopathy, hepatosplenomegaly, serositis
Shnitzler's Disease	Relatively rare (around 100 patients described)	Non-pruritic urticarial-like exanthemas, fever, arthritis or arthralgia, bone pain, lymphadenopathy, hepato-and/or splenomegaly, anemia, fatigue, leukocytosis, thrombocytosis, amyloidosis
Sweet's Disease	<1 / 1 000 000(www.orpha.net)	Fever, painful erythematous cutaneous nodules or plaques, arthralgia, headache, hepatosplenomegaly, eye manifestations, central nervous system involvement, oral lesions, cardio-pulmonary manifestations
CRMO syndrome	<1/1.000.000(www.orpha.net)	Unifocal or multifocal, initially osteolytic, later hyperostotic and sclerotic lesions mainly in the metaphyses of the long bones and shoulder girdle
SAPHO syndrome	Unknown	Bony lesions manifest as severe, recurrent, debilitating pain and tenderness; cutaneous manifestations (palmoplantar pustulosis, severe forms of acne and various forms of psoriasis, especially pustular psoriasis)

genetic researches on Behcet's disease suggest that the *MEFV* gene mutated in FMF is a probable susceptibility gene for Behcet's disease, with respect to their ethnicity [23]. Some authors have also found an association between the presence of *MEFV* mutations and the severity of vasculitis [24]. Furthermore, increased activity of neutrophils and elevated levels of interleukin-1 beta are observed in both Behcet's disease and auto inflammatory diseases. Finally, as in several diseases considered to be auto inflammatory to date, excellent clinical responses have been reported in Behcet's disease patients treated with anakinra, reinforcing the possibility of a role for IL-1 in the pathogenesis of Behcet's disease.

Systemic Juvenile Idiopathic Arthritis (sJIA) or Still's Disease and Adult-Onset Still's Disease (AOSD)

Systemic juvenile idiopathic arthritis (sJIA), also known as Still's disease, in honor of Dr. George Still who first described this syndrome, is a rare systemic inflammatory disease classified as a subtype of JIA. SJIA is defined by [25] the presence of arthritis in one or more joints associated with spiking fever (a typically daily high fever with spike in the evening) persisting for a minimum of 15 days, with at least

one of the following manifestations: skin rash (evanescent, non fixed erythematous rash that accompanies fever spikes), lymphadenopathy, hepatomegaly and/or splenomegaly, serositis (pleuritis or pericarditis). Laboratory tests show a marked inflammatory response, characterized by high white blood cell count, thrombocytosis, anemia, elevated levels of C-reactive protein and erythrocyte sedimentation rate, and finally, an increase in serum level of ferritin. The pathogenesis of sJIA is still unknown. In any event, the emerging consensus in rheumatology is that the innate immunity (cytokines like IL-1, IL-6 and IL-18, and neutrophils and monocytes/macrophages rather than lymphocytes), rather than the adaptive immunity plays a major role in the onset of sJIA, distinguishing sJIA from other JIA-subtypes [26]. Further differences with the other subtypes of JIA include an equal sex ratio (most JIA subset are characterized by female predominance), marked systemic features with spiking fever, a salmon-colored evanescent rash that comes and goes with fever, serositis and the absence of autoantibodies. Another distinctive feature of sJIA is its strong association with macrophage activation syndrome (MAS), a form of reactive hemophagocytic lymphohistiocytosis, characterised by an uncontrolled activation of well-differentiated macrophages releasing a high amount of pro inflammatory cytokines, par-

