Journal of Inflammation Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Improving Diagnosis and Clinical Management of Acquired Systemic Autoinflammatory Diseases

Adam Al-Hakim[1], Anoop Mistry[1], Sinisa Savic[1,2]

[1]Department of Clinical Immunology and Allergy, St James's University Hospital, Leeds, UK; [2]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK

Correspondence: Sinisa Savic, Leeds Institute of Rheumatic and Musculoskeletal Medicine, Clinical Science Building, St James's University Hospital, Leeds, LS9 7TF, UK, Tel +441132065567, Email s.savic@leeds.ac.uk

Abstract: Systemic autoinflammatory diseases (SAID) are conditions caused by dysregulation or disturbance of the innate immune system, with neutrophils and macrophages the main effector cells. Although there are now more than 40 distinct, genetically defined SAIDs, the genetic/molecular diagnosis remains unknown for a significant proportion of patients with the disease onset in adulthood. This review focuses on new developments related to acquired/late onset SAID, including phenocopies of monogenic disorders, Schnitzler's syndrome, Adult onset Still's disease, VEXAS syndrome, and autoinflammatory complications associated with myelodysplastic syndrome.

Keywords: autoinflammation, adult onset Still's disease, inflammasome, VEXAS, Schnitzler's syndrome

Introduction

Systemic autoinflammatory diseases (SAID) are defined as conditions primarily caused by dysregulation or disturbance of the innate immune system, with neutrophils and macrophages the main effector cells. Although there are now more than 40 distinct SAIDs for which the genetic basis has been established,[1] the genetic/molecular diagnosis remains elusive for a significant proportion of patients. This is particularly true for patients with adult onset of the disease, in whom the underlying cause in unknown in at least 50% of all cases.[2]

Inherited or Mendelian forms of SAID are caused by rare pathogenic germline variants arising within relevant genes. These are typically inherited from one or both parents, but in some situations may arise de novo. In all cases, the pathogenic variants are present in most or all tissues and cells of the offspring. Therefore, depending on the penetrance of such variants, most patients are symptomatic from early childhood. In some extreme cases, such as neonatal-onset multisystemic disorders (NOMID), the symptoms might be present from birth. Rarely, disease onset might be in adulthood, particularly in late adulthood. Most patients presenting for the first time in adult life are rarely ever diagnosed with a known monogenic form of SAID.

Recent reports and studies have described late onset SAID due to somatic, post-zygotic mutations. These are either in the known causative genes, or due to pathogenic variants in novel genes such as *UBA1*,[3] as in the case of newly-discovered VEXAS (Vacuoles, E1 ubiquitin, X-linked, autoinflammatory somatic) syndrome. Somatic mutations are those not inherited from a parent, but instead are introduced during the lifetime of the individual as a result of a DNA replication defect or environmental insult (eg, UV radiation). In the case of late onset SAID, such somatic mutations tend to arise within myeloid cell lineage, which is the most relevant for the pathogenies of SAID. It has been reported that the proportions of neutrophils carrying a pathogenic mutation may be as low as 2–5%, and still be enough to cause a full clinical phenotype indistinguishable from a hereditary form of the disease.[4]

Although SAIDs remain relatively rare, their recognition in the pediatric setting has improved. This is particularly the case when making an early diagnosis in more established forms such as hereditary fever syndromes, which has been aided by the development of agreed diagnostic criteria.[5] At the same time, late onset or acquired forms remain difficult to

Received: 14 June 2022
Accepted: 18 August 2022
Published: 10 October 2022

Table 1 Differentials of AOSD and Key Investigations.

Diseases	Key Investigations
Infectious diseases	
Bacterial	
Septicemia	Blood cultures, PCT
Infectious endocarditis	Heart ultrasonography
Bilary, colic or urinary infections	Targeted cultures, CT Scan
Tuberculosis	IGRAs, PCR, CT Scan
Brucellosis, yersiniosis …	Serology, PCR
Viral	
HIV, viral hepatitis, parvovirus B19, Herpes viridae, measles, rubella …	Serology, PCR
Parasitological	
Toxoplasmosis, abscessed parasitosis	Serology, PCR
Malignant diseases	
Hematological	
Hodgkin disease or non-Hodgkin lymphoma	Lymph node biopsy
Angio-immunoblastic lymphadenopathy	Bone marrow examination
Castelman disease	CT scanner
Myeloproliferative disorders	PET/CT scanner
Solid cancers	
Kidney, colon, lung …	CT scanner, PET/CT scanner, Biopsies
Paraneoplastic syndroms	
Systemic diseases	
Autoimmune diseases	
Systemic lupus erythematosus	Antinuclear autoantibodies
Polymyositis, dermatomyositis	MRI, biopsy
Rheumatoid arthritis	RF, ACPA
Polyarteritis nodosa or other vasculitis	ANCA, arteriography
Auto-inflammatory diseases	
Post-streptococcal arthritis	ASLO
Reactive arthritis	HLA-B27, MRI
Hereditary auto-inflammatory syndromes	Family history
Familial Mediterranean fever	*MEFV* gene analysis
Mevalonate kinase deficiency	Urinary mevalonic acid, mevalonate kinase analysis
TNF receptor-associated periodic syndrome	*TNFRSF1A* gene analysis
NLRP3-Associated autoinflammatory disease	*NLRP3* gene analysis
Schnitzler syndrome	
VEXAS syndrome	UBA1 gene analysis
Other Conditions	
Sarcoidosis	ACE, biopsy (granulomatosis)
Neutrophilic dermatosis, Sweet syndrome	Biopsy …
Drug-related hypersensitivity or other pseudo-lymphoma	
Kikuchi-Fujimoto disease	

Notes: Adapted from Mitrovic S, Fautrel B. New markers for adult-onset Still's disease. *Jt Bone Spine*. 2018;85(3):285–293. Copyright © 2018 Elsevier Masson SAS. All rights reserved.[55]

Abbreviations: PCT, procalcitonin; CT, computed tomography; IGRAs, interferon gamma release assays; PCR, polymerase chain reaction; PET, positron emission tomography; RF, rheumatoid factor; ACPA, anti-citrullinated antibody; ANCA, anti-neutrophil cytoplasmic antibodies; ASLO, anti-streptolysin O antibody; HLA, human leukocyte antigen; MRI, magnetic resonance imaging; MEFV, Mediterranean fever; TNFRS1A, tumour necrosis factor receptor superfamily member 1A; ACE, angiotensin converting enzyme.

Table 2 Key Features of Systemic Autoinflammatory Syndromes. Adapted from[3,4,23,24,37,47,118–120,129,130,143,144]

	Late-Onset NLRP3-AID	Schnitzler's Syndrome	AOSD	VEXAS	MDS-SAID
Average age of onset	>40 years of age	Most cases >50 years of age	Possibly two peaks (younger and older adults)	Most cases >60 years of age	Most cases >60 years of age
Gender	M=F	M=F	M<F	M>>>F	M=F
	Clinical characteristics				
Fever	Yes	Yes	Yes	Yes	Not always
Weight loss	No	Possible but not typical	Yes	Yes	Possible
Skin	NUD	NUD	Salmon pink rash (typical), urticaria, NUD	Neutrophilic dermatosis (Sweets syndrome), medium vessel vasculitis, Leukocytoclastic vasculitis	Sweets syndrome, PG
Musculoskeletal	Arthralgia, arthritis, myalgia	Arthralgia, myalgia, deep bone pain	Arthralgia, arthritis, myalgia	Arthralgia, arthritis, chondritis, myalgia	Arthralgia, arthritis, myalgia
GI/liver	No	No	Abdominal pain, hepatomegaly	Hepatomegaly, colitis	Rare, colitis
Cardiac	No	No	Pericarditis, myocarditis	Pericarditis	Not usually
Respiratory	No	No	Pleuritis, pulmonary infiltrations	Pulmonary nodules, neutrophilic alveolitis, pleural effusion	Rare
Neurological	Headaches, aseptic meningitis, sensorineural hearing loss	No	Rare, aseptic meningitis	Rare, aseptic meningitis, sensorineural hearing loss	Rare
Hematological	No	MGUS, IgM>>IgG paraprotein	Splenomegaly, lymphadenopathy, cytopenia (usually as a feature of MAS)	Macrocytic anemia, vacuoles in myeloid and erythroid cells (most cases) cytopenia, MDS	Anemia, cytopenia, vacuoles in myeloid and erythroid cells (some cases)
Other frequent features	Nil	Nil	Sore throat	Periorbital edema	Nil
Complications	Deafness if untreated	Progression into hematological malignancy (MM, WM, MZL, etc)	MAS; Disseminated intravascular coagulopathy;Thrombotic thrombocytopenic purpura; Diffuse alveolar haemorrhage; Fulminant hepatitis; Pulmonary hypertension	MDS, transfusion dependence; infections, thromboembolic events; MAS rare, progression to AML or CMML rare	Progression into AML and CMML

(*Continued*)

Table 2 (Continued).

	Late-Onset NLRP3-AID	Schnitzler's Syndrome	AOSD	VEXAS	MDS-SAID
Pathogenesis/ genetic cause	GOF somatic variants in *NLRP3*	*MYDD88* (p. L265P variant) in selected cases. Significance unclear	Complex, likely polygenic	Somatic mutations in *UBA1*	Complex, somatic variants in MDS related genes likely relevant
	Treatment				
Steroid responsive	Partial	Partial	Yes	Yes	Yes
Colchicine	No	No	No	No	No
Anti-IL-1 blockade	Yes	Yes	Yes	Partial	Yes in some cases
Anti-IL-6	No	Selective cases	Yes	Partial	Yes some cases
Anti-TNF	No	No	Yes, selected cases	Yes, selected cases	Yes, selected cases
JAKi	No	No	Yes, selected cases	Yes (best evidence for ruxolitinib)	Likely beneficial in some cases
Allogeneic HSCT	No	Not routinely	Not routinely	Yes, selected cases	Yes, selected cases
Other	Nil	BTK inhibitor	IL-18BP	Azacytidine	Azacytidine

Abbreviations: AOSD, adult onset Still's disease; NUD, neutrophilic urticarial dermatosis; MDS, myelodysplastic syndrome; SAID, systemic autoinflammatory disease; PG, polyarteritis nodosa; AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; MM, mutiple myeloma; MZL, marginal zone lymphoma; WM, Waldenstrom macroglobulinemia; MGUS, monoclonal gammopathy of undetermined significance; MAS, macrophage activation syndrome.

diagnose in a timely manner. The focus of this review will, therefore, be on this latter group. We will provide updates on new developments in this field and describe our broad approach to the investigation and management of these patients.

