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Review

New data in causes of autoinflammatory diseases

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ABSTRACT

The spectrum of factors known to mediate autoinflammation has broadened recently to include not only interleukin-1 (IL-1) and interferon, but also abnormalities that impair NF-κB pathway negative regulation. The NF-κB pathway is activated upon contact of a ligand with tumor necrosis factor receptor 1 (TNFR1) and plays a pivotal role in triggering the inflammatory process by producing major cytokines such as IL-1, IL-6, and TNF. Negative regulation of the NF-κB pathway, which is essential to stop the inflammatory process, depends on the level of ubiquitination of the proteins associated with TNFR1 and of other intermediate compounds. A20 and otulin are proteins that influence the level of ubiquitination, and a deficiency in either can result in NF-κB activation with overproduction of pro-inflammatory cytokines. Similar to Behçet's disease, A20 haploinsufficiency manifests as oral and genital ulcers and, more rarely, as uveitis. However, transmission is dominant, symptom onset occurs at a younger age, and severe gastrointestinal involvement is at the forefront of the clinical picture. Clinical presentations are extremely diverse. Over their lifetime, affected patients simultaneously or sequentially experience autoinflammatory and autoimmune manifestations. Mild immune deficiency predominantly affecting humoral responses is less common. Otulin deficiency results in systemic inflammatory manifestations at a very young age, with panniculitis, lipodystrophy, and inflammatory bowel disease. The main differential diagnosis is proteasome-associated autoinflammatory syndrome. The treatment of A20 haploinsufficiency and otulin deficiency is challenging and remains unstandardized. The symptoms respond to high-dose glucocorticoid therapy. TNF antagonists and IL-1 antagonists have shown some measure of efficacy.

1. Introduction

The apparently unpredictable flares of systemic inflammatory manifestations that characterize auto inflammatory diseases are due to impairments in the regulation of innate immunity, with overproduction of pro-inflammatory cytokines such as interleukin (IL)-1 IL-18, IL-6, tumor necrosis factor alpha (TNFα), and interferons (IFNs) type I [1–3]. The earliest described auto inflammatory

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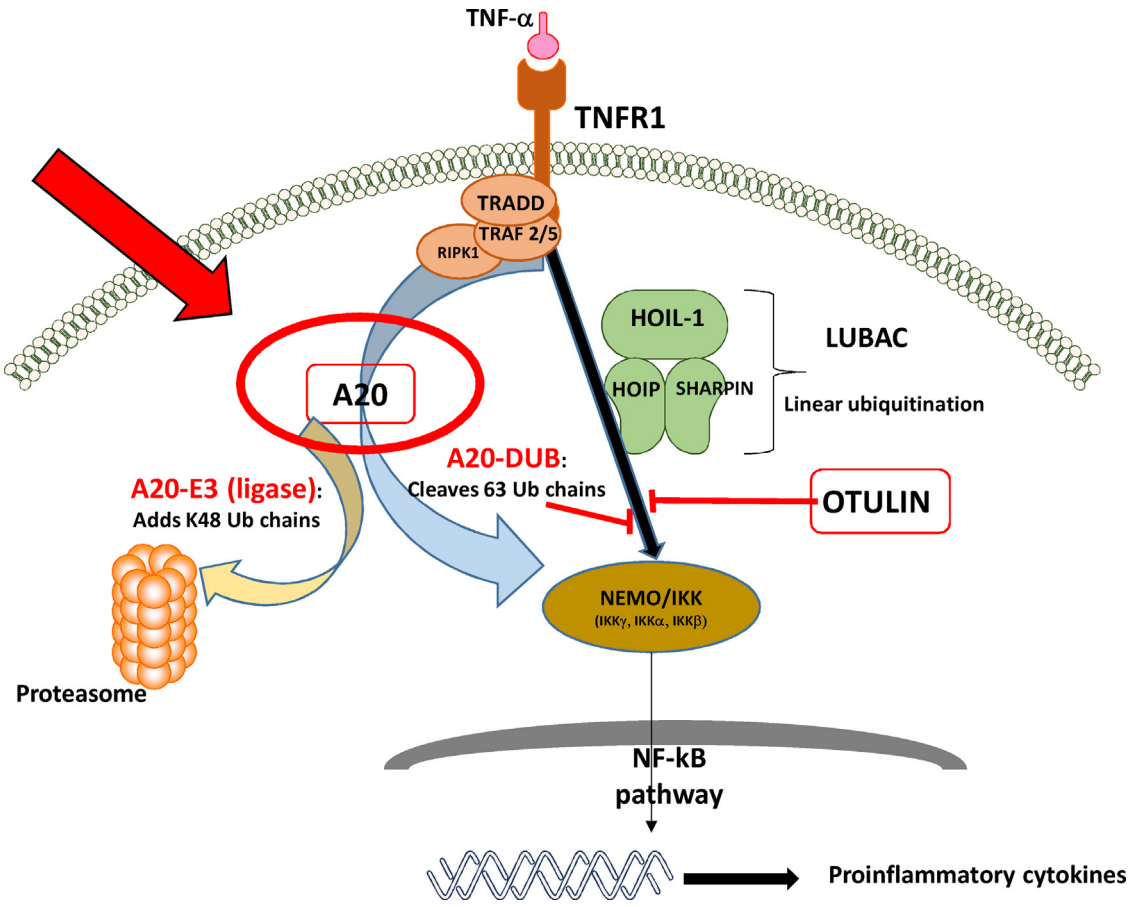