ticularly IL-18, which belongs to the IL-1 family. MAS is a severe, potentially life-threatening disorder clinically characterized by fever, hepatosplenomegaly, lymphadenopathy, neurological dysfunction and coagulopathy and was recently included as an individual group of auto inflammatory diseases in an updated classification proposed by Masters *et al.* [27]. Finally, as in auto inflammatory syndromes, patients with SJIA, in contrast to patients with JIA, are at risk for amyloidosis. On a genomic level, one distinctive feature of the systemic form of JIA is the lack of strong MHC Class II associations, as for the auto inflammatory diseases [28]. This is very different from other clinical forms of JIA in which the contribution of the MHC genes is quite significant. In fact, a recently completed genome-widescreen showed that most of the genetic predisposition to oligo-JIA is contributed by the MHC loci. All these recent insights into the pathogenesis and molecular mechanisms underlying sJIA led to new strategies for the treatment of patients who have been resistant to conventional disease-modifying drugs. Systemic juvenile idiopathic arthritis has a dramatic response to anakinra [29] and the anti-IL6-receptor antibody (to cilizumab) [30], while other subsets of JIA respond to anti-TNF treatments [31]. Based on clinical and laboratory features as well as on the new acquisitions on the pathogenesis, it seems evident that sJIA is an auto inflammatory disease related to an abnormality in the innate immune system. The marked activation of the innate immune system responsible for the multisystem inflammation and the lack of any consistent association with HLA antigens or auto antibodies, allow us to consider sJIA as an auto inflammatory disease rather than a 'classic' autoimmune disease [32].

The same considerations can be also made for adult-onset Still's disease (AOSD), an uncommon clinical entity that predominantly affects young adults. It was initially described in adults by Eric Bywaters in 1971 [33], who also coined the term (AOSD) due to the disease's close resemblance to the pediatric syndrome described by Dr. George Still in 1899. During the first forty years, as for systemic juvenile idiopathic arthritis, the pathophysiology of the disease had remained largely obscure and only recent your understanding of the disease is enhanced by the description of the auto inflammatory syndromes [34]. Indeed a growing number of experimental evidences supports the hypothesis that a dysregulation of inflammasome complex and a related overproduction of the pro inflammatory interleukin 1 β is a pivotal event in the pathogenesis of this disorder, in analogy with other auto inflammatory diseases, including the pediatric variant of Still's disease [35]. In accordance with these findings is the dramatic and sustained efficacy of IL-1blockade on AOSD symptoms, even in refractory forms of the disease. Also inhibitors of IL 6, a pro inflammatory cytokine whose production is increased by IL-1, were effective in controlling the activity of the disease [36]. In conclusion, we can mention both systemic juvenile idiopathic arthritis and adult-onset Still's disease among the expanding group of auto inflammatory diseases.

Crohn's Disease

Crohn's disease is a chronic inflammatory bowel disease that can affect any portion of the gastrointestinal tract from the mouth to the rectum, but most commonly in terminal

ileum, cecum, perianal area and colon. Extra intestinal manifestations are also common. Among these, there are dermatological disorders (such as erythema nodosum and pyoderma gangrenosum), ophthalmological involvement (e.g. episcleritis, uveitis), musculoskeletal manifestations (e.g. spondylitis, isolated sacroiliitis, peripheral arthropathy, osteopenia/osteoporosis), hepatobiliary complications (such as primary sclerosing cholangitis, fatty liver, cholelithiasis, and bile-duct carcinoma), genitourinary and renal manifestations (such as nephrolithiasis, glomerulonephritis, amyloidosis), pancreatitis, hematological disorders (e.g. anemia, thrombocytosis) cardio-pulmonary manifestations (e.g. pleuropericarditis, vasculitis, fibrosis, bronchiectasis, bronchitis, bronchiolitis and granulomatous lung disease) and neurological involvement. In childhood an impaired growth is also observed [5]. The etiopathogenesis of Crohn's disease is still unknown. In any event, a loss of the regulatory capacity of the immune apparatus would be implicated in the onset of the disease. In this respect interestingly enough, as for Blau's disease, the *NOD2* gene mutations have been linked to Crohn's disease [30]. However, in Crohn's disease *NOD2* mutations act as a risk factor, being more common among Crohn's disease patients than the background population, while in Blau's disease *NOD2* mutations are linked directly to this syndrome, as it is an autosomal-dominant disease. Furthermore, even though inflammation is a common theme in both diseases, Crohn's disease is associated with chronic granulomatous inflammation of various intestinal segments, often the distal part of ileum including extra-intestinal manifestations such as arthritis, uveitis and skin lesions, whereas Blau's disease is characterized by more diffuse chronic inflammation [37]. All this new knowledge in the pathogenesis of Crohn's disease allows us to put this multifactorial disease in the group of auto-inflammatory syndromes.