Phenocopies of Monogenic Disorders

Late Onset (Acquired) NLRP3-Associated Autoinflammatory Disease (NLRP3-AID)

Heterozygous gain-of-function (GoF) variants in the *NLRP3* gene are known to cause a spectrum of inflammatory conditions previously known as cryopyrin-associated periodic syndrome (CAPS) and now termed NLRP3-AID. The *NLRP3* gene codes for NACHT (NAIP, CIITA, HET-E, and TP1), LRR (leucin rich repeat), and PYD (pyrin) domain-containing protein 3 or NLRP3, which forms the sensing part of a larger multimolecular complex known as the NLRP3 inflammasome.[145,146] The mutated protein reduces the threshold and/or leads to spontaneous NLRP3 inflammasome activation, resulting in release of the active forms of IL-1beta and IL-18. It is inappropriate release of the IL-1beta that produces most of the symptoms associated with NLRP3-AID, since a therapeutic blockade of this cytokine leads to complete symptom control and the disease remission in most patients.[147]

The range of symptom and disease severity varies significantly across the NLRP3-AID spectrum. The mildest form, also known as familial cold autoinflammatory syndrome (FCAS), is associated with cold induced urticarial-like rash, mild flu-like symptoms, and fever, lasting 1–2 days. Muckle-Wells syndrome (MWS) is of moderate severity, with fever attacks lasting for several days. Before introduction of the modern biological therapies, MWS was also frequently

associated with chronic systemic inflammation resulting in complications such as amyloidosis, sensorineural hearing loss and aseptic meningitis. As the name suggests, NOMID presents in the neonatal period and it is the most severe form of NLRP3-AID. Without treatment, NOMID causes almost continuous fevers, with chronic systemic inflammation leading to the complications seen in MWS in addition to visual loss, epiphyseal enlargements, and cognitive impairment.

The urticarial-like rash which is seen in all forms of NLRP3-AID to a different degree is non-itchy. The lesional biopsy typically shows neutrophilic predominant infiltration, hence the name of this entity being the neutrophilic urticarial dermatosis, which also confirms the central role neutrophils play in the pathogenis of this condition.[148]

Description of late onset NLRP3-AID follows a previous discovery that some cases of NOMID result from somatic mosaicism with de novo rare variants arising within the *NLRP3* gene post-zygotically.[149] Although these patients presented with classical symptoms in the neonatal period, their genetic diagnosis was initially missed by standard Sanger sequencing method. The importance of these discoveries was two-fold. They showed that complete clinical phenotypes can be replicated even when only a relatively small proportion of cells carries a pathogenic mutation, and that next generation sequencing methods are needed to diagnose such cases. Subsequently, late onset NLRP3-AID were described. Here, patients who were previously fit and well and with no relevant family history developed symptoms consistent with FCAS or MWS for the first time in their 4th, 5th and later decades of life.[4,150] These reports showed not only that a small proportion of cells is sufficient to carry a pathogenic mutation, but also that these cells need to be relevant for the disease pathogenesis, which in these cases were cells of the myeloid lineage and in particular neutrophils. This concept was recapitulated recently in a mouse model, where animals were engineered so that only neutrophils carried a pathogenic mutation in *NLRP3*. This was again sufficient to reproduce a complete NLRP3-AID phenotype.[151]

In the largest case series of late onset-NLRP3-AID (8 patients) the symptom onset occurred between 31–71 years. The clonal expansion of those myeloid cells carrying the pathogenic *NLRP3* allele was also noted. In one patient there was an increase in the mutated NLRP3 gene from 5.1% to 45% over 12 years, which interestingly was associated with a greater requirement for anti-IL-1 inhibition for symptom control.[4] An increase like this suggests a mechanism of either increased production, through non-malignant clonal expansion of hematopoietic stem cells with the NLRP3 mutation, or a selective survival advantage in the myeloid cells with the NLRP3 mutation. Neither possibility has yet been determined.

Acquired NLRC4-AID

NLRC4 (NOD-like receptor family CARD-containing 4 protein) is an intracellular receptor whose activation, like NLRP3, leads to the production of an inflammasome and resulting pyroptosis, through caspase-1 mediated cleavage of gasdermin D. Activation of NLRC4, typically by intracellular Gram-negative bacteria, causes it to bind to ASC leading to caspase-1 activation and subsequent cleavage and release of the pro-inflammatory cytokines IL-18>>IL-1β.[6] Germline GoF variants of the NLRC4 gene have been discovered in patients presenting with autoinflammatory phenotypes similar to FCAS, with characteristic rashes and features, as well as infantile enterocolitis and recurrent macrophage activation syndrome (MAS).[7–9] The excess of IL-18 rather than IL-1β is thought to be more important for the pathogenesis of NLRC4-AID, and in particular MAS. Selective targeting of IL-18 in this setting has been shown to have therapeutic benefit.[10]

Up until very recently NLRC4 somatic mosaicism had only been identified in two neonates, both born prematurely and presenting with florid systemic autoinflammation.[11,12] One of these patients (mutation p.Ser171Phe) presented with necrotising enterocolitis and MAS, passing away at 2 months, whilst the other (mutation p.T177A) was given a diagnosis of NOMID and responded well to IL-1 blockade.[11,12]

As of 2022 there have been two reported cases of somatic NLRC4 mutations identified in older adults with no personal or familial history of systemic inflammation. In one case a 69-year-old Chinese woman presented with a history of intermittent prolonged fevers and a recurrent rash. Results showed elevated inflammatory markers, elevated lactate dehydrogenase, and changes consistent with cutaneous vasculitis on skin biopsy. A good clinical response was achieved with Tocilizumab. Genetic analysis revealed a somatic missense variant (p.His443Gln) in the NLRC4 gene with a mosaicism ratio of 2.61%, with the mutation found in both myeloid and lymphoid cells suggesting a late onset mutation occurring in a hematopoietic stem cell progenitor.[13] In another case, a 57 year old Spanish woman was worked up for a

10 year history of periodic symptoms; beginning with 2–3 day episodes of temperatures and features of systemic inflammation occurring every 6–8 weeks and slowly progressing in severity. An excellent clinical and biochemical response, including the resolution of mesenteric lymphadenopathy, was eventually achieved with anakinra 200 mg/day. Canakinumab was later shown to be equally effective.[14] Genetic analysis suggested a likely pathogenic post-zygotic variant (p.Ser171Phe) with a mutant allele fraction of ~3%.[14]

A consideration of both acquired NLRP3-AIDs and acquired NLRC4-AIDs is how a relatively small proportion of peripheral blood cells carrying the pathogenic NLRP3 variants can produce identical phenotypes to their germline counterparts. One possibility is that the activated inflammasome complexes of pathogenic cells retain their enzymatic activity after release via pyroptosis and are taken up by surrounding cells, propagating a "prionoid" inflammatory cascade.[15,16] In support of this, soluble ASC protein specks can be detected in the serum of patients with NLRP3-AIDs and the levels can change in line with disease activity.[4,17] Another possibility is the presence of more pathogenic NLRP3 or NLRC4 variants in somatic cases as a result of somatic mutations rarely found in inherited disease, something seen in the cases of NLRP3 somatic mosaicism.[18] Though these mutations arise at the same gene hotspots, their much greater prevalence in somatic disease suggests when they do occur as germline mutations the resulting severity is not compatible with a viable embryo.[18]

Other Examples

Other acquired SAIDs, in which phenocopies due to somatic mosaicism have been found to occur, include tumour necrosis factor receptor-associated periodic syndrome (TRAPS) and Blau syndrome (BS).

TRAPS, which classically presents in early childhood with periodic fevers, a rash and arthralgia, occurs due to mutations in the TNFRSF1A gene, encoding the TNFR1 (tumor necrosis factor receptor 1) receptor. Patients who carry what is thought to be low penetrance variants (R92Q and P46L) tend to present later, sometimes for the first time in adulthood, and with a phenotype that is overall milder compared to classical TRAPS.[19] Acquired mutations have recently been identified in two patients presenting with symptoms consistent with systemic autoinflammation. One was a 41-year-old gentleman with a deletion mutation in TNFRSF1A (p.Ser86_Glu93del) and 7.6% whole blood mutant allele frequency.[20] The other was a 60-year old gentleman in whom the de novo missense mutation (p.Phe89Leu) was detected in the patients NK cells, neutrophils, and B cells, though not in monocytes and T cells.[21]

BS is a granulomatous autoinflammatory syndrome occurring due to mutations in the NOD2 gene, typically presenting in early childhood with cutaneous sarcoidosis, granulomatous arthritis, and uveitis. A 22 year old male presenting in such a way was found to have a known pathogenic NOD2 mutation (p.Arg334Gln) with 0.9–12.9% somatic NOD2 mosaicism.[22] Interestingly his two daughters presented with the condition in their first year of life, strongly suggesting gonadal tissue mosaicism, engendering "intrafamilial recurrence" or development of a germline mutation in these affected children.[22]

Schnitzler's Syndrome

Schnitzler's syndrome (SchS) is a rare, late onset, acquired autoinflammatory disorder with prominent cutaneous features. Unlike VEXAS syndrome and late onset NLRP3-AID, the genetic basis of it is undeciphered and, hence, diagnostic criteria (Strasbourg criteria) have been devised to make a diagnosis.[23] These include two required features, firstly, a monoclonal protein which is usually IgM and secondly the presence of a chronic urticarial looking rash which is neutrophil rich on biopsy.[24] Other manifestations include recurrent fever, bone pain, lymphadenopathy, peripheral neuropathy, headache, arthralgia, fatigue, weight loss, and raised inflammatory markers.[24]

Patients with SchS have been found to have elevated levels of ASC, IL-6, and IL-18, however the underlying molecular mechanism is unclear.[17] Due to its clinical similarity with NLRP3-AID, it was suggested that SchS in some cases might also be caused by low level somatic mutations in *NLRP3*. However, two studies which included 32 patients in total failed to find any evidence for this.[17,25] More recently another study which included a further 40 SchS cases also did not find any patients with rare variants in *NLRP3*.[26] Interestingly, the same study also showed that SchS patients do not have any pathogenic variants in *UBA1* either, confirming that SchS has a unique pathology. Further clues to possible aetiology of SchS stems from the observation that a proportion of patients with SchS develop Waldenstrom's

macroglobulinaemia (WM) suggesting that both disorders may have a similar cause.[24] Approximately 90% of patients with WM have been found to have the p.L205P variant in MYD88.[27] MYD88 is a cytoplasmic adaptor protein which mediates interaction of toll like receptors and IL-1 receptor families. This is crucial for propagating downstream signalling of NFKB and MAPK pathways. The L265P may have different consequences dependent on the cell affected. In lymphoid cells it is thought to drive lymphoid malignancy via toll like receptor signalling pathways.[28] Conversely, in myeloid cells the same mutation is thought to drive downstream signalling from the IL-1 receptor.[29] The finding that in one study 9/30 patients were found to have this variant supports this hypothesis, simultaneously it does not offer a universal mechanism for all cases of SchS.[25] It is therefore likely that there are other factors at play. The clonal lymphoid expansion seen in SchS may have a role in some cases. Clonal haematopoiesis of undetermined potential (CHIP) is characterised by the acquisition of somatic mutations in stem cells and is associated with an increased level of the pro-inflammatory cytokines IL-1 and IL-6.[30] Additionally, CHIP related somatic mutations in *TET2* and *U2AF1* stimulate the generation of reactive oxygen species and this in turn is thought to trigger the NLRP3 inflammasome.[30–32] This at best may account for a small proportion of cases as only 1/30 patients were found to have a CHIP associated mutation in one study.[25] Finally, the IgM paraprotein may have a direct pathogenic effect, the mechanism for this is unclear but the finding that the disease seems to remit when underlying hematological malignancy is treated and the paraprotein disappears supports this hypothesis.[33,34] Ultimately there continues to be gaps in our understanding of the pathophysiology of SchS which is a promising area for future study.