Fig. 1. Mechanisms of protein ubiquitination in the canonical NF-κB pathway.
The canonical NF-κB pathway is regulated by both K63 (Lys63) and the linear ubiquitin chain (Ub). Downstream from TNFR1 are predominant target proteins for ubiquitination by K63 and the linear Ub chains such as TRADD, TRAF2, TRAF5, and RIPK1. These proteins recruit the NEMO/IKK complex, which is also a target for ubiquitination. After ubiquitination, the IKK complex is less susceptible to degradation by the proteasome. The linear UB chains are added by lubac. A20 and otulin negatively regulate the NF-κB pathway by cleaving the K63 and linear UB chains from the target molecules, including RIPK1. If RIPK1 is subjected to the deubiquitinase function of A20, negative regulation of the NEMO/IKK complex ensues, resulting in decreased NF-κB release. In addition, via its E3 ligase activity, A20 adds K48 Ub chains to RIPK1 and IKKγ, targeting them for increased degradation by the proteasome. Decreased A20 expression in patients with HA20 or of otulin in patients with otulipenia/ORAS results in NF-κB pathway activation, increased expression of pro-inflammatory transcripts in the immune cells, and systemic inflammation. In patients harboring HOIP or HOIL-1 mutations, decreased expression of the lubac complex inhibits the NF-κB pathway in fibroblasts and B cells, causing immune deficiency; however, the monocytes of these patients overproduce pro-inflammatory cytokines. TNFR1, TNF 1 receptor; IKKγ/NEMO, inhibitor of the NF-κB γ subunit; lubac, linear ubiquitin chain assembly complex.

diseases were those mediated by IL-1 and due to single-gene mutations. Biotherapies that target the IL-1 receptor have radically improved the treatment of many diseases in this group, thereby providing quality-of-life gains and probably also extending the survival of those patients at the severe end of the phenotype spectrum [2]. For some time, enormous efforts supplied jointly by clinicians and geneticists, combined with the advent of new high-flow sequencing techniques, have been steadily adding to the list of known auto inflammatory pathways, some of which exhibit overlap with pathways involved in autoimmunity and immune deficiencies [1].

The objective of this review article is to discuss current knowledge about ubiquitination defects. The intracellular fate of proteins can be altered by posttraduction protein modifications consisting in the addition (ubiquitination) or removal (deubiquitinating) of ubiquitin residues [4,5]. These modifications play a central role in the function of the major pro-inflammatory cytokine transcription pathway known as tumor necrosis factor/nuclear factor-κB (NF-κB). Deficiencies in proteins that ensure ubiquitination and/or Deubiquitination (e.g., deubiquitinases), such as A20 and otulin, are responsible for two recently identified autoinflammatory diseases, TNFAIP3/A20 haploinsufficiency or HA20 syndrome and otulin deficiency or otulin-related autoimmunity syndrome (ORAS), respectively. The phenotype of HA20 syndrome was initially believed to resemble that of Behçet's syndrome but was subsequently found to encompass a broader spectrum of presentations combining autoinflammation and autoimmunity. ORAS manifests as chronic diarrhea and shares several features with proteasome-associated autoinflammatory syndrome (PRAAS) [4,6–13].

Otulin is a deubiquitinase that selectively hydrolyzes linear ubiquitin chains assembled by the linear ubiquitin chain assembly complex (lubac) [4,5,7,9]. Lubac is involved in the ubiquitination of two key NF-κB pathway components, receptor-interacting serine/threonine-protein kinase 1 (RIPK1) and NF-κB essential modulator (NEMO). Mutations in the *otulin* gene cause autoinflammatory syndromes with immune deficiencies [14,15]. Thus, deficiency in A20 or otulin results in impaired negative regulation of the NF-κB pathway with overproduction of pro-inflammatory cytokines [4].