Schnitzler's Syndrome

Schnitzler's syndrome is a rare and acquired systemic disease which presents in mid-adulthood with non-pruritic urticaria-like exanthemas and IgM gammopathy, variably accompanied by intermittent fever, fatigue, arthritis or arthralgia, bone pain, lymphadenopathy and hepato- and/or splenomegaly, inflammatory anemia, persistent increase of neutrophils and thrombocytosis [38]. Associated findings include pseudoxanthum elasticum, peripheral neuropathy, impairment of renal function, hearing loss and inflammatory amyloidosis. About 20% of patients will develop a lymphoproliferative disorder, mainly Waldenstrom disease and lymphoma. Both the exact aetiology and pathogenesis of Schnitzler syndrome remain to be clarified. However, the Schnitzler's syndrome shares many features with genetically determined auto inflammatory syndromes:

- The recurrent fever of unknown cause;
- The peculiar eruption, characterized pathologically by a neutrophilic infiltrate very similar to the one observed in the autoinflammatory cryopyrinopathies (CAPS), namely a neutrophilicurticarial dermatosis [39];
- A significant increase of neutrophils in blood and tissues, not otherwise explained;

- Enhanced IL-1 secretion by peripheral blood mononuclear cells [40];
- Elevated free circulating IL-18 levels, a cytokine produced by the inflammasome [41]

An activating NLRP3 mutation (the gene involved in the cryopyrinopathies), reported in a single case, suggests possible involvement of the inflammasome in the pathogenesis [42]; A spectacular response to anakinra [43, 44];

- Amyloidosis is a concern in untreated patients, as in patients with other inherited auto inflammatory syndromes [45].

Thus, Schnitzler's syndrome can be considered today as a paradigm of an acquired/late onset auto inflammatory disease [46]. Recently, Longhurst HJ *et al.* described a case of monoclonal gammopathy-related auto inflammatory syndrome distinguished from Schnitzler's syndrome by complement activation, neutropenia and an absent response to anakinra. They proposed naming this Mullin's syndrome [47].

Sweet's Syndrome

Sweet's syndrome (the eponym for acute febrile neutrophilic dermatosis) is a rare syndrome reported for the first time in 1964 as an acute febrile neutrophilic dermatosis [48]. Sweet's syndrome can present in several clinical settings: classical (or idiopathic) Sweet's syndrome, malignancy associated Sweet's syndrome, and drug-induced Sweet's syndrome. Sweet's syndrome is characterized by a constellation of clinical symptoms, physical features, and pathologic findings which include fever, neutrophilia, tender erythematous skin lesions and a diffuse infiltrate consisting predominantly of mature neutrophils that are typically located in the upper dermis [49]. Other Sweet's syndrome-associated symptoms such as arthralgia, general malaise, headache, myalgia and extracutaneous manifestations (eghepato-splenomegaly, eye manifestations, central nervous system involvement, oral lesions, cardio-pulmonary manifestations, glomerulonephritis and urinalysis abnormalities) may also be present. Systemic corticosteroid therapy remains the gold standard for the clinical management of patients with Sweet's syndrome. Sweet's syndrome satisfies the current criteria for classification as an auto inflammatory disease, notably seemingly unprovoked inflammation in the absence of detectable auto antibodies and evidence of an antigen-specific T-cell response. Furthermore, very encouraging responses to anakinra administration have been recently reported, suggesting that IL-1 and the inflammasome may play a significant role in the pathophysiology of this auto inflammatory disease [50].