SchS is dramatically responsive to IL-1 antagonism, in one study the initiation of anakinra led to a significant reduction in CRP and a meaningful reduction in quality-of-life measures; 95% reported the disappearance of all symptoms accompanied by normalization of plasma CRP concentration.[17] Similarly, canakinumab has also proved to be efficacious.[35] IL-6 blockade may offer an alternate treatment option, as illustrated in an increasing number of case series and reports.[36,37] Notably, it may be an option in patients who fail IL-1 blockade. More recently, Huang et al[38] described a patient with SchS who received Ibrutinib (there was no lymphoplasmacytic lymphoma on bone marrow examination) with the intent of treating his autoinflammatory symptoms, and there was a dramatic symptom improvement in parallel with a reduction in paraprotein levels. In other cases, treating the underlying malignancy proves to be effective.[33,34]

Adult Onset Still's Disease

Adult onset Still's disease (AOSD) is an autoinflammatory condition characterised by prolonged intermittent fevers, arthralgia, and evanescent rash in the absence of infection, malignancy, or rheumatological disease.[39] AOSD and systemic juvenile idiopathic arthritis (sJIA) have different diagnostic criteria but are increasingly understood to be the same disease, with commonality in clinical features, immunological profiles, and responses to treatment.[39]

AOSD typically presents in younger people, with onset occurring in a bimodal pattern, at ages 15–25 and 35–45, though some studies suggesting a further peak between ages 60–65.[40–44] Epidemiological data on AOSD is somewhat limited, with an annual incidence between 0.24–0.62/100,000 and point prevalence of 2.7–6.9/100,000, with women predominantly affected more often than men.[43–46] A retrospective study performed in the USA between 2008–2013 gave an inpatient mortality of 2.6%.[47] The most common clinical features of AOSD are an intermittent fever of ≥39°C lasting ≥1 week, arthralgia lasting ≥2 weeks, and a skin rash that is classically a salmon-pink, non-pruritic, maculopapular eruption occurring during the fever. Myalgias, pharyngitis, lymphadenopathy, and splenomegaly also characteristically feature.[39,48]

AOSD was traditionally felt to occur as one of three broad patterns; monocyclic systemic, polycyclic systemic, and chronic articular. More recently, a dichotomous classification system, with characteristic clinical and immunological profiles, has been proposed, whereby AOSD can be either systemic (high fever, rash, multi-organ involvement, and predominant IL-18/1β cytokine signature) or articular (prominent joint disease and a predominant IL-6 cytokine signature).[49–51] Further work has been done to highlight the clinical heterogeneity of AOSD, with a study showing they may fall into four distinct phenotypes, each characterised by a single prominent clinical feature (high CRP, high ferritin, high systemic score, low CRP/ferritin), raising the possibility of risk stratification and targeted therapies in future.[52]

When comparing presentation by age, those that develop AOSD aged 65 or above similarly present with fever, arthralgia, and skin rashes, though are less likely to develop pharyngitis and more likely to develop pleuritis.[53,54] Those with an elderly onset are 3–5-times more likely to develop life-threatening complications such as disseminated intravascular coagulopathy (DIC) and MAS, highlighting the need for prompt recognition and management in this population.[53]

Biochemical findings include raised CRP/ESR, a neutrophilic leukocytosis, anemia, and thrombocytopenia.[48,55,56] Hyperferritinemia is common in AOSD but in isolation is poorly predictive of the disease.[56] However, ferritin levels have a role in monitoring disease activity in AOSD as they are a reliable marker of disease activity and severity, whilst a profound increase suggests hemophagocytosis and MAS.[48,56] AOSD has a characteristic pattern on FDG PET/CT, showing increased uptake in the bone marrow and spleen with multiple reactive lymph nodes in a symmetrical distribution in the axilla and neck. This characteristic pattern combined with the intensity of uptake has been shown to effectively differentiate AOSD from other rheumatological diseases, though the radiation burden and costs likely preclude it from becoming a key tool of the diagnostic process.[57]

The most widely used and validated criteria for diagnosing AOSD are Yamaguchi's criteria, with a sensitivity of 96.2% and specificity of 92.1%. This classification includes the common clinical features stated above, though requires the exclusion of infections, malignancies, and rheumatic diseases (Table 1), which can significantly delay diagnosis.[56] In 2002, Fautrel et al[59] developed a new classification including glycosylated ferritin fraction ≤20% and removing any exclusion criteria, producing a classification with a sensitivity of 80.6% and an improved specificity of 98.5%.[58] The Fautrel classification has since been validated in a separate study, giving a sensitivity of 96.3%, specificity of 98.9%, and positive and negative predictive values of 94.5% and 99.3%, respectively, providing an effective tool for earlier diagnosis and treatment.[60]

Genetics

Unlike monogenic systemic autoinflammatory syndromes (mSAIDs), AOSD has a presumed polygenic basis. These underlying genetic factors, through unclear immunological pathogenesis, engender a susceptibility to the disease which is then likely triggered by a combination of infective and environmental factors.[61] There is a degree of genetic overlap between AOSD and other SAIDs, with one case series of 162 AOSD/sJIA patients showing 51 (31.4%) carried at least one genetic variant associated with the periodic fever syndromes Familial Mediterranean Fever (FMF), CAPS, TRAPS, or BS.[62] Where these genetic changes indicate shared pathogenic mechanisms of the innate immune system, unique to AOSD is the association of HLA subtypes with the disease, suggesting involvement of the adaptive immune system. HLA-DRB1*11 (OR 2.3), HLA-DQB1*06:02 (OR 2.70), HLA-DRB1*15:01 (OR 2.44), and HLA-DQA1*01:02 (OR 1.97) have all demonstrated association with the disease against healthy controls.[63,64] Furthermore, studies have shown associations with mild, self-limiting disease (HLA-Bw35 and HLA-DRB1*14), chronic disease (HLA-DRB1*2501 and HLA-B1*1501), and those with chronic and systemic AOSD (HLA-DQB1*0602).[65–67]

Pathogenesis

The pathogenesis of AOSD is felt to be driven in large part by a pro-inflammatory cytokine environment with IL-1, IL-6, IL-18, and TNF-α driving an inflammatory cascade. Underpinning this process are new mechanisms gradually being elucidated.

IL-1 is the most potent human endogenous pyrogen and has two forms, IL-1α and IL-1β, both of which stimulate the IL-1R1 receptor and are countered by the endogenous competitive inhibitor IL-1 receptor antagonist (IL-1ra).[39,48] IL-1β, IL-18, which is part of the IL-1 family of cytokines, and IL-6 are all pro-inflammatory cytokines elevated in the context of AOSD.[68–71] IL-6 and IL-18 profiles have even been suggested to indicate clinical subsets, with raised IL-6 increasing the likelihood of articular AOSD (prominent joint disease) and raised IL-18 suggesting an increased risk of developing MAS.[72] Excellent clinical responses in AOSD to anti-IL-1 therapy and anti-IL-6 therapy further underscore the role of these proinflammatory cytokines in active disease.[48]

The interplay between Toll-like receptors (TLRs) and neutrophils, through their various mediators, is emerging as a key component in the development of the sterile inflammation found in AOSD/sJIA.[73] TLRs are pattern recognition

receptors (PRRs) involved in the detection of PAMPS and DAMPS. TLR signalling leads to activation of the NLRP3 inflammasome with downstream promotion of pyroptosis and release of the key pro-inflammatory cytokines IL-1β and IL-18.[74,75]

Neutrophils play a crucial role in this activation, as suggested by the high degree of neutrophilic leucocytosis (>80% of patients) during an acute flare, in part through the production of neutrophil extracellular traps (NETs), which contain the proteins S100A8, S100A9, and S100A12.[76–78] These S100 proteins are DAMPs and ligands for TLR4, inducing activation and further release of chemokines and cytokines to increase neutrophil recruitment and pyroptosis, precipitating a positive feedback loop.[79]

S100A12 and the S100A8/S100A9 dimer (calprotectin) are reliably raised in sJIA a and AOSD, offering a biomarker for diagnosis and disease activity which has shown superiority to CRP in differentiating sJIA from other SAIDs.[72,80–86] Of further interest is the increased type I interferon (IFN) response found in AOSD as neutrophils exposed to IFN-α are primed to form NETs.[73] This recent insight may inform future avenues of research and therapy, particularly as IFNs signal via the Janus kinase (JAK)-signal transducer and JAK inhibitors have shown promise in treating the condition.[73,87,88]

MAS in Context of AOSD

In MAS, also known as secondary hemophagocytic lymphohistiocytosis (sHLH), a pro-inflammatory environment driven by autoinflammation, infection (eg, previous EBV or CMV), malignancy, or autoimmune disease reduces the ability of natural killer (NK) and cytotoxic CD8+ T cells to lyse antigen presenting cells (APC).[89,90] The resulting increased contact time between lytic cells and APCs leads to a pro-inflammatory cascade, involving interferon-gamma (IFN-γ), tumor necrosis factor (TNF), IL-1, IL-6, and IL-18, which in turn leads to macrophage activation and hemophagocytosis. IFN-γ is particularly felt to play a role, supported by its role in macrophage activation, characteristic type 1 polarised T-cell phenotypes seen in the condition, as well as evidence of increased neopterin, an inflammatory marker secreted by IFN-γ activated macrophages and dendritic cells (DCs), in patients with MAS as compared to control groups.[91,92] The role of IFN-γ has been further underscored by the reported success of the anti-IFN-γ antibody Emapalumab in primary HLH, as well as the ongoing trials into its efficacy, specifically in MAS.[93,94] In the context of AOSD and systemic juvenile idiopathic arthritis (a pediatric equivalent of AOSD), MAS occurs in 7–14% of children with sJIA[95,96] and 10–15% of patients with AOSD.[97,98] In another 30–40% of patients MAS might be present in a subclinical form.[99] Elevated IL-18 levels have been shown to be predictive of developing MAS in both sJIA and AOSD.[50,100–102]

Macrophage dysfunction leading to MAS has also been suggested in sJIA lung disease (sJIA-LD), with one study showing 64% (23/36) of patients had pulmonary alveolar proteinosis and/or endogenous lipoid pneumonia (PAP/ELP) as their predominant lung pathology.[103] Interestingly, those with sJIA-LD had significantly higher levels of IL-18, were more likely to develop MAS, and were more likely to have an adverse reaction to biologic therapy, compared to sJIA without lung disease.[104] One observational study showed that those with lung disease in AOSD had an increased mortality compared to those without, suggesting these patients may require a more tailored therapeutic approach to mediate these risks.[105]

It should be noted that excessive inflammatory cytokine production, with a failure of negative feedback mechanisms, leading to hyperinflammation and organ dysfunction, are the hallmark features of a cytokine storm[106] MAS is the archetypal cytokine storm syndrome (CSS), though there are other distinct CSS (eg, driven by sepsis, COVID-19) that have their own unique pathogenesis, immunological profiles, and show marked heterogeneity on attempts to apply pre-existing classification systems, like those used for MAS.[106,107]

MAS classically presents with a triad of fever, hyperferritinemia, and pancytopenia, with an accompanying clinical picture of multi-organ dysfunction.[89,90] Any patient presenting this way, with no clear evidence of underlying infection, malignancy, or autoimmunity should be referred for specialist consideration of autoinflammatory disease, including AOSD.