Pathophysiology (Fig. 1)

2. Ubiquitination

Ubiquitination is a post-traduction protein modification involved in regulating signal transduction in response to stimulation via innate immunity receptors [4,5]. Stimulation results in the assembly of ubiquitin chains, which then attach to the

Table 1
Comparison of the main features of A20 haploinsufficiency and otulipenia/ORAS.

Disease	HA20	Otulipenia/ORAS
Gene	*TNFAIP3*	*Otulin*
Protein	A20	Otulin
Transmission	Autosomal dominant	Autosomal recessive
Type of mutation	Stop or missense mutations or deletion Loss of function	Missense mutations and deletion Loss of function
Distribution	Worldwide but 60% Japanese	3 families, from Turkey and Pakistan
Main clinical manifestations	In nearly 85% of cases: oral and genital ulcers, fever In nearly 50% of cases: gastrointestinal and cutaneous manifestations In 30% of cases: arthralgia and myalgia Rarely: ocular involvement	In 100% of cases: fever, rash, nodular panniculitis, arthritis In 66% of cases: diarrhea and abdominal pain In 50% of cases: lymphadenopathy and enlargement of the liver and spleen In 33% of cases: pustules
Age at onset	Before 10 years of age	Before 3 months of age
Duration of the flares	3 to 14 days	More than 10 days
Inflammation	Yes	Yes

Table 2
Main features of HA20 with autoinflammation based on the 51 cases reported to date.

Demographics	Country of origin/Ethnicity	Frequency (%)
	Japan	60%
	Caucasian	30%
	Turkey	10%
	Females	68.6%
Age at onset	2 months to 20 years	92% in childhood
Duration of flares	3 to 14 days. Permanent manifestations in some patients	
Frequency of flares	1 to 12 per year	
Clinical manifestations	Oral ulcers	88%
	Recurrent fever	78%
	Genital ulcers	68%
	Gastrointestinal manifestations	57%
	Cutaneous manifestations	45%
	Musculoskeletal manifestations	31%
	Ocular manifestations	10%
	Cardiovascular manifestations	8%
	Immune deficiency	6%
	Central nervous system involvement	4%
Laboratory test abnormalities	Auto-antibodies ($n = 17$) including: antithyroid ($n = 8$); antinuclear ($n = 4$)	33%
Effective treatments	Colchicine ($n = 8$)	15.7%
	Infliximab ($n = 6$)	11.7%
	Anakinra ($n = 2$) and adalimumab ($n = 2$)	8%

protein whose function and fate they regulate. Ubiquitin chains take a variety of forms depending on their site and mode of fixation. Ubiquitination starts with the attachment of a simple ubiquitin motif to the target protein via a three-stage enzymatic process that sequentially involves a ubiquitin-activating enzyme (E1), a ubiquitin-conjugating enzyme (E2), and a ubiquitin-ligating enzyme (E3) [4,5]. Ubiquitin chains are produced via the attachment of ubiquitin monomers to either lysine residues (Lys-Ub; K48, K63) or methionine residues (Met-Ub, Met1). Bound ubiquitin chains can then undergo modifications and/or be identified by receptors or sensors that determine the fate of their targets [4]. For instance, enzymes conjugated via lysines at position 48 (K48) undergo degradation via the ubiquitin-proteasome system (UPS) within the proteasomes. Deubiquitinases hydrolyze the ubiquitin chains off the modified proteins. The deubiquitinases A20, otulin, CYLD, and Cezanne negatively regulate the NF-κB pathway [4,5]. Polymorphisms of these deubiquitinases have been linked to various autoimmune diseases, malignancies, and neurodegenerative diseases [5,16–19].

3. A20 protein haploinsufficiency

The A20 protein negatively regulates the NF-κB signaling pathway. Polymorphisms of *TNFAIP3*, which encodes A20, are associated with several autoimmune diseases including lupus, rheumatoid arthritis, psoriasis, Crohn's disease, and type 1 diabetes [17]. A20 has a dual function, inducing deubiquitination via its OTU domain and ubiquitination (E3 ligase) via its seven zinc finger (ZnF) domain. Deubiquitination by A20 consists in the removal of ubiquitin chains bound to K63 on signaling proteins such as TNFR-associated factor 6 (TRAF6) and RIPK1 in the NF-κB pathway [4,17,18]. Ubiquitination by A20 consists in the ligation of ubiquitin chains bound to K48 on RIPK1, which is then directed toward the proteasome for degradation. In A20 haploinsufficiency, one of the *A20* (*TNFAIP3*) gene copies is missing. As a result, the A20 protein is not produced in sufficient amounts to ensure normal function [4,8].