Chronic Recurrent Multifocal Osteomyelitis (CRMO), and Synovitis Acne Pustulosis Hyperostosis Osteitis (SAPHO) Syndrome

CRMO is a human disorder which usually presents itself early in life. Sterile bone lesions resembling osteomyelitis are the hallmark of CRMO. Radiographs reveal osteolytic lesions with surrounding sclerosis. Bacterial and fungal cultures from blood and bone biopsies are negative, and the granulocytic infiltrate seen on histology of affected lesions is

non specific. Clinically CRMO presents itself with bone pain that is worse at night and occurs in the presence of fever. The onset is typically insidious. Swelling and warmth can occur overlying the affected areas. Laboratory investigations often reveal mild elevations in white blood cell count and erythrocyte sedimentation rate, but both of these may be normal. A strong association with other inflammatory diseases (such as inflammatory bowel diseases, palmar-plantar pustulosis, psoriasis vulgaris, Sweet syndrome, sclerosing cholangitis, arthritis, sacroiliac joint involvement, Still disease, Takayasu arteritis, ANCA-positive vasculitis, parenchymal lung disease and dermatomyositis) has been described [51]. Despite being recognized as a clinical entity for more than thirty years, little is known about the pathophysiology of CRMO. However, it would seem that the disease may be classified as auto inflammatory. In fact, the existence of a monogenic auto inflammatory disease associated with CRMO, called Majeed's syndrome (previously described), has raised the hypothesis that isolated sporadic CRMO could also be included in the group of auto inflammatory diseases.

SAPHO syndrome is characterized by the conditions abbreviated in its acronym (synovitis, acne, pustulosis, hyperostosis, and osteitis). Most of these are coincident with CRMO, although skin involvement plays a larger role in SAPHO. For this reason numerous authors have suggested that the two syndromes lie along the same clinical spectrum. In fact, some believe that CRMO is the pediatric presentation of SAPHO [52].

CONCLUSION

Recent evidence has shown that the same pathogenetic mechanisms responsible for the activation of innate immunity in inherited auto inflammatory diseases may also play a crucial role in sustaining inflammation in several extremely frequent multifactorial illness, such as type II diabetes [53], gout, pseudogout [54] and atherosclerosis [55], opening new perspectives on the management of these diseases.

Originally with the name of auto inflammatory diseases we referred to a group of hereditary recurrent fever syndromes, but with time advances in the understanding of the auto inflammatory syndromes have provided new insight into the role of innate immune system in other more common diseases. Also other pathophysiological conditions, apparently not related to overt inflammation and/or autoimmunity, such as aging, obesity, osteoporosis and metabolic syndrome, in some sense could be included in the wide spectrum of auto inflammation. The recent discoveries in the field of innate immune system, inflammasomes (mainly NLRP3 inflammasome), inflammatory cytokine signaling systems (for example caspase 1-cleaved cytokines and their pathways), open new perspectives in the treatment of both "classic" and "new" auto inflammatory diseases.

In conclusion, during the years, the term auto inflammatory diseases has expanded to include a broader range of diseases and probably in the future new syndromes will join the group.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

Reference 56 is related article recently published.

