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REVIEW

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Break down the barriers of auto-inflammation: How to deal with a monogenic auto-inflammatory disease and immuno-haematological features in 2022?

Hélène Vergneault[1] | **Capucine Picard**[2,3] | **Sophie Georgin-Lavialle**[1]

[1]Internal Medicine Department, APHP, Tenon Hospital, National Reference Center for Autoinflammatory Diseases and Inflammatory Amyloidosis (CEREMAIA), Sorbonne University, Paris, France

[2]Study Center for Primary Immunodeficiencies, Necker Hospital for Sick Children, APHP, Université de Paris, Paris, France

[3]Laboratory of Lymphocyte Activation and Susceptibility to EBV, INSERM UMR1163, Imagine Institute, Necker Hospital for Sick Children, Université de Paris, Paris, France

Correspondence
Hélène Vergneault, Department of Internal Medicine, Assistance Publique—Hôpitaux de Paris, Hôpital Tenon, Sorbonne University, 4, rue de la Chine, Paris 75020, France.
Email: helene.vglt@gmail.com

Abstract

In the past few years, the spectrum of monogenic systemic auto-inflammatory diseases (MSAID) has widely expanded beyond the typical recurrent fever. Immuno-haematological features, as cytopenias, hypogammaglobulinemia, hypereosinophilia, lymphoproliferation and immunodeficiency, have been described in association of several MSAID. The objective of this review was to describe these particular MSAID. MSAID must be suspected in front of immuno-haematological features associated with non-infectious recurrent fever, chronic systemic inflammation, inflammatory cutaneous manifestations, arthritis or inflammatory bowel disease. Genes and cellular mechanisms involved are various but some of them are of special interest. Defects in actine regulation pathway are notably associated with cytopenia and immune deficiency. Because of their frequency, ADA2 deficiency and Vacuoles, E1-Enzyme, X-linked, auto-inflammatory, Somatic (VEXAS) syndrome deserve to be noticed. ADA2 deficiency results in polyarteritis nodosa-like presentation with a wide panel of manifestations including cytopenia(s), lymphoproliferation and immune deficiency. Neutrophilic dermatosis or chondritis associated with macrocytic anaemia or myelodysplasia should lead to screen for VEXAS. Of note, most of MSAID are associated with inflammatory anaemia. We proposed here a clinical and pragmatic approach of MSAID associated with immuno-haematological features.

KEYWORDS
anaemia, autoinflammation, hypogammaglobulinemia, immunodeficiency, thrombocytopenia, VEXAS

INTRODUCTION

Monogenic systemic auto-inflammatory diseases (MSAID) are a distinct group of diseases caused by errors of the innate inflammatory response. They are classically associated with abnormal systemic inflammation in the absence of infection or auto-immunity. Since the identification of *MEFV* mutation responsible for Familial Mediterranean Fever (FMF) and the further description of the other historic periodic fevers due to mutation of

TNFRSF1A (Tumour necrosis factor-Receptor-Associated Periodic Syndrome), *MVK* (mevalonate kinase deficiency) and *NLRP3* (cryopyrinopathy), the spectrum of MSAID has broadened with actually 50 or more genes involved. Main pathophysiological pathways affect respectively inflammasomes, downstream TNFR1 pathway, reticulum endoplasmic stress, interferon pathway, actin polymerization regulation or the production of endogenous interleukin antagonists.

MSAID are usually suspected in front of recurrent attacks of fever or chronic systemic inflammation associated with cutaneous manifestations (urticaria, aseptic abscess, aphthous), arthritis or inflammatory bowel disease (IBD). However, the diagnosis of MSAID can also be made in the presence of other manifestations such as cytopenia and lymphoproliferation. The dichotomous view of innate immunity defects classifying on the one side MSAID and on the other primary immune deficiency (PID), has been shattered by recent identification of defective regulation of cellular pathways leading to auto-inflammation and susceptibility to infections and/or hypogammaglobulinemia. In clinical practice, the hypothesis of MSAID is first evocated by integrating a set of elements including the presence of an inflammatory syndrome, the age and a familial context suggesting a genetic transmission. In a second time, the presence of specific clinical or biological features drives the diagnosis towards a specific disease.

Our objective was to review MSAID associated with immuno-haematological features and to propose a pragmatic and clinical approach for clinicians.

MATERIALS AND METHODS

A literature review was performed to identify MSAID associated with immuno-haematological features. We focused on haemogram abnormalities including cytopenias and hypereosinophilia, lymphoproliferation, hypogammaglobulinemia and immunodeficiency. The database Medline (PubMed) was screened by three investigators from 1997 to 2021. The search involved the terms ‘autoinflammation’, ‘inborn errors of immunity’, ‘cytopenia’, ‘anaemia’, ‘thrombopenia’, ‘neutropenia’, ‘hypereosinophilia’, ‘haemophagocytosis lymphohistiocytosis’, ‘hypogammaglobulinemia’, ‘antibody deficiency’, ‘immuno deficiency’. After a screening of 220 references, 37 MSAID were identified. Their description was based on the following features cytopenias (anaemia, thrombopenia, neutropenia, haemophagocytosis lymphohistiocytosis), hypereosinophilia, hypogammaglobulinemia, primary immunodeficiency (Table 1).

RESULTS

Cytopenias

Anaemia

Anaemia is a frequent cytopenia associated with MSAID. It is necessary to specify the characteristics of this anaemia to orient the diagnosis (Figure 1).

Microcytic anaemia is the most frequent. It can occur in any MSAID because of the systemic inflammation.

Microcytic anaemia, due to congenital dyserythropoiesis, associated with chronic recurrent multifocal osteomyelitis and recurrent fever occurring in the first years of life is highly evocative of Majeed syndrome, which include neutrophilic dermatosis in less than 25% of cases [1]. Majeed syndrome is due to homozygous LOF mutations in *LPIN2*, which encodes LIPIN2 [2]. This phosphatidic acid phosphatase is implicated in triglyceride synthesis and probably in inflammation through its interaction with NLRP3 inflammasome [3].

Microcytic anaemia is especially frequent in the course of *TANK binding kinase 1* (*TBK1*) deficiency characterized by fever, polyarthritis beginning in the first year of life, cutaneous vasculitis and seizures [4]. *TBK1* homozygous loss of function (LOF) mutation has been described in four patients from three unrelated families. TBK1 is a crucial regulator of RIPK1 (Figure 2). It steers TNF receptor engagement through phosphorylation of RIPK1 and inhibition of the deubiquitinase CYDL. In absence of TBK1, RIPK1 can dissociates from TNFR1 and induces cell-death trough caspase 8 and RIPK3 pathways.

In context of auto-inflammation, macrocytic anaemia is highly suggestive of *Vacuoles, E1-Enzyme, X-linked, auto-inflammatory, Somatic (VEXAS) syndrome*. VEXAS syndrome is a late-onset inflammatory syndrome described for the first time in 2020; it affects mostly males and is characterized by recurrent fever, asthenia, cutaneous features such as neutrophilic dermatosis or cutaneous vasculitis, chondritis and pulmonary infiltration in a context of chronic peripheral inflammation [5]. Patients display macrocytic anaemia with lipid vacuoles in bone marrow and between 26% and 50% of patients have myelodysplasia [6, 7]. VEXAS syndrome is associated with somatic mutations in *UBA1* lying on the X chromosome and encoding the ubiquitin-activating enzyme-1 [6]. *UBA1* is expressed in haematopoietic stem cells and myeloid lineage cells; most mutations are in exon 3 and promote the production of an impaired isoform of UBA1. This leads to the reduction of cytoplasmic UBA1 function and therefore to the decrease of ubiquitylation and innate immune pathways activation.