Treatment

First line therapy of AOSD involves corticosteroids (0.5–1 mg/kg/day), with studies suggesting higher initial doses (eg, ≥40 mg or ≥0.8 mg/kg/day) lead to quicker resolution with fewer relapses.[108,109] The response to corticosteroids should be seen within a few days.[48,109] DMARDs such as methotrexate are then utilised as steroid sparing agents and even in

low doses (7.5–17.5 mg/week) can effectively induce remission and allow the cessation of corticosteroids.[110] Despite this, a significant number (~22%) fail on this combination of corticosteroids and DMARDs, a condition termed refractory AOSD.[40,48,111] This cohort requires biologics, typically in the form of either IL-1 antagonists, IL-6 antagonists, or TNF-inhibitors.[40,48] However, in patients with severe and rapidly progressing disease and those at risk of developing MAS, use of biologics, particularly anti-IL-1 therapy, should be considered early and before conventional synthetic DMARD's.

The IL-1 inhibitor anakinra, the IL-1β inhibitor canakinumab, and the IL-6 inhibitor Tocilizumab have all been shown to cause rapid and sustained improvement in clinical symptoms and inflammatory markers associated with AOSD.[112–114] In an observational study of anakinra assessing 140 patients over 12 months, there was a significant reduction in clinical and biochemical features and steroid sparing effect, with 69.2% of patients remaining on the therapy at 12 months and 28.1% stopping due to clinical remission.[112] In an observational study of 50 patients receiving canakinumab for refractory disease, there was complete response in 78% of patients within 3 months (median) and a partial response in 20%, with around 51% benefiting from a sustained corticosteroid wean.[114] After 27 months (median), 44% of patients were still on canakinumab treatment whilst 18% achieved clinical remission.[114] A Phase II, randomised, double-blind placebo-controlled trial for canakinumab showed significantly superior per-protocol response rates in those receiving canakinumab, as measured by the American College of Rheumatology criteria (ACR30, 50 and 70) after 12 weeks.[115]

It has been suggested that TNF inhibitors and Tocilizumab should be prioritised in refractory AOSD with pronounced joint disease, whereas Anakinra should be first line in so-called systemic AOSD.[111] Other therapies that are beginning to show promise include JAK inhibitors and the IL-18 binding protein tadekinig alfa.[87,88,116] In an observational study of 14 patients the JAK1/3 inhibitor tofacitinib was shown to induce complete remission in 50%, partial remission in 43%, and reduce the average dose of daily prednisolone from 37.3 mg to 5 mg/day at 12 months.[87] A Phase II safety and efficacy trial of tadekinig alfa in AOSD found that both 80 mg and 160 mg, three times a week, had a favourable safety profile and produced a biochemical and/or clinical response in 50% of participants, irrespective of dose.[116] These results highlight the way in which elucidating the pathogenesis of these rare syndromes informs the development of highly targeted, effective treatments.

VEXAS

VEXAS syndrome (vacuoles, E1 enzyme, autoinflammatory, somatic) was originally described in 2020, the disorder represents the prototype of the newly-proposed group of "hematoinflammatory" diseases.[3] It is caused by somatic mutations in *UBA1* which encodes the E1 ubiquitin ligase, an enzyme that plays a key role in post-translational ubiquitination of cellular proteins. The ubiquitin system regulates innate immune-signaling pathways and plays a crucial role in adaptive immune responses and tolerance.[117] *UB1* lies on the X-chromosome, hence the disease almost exclusively effects males. In the original report all 25 men had missense mutations in codon 41 affecting the methionine-41 codon (p.Met41) leading to a loss of the cytoplasmic isoform UBA1b, and the subsequent gain of a new isoform, UBA1c. This catalytically impaired isoform is thought to drive inflammation. More recently, mutations effecting regions outside of codon 41 have been described.[118,119] Affected patients have highly activated inflammatory signatures in pathways associated with myeloid related inflammation such as TNF, IL-6, and IFN-γ.[3] Indeed, animal models replicating loss of UBA1 replicate upregulation of multiple cytokines, as seen in VEXAS syndrome.[3]

VEXAS is severe and progressive, initially thought to be rare and the rapid rate of increasingly published reports suggest that the true prevalence may be under-appreciated. Clinically the disease presents with the cardinal features of fever, fatigue, and raised inflammatory markers combined with both rheumatological and hematologic features. There is systemic inflammation of multiple organ systems leading to various manifestations including Sweet's syndrome, relapsing polychondritis, inflammatory arthritis, polyarteritis nodosa, pulmonary infiltrates, and giant cell arteritis.[120] Hematologic features include macrocytic anemia, thrombocytopenia, thromboembolic disease, and progressive bone marrow failure, which rarely evolves to hematologic malignancy.[120] Our understanding of the phenotype is constantly evolving with hemophagocytic lymphohistiocytosis,[121] myofasciitis,[122] and Behcet's syndrome[123] being described in association with the disease. The combination of relapsing polychondritis, a mean corpuscular volume of >100 fL or platelet count <200x10^9/l in a male patient is highly predictive of a patient with VEXAS.[124]

Vacuoles are a characteristic feature of VEXAS. Vacuoles are rare in marrow myeloid and erythroid precursor cells, when found there is a limited range of differentials including copper deficiency/zinc toxicity[125] and myeloid neoplasms.[126] Consequently, sequencing of *UBA1* must be considered when cytoplasmic vacuoles are seen on hematopathological examination of a specimen. Distinguishing features include the finding that the cytoplasmic vacuoles in VEXAS patients ubiquitination are predominantly localized in promyelocytes, myelocytes, erythroid precursors, and blasts in bone marrow aspirates.[127]

There is currently no approved cure for VEXAS. High dose steroid therapy is effective but a reduction in dose invariably leads to disease relapse. Various drugs have been used to treat patients including methotrexate, calcineurin inhibitors, TNF alpha blockade, IL-1 blockade, IL-6 blockade, as well as JAK inhibitors. Bourbon et al[118] compared the effectiveness of different therapeutic strategies by evaluating the time to change between drugs in a case series, hypomethylating agent and signaling inhibitors achieved notable results; the median time to next treatment was 12.7 months for cyclosporine, 21.9 months for azacytidine. Moreover, a marked regression of cutaneous lesions was observed after the introduction of ruxolitinib in one patient. Azacytidine holds potential promise. It is currently used to manage high risk myelodysplastic syndromes and may target myeloid cells harboring *UBA1* mutations. Notably, Azacytidine has been proposed as a treatment for autoimmune disorders associated with MDS, based on data reporting control of the inflammatory manifestations in two-thirds of the patients.[128] Allogenic hemopoetic stem cell transplantation is more likely to offer a curative treatment, recently a case series of six patients who received a transplant were described.[129] At the time of publication five of the six patients were in complete remission, one unfortunately died post-transplant.[129] The lack of effective safe treatments requires further evaluation.

Myelodysplastic Syndromes and Systemic Inflammation

Prior to the discovery of VEXAS, a number of studies had already established a close link between myelodysplastic disorders (MDS) and systemic inflammation.[130] MDS is a pre-malignant bone marrow condition characterised by persistent peripheral blood cytopaenias. These result from ineffective stem cell maturation due to acquired genetic abnormalities, leading to clonal hematopoiesis. The pathogenesis of MDS involves progressive accumulation of somatic mutations, affecting various cellular processes such as transcription, epigenetic regulation, cohesin complex, RNA splicing, translation, and telomerase function.[131] A proportion of patients (up to 33%) progress to develop acute myeloid leukemia.[132]

The link between MDS and systemic inflammation is bi-directional. For example, evolving evidence suggests that NLRP3 inflammasome activation is a core feature of MDS.[133] A recent mechanistic study also identified that chronic IL-1β exposure can trigger selective expansion of CEBPα-deficient multipotent hematopoietic progenitors, indicating a role for inflammation.[134] Conversely, given the effector role of myeloid cells in SAID pathogenesis, somatic mutations in genes such as *TET2* which initiate MDS development and lead to NLRP3 inflammasome activation[30] might also be responsible for evolution of inflammatory complications seen in this condition. Both autoimmune and autoinflammatory complications occur in MDS. The latter include, among others, inflammatory seronegative arthritis, polymyalgia rheumatica, giant-cell arteritis and various neutrophilic dermatosis such as Sweet's syndrome and pyoderma gangrenosum.[130] A recent study demonstrated that autoinflammatory complications might be more frequent than autoimmune conditions in MDS and that the former were probably under-recognised.[135] Many patients demonstrated an undifferentiated autoinflammatory state, defined by the presence of inflammatory symptoms such as fever, non-specific myalgia, and arthralgia, and associated with elevated CRP in the absence of overt infection. Such patients were found to be younger (on average 3 years) and also had the type of MDS which had higher risk of progression to AML.[135]

The treatment of autoinflammatory complications associated with MDS is challenging for several reasons. Firstly, patients often present with an indistinct clinical picture which makes diagnosis difficult and means it can be problematic to follow a specific treatment guideline. There is an overall lack of defined treatment targets, and the use of immuno-suppressive treatments is further complicated by the pre-existing risk of infection and cytopenia.