- [1] McDermott, M.F.; Aksentijevich, I.; Galon, J.; McDermott, E.M.; Ogunkolade, B.W.; Centola, M.; Mansfield, E.; Gadina, M.; Karenko, L.; Pettersson, T.; McCarthy, J.; Frucht, D.M.; Aringer, M.; Torosyan, Y.; Teppo, A.M.; Wilson, M.; Karaarslan, H.M.; Wan, Y.; Todd, I.; Wood, G.; Schlimgen, R.; Kumarajeewa, T.R.; Cooper, S.M.; Vella, J.P.; Amos, C.I.; Mulley, J.; Quane, K.A.; Molloy, M.G.; Ranki, A.; Powell, R.J.; Hitman, G.A.; O'Shea, J.J.; Kastner, D.L. Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes. *Cell*, **1999**, *97*(1), 133-144.
- [2] Ginaldi, L.; Di Benedetto, M.C.; De Martinis, M. Osteoporosis, inflammation and ageing. *Immun. Ageing.*, **2005**, *2*, 14.
- [3] Franceschi, C.; Bonafe, M.; Valensin, S.; Olivieri, F.; De Luca, M.; Ottaviani, E.; De Benedictis, G. Inflamm-aging. An evolutionary perspective on immunosenescence. *Ann. N. Y. Acad. Sci. USA*, **2000**, *908*, 244-254.
- [4] Salminen, A.; Kaamiranta, K.; Kauppinen, A. Inflammaging: disturbed interplay between autophagy and inflammasomes. *Ageing*, **2012**, *4*(3), 166-175.
- [5] Folashade, A.J.; Melvin, B.H. Extraintestinal manifestations of Inflammatory Bowel Disease. *J. Pediatr. Gastroenterol. Nutr.*, **2008**, *46*(2), 124-133.
- [6] Dinarello, C.A.; Wolff, S.M.; Goldfinger, S.E.; Dale, D.C.; Alling, D.W. Colchicine therapy for familial mediterranean fever. A double-blind trial. *N. Engl. J. Med.*, **1974**, *291*, 934.
- [7] Simon, A.; Cuisset, L.; Vincent, M.F.; van Der Velde-Visser, S.D.; Delpech, M.; van Der Meer, J.W.; Drenth, J.P. Molecular analysis of the mevalonate kinase gene in a cohort of patients with the hyper-Igd and periodic fever syndrome: its application as a diagnostic tool. *Ann. Intern. Med.*, **2001**, *135*(5), 338-343.
- [8] Goldfinger, S. The inherited autoinflammatory syndrome: a decade of discovery. *Trans. Am. Clin. Climatol. Assoc.*, **2009**, *120*, 413-418.
- [9] Cailliez, M.; Garaix, F.; Rousset-Rouviere, C.; Bruno, D.; Kone-Paut, I.; Sarles, J. Anakinra is safe and effective in controlling hyperimmunoglobulinaemia D syndrome-associated febrile crisis. *J. Inherit. Metab. Dis.*, **2006**, *29*(6), 763.
- [10] Bulua, A.C.; Mogul, D.B.; Aksentijevich, I.; Singh, H.; He, D.; Muenz, L.R.; Ward, M.M.; Yarboro, C.H.; Kastner, D.L.; Siegel, R.M.; Hull, K.M. Efficacy of etanercept in the tumor necrosis factor receptor-associated periodic syndrome: a prospective, open-label, dose-escalation study. *Arthritis Rheum.*, **2012**, *64*(3), 908-913.
- [11] Iacobelli, S.; Andre, M.; Alexandra, J.F.; Dode, C.; Papo, T. Failure of antiTNF therapy in TNF receptor 1 associated periodic syndrome (TRAPS). *Rheumatology*, **2007**, *46*, 1211-1212.
- [12] Gattorno, M.; Pelagatti, M.A.; Meini, A.; Obici, L.; Barcellona, R.; Federici, S. Persistent efficacy of anakinra in patients with tumor necrosis factor receptor-associated periodic syndrome. *Arthritis Rheum.*, **2008**, *58*(5), 1516-1520.