TABLE 1 Genes involved according to the main immuno-haematological features

Anaemia	Thrombocytopenia	Neutropenia	Myelodysplasia	Haemophagocytosis	Hypogammaglobulinemia	Hypereosinophilia	Splenomegalia lymphadenopathies	Immune deficiency
PIGT	*ARPC1B*	*G6PC3*[a]	*SMAD9L*	*NLRC4*	*ADA2*	*NLRP3*	*CDC42*	*ARPC1B*
PSTPIP1	*IKBKG* del ex5	*PSTPIP1*	*UBA1*	*CDC42*	*IKBKG* del ex5	*MEVF*-ex2	*IKBKG- del ex5*	*CEBPE*[a]
TBK1	*LRBA*			*XIAP*[b]	*LRBA*	*NOD* 2	*LRBA*	*ISG15*
TRNT1	*PSTPIP1*				*NFKB1*[a]		*MEFV*	*NFKB1*[a]
UBA1	*SOCS1*				*OAS1* GOF		*MVK*[b]	*NFKBIA* GOF
LPIN2	*WDR1*				*PLGC2*		*PSTPIP1*	*PLGC2*
					PSMB9		*RIPK1* Htz	*POMP*
					RNF31		*SOCS1*	*PSMB9*
					SYK GOF		*STAT2*	*RIPK1* Hmz[b]
					TRNT1		*XIAP*[b]	*TRNT1*
					XIAP[b]			*WDR1*
	ADA2[c]				*TNFAIP3*[a,c]			
ADA2[c]							*RBCK1*[b]	
							RNF31	
							ADA2	

Abbreviations: *ADA2*, adenosine deaminase 2; *ARPC1B*, actin related protein 2/3 complex subunit 1B; *CDC42*, cell division cycle 42; *CEBPE*, CCAAT enhancer binding protein epsilon; *ex*, exon; *G6PC3*, glucose-6-phosphatase catalytic subunit 3; *GOF*, gain of function; *Hmz*, homozygous mutation; *Htz*, heterozygous mutation; *IKBKG*, inhibitor of nuclear factor kappa B kinase regulatory subunit gamma; *ISG15*, interferon-stimulated gene 15; *LRBA*, LPS responsive beige-like anchor protein; *MVK*, mevalonate kinase; *NFKB1*, nuclear-factor kappa B subunit 1; *NFKBIA*, NFKB inhibitor alpha; *NLRC4*, NLR family CARD domain containing 4; *OAS1*, 2′-5′-oligoadenylate synthetase 1; *PIGT*, phosphatidylinositol glycan T; *PLGC2*, phospholipase C gamma 2; *POMP*, proteasome maturation protein; *PSMB9*, proteasome subunit β-type 9; *PSTPIP1*, proline–serine–threonine phosphatase interacting protein 1; *RIPK1*, receptor-interacting serine/threonine-protein kinase 1; *RNF31*, ring finger protein 31; *SAMD9L*, sterile alpha motif domain containing 9 like; *SOCS1*, suppressor of cytokine signalling protein 1; *STAT2*, signal transducer and activator of transcription 2; *SYK*, spleen associated tyrosine kinase; *TBK1*, TANK binding kinase 1; TNFAIP3, TNF alpha induced protein 3; *TRNT1*, tRNA nucleotidyl transferase 1; *UBA1*, ubiquitin like modifier activating enzyme 1; *WDR1*, WD repeat domain 1; *XIAP*, X-linked inhibitor of apoptosis protein.

[a]With aphtosis.

[b]With inflammatory bowel disease.

[c]Features that are generally not in foreground and/or of rare occurrence but which could lead to the diagnosis.

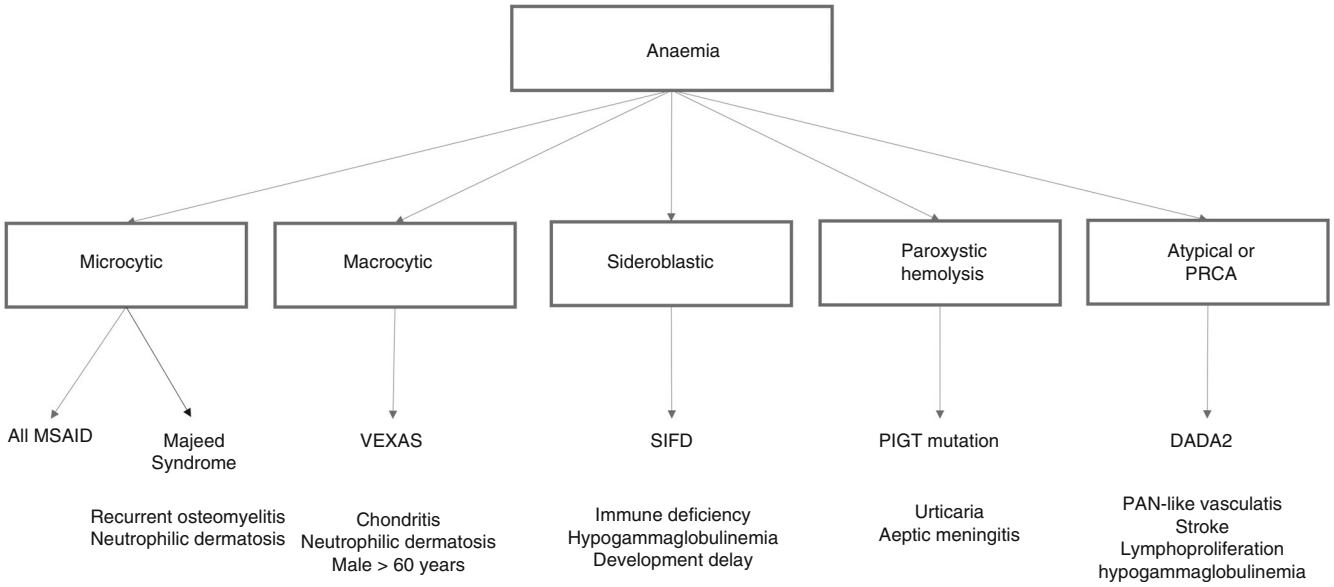

FIGURE 1 Orientation in front of anaemia with autoinflammation. Bottom notes precise main suggestive features.

Sideroblastic anaemia is characteristic of *SIFD syndrome: Sideroblastic anaemia, Immunodeficiency, Fever, Developmental delay*. Manifestations of SIFD occur in two-third of cases in neonatal period generally by non-infectious periodic attacks of fever with elevated inflammatory markers [8], vomiting and diarrhoea, oral ulcers, skin cellulitis, arthralgia or arthritis [9]. Patients suffered from congenital sideroblastic anaemia and immune deficiency manifested by sinopulmonary bacterial infections secondary to B-cell lymphopenia and hypogammaglobulinemia [8]. Affected children also display development delay characterized by impaired motricity, comprehension and communication. Other neurological manifestations may occur as seizure, cerebellar ataxia, cerebral atrophy on neuroimaging, sensorineural hearing loss. Exact physiopathology of SFID remains to be clarified. It is caused by bi-allelic LOF mutations in *TRNT1* which encodes the CCA-adding enzyme, an essential molecule for tRNAs maturation. TRNT1 deficiency is responsible for impaired maturation of mitochondrial and cytosolic tRNAs [9] and increased reactive oxygen species production leading to enhanced IL-1β secretion.

Haemolytic anaemia secondary to paroxysmal nocturnal haemoglobinuria with neutrophilic urticaria, arthralgia, fever and aseptic meningitis has been described in four patients with *mutations of PIGT* which encodes a GPI-anchor. Its results from biallelic mutation including a germline heterozygous mutation and a somatic mutation occurring in haematopoietic stem cells, leading to the expression on cell surface of a defective GPI-anchor which is enabled to interact with proteins [10]. Free GPI is responsible of increased IL-1β secretion, activation of the lectin pathway of complement and generation of C5b-9 complexes.