4. Otulin deficiency (ORAS)

Lubac is a ubiquitinase (E3 ligase) that preserves the stability of many proteins involved in regulating innate immunity such as the tumor necrosis factor receptor 1 (TNFR1), toll-like receptors (TLRs), the IL-1 receptor (IL-1R), CD40, and inflammasome receptor signaling complexes (RSCs) [4,14,15]. In response to pro-inflammatory signals, lubac is recruited and adds linear ubiquitination chains to its substrates IKK (NEMO), RIPK1, RIPK2, IRAKs, MyD88, and ASC (Fig. 1). Linear ubiquitination by lubac is required for inflammasome assembly [5]. Lubac is composed of HOIL-1 interacting protein

Table 3
Clinical manifestations in patients with HA20 based on a literature review.

N Pts/Sex [ref]	Age at onset	Mucosal ulcers	Skin	Gastro-intestinal	Joints	Eyes	Nervous system	Cardio-vascular	Infections	Auto-immunity
16/13F3M [6]	7 months to 16 years	16/16 Oral 16/16 Genital 15/16 Perineal 2/16	8/16 Acne 2/16 Folliculitis 4/16 Pustules 4/16 Subcutaneous abscesses 2/16 Malar rash 1/16 Papules 1/16 Stevens Johnson 1/16	9/16 Ulcerative colitis 6/16 Malabsorption 1/16 Weight loss, anorexia 1/16	9/16 Arthralgia 2/16 Polyarthritis 7/16	3/16 Anterior uveitis 2/16 Necrotizing retinal vasculitis 1/16	1/16 CNS vasculitis with chorea 1/16	3/16 Pericarditis 2/16 Pulmonary embolus 1/16	2/16 Viral and bacterial (IgG subclass deficiencies and lymphopenia)	6/16 ANA 4/10 Anti-DNA 2/6 LAC 6/7 Anti- cardiolipin 1/16
6/5F1M [10]	8 years to 17 years	6/6 Oral 6/6 Genital 4/6	6/6 Folliculitis 4/6 Perianal ulcer 1/6 Erythema nodosum 4/6 Erythema 1/6	1/6 Ulcerative colitis 1/6	0	0	0	0	0	Nephrotic syndrome
3/2F1M [11]	9 months to 11 years	3/3 Oral 2/3 Genital 1/3	0/3	3/3 Ulcerative colitis 3/3	2/3 Polyarthritis 2/3	3/3 Anterior uveitis 1/3 Conjunctival ulcer 1/3	0	0	0	0
3/2F1M [20]	6 months to 6 years	Oral 3/3 Genital 2/3	Folliculitis 1/3 Local injection reaction to the pneumococcal vaccine 1/3 Urticaria 1/3	Ulcerative colitis 3/3	Arthritis 2/3	Episcleritis 1/3	0	Deep vein thrombosis of the lower limbs (1/3 with 2 episodes)	Pneumonia during IL-1 antagonist therapy 1/3	ANCA 1/3 Hashimoto 1/3
22/13F1M [12]	2 months to 20 years	22/22 Oral 17/22 Genital 12/22	8/22	12/22	3/22	0	1/22	0	0	8/22 Anti-thyroid 7/22 ANA 1/22

ANA: anti-nuclear antibodies; LAC: lupus anticoagulant; ANCA: anti-neutrophil cytoplasmic antibody.

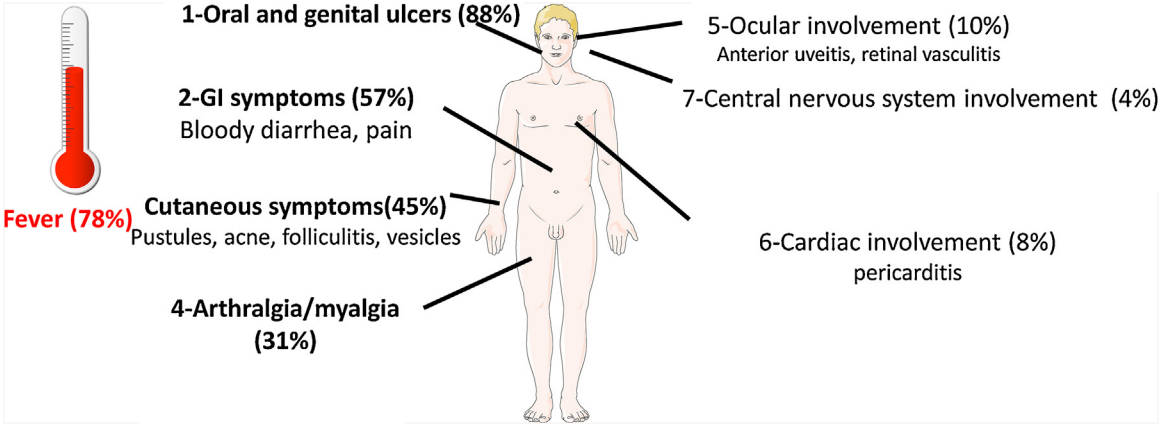

Fig. 2. Main clinical manifestations of A20 haploinsufficiency (HA20).