- [13] Feldmann, J.; Prieur, A.M.; Quartier, P.; Berquin, P.; Certain, S.; Cortis, E. Chronic infantile neurological cutaneous and articular syndrome is caused by mutations in CIAS1, a gene highly expressed in polymorphonuclear cells and chondrocytes. *Am. J. Hum. Genet.*, **2002**, *71*(1), 198-203.
- [14] De Sanctis, S.; Nozzi, M.; Del Torto, M.; Scardapane, A.; Gaspari, S.; de Michele, G.; Breda, L.; Chiarelli, F. Autoinflammatory syndromes: diagnosis and management. *Ital. J. Pediatr.*, **2010**, *36*, 57.
- [15] Jéru, I.; Duquesnoy, P.; Fernandes-Alnemri, T.; Cochet, E.; Yu, J.W.; Lackmy-Port-Lis, M.; Grimprel, E.; Landman-Parker, J.; Hentgen, V.; Marlin, S.; McElreavey, K.; Sarkisian, T.; Grateau, G.; Alnemri, E.S.; Amselem, S. Mutations in NALP12 cause hereditary periodic fever syndromes. *Proc. Natl. Acad. Sci. USA*, **2008**, *105*, 1614-1619.
- [16] Aksentijevich, I.; Masters, S.L.; Ferguson, P.J.; Dancey, P.; Frenkel, J.; van Royen-Kerkhoff, A.; Laxer, R.; Tedgård, U.; Cowen, E.W.; Pham, T.H.; Booty, M.; Estes, J.D.; Sandler, N.G.; Plass, N.; Stone, D.L.; Turner, M.L.; Hill, S.; Butman, J.A.; Schneider, R.; Babyn, P.; El-Shanti, H.I.; Pope, E.; Barron, K.; Bing, X.; Laurence, A.; Lee, C.C.; Chapelle, D.; Clarke, G.I.; Ohson, K.; Nicholson, M.; Gadina, M.; Yang, B.; Korman, B.D.; Gregersen, P.K.; van Hagen, P.M.; Hak, A.E.; Huizinga, M.; Rahman, P.; Douek, D.C.; Remmers, E.F.; Kastner, D.L.; Goldbach-Mansky, R. An autoinflammatory disease with deficiency of the interleukin-1-receptor antagonist. *N. Engl. J. Med.*, **2009**, *360*, 2426-2437.
- [17] Dierselhuis, M.P.; Frenkel, J.; Wulffraat, N.M.; Boelens, J.J. Anakinra for flares of pyogenic arthritis in PAPA syndrome. *Rheumatology (Oxford)*, **2005**, *44*(3), 406-408.
- [18] Majeed, H.A.; Kalaawi, M.; Mohanty, D.; Teebi, A.S.; Tunjekar, M.F.; al-Gharbawy, F.; Majeed, S.A.; al-Gazzar, A.H. Congenital dyserythropoietic anemia and chronic recurrent multifocal osteomyelitis in three related children and the association with Sweet syndrome in two siblings. *J. Pediatr.*, **1989**, *115*(5Pt1), 730-734.
- [19] Arostegui, J.I.; Arnal, C.; Merino, R.; Modesto, C.; Antonia, C.M.; Moreno, P. NOD2 gene-associated pediatric granulomatous arthritis: clinical diversity, novel and recurrent mutations, and evidence of clinical improvement with interleukin-1 blockade in a Spanish cohort. *Arthritis Rheum.*, **2007**, *56*(11), 3805-3813.
- [20] Ogura, Y.; Bonen, D.K.; Inohara, N.; Nicolae, D.L.; Chen, F.F.; Ramos, R.; Britton, H.; Moran, T.; Karaliuskas, R.; Duerr, R.H.; Achkar, J.P.; Brant, S.R.; Bayless, T.M.; Kirschner, B.S.; Hanauer, S.B.; Nuñez, G.; Cho, J.H. A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. *Nature*, **2001**, *411*(6837), 603-606.