Thrombocytopenia

Thrombocytopenia was found to be associated with a subgroup of MSAID called actinopathies where mutations in genes involved in actin polymerization regulation were detected. The complete clinical picture of the following two MSAID includes immune deficiency:

- *Periodic fever with immunodeficiency and thrombocytopenia (PFIT)* is characterized by periodic fever attacks arising from the first week of life and lasting 3–7 days with increased inflammatory markers. Recurrent oral inflammation and recurrent perianal ulcerations are associated as well as recurrent severe bacterial infections due to impaired neutrophil function [11]. Half patients display thrombocytopenia. PFIT is caused by homozygous mutation in *WDR1* which encodes a protein promoting the disassembly of actin filaments. This was found to induce increased caspase-1 cleavage and excessive IL-18 production by monocytes [12].
- The association of autoinflammation and thrombocytopenia to atopy, lymphadenopathy and combined immune deficiency can evoke mutation in *ARPC1B* gene [13]. Clinical manifestations appear in the first months of life. Patients are stunted and present extensive eczema and allergies, skin vasculitis, haemorrhagic colitis and less frequently arthritis. Patients present recurrent respiratory tract infections and skin

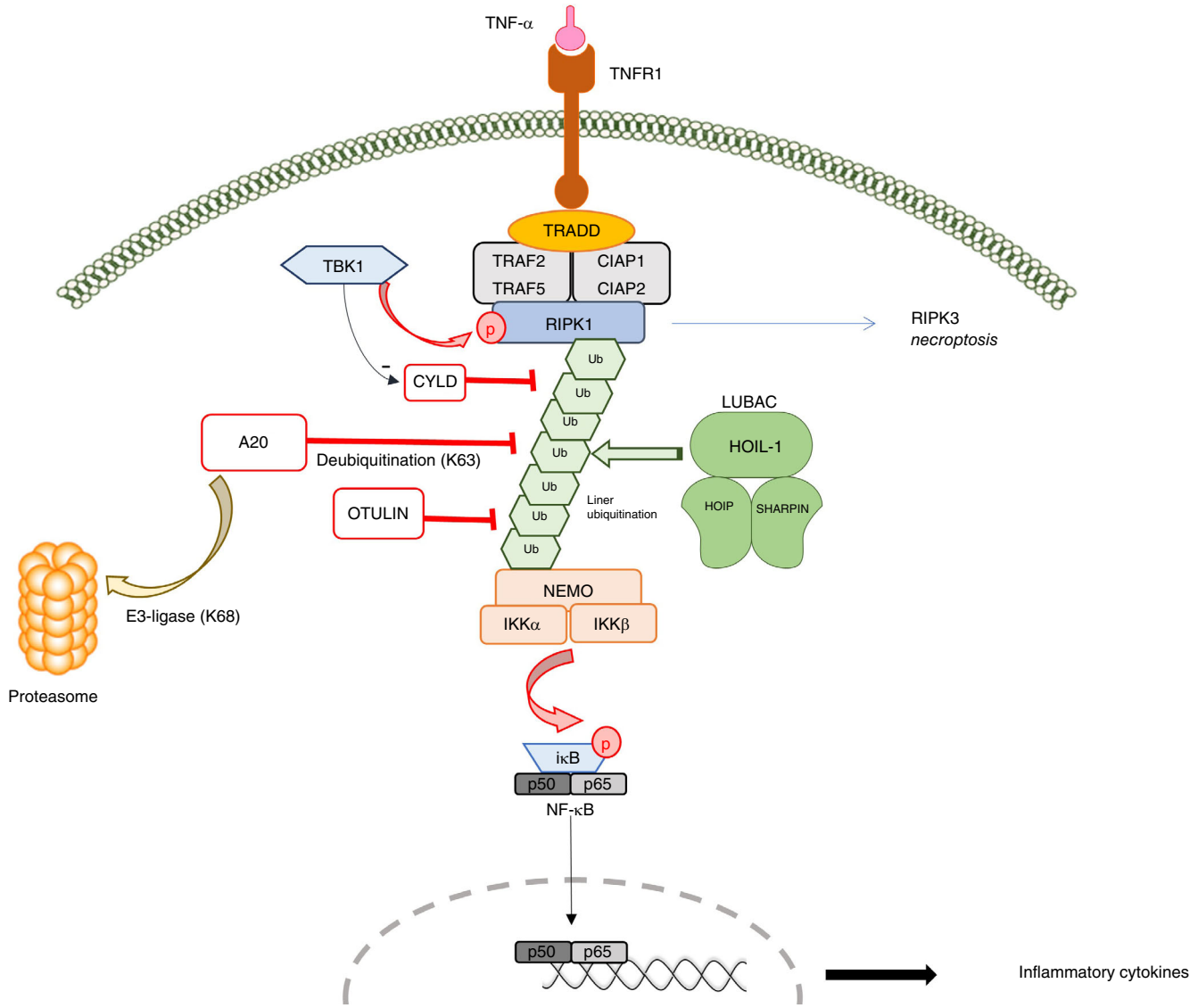

FIGURE 2 Pathway downstream TNFR1. Pathways downstream TNFR include RIPK1 pathway and NF-κB pathway. RIPK1 (receptor-interacting serine/threonine kinase 1) mediates multimodal signalling downstream TNFR1. Modulation of intracellular signalling cascade can promote cell survival and inflammatory signalling through NF-κB nuclear translocation or induce caspase-8 mediated apoptosis or RIPK3-dependent necroptosis in the absence of caspase 8. NF-κB activation is regulated by a series of ubiquitination, deubiquitination and phosphorylation events triggered by various stimuli: cytokines including TNFα (shown on this figure) and interleukin-1, bacterial or viral proteins via Toll- like receptors and various stress signals. All these pathways converge to the activation of a complex composed of two catalytic subunits (IKKα and IKKβ) and a regulatory subunit (NEMO also called IKKγ) resulting in phosphorylation and subsequent degradation of the inhibitor of NF-κB, IκB. This enables NF-κB to translocate into nucleus. The activation of NF-κB pathway by TNF receptor 1 (TNFR1) requires the formation of the signalling complex I composed of TRADD (TNFR1-associated death domain) and RIPK1. This permits the recruitment of diverse E3 ubiquitin ligase, including LUBAC (linear ubiquitin chain assembly complex). The linear ubiquitination of NEMO by LUBAC increase the phosphorylation and activation of IKKβ. OTULIN and A20 are negative regulators of linear ubiquitination-dependent NF-κB activation. TBK1 phosphorylates RIPK1 and inhibits the deubiquitinase CYDL, promoting TFNR1 engagement towards NF-κB pathway rather than RIPK induced cell-death.

infections including bacterial infections, molluscum and warts. Thrombocytopenia is characterized by microthrombocytes with dense granule deficiency and is responsible of gastric haemorrhage [14]. T-cells are low, and levels of immunoglobulin E (IgE) and IgA are increased. Haemophagocytosic lymphohistiocytosis (HLH) has been reported [13]. ARPC1B is a haematological linear cells isoform of ARPC1, a component of actin-related protein 2/3 complex (Arp2/3) which plays a key role for actin polymerization [13, 14]. ARPC1B deficiency due to homozygous LOF mutation is responsible for impaired cytoskeleton rearrangement leading to

alteration of chemotaxis, endocytosis and immunological synapse formation in neutrophils, NK-cells and Treg.

Thrombocytopenia was also described in one third patients suffering from CANDLE-like syndrome due to *LRBA deficiency* and *IKBKG-deleted exon 5 auto-inflammatory syndrome*, we will detailed further [15].