(HOIP; RNF31) and of two ancillary protein, namely, heme-oxidized IRP2 ubiquitin ligase 1 (HOIL-1; RBCK1) and heme-oxidized IRP2 ubiquitin ligase 1 (SHARPIN; RBCK1). The otulin protein (Gumby; FAM105B) negatively regulates linear ubiquitination by lubac via linear hydrolysis of ubiquitin chains linked via Met1 [4,7,9].

Thus, mutations in the *TNFAIP3* and *otulin* genes for A20 and otulin, respectively, result in impairments of the protein ubiquitination/deubiquitination system, thereby potentially causing NF-κB pathway overactivation with manifestations of autoinflammation [4] (Table 1).

5. Epidemiology

5.1. *Haploinsufficiency of the* TNFAIP3 *gene for the A20 protein*

Neither the incidence nor the prevalence of the recently described HA20 syndrome have been determined. To date, 51 cases have been reported in various parts of the world. Most patients had oral and genital ulcers simulating Behçet's disease [6,8,10–13,20]. Females contribute 68% of the identified patients, among whom 60% are Japanese, 30% Caucasian, and 10% Turkish (Table 2). Symptom onset was in childhood in 92% of patients. Of the 22 patients from 9 families reported by Kadowaki et al., 9 had Behçet-like presentations and 13 more complex clinical pictures combining autoinflammatory manifestations and autoimmunity [12]. Given this clinical variability, many cases of HA20 syndrome may still be unidentified.

5.2. *Otulin deficiency*

Only six patients from 3 consanguineous families, 2 from Turkey and 1 from Pakistan, have been identified to date. In one of these families, 2 patients died in early childhood, probably due to otulipenia. Symptom onset was within the first 3 postnatal months. In one patient, the presence of panniculitis and lipodystrophy created a picture reminiscent of PRAAS. Finally, 3 of the 6 patients were born prematurely [7,9].

6. Clinical spectrum (Table 1)

6.1. *HA20*

The initial description by Zhou et al. has been expanded upon in a recent article by the same group [6,8] (Tables 1–3 and Fig. 2). The 16 patients belong to 7 families, of which 5 are multiplex families with dominant inheritance. Symptom onset was in early childhood. Most patients had oral and genital ulcers, as well as ocular inflammation, creating some resemblance with Behçet's disease [6] (Fig. 2). Distinguishing features included fever spikes in most patients; the consistent presence during flares of laboratory evidence of inflammation (in Behçet's disease, in contrast, laboratory signs of inflammation are usually found only during flares of serositis or vasculitis and in the event of gastrointestinal involvement, which is extremely rare in non-Asian patients); a predominance of anterior uveitis; and a fairly high frequency of ulcerative colitis with bloody diarrhea (6/11 patients). Another major difference with Behçet's disease is that some of the patients experience recurrent upper and lower respiratory tract infections. Cerebral vasculitis developed in 2 patients and pulmonary embolus related to vasculitis in 1 patient. Laboratory evidence of autoimmunity was present in some patients. Behçet's disease was the most common initial diagnosis. Other initial diagnoses were periodic fever/aphthous stomatitis/pharyngitis/adenitis (PFAPA), juvenile idiopathic arthritis (JIA), lupus, and Crohn's disease [6]. Kadowaki et al. reported 22 other patients with HA20 from 9 families [12]. Among them, 9 had Behçet-like presentations with symptom onset in childhood or adolescence. The initial presentation suggested PFAPA in 4 patients and polyarticular JIA in 2. In the remaining patients, the manifestations initially suggested Kawasaki disease, familial Mediterranean fever, or recurrent oral ulcers [12]. In addition to autoinflammation, 9 patients (different from the 9 with Behçet-like disease) had autoimmune manifestations including psoriasis, autoimmune thyroiditis, Crohn's disease, and lupus with progression to autoimmune lymphoproliferative syndrome. In addition to these two large case-series, 10 other cases manifesting as mucosal ulcers and recurrent fever have been reported. Thus, the total number of cases reported to date is 51 (Tables 2 and 3). However, a patient with an unusual combination of multiple birth defects, recurrent IgA vasculitis, and autoimmunity but no recurrent fever had an extensive deletion involving 60 genes on chromosome 6 including CITED2, IFNGR1, and *TNFAIP3*; this patient is not shown in Table 3 [21].