- [21] Stojanov, S.; Lapidus, S.; Chitkara, P.; Feder, H.; Salazar, J.C.; Fleisher, T.A.; Brown, M.R.; Edwards, K.M.; Ward, M.M.; Colbert, R.A.; Sun, H.W.; Wood, G.M.; Barham, B.K.; Jones, A.; Aksentijevich, I.; Goldbach-Mansky, R.; Athreya, B.; Barron, K.S.; Kastner, D.L. Periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) is a disorder of innate immunity and Th1 activation responsive to IL-1 blockade. *Proc. Natl. Acad. Sci. USA*, **2011**, *108*, 7148-7153.
- [22] Saadoun, D.; Wechsler, B. Behcet's disease. *Orphanet J. Rare Dis.*, **2012**, *7*, 20.
- [23] Taitou, I.; Magne, X.; Molinari, N.; Navarro, A.; Le Quellec, A.; Picco, P. MEFV mutations in Behcet's diseases. *Hum. Mutat.*, **2000**, *16*, 271-272.
- [24] Atagundunz, P.; Ergun, T.; Direskeneli, H. MEFV mutations are increased in Behcet's disease and are associated with vascular involvement. *Clin. Exp. Rheumatol.*, **2003**, *21*(Suppl30), S35-S37.
- [25] Petty, R.E.; Southwood, T.R.; Manners, P. International league of associations for rheumatology classification of juvenile idiopathic arthritis: second revision, edmonton, **2001**. *J. Rheumatol.*, **2004**, *31*(2), 390-392.
- [26] Pascual, V.; Allantaz, F.; Arce, E.; Punaro, M.; Banchereau, J. Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade. *J. Exp. Med.*, **2005**, *201*, 1479-1486.
- [27] Masters, S.L.; Simon, A.; Aksentijevich, I.; Kastner, D.L. Horror autoinflammatory: the molecular pathophysiology of autoinflammatory disease. *Ann. Rev. Immunol.*, **2009**, *27*, 621-668.
- [28] Nepom, B.G.; Glass, D.N. Juvenile rheumatoid arthritis and HLA: report of the Park City III workshop. *J. Rheumatol.*, **1992**, *33*, 70-74.
- [29] Verbsky, J.W.; White, A.J. Effective use of the recombinant interleukin 1 receptor antagonist anakinra in therapy resistant systemic onset juvenile rheumatoid arthritis. *J. Rheumatol.*, **2004**, *31*, 2071-2075.
- [30] Yokota, S.; Miyamae, T.; Imagawa, T.; Iwata, N.; Katakura, S.; Mori, M.; Woo, P.; Nishimoto, N.; Yoshizaki, K.; Kishimoto, T. Therapeutic efficacy of humanized recombinant anti-interleukin-6 receptor antibody in children with systemic-onset juvenile idiopathic arthritis. *Arthritis Rheum.*, **2005**, *52*, 818-825.
- [31] Frosch, M.; Roth, J. New insights in systemic juvenile idiopathic arthritis--from pathophysiology to treatment. *Rheumatology (Oxford)*, **2008**, *47*, 121-125.
- [32] Rossi-Semerano, L.; Koné-Paut, I. Is Still's Disease an Autoinflammatory Syndrome? *Int. J. Inflamm.*, **2012**, *2012*, 480373.
- [33] Bywaters, E.G. Still's disease in the adult. *Ann. Rheum. Dis.*, **1971**, *30*, 121-133.
- [34] Efthimiou, P.; Nandini Moorthy, L.; Mavragani, L.; Skokos, D.; Fautrel, B. Adult Onset Still's Disease and Autoinflammation. *Int. J. Inflamm.*, **2012**, *2012*, 964751.