Early-onset immune thrombocytopenia, sometimes as part of Evans syndrome or accompanied by lymphoproliferative manifestations, can be due to *SOCS1 haploinsufficiency* [16]. The protein SOCS1 is a downregulator of the JAK-STAT pathway. SOCS1 haploinsufficiency leads to cytokine hypersensitivity of monocytes, T- and B-cells which is responsible of auto-immune manifestations as auto-immune cytopenias or systemic lupus erythematosus [16].

Neutropenia

The association of neutropenia and inflammatory manifestations is suggestive of *Glucose-6-phosphatase (G6PC3) deficiency*. This heterogeneous syndrome associates congenital neutropenia with cardiac and urogenital developmental defects. In some cases, it associates with inflammatory bowel disease presenting as Crohn-like disease but without granuloma on biopsy [17]. G6PC3 is an ubiquitous enzyme that regulates cytoplasmic glucose availability through hydrolysis of glucose-6-phosphate during glycolysis and glycogenolysis. Neutrophils deficient in G6PC3, due to bi-allelic LOF mutations, display higher levels of activation markers, excessive IL-8 and reactive oxygen species and increased apoptosis [18].

Pancytopenia and haemophagocytic lymphohistiocytosis

Pancytopenia in context of susceptibility to haemophagocytic lymphohistiocytosis (HLH) occurs in three MSAID: somatic mutations of *NLRC4*, X-linked lymphoproliferative syndrome type 2 (*XIAP* gene) and NOCARH syndrome (*CDC42* gene).

- *NLRC4 mutations* cause a constitutive activation of NRLC4 inflammasome leading to enhanced production of cytokines IL-1β and IL-18. Heterozygous gain of function (GOF) mutations of *NLRC4* are associated with two phenotypes [19]. Familial mutations manifest by familial cold urticaria associated with recurrent fever in only half of cases. Sporadic mutations are responsible of severe disease occurring earlier, in first months of life, with recurrent fever, severe inflammatory bowel disease, pulmonary or neurological involvement in some cases and HLH [20].
- *X-linked lymphoproliferative syndrome type 2* (XLP2) due to *XIAP deficiency* is a X-linked disorder characterized by paediatric-onset Crohn-like inflammatory bowel disease, recurrent splenomegaly and susceptibility to develop HLH frequently triggered by Epstein Barr virus (EBV) [21, 22]. There is individual variability: in a same family, dominant phenotype (IBD, lymphoproliferation or HLH) and severity differ from one individual to another. Some patients also display hypogammaglobulinemia or other inflammatory manifestations like arthritis, cutaneous abscesses, erythema nodosum, uveitis and nephritis. XLP2 is caused by mutation in *XIAP* gene located on X chromosome [21]. XIAP is an ubiquitous anti-apoptotic protein. Through its ubiquitinase activity, it is also involved in many intra-cellular pathways including activation of NF-κB and MAP-kinases pathways. XIAP plays a role in innate and adaptative immunity. It participates in signalling pathway of the pattern recognition receptor NOD2 and inhibits caspase in activated T lymphocytes promoting their survival. XIAP-deficiency leads to pathogen clearance defect, uncontrolled activation of inflammasomes accumulation of the pro-inflammatory cytokines TNF-α, IL-1β and IL-18.
- Neonatal Onset of Cytopenia, Autoinflammation, Rash, and HLH define *NOCARH syndrome*. From the first days of life, patients present recurrent fever associated with chronically elevated inflammatory markers, psoriasiform skin rash, pancytopenia, hepatomegaly with frequent cytolysis, splenomegaly and predisposition to haemophagocytic lymphohistiocytosis [23, 24]. All patients display failure to thrive and some of them display facial dysmorphia [24]. NOCARH syndrome was described associated to *CDC42* heterozygous mutation which belongs to Rho GTPase family and regulates multiple intracellular signalling pathways including polarization and migration of the cell via actin filaments, cytoskeleton architecture, endocytosis and progression through the cell cycle. It regulates actin polymerization by binding to Wiskott–Aldrich protein (WASp), which subsequently activates Arp2/3 complex. *De novo* heterozygous mutation in the C-terminal region of CDC42 is responsible for impaired active/inactive cycling of Cdc42 leading to defects in actin polymerization and hyperactivating of NF-κB signalling [25]. IL-1b and anti-IL-18 production are increased as well as INFγ [23].

A pancytopenia in context of arthritis and skin inflammation including pyoderma gangrenosum and other ulcerative lesions, pustular lesions, abscesses and

acne suggest *PAMI syndrome* (*PSTPIP1*-associated myeloid-related-proteinemia inflammatory syndrome) also known as hypercalprotectinemia and hyperzincemia syndrome [26]. PAMI syndrome is characterized by chronic inflammatory syndrome and high levels of calprotectinemia and zincemia. Anaemia and neutropenia are almost systematically present while thrombocytopenia occurs in half of cases [26]. Hepatosplenomegaly and less frequently lymphadenopathy are associated. PAMI syndrome is caused by a heterozygous mutation of *PSTPIP1* distinct from those responsible of PAPA (pyogenic arthritis, pyoderma gangrenosum, acne) syndrome [27]. *PSTPIP1* encodes *a* cytoskeleton-associated adaptor protein implicated in cytoskeletal organization and T-cell activation. p.E250K and p.E257K mutants are associated with an enhanced binding to pyrin and increased levels of calprotectin which is composed by the two alarmin MRP8 and MRP14.

Unexplained cytopenia(s) can also be a way to evoke a *deficiency in adenosine deaminase 2 (ADA2)* which we will describe below. Anaemia and thrombocytopenia occur in respectively 13%–45% and 6%–10% of cases [28, 29]. Bone marrow failure with neutropenia or pancytopenia as well as pure red cell aplasia have been reported [30, 31].

Myelodysplasic syndrome

Myelodysplasic syndrome (MDS) associated with chronic inflammatory syndrome, Sweet syndrome or relapsing polychondritis in a patient over 60 years old should lead to investigate *UBA1* mutation responsible for *VEXAS syndrome*.

Paediatric onset MDS with atypical CANDLE syndrome combining neutrophilic panniculitis with interstitial lung disease, basal ganglion calcification and B-cell lymphopenia can reveal *SAMD9L associated autoinflammatory disease (SAAD)*. *SAMD9L* mutations are usually associated to familial and paediatric MDS and to ataxia pancytopenia syndrome [32, 33]. Rare variants producing a truncated-SAMD9L are responsible for a broaded syndrome including autoinflammation [15, 34].

Hypogammaglobulinemia

Serum protein electrophoresis is a simple and cost-effective test to guide the clinician. Some MSAID combine auto-inflammation and common variable immunodeficiency (CVID)-like with recurrent infections of respiratory tract and hypogammaglobulinemia (Table 2). They are distinguished by their type of auto-inflammatory presentation (Figure 3).

Aphtosis and Behçet-like vasculitis are suggestive of defect in the pathway of the transcription factor NF-κB which plays an important role in immune and inflammatory responses (Figure 2).

NFKB1 heterozygous mutations are a frequent cause of CVID [35, 36]. Some mutations also induce autoinflammatory features [37]. Phenotype differs from one patient to another depending on the causal mutation. Small vessel vasculitis with a variable association of arthritis, mucosal aphtous lesions, gut disease and fever flares are caused by p.H67R substitution whereas life-threatening postoperative hyperinflammatory reactions are associated with p.R157X variant. NFKB1 encodes the protein p105 which is the precursor of the subunit p50 of NF-κB. LOF *NFKB1* mutations lead to p50 haploinsufficiency and subsequent NF-κB defect.

A20 haploinsufficiency (HA20) presents with early-onset Behçet-like disease characterized by recurrent fever and bipolar aphtosis in about 90% of cases, arthritis, folliculitis or axillary abscess, ulcerative colitis and ocular inflammation. In rare cases, patients present recurrent infections due to hypogammaglobulinemia or even combined immunodeficiency [38, 39]. HA20 is caused by heterozygous LOF mutation of *TNFAIP3* which encodes the protein A20, a crucial inhibitor of the NF-κB pathway (Figure 2). Defective ubiquitinase and deubiquitinase activities of truncated A20 proteins leads to increased expression of NF-κB–mediated proinflammatory cytokines [40].