6.2. *Otulipenia or otulin-related autoinflammatory syndrome (ORAS)*

ORAS is characterized by severe neonatal systemic inflammatory manifestations including prolonged fever, joint swelling, and severe diarrhea with failure to thrive. The flares are prolonged and do not resolve without treatment [7,9]. A variety of skin lesions have been reported including erythema, pustules, subcutaneous nodules, panniculitis, and lipodystrophy.

Table 1 and Fig. 3 show the main manifestations of NF-κB pathway abnormalities due to mutations in the *TNFAIP3* and *otulin* genes.

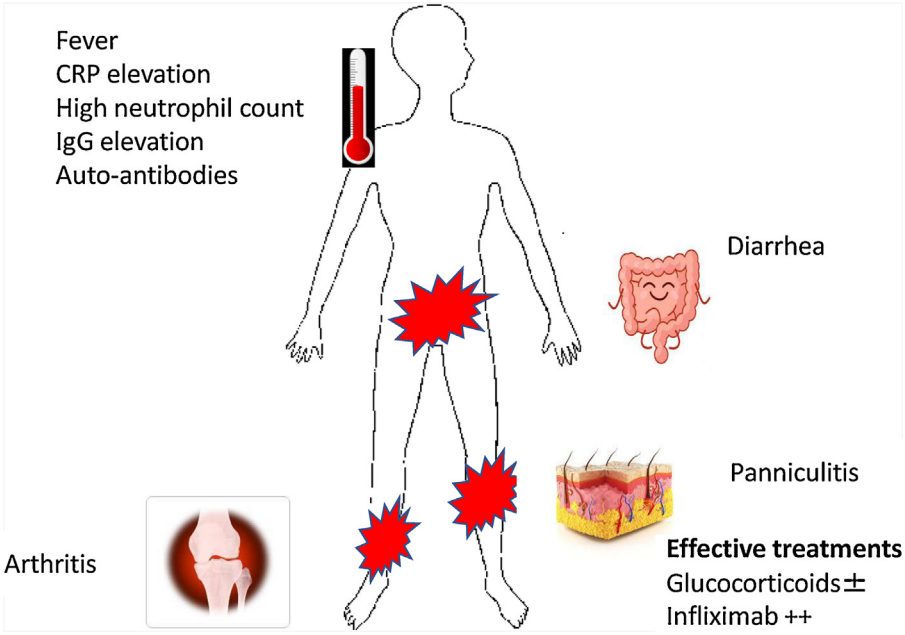

Fig. 3. Main clinical manifestations of otulipenia/ORAS.

7. Genetic aspects

7.1. HA20

The tumor necrosis factor α-induced protein 3 gene (*TNFAIP3* or *A20*) that encodes protein A20 is composed of 9 exons on chromosome 6. The first is a non-coding exon. The other 5 exons contribute to formation of the ovarian tumor (OTU) domain and 3 exons contribute to the zinc finger domain. Finally, the last exon, which is partially non-coding, encodes a protein that has two main domains, an OTU domain at its N-terminus that plays a key role in the deubiquitinase activity of A20 (this domain is a C103 cysteine that confers K63 deubiquitination) and a seven zinc fingers (7ZF) domain at its C-terminus that confers ubiquitinase activity [3,4,8,17,18]. Among mutations reported to date, most are nonsense mutations or small frameshift deletions that result in truncation of the OTU or 7ZF domain, thereby impairing the function of the A20 protein. The data needed to establish genotype-phenotype correlations are not yet available. The extraordinary variability of the clinical presentations and outcomes in reported patients with HA20 syndrome suggest a role for other factors such as modifying genes or epigenetic regulation [4]. Nevertheless, patients with mutations affecting the ZF ubiquitination domain seem to share the same phenotype as patients with mutations in the OTU domain [4].

7.2. Otulin deficiency

The otulin (FAM105B) gene has 5 exons on chromosome 5. Otulipenia is caused by recessive loss-of-function mutations including frameshift missense mutations and small deletions. Damgaard et al. described 3 patients from a single consanguineous family who had a homozygous missense mutation of the *otulin* gene (c.815T > C; p.Leu272Pro; L22P in exon 6). This mutation destabilizes otulin and impairs its function. The cells of the affected patients overexpressed Met1-Ub compared to controls [7]. Zhou et al. reported two other mutations in the OTU domain, a deletion in exon 5 (c.517delC) and a substitution in exon 6 (c.731A > G) [9].