Typically, systemic corticosteroids have been the mainstay of the early treatment approach. In many cases, steroid treatment will lead to initial disease remission. However, refractory cases with steroid dependence are common. There is no unified approach to treatment beyond steroids, but this might involve a trial of traditional DMARDs or, increasingly,

biological and synthetic DMARDs.[136] There is emerging evidence that treatments such as azacytidine, a hypomethylating agent used in the treatment of high risk MDS, might be helpful in these cases.[128] Ultimately, some patients require allogenic stem cell transplantation, which has been effective for treating both MDS and inflammatory complications.[137,138]

Conclusion

The recognition, diagnosis, and treatment of patients with late onset or acquired SAID remains challenging and requires a high degree of clinical suspicion. In part this is due to their rarity, but also results from overlapping clinical features and pathogenesis (Table 2). Furthermore, they share many of the non-specific clinical manifestations seen in very common conditions such as infection, autoimmune disorders, and malignancies, which must be excluded first. In malignancy, the situation is further complicated by the fact that some acquired SAID's such as VEXAS and SchS often develop on a background of pre-malignant disease states. Therefore, the boundary between the autoinflammation seen in acquired SAID and that resulting from malignancy, is increasingly blurred.

There are few specific diagnostic tests beyond genetic investigation, so patients with suspected late-onset SAID's require detailed diagnostic work up which is predominantly focused on the exclusion of overlapping conditions. The value of PET-CT in investigating patients with pyrexia of unknown origin has largely been the exclusion of malignancy, since findings in SAID patients are largely non-specific.[139] A retrospective study demonstrated that bone scans can show a district pattern of inflammation in SchS and that the scintigraphic score correlates with disease activity and treatment response.[140] Patients with SchS often complain of non-specific, deep bone pain, and bone imaging might prove useful in the titration of anti-IL-1 therapy, beyond just measuring CRP.

Routine genetic investigations form an important part of the diagnostic work up. Even if the onset of symptoms is in adulthood, it is still important to screen for the known monogenic forms of SAID, since several conditions such as FMF, NLRP12-AID, and haploinsufficiency A20 can all present for the first time in later life. However, in the investigation of late-onset or acquired SAID, additional testing might be necessary to identify the relevant genetic changes. For example, sequencing analysis pipelines, predominantly focused on detection of germline variants in hereditary diseases, should be updated to include somatic-aware variant calling, such as MuTECT2. Furthermore, sequencing should be performed using modern, massive parallel techniques so that sufficient coverage is provided in order to detect low-level mutation down to 2–5%. Lastly, it might occasionally be necessary to perform cell separation and sequence DNA from each relevant cell type.

Whilst for some conditions, such as SchS, treatment options are well established, for others such as VEXAS the optimum medical management is poorly understood. There are a significant proportion of patients with undifferentiated SAID in whom the precise cause of disease is unknown, but who nevertheless require treatment. In such cases, empirical trials of medications typically used to treat SAID, such as colchicine and anakinra, might prove effective and safe in the long-term.[2,141] In addition, their use may improve our understanding of the possible pathological mechanisms driving such conditions. In patients who fail colchicine and anti-IL-1 therapy, JAKi are increasingly used in a similar, empirical fashion.[142]

Recent discovery of VEXAS syndrome provides a paradigm shift in thinking around the role of somatic mutations in the disease pathogenesis other than malignancy. The role of such acquired process in the development of many more common disorders is just starting to be fully appreciated.[118]

Acknowledgments

SS is supported by the National Institute for Health Research (NIHR) Leeds Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health.

Disclosure

SS has contributed to advisory boards for Novartis, and has research funding from SOBI during the conduct of the study; grants, personal fees from CSL Behring, personal fees from Takeda, personal fees from KalVista, personal fees from Biocryst, outside the submitted work. The authors report no other conflicts of interest in this work.

References

1. Savic S, Caseley EA, McDermott MF. Moving towards a systems-based classification of innate immune-mediated diseases. *Nat Rev Rheumatol*. 2020;16(4):222–237. doi:10.1038/s41584-020-0377-5
2. Harrison SR, McGonagle D, Nizam S, et al. Anakinra as a diagnostic challenge and treatment option for systemic autoinflammatory disorders of undefined etiology. *JCI Insight*. 2016;1(6):86336. doi:10.1172/jci.insight.86336
3. Beck DB, Ferrada MA, Sikora KA, et al. Somatic mutations in UBA1 and severe adult-onset autoinflammatory disease. *N Engl J Med*. 2020;383(27):2628–2638. doi:10.1056/NEJMoa2026834
4. Rowczenio DM, Gomes SM, Aróstegui JI, et al. Late-onset cryopyrin-associated periodic syndromes caused by somatic NLRP3 mosaicism-UK single center experience. *Front Immunol*. 2017;8:1410. doi:10.3389/fimmu.2017.01410
5. Romano M, Arici ZS, Piskin D, et al. The 2021 EULAR/American College of Rheumatology points to consider for diagnosis, management and monitoring of the interleukin-1 mediated autoinflammatory diseases: cryopyrin-associated periodic syndromes, tumour necrosis factor receptor-associated periodic syndrome, mevalonate kinase deficiency, and deficiency of the interleukin-1 receptor antagonist. *Ann Rheum Dis*. 2022;81(7):907–921. doi:10.1136/annrheumdis-2021-221801
6. Bauer R, Rauch I. The NAIP/NLRC4 inflammasome in infection and pathology. *Mol Aspects Med*. 2020;76:100863. doi:10.1016/j.mam.2020.100863
7. Romberg N, Al Moussawi K, Nelson-Williams C, et al. Mutation of NLRC4 causes a syndrome of enterocolitis and autoinflammation. *Nat Genet*. 2014;46(10):1135. doi:10.1038/ng.3066
8. Kitamura A, Sasaki Y, Abe T, Kano H, Yasutomo K. An inherited mutation in NLRC4 causes autoinflammation in human and mice. *J Exp Med*. 2014;211(12):2385. doi:10.1084/jem.20141091
9. Canna SW, De Jesus AA, Gouni S, et al. An activating NLRC4 inflammasome mutation causes autoinflammation with recurrent macrophage activation syndrome. *Nat Genet*. 2014;46(10):1140. doi:10.1038/ng.3089
10. Liang J, Alfano DN, Squires JE, et al. Novel NLRC4 mutation causes a syndrome of perinatal autoinflammation with hemophagocytic lymphohistiocytosis, hepatosplenomegaly, fetal thrombotic vasculopathy, and congenital anemia and ascites. *Pediatr Dev Pathol*. 2017;20(6):498–505. doi:10.1177/1093526616686890
11. Kawasaki Y, Oda H, Ito J, et al. Identification of a high-frequency somatic NLRC4 mutation as a cause of autoinflammation by pluripotent cell–based phenotype dissection. *Arthritis Rheumatol*. 2017;69(2):447–459. doi:10.1002/art.39960
12. Wang J, Ye Q, Zheng W, et al. Low-ratio somatic NLRC4 mutation causes late-onset autoinflammatory disease. *Ann Rheum Dis*. 2022;2022:annrheumdis-2021-221708.
13. Ionescu D, Peñín-Franch A, Mensa-Vilaró A, et al. First description of late-onset autoinflammatory disease due to somatic NLRC4 mosaicism. *Arthritis Rheumatol*. 2022;74(4):692–699. doi:10.1002/art.41999
14. Franklin BS, Bossaller L, De Nardo D, et al. The adaptor ASC has extracellular and "prionoid" activities that propagate inflammation. *Nat Immunol*. 2014;15(8):727–737. doi:10.1038/ni.2913
15. Baroja-Mazo A, Martín-Sánchez F, Gomez AI, et al. The NLRP3 inflammasome is released as a particulate danger signal that amplifies the inflammatory response. *Nat Immunol*. 2014;15(8):738–748. doi:10.1038/ni.2919
16. Rowczenio DM, Pathak S, Arostegui JI, et al. Molecular genetic investigation, clinical features, and response to treatment in 21 patients with Schnitzler syndrome. *Blood*. 2018;131(9):974–981. doi:10.1182/blood-2017-10-810366
17. Louvrier C, Assrawi E, El Khouri E, et al. NLRP3-associated autoinflammatory diseases: phenotypic and molecular characteristics of germline versus somatic mutations. *J Allergy Clin Immunol*. 2020;145(4):1254–1261. doi:10.1016/j.jaci.2019.11.035
18. Cantarini L, Rigante D, Merlini G, et al. The expanding spectrum of low-penetrance TNFRSF1A gene variants in adults presenting with recurrent inflammatory attacks: clinical manifestations and long-term follow-up. *Semin Arthritis Rheum*. 2014;43(6):818–823. doi:10.1016/j.semarthrit.2013.12.002
19. Rowczenio DM, Trojer H, Omoyinmi E, et al. Brief report: association of tumor necrosis factor receptor-associated periodic syndrome with gonosomal mosaicism of a novel 24-nucleotide TNFRSF1A deletion. *Arthritis Rheumatol*. 2016;68(8):2044–2049. doi:10.1002/art.39683
20. Kontzias A, Zarabi SK, Calabrese C, et al. Somatic mosaicism in adult-onset TNF receptor-associated periodic syndrome (TRAPS). *Mol Genet Genomic Med*. 2019;7(8). doi:10.1002/mgg3.791
21. Mensa-Vilaro A, Teresa Bosque M, Magri G, et al. Brief report: late-onset cryopyrin-associated periodic syndrome due to myeloid-restricted somatic NLRP3 mosaicism. *Arthritis Rheumatol*. 2016;68(12):3035–3041. doi:10.1002/art.39770
22. Simon A, Asli B, Braun-Falco M, et al. Schnitzler's syndrome: diagnosis, treatment, and follow-up. *Allergy Eur J Allergy Clin Immunol*. 2013;68(5):562–568. doi:10.1111/all.12129
23. De Koning HD. Schnitzler's syndrome: lessons from 281 cases. *Clin Transl Allergy*. 2014;4(1):1–15. doi:10.1186/2045-7022-4-41
24. Pathak S, Rowczenio DM, Owen RG, et al. Exploratory study of MYD88 L265P, rare NLRP3 variants, and clonal hematopoiesis prevalence in patients with schnitzler syndrome. *Arthritis Rheumatol*. 2019;71(12):2121–2125. doi:10.1002/art.41030
25. Louvrier C, Awad F, Amselem S, Lipsker D, Giurgea I. Absence of NLRP3 somatic mutations and VEXAS-related UBA1 mutations in a large cohort of patients with Schnitzler syndrome. *Allergy*. 2022. doi:10.1111/all.15411
26. Varettoni M, Arcaini L, Zibellini S, et al. Prevalence and clinical significance of the MYD88 (L265P) somatic mutation in Waldenström's macroglobulinemia and related lymphoid neoplasms. *Blood*. 2013;121(13):2522–2528. doi:10.1182/blood-2012-09-457101
27. Ngo VN, Young RM, Schmitz R, et al. Oncogenically active MYD88 mutations in human lymphoma. *Nature*. 2011;470(7332):115–121. doi:10.1038/nature09671
28. Warner N, Núñez G. MyD88: a critical adaptor protein in innate immunity signal transduction. *J Immunol*. 2013;190(1):3–4. doi:10.4049/jimmunol.1203103
29. Sano S, Oshima K, Wang Y, et al. Tet2-mediated clonal hematopoiesis accelerates heart failure through a mechanism involving the IL-1β/NLRP3 inflammasome. *J Am Coll Cardiol*. 2018;71(8):875–886. doi:10.1016/j.jacc.2017.12.037
30. Basiorka AAA, McGraw KLL, Abbas-Aghababazadeh F, et al. Assessment of ASC specks as a putative biomarker of pyroptosis in myelodysplastic syndromes: an observational cohort study. *Lancet Haematol*. 2018;5(9):e393–402. doi:10.1016/S2352-3026(18)30109-1