Bullous cutaneous lesions are suggestive of *APLAID syndrome (auto-inflammation and PLCγ2-associated antibody deficiency and immune dysregulation)* mutation described in a father and his daughter who developed in childhood an epidermolysis-bullosa-like eruption and recurrent blistering lesions, which over time become sensitive to heat and sun exposure. They also presented non-specific interstitial pneumonitis with respiratory bronchiolitis, arthralgia, eye inflammation and enterocolitis. Biological inflammatory markers were increased [41]. They both experienced recurrent sino-pulmonary infections associated with low serum levels of IgM and IgA immunoglobulins and low circulating switched memory B-cells. PLCγ2 is a phospholipase mainly expressed in haematopoietic cells and playing a key role in the regulation of immune response. Its activity is autoregulated by the sH2 domain inhibitor. APLAID syndrome is caused by heterozygous mutation in sH2 domain leading to enhanced PLCγ2 activity [41]. Patients with PLAID syndrome (PLCγ2-associated antibody deficiency and immune dysregulation), caused by caused by genomic large deletions in sH2 domain, have cold urticaria,

TABLE 2 MSAID associated with immunodeficiency

Mechanism	Gene	Condition	Infections	Auto-inflammatory features	Others features	Transmission
Humoral deficiency	*PLCγ2*[a]	APLAID	Recurrent sino-pulmonary infections	EB-like eruption; arthralgia, eye inflammation, enterocolitis	RB-ILD	AD
	ADA2[b]	ADA2	Bacterial infections ±HSV	PAN-like vasculitis; stroke	Lymphoproliferation (ADP, SPM) cytopenia	AR
	RBCK1[b]	HOIL1 deficiency	Recurrent invasive pyogenic infections	Recurrent fever; early-onset IBD	Lymphoproliferation (ADP, HPSM); systemic amylopectinosis	AR
	NFKB1[b]	NF-kB1 deficiency	Recurrent sino-pulmonary infections	Recurrent fever; Behçet-like vasculitis: arthritis, aphtosis, diarrhoea		AD
	TRNT1[b]	SIFD	Recurrent sino-pulmonary infections	Recurrent fever; vomiting/ diarrhoea, oral ulcers, skin cellulitis, arthritis	Sideroblastic anaemia; developmental delay; seizure, cerebellar ataxia	AR
	SYK[b]	SYK constitutive activation	Recurrent invasive bacterial infection ±HSV	Colitis; skin rash, arthritis	Susceptibility to B-cells lymphoma	AD
Combined immunodeficiency	*ARPC1B*[b]	ARPC1B deficiency	Recurrent sino-pulmonary and skin bacterial infections; molluscum, warts	Skin vasculitis; haemorrhagic colitis arthritis	Eczema, allergies; thrombopenia; lymphoproliferation (ADP)	AR
	RNF31[b]	HOIP deficiency	Bacterial, viral, fungal infections; recurrent warts	Recurrent fever; diarrhoea, oral ulcers	Lymphoprolifération (SPM); subclinical amylopectinosis; lymphangectasia	AR
	POMP[b]	PRAID	Bacterial, viral and opportunistic infections	Neutrophilic dermatosis	Auto-immunity	AD
	PSMB9	PRAAS-ID	BK and JC viruses	Fever; skin rash; myositis	Pulmonary hypertension; basal ganglia calcification; liver dysfunction	AD
	RIPK1[b]	RIPK1 deficiency	Recurrent otitis media, pneumonia and invasive bacterial infections; viral and fungal infections	Early-onset IBD; aphtosis; arthritis		AR
	IKBKB[a]	IKK2		Suppurative hydradenitis	Ectodermal dysplasia; eczema; cataract	AD

(Continues)

TABLE 2 (Continued)

Mechanism	Gene	Condition	Infections	Auto-inflammatory features	Others features	Transmission
			Reccurent respiratory tract infections; Mucocutaneous candidiasis			
Neutrophils impairment	*CEBPE*[b]	CAIN	Tongue and gluteal abscesses; paronychia; pulmonary infections	Recurrent fever and abdominal pains; oral ulcers; PG and abdominal granuloma	Epistaxis, haematomas	AR
	WDR1[b]	PFIT	Severe bacterial infection	Recurrent fever Peri-anal ulceration	Thrombocytopenia	AR
Interferon-γ impairment	*NFKBIA*[a]	NFKBIA deficiency	Invasive bacterial and mycobacterial infections	Systemic inflammation; liver infiltration by neutrophils		AD
	ISG15[b]	ISG15 deficiency	Mycobacterial infections	Necrotic skin ulcers	Intra-cerebral calcification	AR
Type 1 interferon impairment	*OAS1*	OAS1 mutation[a]	Viral infections of respiratory tract	Recurrent fever; ulcerative skin rash IBD	Pulmonary alveolar proteinosis hypogammaglobulinemia	AD

Abbreviations: ADP, adenopathies; APLAID, autoinflammation and PLCG2-associated antibody deficiency and immune dysregulation; CAIN, CEBPE associated autoinflammation and immune impairment of neutrophils; DADA2, deficiency in adenosine deaminase 2; EB, epydermolysis bullosa; HEM-1, haematopoietic protein 1; HLH, haemophagocytic lymphohistiocytosis; HOIL-1, heme-oxidized IRP2 ubiquitin ligase 1; HOIP, HOIL-1-interacting protein; HSV, herpes simplex virus; HPSM, hepatosplenomegaly; IBD, inflammatory bowel disease; ISG15, interferon-stimulated gene 15; NF-κB, nuclear-factor kappa B; NFKBIA, NFKB inhibitor alpha; OAS1, oligoadenylate synthetase 1; PAN, polyarteritis nodosa; PFIT, periodic fever, immunodeficiency, thrombocytopenia; PG, pyoderma gangrenosum; PRAAS-ID, proteasome associated autoinflammatory syndrome with immune deficiency; PRAID, POMP-related autoinflammation and immune dysregulation; RB-ILD, respiratory bronchiolitis-associated interstitial lung disease; SIFD, Sideroblastic anaemia, Immune deficiency, periodic Fever, Developmental delay; SPM, splenomegaly.

[a]Gain of function mutation.

[b]Loss of function mutation.

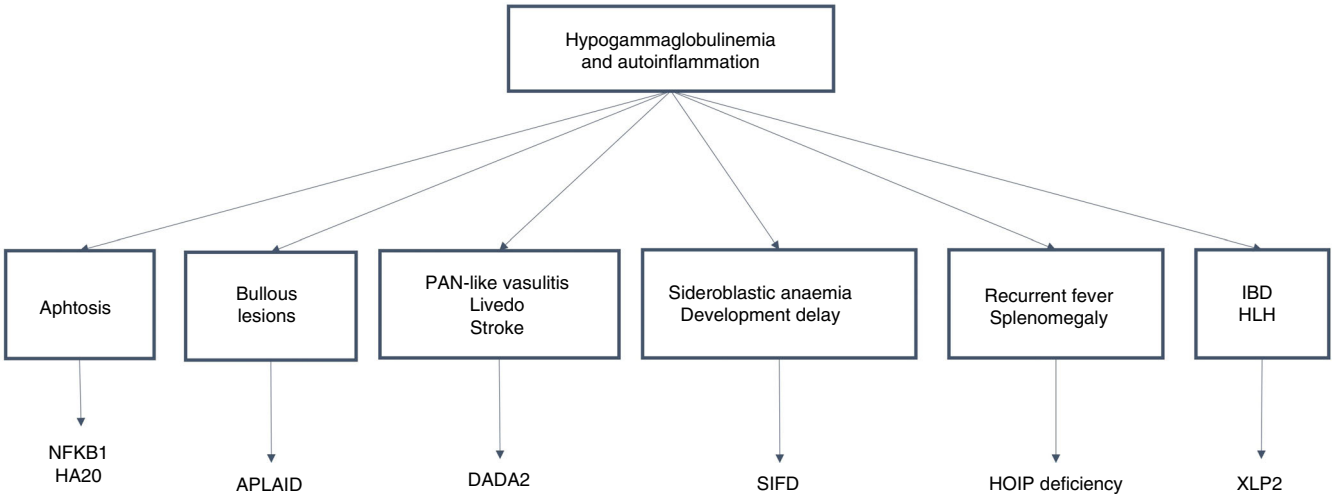

FIGURE 3 Orientation in front of hypogammaglobulinemia with auto-inflammation.

infections, auto-immunity, allergies and hypogammaglobulinemia. Contrary to PLAID syndrome, patients with APLAID did not experience cold urticaria and were negative for auto-antibodies.