8. Differential diagnoses

8.1. HA2O syndrome

8.1.1. Polygenic autoinflammatory diseases

8.1.1.1. Behçet's disease. The main differential diagnosis is Behçet's disease, particularly in its pediatric presentation. Fig. 4 shows the differences between HA20 syndrome and Behçet's disease. Very early symptom onset, a pedigree consistent with dominant inheritance, and the occurrence of febrile flares should suggest HA20 syndrome. In sporadic Behçet's disease, the symptoms start in adulthood, often at about 30 years of age; there is usually no fever or laboratory evidence of inflammation during the episodes of oral and genital ulcers; and the oral ulcers heal without leaving scars. In addition, the uveitis seen in sporadic Behçet's disease usually affects the posterior chamber or both chambers, and the retinal vasculitis manifests as blood leakage in a fern pattern. The gastrointestinal manifestations of Behçet's disease are usually mild, consisting in isolated abdominal pain. Hemorrhagic colitis with prominent aphthous ulcers is rare. The polyarthritis seen in HA20 syndrome is very different from the joint involvement in Behçet's disease, which usually consists in oligoarthritis of the lower limbs [6].

8.1.1.2. PFAPA. PFAPA manifests as periodic fever, cervical lymphadenopathy, exudative pharyngitis, and oral ulcers. PFAPA may mask HA20 syndrome. In the usual pediatric form of PFAPA, which affects children younger than 5 years, the oral ulcers are mild, there are no genital ulcers, and the gastrointestinal symptoms consist only in abdominal pain due to mesenteric lymphadenopathy, with no diarrhea or colitis. PFAPA usually resolves after a few months or years. However, PFAPA may be a mode of onset of a more complex inflammatory disease such as Behçet's disease or HA20 syndrome [22].

8.1.1.3. Systemic juvenile idiopathic arthritis. Pediatric Still disease is an autoinflammatory disease characterized by prolonged episodes of fever with a macular rash and musculoskeletal symptoms ranging from isolated arthralgia/myalgia to destructive

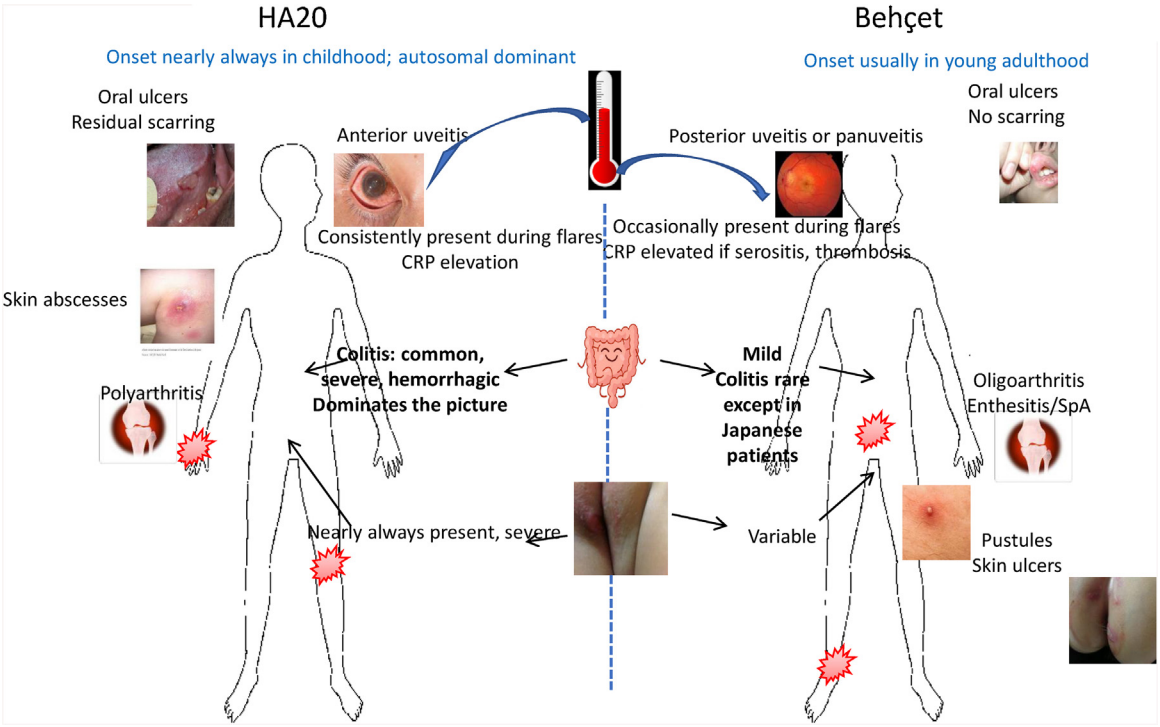

Fig. 4. Main features that differentiate Behçet-like HA20 from Behçet's disease.

polyarthritis. No reliable markers are available for confirming the diagnosis. As with PFAPA, some of the patients with HA20 syndrome reported by Kadowaki et al. [12] presented with Still-like manifestations that progressed over time to an apparently autoimmune condition resembling psoriatic arthritis [23].