31. Basiorka AA, McGraw KL, Eksioglu EA, et al. The NLRP3 inflammasome functions as a driver of the myelodysplastic syndrome phenotype. *Blood*. 2016;128(25):2960–2975. doi:10.1182/blood-2016-07-730556
32. Claves F, Siest R, Lefebvre C, Valmary-Degano S, Carras S. Dramatic efficacy of ibrutinib in a Schnitzler syndrome case with indolent lymphoma. *J Clin Immunol*. 2021;41(6):1380–1383. doi:10.1007/s10875-021-01038-y
33. Paladini A, Vitale A, Frediani B, Cantarini L. Resolution of Schnitzler's syndrome after haematopoietic stem cell transplantation. *Clin Exp Rheumatol*. 2021;39:704. doi:10.55563/clinexprheumatol/1r3i7i
34. Betrains A, Staels F, Vanderschueren S. Efficacy and safety of canakinumab treatment in schnitzler syndrome: a systematic literature review. *Semin Arthritis Rheum*. 2020;50(4):636–642. doi:10.1016/j.semarthrit.2020.05.002
35. Bonnekoh H, Frischbutter S, Roll S, Maurer M, Krause K. Tocilizumab treatment in patients with Schnitzler syndrome: an open-label study. *J Allergy Clin Immunol Pract*. 2021;9(6):2486–2489.e4. doi:10.1016/j.jaip.2021.01.024
36. Yan R, Cao W, Liu X, Li F, Shen M. A Chinese case series of Schnitzler syndrome and complete remission in one tocilizumab-treated patient. *Clin Rheumatol*. 2020;39(12):3847–3852. doi:10.1007/s10067-020-05204-2
37. Huang Y, Wang Y, Yu F, et al. Case report: therapeutic use of ibrutinib in a patient with Schnitzler syndrome. *Front Immunol*. 2022;13:1–4.
38. Nigrovic PA, Schneider R. Systemic juvenile idiopathic arthritis and adult onset Still disease. In: Hashkes PJ, Laxer RM, Simon A, editors. *Textbook of Autoinflammation*. Cham, Switzerland: Springer Nature Switzerland AG; 2019:587–616.
39. Sfriso P, Priori R, Valesini G, et al. Adult-onset Still's disease: an Italian multicentre retrospective observational study of manifestations and treatments in 245 patients. *Clin Rheumatol*. 2016;35(7):1683–1689. doi:10.1007/s10067-016-3308-8
40. Wakai K, Ohta A, Tamakoshi A, et al. Estimated prevalence and incidence of adult Still's disease: findings by a nationwide epidemiological survey in Japan. *J Epidemiol*. 1997;7(4):221–225. doi:10.2188/jea.7.221
41. Magadur-Joly G, Billaud E, Barrier JH, et al. Epidemiology of adult Still's disease: estimate of the incidence by a retrospective study in west France. *Ann Rheum Dis*. 1995;54(7):587. doi:10.1136/ard.54.7.587
42. Bogdan M, Nitsch-Osuch A, Samel-Kowalik P, Goryński P, Tyszko P, Kanecki K. Adult-onset Still's disease in Poland - a nationwide population-based study. *Ann Agric Environ Med*. 2021;28(2):250–254. doi:10.26444/aaem/132451
43. Evensen KJ, Nossent HC. Epidemiology and outcome of adult-onset Still's disease in Northern Norway. *Scand J Rheumatol*. 2006;35(1):48–51. doi:10.1080/03009740510026616
44. Hocevar A, Rotar Z, Krosel M, Novljan MP, Praprotnik S, Tomsic M. SAT0524 the incidence rate of adult onset Still's disease in Slovenia. *Ann Rheum Dis*. 2020;79(Suppl 1):1218–1219. doi:10.1136/annrheumdis-2020-eular.1738
45. Balci MA, Pamuk ON, Pamuk GE, Uzundere FK, Donmez S. AB1142 epidemiology and outcome of adult-onset still's disease in Northwestern Thrace Region in Turkey. *Ann Rheum Dis*. 2015;74(Suppl 2):1284. doi:10.1136/annrheumdis-2015-eular.1929
46. Mehta BY, Ibrahim S, Briggs W, Efthimiou P. Racial/ethnic variations in morbidity and mortality in adult onset Still's disease: an analysis of national dataset. *Semin Arthritis Rheum*. 2019;49(3):469–473. doi:10.1016/j.semarthrit.2019.04.004
47. Giacomelli R, Ruscitti P, Shoenfeld Y. A comprehensive review on adult onset Still's disease. *J Autoimmun*. 2018;(93):24–36. doi:10.1016/j.jaut.2018.07.018
48. Mitrovic S, Fautrel B. Clinical phenotypes of adult-onset Still's disease: new insights from pathophysiology and literature findings. *J Clin Med*. 2021;10(12):2633. doi:10.3390/jcm10122633
49. Inoue N, Shimizu M, Tsunoda S, Kawano M, Matsumura M, Yachie A. Cytokine profile in adult-onset Still's disease: comparison with systemic juvenile idiopathic arthritis. *Clin Immunol*. 2016;169:8–13. doi:10.1016/j.clim.2016.05.010
50. Jamilloux Y, Gerfaud-Valentin M, Martinon F, Belot A, Henry T, Sève P. Pathogenesis of adult-onset Still's disease: new insights from the juvenile counterpart. *Immunol Res*. 2014;61(1):53–62. doi:10.1007/s12026-014-8561-9
51. Berardicurti O, Conforti A, Iacono D, et al. Dissecting the clinical heterogeneity of adult-onset Still's disease: results from a multi-dimensional characterization and stratification. *Rheumatology*. 2021;60(10):4844–4849. doi:10.1093/rheumatology/keaa904
52. Kishida D, Ichikawa T, Takamatsu R, et al. Clinical characteristics and treatment of elderly onset adult-onset Still's disease. *Sci Rep*. 2022;12(1):1–7.
53. Di Cola I, Di Muzio C, Conforti A, et al. Adult-onset Still's disease with elderly onset, results from a multicentre study. *Clin Exp Rheumatol*. 2022. doi:10.55563/clinexprheumatol/0215kv
54. Colafrancesco S, Priori R, Valesini G. Presentation and diagnosis of adult-onset Still's disease: the implications of current and emerging markers in overcoming the diagnostic challenge. *Expert Rev Clin Immunol*. 2015;11(6):749–761. doi:10.1586/1744666X.2015.1037287
55. Mitrovic S, Fautrel B. New markers for adult-onset Still's disease. *Jt Bone Spine*. 2018;85(3):285–293. doi:10.1016/j.jbspin.2017.05.011
56. Zhou X, Li Y, Wang Q. FDG PET/CT used in identifying adult-onset Still's disease in connective tissue diseases. *Clin Rheumatol*. 2020;39(9):2735–2742. doi:10.1007/s10067-020-05041-3
57. Hofheinz K, Schett G, Manger B. Adult onset Still's disease associated with malignancy-cause or coincidence? *Semin Arthritis Rheum*. 2016;45(5):621–626. doi:10.1016/j.semarthrit.2015.10.003
58. Fautrel B, Zing E, Golmard JL, et al. Proposal for a new set of classification criteria for adult-onset still disease. *Medicine*. 2002;81(3):194–200. doi:10.1097/00005792-200205000-00003
59. Lebrun D, Mestrallet S, Dehoux M, et al. Validation of the Fautrel classification criteria for adult-onset Still's disease. *Semin Arthritis Rheum*. 2018;47(4):578–585. doi:10.1016/j.semarthrit.2017.07.005
60. Gaggiano C, Rigante D, Vitale A, et al. Hints for genetic and clinical differentiation of adult-onset monogenic autoinflammatory diseases. *Mediators Inflamm*. 2019;2019:1–29. doi:10.1155/2019/3293145
61. Li H, Abramova I, Chesoni S, Yao Q. Molecular genetic analysis for periodic fever syndromes: a supplemental role for the diagnosis of adult-onset Still's disease. *Clin Rheumatol*. 2018;37(8):2021–2026. doi:10.1007/s10067-018-4178-z
62. Ombrello MJ, Remmers EF, Tachmazidou I, et al. HLA-DRB1*11 and variants of the MHC class II locus are strong risk factors for systemic juvenile idiopathic arthritis. *Proc Natl Acad Sci U S A*. 2015;112(52):15970–15975. doi:10.1073/pnas.1520779112
63. Teng J, Chen X, Chen J, et al. The amino acid variants in HLA II molecules explain the major association with adult-onset Still's disease in the Han Chinese population. *J Autoimmun*. 2021;116:102562. doi:10.1016/j.jaut.2020.102562
64. Terkeltaub R, Esdaile JM, Décary F, Harth M, Lister J, Lapointe N. HLA-Bw35 and prognosis in adult Still's disease. *Arthritis Rheum*. 1981;24(12):1469–1472. doi:10.1002/art.1780241203