PAN (polyarteritis nodosa)-like presentation characterize ADA2-deficient patients which present a vasculitis of small- and medium-vessels with a peculiar early-onset, mostly before the age of ten. Cutaneous manifestations are the most frequent and consist in livedoid reticularis/racemosa rash and ulceration. About half of patients experience neurologic manifestations mainly haemorrhagic or ischaemic stroke [31]. Digestive, liver, renal and coronary involvements are possible. Hypogammaglobulinemia occurs in 22% of cases and can be responsible of recurrent bacterial infections [28, 29]. Susceptibility to herpetic infections is also increased. Immunodeficiency due to B-cells deficiency is not so uncommon and can be in the foreground [42]. As stipulate above, cytopenia(s) and lymphoproliferation are also common features of *ADA2 deficiency* [31]. The exact pathogenesis of *ADA2 deficiency* is not fully established. It results from bi-allelic LOF *ADA2* mutations. Lack of ADA2 leads to chronic increased extracellular levels of adenosine. This promotes differentiation of monocytes towards proinflammatory M1 macrophages [43] and enhances NET (neutrophil extracellular traps) formation [44] leading to macrophage activation and secretion of anti-TNFα. In addition to its deaminase activity, ADA2 may have a growth factor activity especially in haematopoiesis which could explain haematological and immunological manifestations of ADA2-deficient patients [45].

A CANDLE-like (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature) presentation resistant to JAK inhibitor can be associated with impairment of INF-signalling [15]. The association to ectodermal dysplasia suggests a splice site variants of IKBKG causing *NEMO-Deleted exon 5 autoinflammatory syndrome (NEMO-NDAS)* [46]. The association to interstitial lung disease, hepatosplenomegaly with granulomatous hepatitis suggests LRBA (LPS-responsive beige-like anchor protein) deficiency. These both conditions are characterized by INF-signature. Patients present hypogammaglobulinemia due to progressive B-cells lymphopenia without evidence of susceptibility to infections and thrombocytopenia occurred in one third of patients [15].

Recurrent fever with skin rash, pulmonary alveolar proteinosis, inflammatory bowel disease and susceptibility to viral respiratory infections evokes *OA1S GOF heterozygous mutations* [47]. Patients display hypogammaglobulinemia and low B-cells count during flares.

Chron-like colitis associated with skin rash and erosive arthritis is caused by *SYK mutation* [48]. Most of the six patients display recurrent bacterial infections due to antibody deficiency but some also present low CD4+ T-cells. Susceptibility to B-cells lymphoma has also been reported in two patients [48]. SYK is a tyrosine kinase involved in downstream signalling of immune -receptors like T- and B-cells receptors or Toll-like receptors. Heterozygous GOF mutation leads to constitutive activation of SYK and consequent enhanced response to immunoreceptor engagement. The SYK variants increased phosphorylation and enhanced downstream signalling.

The combination of immune deficiency due to hypogammaglobulinemia, sideroblastic anaemia and developmental delay is suggestive of SIFD [8].

In XLP-2, hypogammaglobulinemia is associated with IBD and/or HLH.

Hypogammaglobulinemia can also occur in mutations of HOIP, HOIL1 and PSMB9 described in other sections.

Hypereosinophilia

Hypereosinophilia is a marker of a particular recurrent fever due to homozygous Serine-208 mutations in *MEFV* [49]. Oral ulcers, hepatosplenomegaly and lymphadenopathy with eosinophils infiltrates as well as recurrent purpuric lesions due to leucocytoclastic vasculitis are associated. p.S208T mutation in exon 2 of *MEVF* is distinct of those responsible for FMF. It leads to constitutive pyrin inflammasome activation and increased levels of C-C-motif chemokine ligand 5 (CCL5) [49].

Hypereosinophilia can also been associated with other autoinflammatory diseases.

- Recurrent fever with urticaria are suggestive of cryopyrinopathy (CAPS). Hypereosinophilia occurs in Muckle–Wells syndrome, distinguished by hearing loss and especially in neonatal-onset multisystem inflammatory disease (CINCA/NOMID), characterized by supplemental neurological involvement and arthropathy [50, 51]. These are associated with heterozygous *NLRP3* GOF mutations.
- Juvenile sarcoidosis can evocate Blau syndrome which is characterized by polyarthritis with granuloma, uveitis and skin rashes beginning in the early childhood due to heterozygous *NOD2* mutation which impairs CARD15 binding causing a deregulated activity of caspase 1 with excessive IL-1 production [51].

Lymphoproliferation

Lymphoproliferation, consisting in lymphadenopathy and/or hepatosplenomegaly is a common feature of certain MSAID. The occurrence of recurrent fever and a neonatal onset make the clinician suspect auto-inflammatory disease.

Lymphadenopathies associated with recurrent fever beginning in the first year of life are evocative of Mevalonate kinase Deficiency (MKD) or cleavage-resistant RIPK1-induced autoinflammatory (CRIA) syndrome.

- In *MKD*, attacks begin in early childhood with recurrent fevers and predominant digestive features. Lymphoproliferation consist mainly in painful cervical lymphadenopathies with hepatosplenomegaly in some cases. During attacks, patients may also display aphtous, abdominal pain and diarrhoea, arthralgia, skin rash or headaches. MKD is caused by homozygous LOF mutation in *MVK* encoding mevalonate kinase, a protein involved in cholesterol production pathway. Its deficiency leads to mevalonic acid accumulation.
- In *CRIA syndrome*, fever attacks usually last several days and occur every 2–4 weeks. Lymphoproliferation consist mainly in intermittent diffuse lymphadenopathy with splenomegaly or tonsilitis in some cases. During attacks, patients may also display abdominal pain but arthritis and cutaneous rash are absent. CRIA syndrome is also characterized by chronic increased levels of inflammatory markers. RIPK1 is a key determinant of cell response to TNF stimulation. Its ubiquitination status shifts the cell towards either a pro-survival inflammatory pathway via NF-κB activation, or cell death pathway via activation of caspase-8-dependent apoptosis or RIPK3/MLKL-dependent necroptosis [52]. Heterozygous mutation of a key aspartate, described in 12 patients, residue prevents caspase-6/8 cleavage of RIPK1 and sensitizes cells to TNF-induced cell death [53]. Of note, the phenotype is milder than RIPK1 deficiency described below as no vital organ are involved and tocilizumab provide markedly improvement.

Aseptic fistulizing adenitis and hepatosplenomegaly with systemic inflammation and intracranial calcifications have been described in three infants carrying a GOF variant of *STAT2* gene [54, 55]. STAT2 is a transcription factor belonging to IFNα/β pathway. This STAT2 R148W variant was associated with elevated responses to IFNα/β and prolonged JAK-STAT signalling [54].