- [35] Kalliolias, G.D.; Georgiou, P.E.; Antonopoulos, I.A.; Andonopoulos A.P.; Lioussis, S.N.C. Anakinra treatment in patients with adult-onset Still's disease is fast, effective, safe and steroid sparing: experience from an uncontrolled trial. *Ann. Rheumatic Dis.*, **2007**, *66*(6), 842-843.
- [36] Efthimiou, P.; Georgy, S. Pathogenesis and management of adult-onset Still's disease. *Semin. Arthritis Rheum.*, **2006**, *36*, 144-152.
- [37] Ferrero-Miliani, L.; Nielsen, O.H.; Andersen, P.S. Chronic inflammation: importance of NOD2 and NALP3 in interleukin-1 β generation. *Clin. Exp. Immunol.*, **2007**, *147*(2), 227-235.
- [38] Asahina, A.; Sakurai, N.; Suzuki, Y.; Narushima, K. Schnitzler's syndrome with prominent neutrophil infiltration misdiagnosed as Sweet's syndrome: a typical example of urticarial neutrophilic dermatosis. *Clin. Exp. Dermatol.*, **2010**, *35*(4), e123-e126.
- [39] Kieffer, C.; Cribier, B.; Lipsker, D. Neutrophilic urticarial dermatosis: a variant of neutrophilic urticaria strongly associated with systemic disease. Report of 9 new cases and review of the literature. *Medicine (Baltimore)*, **2009**, *88*(1), 23-31.
- [40] Pizzirani, C.; Falzoni, S.; Govoni, M.; La Corte, R.; Donadei, S.; Di Virgilio, F.; Trotta, F.; Lo Monaco, A. Dysfunctional inflammasome in Schnitzler's syndrome. *Rheumatology (Oxford)*, **2009**, *48*(10), 1304-1308.
- [41] Migliorini, P.; Del Corso, I.; Tommasi, C.; Boraschi, D. Free circulating interleukin-18 is increased in the Schnitzler syndrome: a new autoinflammatory disease. *Eur. Cytokine Netw.*, **2009**, *20*, 108-111.
- [42] Loock, J.; Lamprecht, P.; Timmann, C.; Mrowietz, U.; Csernok, E.; Gross, W.L. Genetic predisposition (NLRP3 V198M mutation) for IL-1-mediated inflammation in a patient with Schnitzler syndrome. *J. Allergy Clin. Immunol.*, **2010**, *125*(2), 500-502.
- [43] Besada, E.; Nossent, H. Dramatic response to IL1-RA treatment in longstanding multidrug resistant Schnitzler's syndrome: a case report and literature review. *Clin. Rheumatol.*, **2010**, *29*, 567-571.
- [44] Schuster, C.; Kränke, B.; Aberer, E.; Arbab, E.; Sturm, G.; Aberer, W. Schnitzler syndrome: response to anakinra in two cases and review of the literature. *Int. J. Dermatol.*, **2009**, *48*, 1190-1194.
- [45] Claes, K.; Bammens, B.; Delforge, M.; Evenepoel, P.; Kuypers, D.; Vanrenterghem, Y. Another devastating complication of the Schnitzler syndrome: AA amyloidosis. *Br. J. Dermatol.*, **2008**, *158*(1), 182-184.
- [46] Lipsker, D. The Schnitzler syndrome. *Orphanet J. Rare Dis.*, **2010**, *5*, 38.
- [47] Longhurst, H.J.; Yong, P.F.; Manson, A.L.; Cavenagh, J.D.; Grigoriadou, S.; Buckland, M.S. Mullins' syndrome: a new gammopathy-related autoinflammatory syndrome resistant to anakinra. *QJM.*, **2012**, [Epub ahead of print] PMID: 23108029.
- [48] Sweet, R.D. An Acute Febrile Neutrophilic Dermatitis. *Br. J. Dermatol.*, **1964**, *76*, 349-356.
- [49] Cohen, P.R. Sweet's syndrome – a comprehensive review of an acute febrile neutrophilic dermatosis. *Orphanet J. Rare Dis.*, **2007**, *2*, 34.
- [50] Kluger, N.; Gil-Bistes, D.; Guillot, B.; Bessis, D. Efficacy of anti-interleukin-1 receptor antagonist anakinra (Kineret(R)) in a case of refractory Sweet's syndrome. *Dermatology*, **2011**, *222*(2), 123-127.
- [51] Ferguson, P.J. Current understanding of the pathogenesis and management of chronic recurrent multifocal osteomyelitis. *Curr. Rheumatol. Rep.*, **2012**, *14*(2), 130-141.
- [52] Tloutan, B.E.; Podjasek, J.O.; O'Haver, J.; Cordova, K.B.; Nguyen, X.H.; Tee, R.; Pinckard-Hansen, K.C.; Hansen, R.C. Chronic recurrent multifocal osteomyelitis (CRMO) and synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome with associated neutrophilic dermatoses: a report of seven cases and review of the literature. *Pediatr. Dermatol.*, **2009**, *26*(5), 497-505.
- [53] Schroder, K.; Zhou, R.; Tschopp, J. The NLRP3 inflammasome: a sensor for metabolic danger? *Science*, **2010**, *327*(5963), 296-300.
- [54] Martinon, F.; Pettrilli, V.; Mayor, A.; Tardivel, A.; Tschopp, J. Gout-associated uric acid crystals activate the NALP3 inflammasome. *Nature*, **2006**, *440*, 237-241.
- [55] Duewell, P.; Kono, H.; Rayner, K.J.; Sirois, C.M.; Vladimer, G.; Bauernfeind, F.G.; Abela, G.S.; Franchi, L.; Nuñez, G.; Schnurr, M.; Espevik, T.; Lien, E.; Fitzgerald, K.A.; Rock, K.L.; Moore, K.J.; Wright, S.D.; Hornung, V.; Latz, E. NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. *Nature*, **2010**, *466*(7306), 652.
- [56] Aslam, R.; Atindehou, M.; Lavaux, T.; Haïkel, Y.; Schneider, F.; Metz-Boutigue, M.H. Chromogranin A-derived peptides are involved in innate immunity. *Curr. Med. Chem.*, **2012**, *19*(24), 4115-4123.