65. Wouters JM, Reekers P, Van De Putte LB, et al. Adult-onset still's disease. Disease course and HLA associations. *Arthritis Rheum*. 1986;29(3):415–418. doi:10.1002/art.1780290316
66. Fujii T, Nojima T, Yasuoka H, et al. Cytokine and immunogenetic profiles in Japanese patients with adult Still's disease. Association with chronic articular disease. *Rheumatology*. 2001;40(12):1398–1404. doi:10.1093/rheumatology/40.12.1398
67. 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(9):1479. doi:10.1084/jem.20050473
68. Colafrancesco S, Priori R, Alessandri C, et al. IL-18 serum level in adult onset Still's disease: a marker of disease activity. *Int J Inflam*. 2012;2012. doi:10.1155/2012/156890
69. Choi J-H, Suh C-H, Lee Y-M, et al. Serum cytokine profiles in patients with adult onset Still's disease. *J Rheumatol*. 2003;30:11.
70. Chen D-Y, Lan J-L, Lin F-J, Hsieh T-Y. Proinflammatory cytokine profiles in sera and pathological tissues of patients with active untreated adult onset Still's disease. *J Rheumatol*. 2004;31(11):2189–2198.
71. Frediani B, Millucci L, Bernardini G, et al. SAT0621 Clinical significance of interleukin-18 and interleukin −6 on disease course of adult-onset still's disease. *Ann Rheum Dis*. 2018;77(Suppl 2):1162.
72. Ma Y, Wang M, Jia J, et al. Enhanced type I interferon signature induces neutrophil extracellular traps enriched in mitochondrial DNA in adult-onset Still's disease. *J Autoimmun*. 2022;127:102793. doi:10.1016/j.jaut.2022.102793
73. Nyström S, Antoine DJ, Lundbäck P, et al. TLR activation regulates damage-associated molecular pattern isoforms released during pyroptosis. *EMBO J*. 2013;32(1):86. doi:10.1038/emboj.2012.328
74. Gurung P, Subbarao Malireddi RK, Anand PK, et al. Toll or interleukin-1 receptor (TIR) domain-containing adaptor inducing interferon-β (TRIF)-mediated caspase-11 protease production integrates Toll-like receptor 4 (TLR4) protein- and Nlrp3 inflammasome-mediated host defense against enteropathogens. *J Biol Chem*. 2012;287(41):34474–34483. doi:10.1074/jbc.M112.401406
75. Kim JW, Ahn MH, Jung JY, Suh CH, Kim HA. An update on the pathogenic role of neutrophils in systemic juvenile idiopathic arthritis and adult-onset Still's disease. *Int J Mol Sci*. 2021;22(23):13038. doi:10.3390/ijms222313038
76. Austermann J, Spiekermann C, Roth J. S100 proteins in rheumatic diseases. *Nat Rev Rheumatol*. 2018;14(9):528–541. doi:10.1038/s41584-018-0058-9
77. Sprenkeler EGG, Zandstra J, Van Kleef ND, et al. S100A8/A9 is a marker for the release of neutrophil extracellular traps and induces neutrophil activation. *Cells*. 2022;11(2):236. doi:10.3390/cells11020236
78. Frosch M, Ahlmann M, Vogl T, et al. The myeloid-related proteins 8 and 14 complex, a novel ligand of toll-like receptor 4, and interleukin-1beta form a positive feedback mechanism in systemic-onset juvenile idiopathic arthritis. *Arthritis Rheum*. 2009;60(3):883–891. doi:10.1002/art.24349
79. Holzinger D, Foell D, Kessel C. The role of S100 proteins in the pathogenesis and monitoring of autoinflammatory diseases. *Mol Cell Pediatr*. 2018;5(1). doi:10.1186/s40348-018-0085-2
80. Holzinger D, Frosch M, Kastrup A, et al. The Toll-like receptor 4 agonist MRP8/14 protein complex is a sensitive indicator for disease activity and predicts relapses in systemic-onset juvenile idiopathic arthritis. *Ann Rheum Dis*. 2012;71(6):974–980. doi:10.1136/annrheumdis-2011-200598
81. Aljaberi N, Tronconi E, Schulert G, et al. The use of S100 proteins testing in juvenile idiopathic arthritis and autoinflammatory diseases in a pediatric clinical setting: a retrospective analysis. *Pediatr Rheumatol Online J*. 2020;18(1). doi:10.1186/s12969-020-0398-2
82. Kim HA, An JM, Nam JY, Jeon JAY, Suh CH. Serum S100A8/A9, but not follistatin-like protein 1 and interleukin 18, may be a useful biomarker of disease activity in adult-onset Still's disease. *J Rheumatol*. 2012;39(7):1399–1406. doi:10.3899/jrheum.120079
83. Kim HA, Han JH, Kim WJ, et al. TLR4 endogenous ligand S100A8/A9 levels in adult-onset Still's disease and their association with disease activity and clinical manifestations. *Int J Mol Sci*. 2016;17(8):1342. doi:10.3390/ijms17081342
84. Wittkowski H, Frosch M, Wulffraat N, et al. S100A12 is a novel molecular marker differentiating systemic-onset juvenile idiopathic arthritis from other causes of fever of unknown origin. *Arthritis Rheum*. 2008;58(12):3924–3931. doi:10.1002/art.24137
85. Bae CB, Suh CH, An JM, et al. Serum S100A12 may be a useful biomarker of disease activity in adult-onset Still's disease. *J Rheumatol*. 2014;41(12):2403–2408. doi:10.3899/jrheum.140651
86. Hu Q, Wang M, Jia J, et al. Tofacitinib in refractory adult-onset Still's disease: 14 cases from a single centre in China. *Ann Rheum Dis*. 2020;79(6):842–844. doi:10.1136/annrheumdis-2019-216699
87. Ladhari C, Jorgensen C, Pers YM. Treatment of refractory adult onset Still's disease with combination anakinra and baricitinib therapy. *Rheumatology*. 2019;58(4):736–737. doi:10.1093/rheumatology/key414
88. Crayne CB, Albeituni S, Nichols KE, Cron RQ. The immunology of macrophage activation syndrome. *Front Immunol*. 2019;10:119. doi:10.3389/fimmu.2019.00119
89. Eloseily EM, Cron RQ. Macrophage activation syndrome. *Microbiome Rheum Dis Infect*. 2018;151:927–941.
90. Di Cola I, Ruscitti P, Giacomelli R, Cipriani P. The pathogenic role of interferons in the hyperinflammatory response on adult-onset Still's disease and macrophage activation syndrome: paving the way towards new therapeutic targets. *J Clin Med*. 2021;10(6):1–12. doi:10.3390/jcm10061164
91. Chaturvedi VV, Marsh RA, Zoref-Lorenz A, et al. T-cell activation profiles distinguish hemophagocytic lymphohistiocytosis and early sepsis. *Blood*. 2021;137(17):2337–2346. doi:10.1182/blood.2020009499
92. Grom AA, Bachir J, Asnaghi V, De Benedetti F. Trials in progress: a two-cohort, open-label, single-arm study of emapalumab, an anti-interferon gamma (IFNγ) monoclonal antibody, in patients with macrophage activation syndrome (MAS) in rheumatic diseases. *Blood*. 2021;138(Supplement 1):4195. doi:10.1182/blood-2021-146770
93. Locatelli F, Jordan MB, Allen C, et al. Emapalumab in children with primary hemophagocytic lymphohistiocytosis. *N Engl J Med*. 2020;382(19):1811–1822. doi:10.1056/NEJMoa1911326
94. Sawhney S, Woo P, Murray KJ. Macrophage activation syndrome: a potentially fatal complication of rheumatic disorders. *Arch Dis Child*. 2001;85(5):421–426. doi:10.1136/adc.85.5.421
95. Moradinejad MH, Ziaee V. The incidence of macrophage activation syndrome in children with rheumatic disorders. *Minerva Pediatr*. 2011;63(6):459–466.