Some MSAID combine lymphoproliferative features to immunodeficiency.

Recurrent fever with splenomegaly, infections and amylopectinosis characterize mutations of Linear ubiquitin chain assembly (LUBAC) complex composed of three proteins (Figure 2): HOIP (HOIL1 interacting protein), HOIL1 (Heme-Oxizidized IRP2 Ubiquitin Ligase 1) and SHARPIN (SHANK interacting protein 1). LUBAC conjugates linear ubiquitin chains on NEMO to stabilize its recruitment to cytokine receptor (TNFR and IL1R). Consequences of LUBAC deficiency differed between cell types. It leads to impaired NF-κB dependent response to TNFα and IL-1β in fibroblast and B cells whereas in mononuclear leukocytes, it induces constitutive increased production of pro-inflammatory cytokines and enhance response to IL-1β.

Homozygous mutations of *RBCK1* encoding HOIL1 and of *RNF31* encoding HOIP have been described in respectively three patients [56] and two patients [57, 58]. In both situations, patients displayed recurrent fever attacks from the first year of life with persistent increase of biological inflammatory markers between flares.

HOIL1 deficiency is characterized by recurrent fever episodes with lymphadenopathies and hepatosplenomegaly with early onset and in some patients IBD with

bloody and mucus stools, humoral deficiency with low switch memories B cells responsible of invasive and severe bacterial infections and symptomatic myocardiopathy after the age of 4 years caused by muscle amylopectinosis deposits.

Patients with *HOIP deficiency* presented diarrhoea, oral ulcers and persistent splenomegaly without lymphadenopathy. The first patient presented combined immunodeficiency with T cell lymphopenia, switch-memories B cells deficiency and hypogammaglobulinemia. The second patient displayed recurrent bacterial, viral and fungal infections without hypogammaglobulinemia nor lymphopenia but lacked response to pneumococcal antigens upon vaccination with polysaccharides non-conjugate pneumococcal vaccine. Systemic lymphangiectasia and subclinical amylopectinosis were associated.

Lymphoproliferative manifestations are also important features of deficiency in ADA2 previously detailed. Patients may present splenomegaly (up to 30%) or lymphadenopathy [28]. Autoimmune lymphoproliferative syndrome (ALPS)-like phenotype [59], T cell large granular lymphocytic (LGL) proliferation [60] and EBV-driven lymphoproliferation [61] have also been reported.

Lymphoproliferative manifestations including hepatosplenomegaly and lymphadenopathy in context of auto-immune features can be due to *SOCS1* haploinsufficiency [16].

Lymphoproliferation with pancytopenia accompanying arthritis and inflammatory skin manifestations as pyoderma gangrenosum, pustular lesion or abscesses suggest PAMI syndrome described above (*PSTPIP1* mutations) [26].

Splenomegaly occurs frequently in conditions providing susceptibility to HLH. Associated symptoms of IBD are suggestive of *XIAP* mutations whereas recurrent fever and psoriasic lesions suggest NOCARH syndrome.

Of note, persistent splenomegaly with or without hepatomegaly in a patient of Mediterranean origin who present recurrent attack of fever and abdominal pain can revealed FMF which is associated with *MEVF* exon 10 mutations. Splenomegaly occurs up to more than 50% of patients with FMF [62]. It is more frequent in children and during attacks but can persist out of attacks especially in case of uncontrolled disease and even in absence of AA amyloidosis. p.S208T *MEVF* mutation are also associated hepatosplenomegaly as well as lymphadenopathies due to eosinophils infiltration [49].

Combined immunodeficiency

Combined immunodeficiency (CID) is defined by impairment of humoral and cellular immunity, responsible of bacterial, viral, fungal and opportunistic infections susceptibility. This syndrome covers a wide spectrum of genetic diseases including MSAID, which may be suspected before digestive or dermatological inflammatory symptoms (Table 2).

Combined immune deficiency associated with neonatal-onset IBD is suggestive *of RIPK1 deficiency*. Some patients also present aphthous lesion and/or polyarthritis. RIPK1 is a key determinant of cell response to TNF stimulation (Figure 2). Its ubiquitination status shifts the cell towards either a pro-survival inflammatory pathway via NF-κB activation, or cell death pathway via activation of caspase-8-dependent apoptosis or RIPK3/MLKL-dependent necroptosis [52]. RIPK1 deficiency, due to homozygous *RIPK1* LOF mutation, leads to reduced NF-κB activity, increased NLRP3 inflammasome activity and impaired T-cell and B-cell development. The prognosis is poor with high mortality rate.

Other even more rare defects of NF-κB pathway associated autoinflammation and combined immune deficiency: *mutations of HOIP*, characterized by recurrent fever with oral ulcers, diarrhoea and splenomegaly [57] and GOF *mutation of IKBKB* characterized by ectodermal dysplasia and suppurative hydradenitis [63]. This mutation of *IKBKB*, encoding IKK2, has been described in four patients from two kindreds. Its lead to enhanced NF-κB signalling as well as T and B cell functional defects [64].

Neutrophilic dermatosis and auto-immunity have been described in *POMP-Related Autoinflammation and Immune Dysregulation (PRAID)* [65]. POMP deficiency is characterized by papulo-erythematous skin lesions on face, trunk and extremities and progressing to necrotizing lesions then scarring without lipodystrophy. Auto-immunity features consist in presence of anti-nuclear antibodies, anti-b2-glycoprotein and anti-thyroid. Proteasome maturation protein (POMP) is a chaperone essential for the assembly of standard proteasome and immunoproteasome. The synthesis of a truncated protein due to heterozygous mutation of POMP has been reported in two unrelated patients. It results in impaired proteasome assembly, enhanced endoplasmic reticulum stress and increased expression of type-1-IFN-induced genes.

Fever, skin rash, myositis and basal ganglia calcification is evocative of another particular proteasome-associated autoinflammatory syndrome (PRAAS) due to *PSMB9 mutation* [66]. Other manifestations include liver dysfunction and pulmonary arterial hypertension but not lipoatrophy contrary to CANDLE syndrome caused by *PSMB8* mutation [66]. This PRAAS with immune deficiency has been described in two newborns who displayed susceptibility to viral infection especially BK and JC virus. One presented hypogammaglobulinemia with B- and T-cells deficiency meanwhile the other presented

T- and NK-cells deficiency. *PSMB9* encodes for β1i subunit of immunoproteasome. Heterozygous mutation leads to 26S proteasome defect.

The combination of thrombocytopenia, lymphadenopathy, skin and digestive autoinflammatory manifestations and atopy associated to combined immunodeficiency occurs in mutation of *ARPC1B* describe above.

Other primary immunodeficiencies

Interferon-γ impairment

Interferon-γ impairment results in susceptibility to mycobacterial infections.

Mycobacterial infection associated with calcification of cerebral basal ganglia during childhood and necrotic skin ulcers are characteristic of *Interferon-stimulated gene 15 (ISG15) deficiency* [67]. ISG15 encodes an INF inducible ubiquitine-like protein acting by its conjugation to a target protein (ISGylation). ISG15 deficiency, caused by bi-allelic LOF mutations of *ISG15* gene, leads to impaired USP18 stabilization and subsequent loss of negative regulation of INF-α/β explaining autoinflammatory manifestations. The lack of free extracellular ISG15 resulted in lower IFN-γ production by lymphocyte conferring susceptibility to mycobacterial infection.

Mycobacterial infection associated with anhidrotic ectodermal dysplasia (EDA) and inflammatory liver damage mediated by neutrophils has been described in one patient carrying an *heterozygous NFKBIA missense GOF mutation* [68]. This gene encodes IκBα which is one of the inhibitors of NF-κB (Figure 2). Mutations of *NFKBIA* are associated to EDA with immunodeficiency. L34P *IκBα* variant lead to impaired NF-κB activation in fibroblasts and macrophages but paradoxical hyperproduction of IL-1β [69].