96. Fukaya S, Yasuda S, Hashimoto T, et al. Clinical features of haemophagocytic syndrome in patients with systemic autoimmune diseases: analysis of 30 cases. *Rheumatology*. 2008;47(11):1686–1691. doi:10.1093/rheumatology/ken342
97. Mitrovic S, Fautrel B. Complications of adult-onset Still's disease and their management. *Expert Rev Clin Immunol*. 2018;14(5):351–365. doi:10.1080/1744666X.2018.1465821
98. Behrens EM, Beukelman T, Paessler M, Cron RQ. Occult macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis. *J Rheumatol*. 2007;34(5):1133–1138.
99. Shimizu M, Yokoyama T, Yamada K, et al. Distinct cytokine profiles of systemic-onset juvenile idiopathic arthritis-associated macrophage activation syndrome with particular emphasis on the role of interleukin-18 in its pathogenesis. *Rheumatology*. 2010;49(9):1645–1653. doi:10.1093/rheumatology/keq133
100. Mizuta M, Shimizu M, Inoue N, et al. Clinical significance of interleukin-18 for the diagnosis and prediction of disease course in systemic juvenile idiopathic arthritis. *Rheumatology*. 2021;60(5):2421–2426. doi:10.1093/rheumatology/keaa634
101. Shiga T, Nozaki Y, Tomita D, et al. Usefulness of interleukin-18 as a diagnostic biomarker to differentiate adult-onset Still's disease with/without macrophage activation syndrome from other secondary hemophagocytic lymphohistiocytosis in adults. *Front Immunol*. 2021;12:1. doi:10.3389/fimmu.2021.750114
102. Saper VE, Chen G, Deutsch GH, et al. Emergent high fatality lung disease in systemic juvenile arthritis. *Ann Rheum Dis*. 2019;78(12):1722. doi:10.1136/annrheumdis-2019-216040
103. Schulert GS, Yasin S, Carey B, et al. Systemic juvenile idiopathic arthritis-associated lung disease: characterization and risk factors. *Arthritis Rheumatol*. 2019;71(11):1943–1954. doi:10.1002/art.41073
104. Ruscitti P, Berardicurti O, Iacono D, et al. Parenchymal lung disease in adult onset Still's disease: an emergent marker of disease severity—characterisation and predictive factors from Gruppo Italiano di Ricerca in Reumatologia Clinica e Sperimentale (GIRRCS) cohort of patients. *Arthritis Res Ther*. 2020;22(1). doi:10.1186/s13075-020-02245-5
105. Fajgenbaum DC, June CH. Cytokine Storm. *The New England Journal of Medicine*. 2020;383(23):2255–2273. doi:10.1056/NEJMra2026131
106. Reiff DD, Cron RQ. Performance of cytokine storm syndrome scoring systems in pediatric COVID-19 and multisystem inflammatory syndrome in children. *ACR Open Rheumatol*. 2021;3(12):820–826. doi:10.1002/acr2.11331
107. Colina M, Zucchini W, Ciancio G, Orzincolo C, Trotta F, Govoni M. The evolution of adult-onset Still disease: an observational and comparative study in a cohort of 76 Italian patients. *Semin Arthritis Rheum*. 2011;41(2):279–285. doi:10.1016/j.semarthrit.2010.12.006
108. Kong XD, Xu D, Zhang W, Zhao Y, Zeng X, Zhang F. Clinical features and prognosis in adult-onset Still's disease: a study of 104 cases. *Clin Rheumatol*. 2010;29(9):1015–1019. doi:10.1007/s10067-010-1516-1
109. Fautrel B, Borget C, Rozenberg S, et al. Corticosteroid sparing effect of low dose methotrexate treatment in adult Still's disease. *J Rheumatol*. 1999;26(2):373–378.
110. Jamilloux Y, Gerfaud-Valentin M, Henry T, Sève P. Treatment of adult-onset Still's disease: a review. *Ther Clin Risk Manag*. 2015;11:33. doi:10.2147/TCRM.S64951
111. Colafrancesco S, Priori R, Valesini G, et al. Response to interleukin-1 inhibitors in 140 Italian patients with adult-onset Still's disease: a multicentre retrospective observational study. *Front Pharmacol*. 2017;8. doi:10.3389/fphar.2017.00369
112. Ortiz-Sanjuán F, Blanco R, Calvo-Rio V, et al. Efficacy of tocilizumab in conventional treatment-refractory adult-onset Still's disease: multicenter retrospective open-label study of thirty-four patients. *Arthritis Rheumatol*. 2014;66(6):1659–1665. doi:10.1002/art.38398
113. Laskari K, Tektonidou PMG, Katsiari PC, et al. Outcome of refractory to conventional and/or biologic treatment adult Still's disease following canakinumab treatment: countrywide data in 50 patients. *Semin Arthritis Rheum*. 2021;51(1):137–143. doi:10.1016/j.semarthrit.2020.10.011
114. Kedor C, Listing J, Zernicke J, et al. Canakinumab for treatment of adult-onset Still's disease to achieve reduction of arthritic manifestation (CONSIDER): phase II, randomised, double-blind, placebo-controlled, multicentre, investigator-initiated trial. *Ann Rheum Dis*. 2020;79(8):1090–1097. doi:10.1136/annrheumdis-2020-217155
115. Gabay C, Fautrel B, Rech J, et al. Open-label, multicentre, dose-escalating phase II clinical trial on the safety and efficacy of tadekinig alfa (IL-18BP) in adult-onset Still's disease. *Ann Rheum Dis*. 2018;77(6):840–847. doi:10.1136/annrheumdis-2017-212608
116. Moudry P, Lukas C, Macurek L, et al. Ubiquitin-activating enzyme UBA1 is required for cellular response to DNA damage. *Cell Cycle*. 2012;11(8):1573–1582. doi:10.4161/cc.19978
117. Bourbon E, Heiblig M, Gerfaud Valentin M, et al. Therapeutic options in VEXAS syndrome: insights from a retrospective series. *Blood*. 2021;137(26):3682–3684. doi:10.1182/blood.2020010177
118. Poulter JA, Collins JC, Cargo C, et al. Novel somatic mutations in UBA1 as a cause of VEXAS syndrome. *Blood*. 2021;137(26):3676–3681. doi:10.1182/blood.2020010286
119. Grayson PC, Patel BA, Young NS. VEXAS syndrome. *Blood*. 2021;137(26):3591–3594. doi:10.1182/blood.2021011455
120. Grey A, Cheong PL, Lee FJ, et al. A case of VEXAS syndrome complicated by hemophagocytic lymphohistiocytosis. *J Clin Immunol*. 2021;41(7):1648–1651. doi:10.1007/s10875-021-01070-y
121. Cordts I, Hecker JS, Gauck D, et al. Successful treatment with azacitidine in VEXAS syndrome with prominent myofasciitis. *Rheumatology*. 2021;61(5):e117–9. doi:10.1093/rheumatology/keab866
122. Muratore F, Marvisi C, Castrignanò P, et al. VEXAS syndrome: a case series from a single-center cohort of Italian patients with vasculitis. *Arthritis Rheumatol*. 2022;74(4):665–670. doi:10.1002/art.41992
123. Ferrada MA, Sikora KA, Luo Y, et al. Somatic mutations in UBA1 define a distinct subset of relapsing polychondritis patients with VEXAS. *Arthritis Rheumatol*. 2021;73(10):1886–1895. doi:10.1002/art.41743
124. Lazarchick J. Update on anemia and neutropenia in copper deficiency. *Curr Opin Hematol*. 2012;19(1):58–60. doi:10.1097/MOH.0b013e32834da9d2
125. Houwerzijl EJ, Pol HWD, Blom NR, van der Want JJL, de Wolf JTM, Vellenga E. Erythroid precursors from patients with low-risk myelodysplasia demonstrate ultrastructural features of enhanced autophagy of mitochondria. *Leukemia*. 2009;23(5):886–891. doi:10.1038/leu.2008.389
126. Gurnari C, Pagliuca S, Durkin L, et al. Vacuolization of hematopoietic precursors: an enigma with multiple etiologies. *Blood*. 2021;137(26):3685–3689. doi:10.1182/blood.2021010811
127. Fraison JB, Mekinian A, Grignano E, et al.Efficacy of Azacitidine in autoimmune and inflammatory disorders associated with myelodysplastic syndromes and chronic myelomonocytic leukemia. *Leuk Res*. 2016;(43):13–17. doi:10.1016/j.leukres.2016.02.005

128. Diarra A, Duployez N, Fournier E, et al. Successful allogeneic hematopoietic stem cell transplantation in patients with VEXAS syndrome: a 2-center experience. *Blood Adv*. 2022;6(3):998–1003. doi:10.1182/bloodadvances.2021004749
129. Oganesyan A, Hakobyan Y, Terrier B, Georgin-Lavialle S, Mekinian A. Looking beyond VEXAS: coexistence of undifferentiated systemic autoinflammatory disease and myelodysplastic syndrome. *Semin Hematol*. 2021;58(4):247–253. doi:10.1053/j.seminhematol.2021.10.003
130. Papaemmanuil E, Gerstung M, Malcovati L, et al. Clinical and biological implications of driver mutations in myelodysplastic syndromes. *Blood*. 2013;122(22):3616–3627. doi:10.1182/blood-2013-08-518886
131. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127(20):2391–2405. doi:10.1182/blood-2016-03-643544
132. Chakraborty S, Shapiro LC, de Oliveira S, Rivera-Pena B, Verma A, Shastri A. Therapeutic targeting of the inflammasome in myeloid malignancies. *Blood Cancer J*. 2021;11(9). doi:10.1038/s41408-021-00547-8
133. Higa KC, Goodspeed A, Chavez JS, et al. Chronic interleukin-1 exposure triggers selection for Cebpa-knockout multipotent hematopoietic progenitors. *J Exp Med*. 2021;218(6). doi:10.1084/jem.20200560
134. Watad A, Kacar M, Bragazzi NL, et al. Somatic mutations and the risk of undifferentiated autoinflammatory disease in MDS: an under-recognized but prognostically important complication. *Front Immunol*. 2021;12. doi:10.3389/fimmu.2021.610019
135. Mekinian A, Grignano E, Braun T, et al. Systemic inflammatory and autoimmune manifestations associated with myelodysplastic syndromes and chronic myelomonocytic leukaemia: a French multicentre retrospective study. *Rheumatology*. 2015;55(2):291–300. doi:10.1093/rheumatology/kev294
136. Kook MH, Yhim HY, Lee NR, et al. Successful treatment of myelodysplastic syndrome and Behcet colitis after allogeneic hematopoietic stem cell transplantation. *Korean J Intern Med*. 2014;29(1):123. doi:10.3904/kjim.2014.29.1.123
137. Simonetta F, Guerne PA, Tirefort Y, Masouridi-Levrat S, Roosnek E, Chalandon Y. Complete and sustained remission of spondyloarthritis after allogeneic hematopoietic stem cell transplantation for myelodysplastic syndrome. *J Bone Spine*. 2015;82(3):216–217. doi:10.1016/j.jbspin.2014.10.011
138. Alix L, Néel A, Cador B, et al. Diagnostic value of 18-F fluorodeoxyglucose PET/CT and bone scan in Schnitzler syndrome. *Autoimmunity*. 2019;52(7–8):264–271. doi:10.1080/08916934.2019.1680649
139. Darrieutort-Laffite C, Ansquer C, Aubert H, et al. Rheumatic involvement and bone scan features in Schnitzler syndrome: initial and follow-up data from a single-center cohort of 25 patients. *Arthritis Res Ther*. 2020;22(1):1–10. doi:10.1186/s13075-020-02318-5
140. Sutera D, Bustaffa M, Papa R, et al. Clinical characterization, long-term follow-up, and response to treatment of patients with syndrome of undifferentiated recurrent fever (SURF). *Semin Arthritis Rheum*. 2022;55:152024. doi:10.1016/j.semarthrit.2022.152024
141. Hadjadj J, Frémond ML, Neven B. Emerging place of JAK inhibitors in the treatment of inborn errors of immunity. *Front Immunol*. 2021;12. doi:10.3389/fimmu.2021.717388
142. Heiblig M, Ferrada MA, Koster MJ, et al. Ruxolitinib is more effective than other JAK inhibitors to treat VEXAS syndrome: a retrospective multi center study. *Blood*. 2022. doi:10.1182/blood.2022016642
143. Comont T, Heiblig M, Rivière E, et al. Azacitidine for patients with Vacuoles, E1 Enzyme, X-linked, Autoinflammatory, Somatic syndrome (VEXAS) and myelodysplastic syndrome: data from the French VEXAS registry. *Br J Haematol*. 2022;196(4):969–974. doi:10.1111/bjh.17893
144. Canna SW, Girard C, Malle L, et al. Life-threatening NLRC4-associated hyperinflammation successfully treated with IL-18 inhibition. *J Allergy Clin Immunol*. 2017;139(5):1698–1701. doi:10.1016/j.jaci.2016.10.022
145. Booshehri LM, Hoffman HM. CAPS and NLRP3. *J Clin Immunol*. 2019;15;39(3):277–86.
146. Agostini L, Martinon F, Burns K, McDermott MF, Hawkins PN, Tschopp J. NALP3 forms an IL-1beta-processing inflammasome with increased activity in Muckle-Wells autoinflammatory disorder. 2004;20(3):319–25. doi: 10.1016/s1074-7613(04)00046-9
147. Koné-Paut I, Galeotti C. Anakinra for cryopyrin-associated periodic syndrome. *Expert Rev Clin Immunol*. 2014;10(1):7–18.
148. 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.
149. Poulter JA, Savic S. Genetics of somatic auto-inflammatory disorders. *Semin Hematol*. 2021;58(4):212–217.
150. Zhou Q, Aksentijevich I, Wood GM, Walts AD, Hoffmann P, Remmers EF, et al. Brief Report: Cryopyrin-Associated Periodic Syndrome Caused by a Myeloid-Restricted Somatic NLRP3 Mutation. *Arthritis Rheumatol (Hoboken, NJ)*. 2015;67(9):2482–2486.
151. Stackowicz J, Gaudenzio N, Serhan N, Conde E, Godon O, Marichal T, et al. Neutrophil-specific gain-of-function mutations in Nlrp3 promote development of cryopyrin-associated periodic syndrome. *J Exp Med*. 2021 Sep 3;218(10).