Neutrophils impairment

Combination of recurrent fever and PID due to neutrophils impairment has been described in *PFIT* syndrome, described above, and in *CEBPE associated autoinflammation and immune impairment of neutrophils (CAIN) syndrome*.

In *PFIT syndrome*, fever attacks arise from the first week of life and last 3–7 days and neutrophils impairment results in recurrent severe bacterial infections [11]. Other features include recurrent oral inflammation, recurrent perianal ulcerations and thrombocypenia.

In *CAIN syndrome*, fever attacks arise in the puberty, last 4–5 days and are associated with abdominal pains. Neutrophils impairment results neutrophils hyposegmentation, recurrent nails, tongue, submandibular and gluteal abscesses, purulent wounds with delayed healing, paronychia complicated by lymphangitis and pulmonary infections. Other features include ulcers of buccal mucosal, intra-abdominal granuloma and pyoderma gangrenosum as well as moderate bleeding diathesis with epistaxis and a tendency towards haematomas without thrombocytopenia. CAIN has been identified in a family whose three members carried homozygous germline mutations of *CEBPE* encoding the transcription factor CCAAT-enhancer–binding protein epsilon (C/EBPε) [70]. C/EBPε is involved in terminal differentiation of neutrophils and expression of specific granule genes. The Arg219His mutation in the DNA-binding domain is responsible of decreased C/EBPε association with transcriptional repressor and increased chromatin binding leading to dysregulated transcription. It results in neutrophil dysfunction, alteration of interferon pathways and aberrant activation of noncanonical caspase-4/5 inflammasome. Heterozygous carriers present also widely dysregulated transcription, but homozygous mutations are required for clinical manifestations.

Type I interferon response impairment

Recurrent viral bronchitis in a context of recurrent fever, skin rash, inflammatory bowel disease, pulmonary alveolar proteinosis and hypogammaglobulinemia are caused by heterozygous *OAS1 GOF mutation* [47]. *OAS1* encodes oligoadenylate synthetase 1 which is a type 1 INF-inducible enzyme implicated in the antiviral immune response through the activation of ribonuclease L (RNase-L). GOF variants lead to inappropriate cellular RNA cleavage and therefore dysfunction and apoptosis of monocytes, macrophages and B cells.

DISCUSSION

Progress in genetic have allowed to expand the field of MSAID to cytopenias, lymphoproliferation and immune deficiency. Many MSAID have been identified through exome sequencing of patients suffering from PID with unknown genetic etiology. Most of them associate immune deficiency to cytopenias, especially thrombocytopenia, or to lymphoproliferation. Certain conditions offer a very florid picture of immuno-haematological features like in ADA2 deficiency, one of the most common, which presents typically as vasculopathy but also

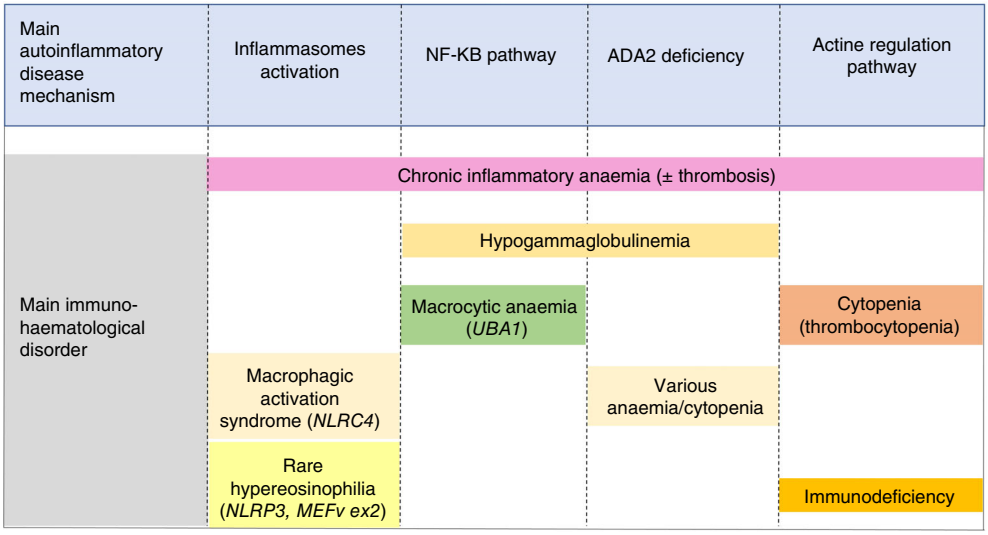

FIGURE 4 Mains immuno-haematological features according to the main pathophysiological mechanism involved.

with cytopenias, lymphoproliferation and/or humoral deficiency.

Genes and cellular mechanisms involved are various but two main pathophysiological pathways stand out: cytoskeletal abnormalities (*WDR1*, *ARPC1B* and *CDC42*), which all combine autoinflammation with cytopenia, and the defect of downstream TNFR1 pathway including RIPK1 and NF-κB pathway. Figure 4 summarizes main immuno-haematological features according to underlying mechanism. The type of mutation and its consequences for a same protein or the stage of the defect on a same pathway can result in different phenotypes. For example, homozygous *RIPK1* LOF mutation leads to immune deficiency whereas a peculiar heterozygous mutation leads to lymphoproliferation. *NFKBIA* GOF mutations have been associated with immunodeficiency and EDA, but the L34P IκBα variant provide additional autoinflammatory manifestations [68]. Defects on pathway downstream TNFR1 provide various phenotypes from exclusive autoinflammation in *OTULIN* deficiency to autoinflammation with susceptibility to infection in *RIPK1* deficiency, passing by a blended phenotype with autoinflammation, lymphoproliferation and immunodeficiency in LUBAC defect [71].

Suspect MSAID in front of haematological presentation or recurrent infections is challenging but some features may help. Recurrent fever and increased inflammatory markers without any infectious episode are the first sign that should arouse suspicion. The clinician can be guided by simple clinical signs as aphtosis or skin vasculitis which are atypical for a PID. The age and the family context are also essential aspects to considered. Most of MSAID we described are characterized by a very early-onset of inflammatory diseases like IBD, Behçet or vasculitis. Drawing family tree is here essential to identify the inheritance (recessive or dominant). In context of autoinflammation, blood count and hypogammaglobulinemia are basic features to orient the diagnosis.

This review is expected to evolve. Next generation sequencing (NGS) allowed to identified causative mutation of unexplained presentation in one family or even in one individual. Probably many other gene defects can be responsible for autoinflammation with immuno-haematological features and used wisely, whole-exome/genome sequencing will continue to help identify new MSAID. The comprehension of the pathophysiological pathways and the occurrence of haematological features set the stage for invasive therapeutic like HSCT whose effectiveness on auto-inflammatory manifestations has been reported [72, 73]. The purpose of this review was partly to make clinicians aware about the overlap between autoinflammation, immune deficiency, lymphoproliferation and to propose some keys for reasoning in daily clinical practice.

CONCLUSION

Borders between autoinflammation and haematology are now blurred. Cytopenias, hypogammaglobulinemia, susceptibility to infections and lymphoproliferation are part of the spectrum of MSAID. The current review provides an update and propose a practical description of MSAID with immuno-haematological features. These disorders belong largely to the inborn errors of immunity.

AUTHOR CONTRIBUTIONS

Hélène Vergneault wrote the manuscript. Hélène Vergneault and Sophie Georgin-Lavialle collected the data. Sophie Georgin-Lavialle contributed to the conceptualization of the study. Sophie Georgin-Lavialle and Capucine Picard revised the manuscript.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Hélène Vergneault https://orcid.org/0000-0001-7644-2903

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