8.1.2. Monogenic autoinflammatory diseases of the small bowel and colon

In addition to the familial forms of Crohn's disease due to mutations in the *NOD2/CARD15* gene, whose diagnosis can be provided by histological studies of biopsy specimens, several forms of ulcerative colitis are due to monogenic abnormalities. Onset is during the neonatal period or within the first few postnatal months. The manifestations may be so severe as to require allogeneic bone marrow grafting. Depending on the concomitant manifestations, the picture may suggest immune dysregulation/polyendocrinopathy/enteropathy/X-linked syndrome (IPEX), X-linked inhibitor of apoptosis (XIAP) deficiency, or causes of autoinflammatory disease such as IL-10 and IL-10 receptor deficiencies or mevalonate kinase deficiency.

8.1.3. Other monogenic autoinflammatory diseases

Mucosal ulcers can develop in several conditions characterized by recurrent fever such as mevalonate kinase deficiency, the cryopyrinopathies, and familial Mediterranean fever. TNF receptor-associated periodic syndrome (TRAPS) can manifest as prolonged febrile episodes [1]. The geographic origin of the patient should be specified and a pedigree drawn.

8.2. Otulipenia

8.2.1. Polygenic autoinflammatory diseases

Several early-onset chronic inflammatory diseases of the gastrointestinal tract can mimic otulipenia [1]. The cutaneous manifestations of otulipenia may suggest neutrophilic dermatosis or Sweet syndrome [24]

8.2.2. Monogenic autoinflammatory diseases

Majeed syndrome due to a mutation in the *LPIN2* gene is characterized by the neonatal onset of neutrophilic dermatosis [1]. Monogenic Crohn's disease can simulate otulipenia. Finally, pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND) can be responsible for cutaneous, gastrointestinal, and even cardiac manifestations similar to those seen in otulipenia [25]. PRAAS is due to point mutations that cause loss of function of the constitutive proteasome (PMSB4, PMSA3), the inducible proteasome or immunoproteasome (PSMB8, PSMB9), or the chaperone protein (POMP). Patients may be homozygotes, composite heterozygotes, double heterozygotes, or simple heterozygotes. All the mutations reported to date alter the assembly of the various sub-units, thereby impairing the key function, which is protein degradation [1,2,26]. PRAAS manifests as prolonged spiking fever of neonatal onset, panniculitis, progressive lipodystrophy, myositis, purplish periorbital eruptions, and calcifications in the brain and blood vessels. Common laboratory test findings include C-reactive protein elevation, hypergammaglobulinemia, and evidence of autoimmunity. However, the severe gastrointestinal manifestations seen in otulipenia do not occur in patients with PRAAS.

9. Treatment

Information on the nature and effectiveness of treatments used in HA20 syndrome and otulipenia is somewhat limited and comes only from retrospective case-series studies.

9.1. HA20

All the patients reported to date have required treatment. The medications used to date have ranged from colchicine alone, which was effective in 8 patients, to glucocorticoid combined with immunosuppressants (methotrexate, azathioprine, thalidomide, cyclophosphamide, tofacitinib). Although glucocorticoid therapy

has been effective overall, the high dosages required and development of steroid dependency have been responsible for major adverse events. Biotherapies including anakinra, tocilizumab, and TNFα antagonists have been used and considered potentially capable of suppressing the systemic inflammation. Intravenous immunoglobulin therapy has been given to a few patients who had concomitant humoral immune deficiencies [6,8,10–13,20]. A therapeutic strategy that is tailored to the needs of each patient based in part on the cytokine levels is probably the best approach, as the considerable phenotype variability does not argue in favor of a standardized management protocol. A patient who had severe disease with cerebral vasculitis received an allogeneic bone marrow transplant and subsequently experienced a lupus-like recurrence; another patient experienced fatal gastrointestinal bleeding [6,12].

9.2. Otulipenia

Of the 6 reported patients with ORAS, 5 have received TNFα antagonist therapy. The remaining patient was treated with glucocorticoids and anakinra [7,9].

10. Outcomes

10.1. HA20

Overall, changes in both directions between an autoinflammatory profile and an autoimmune profile occur throughout the lifetime of patients with HA20. Two reported patients with HA20 developed autoimmune lymphoproliferative syndrome, a condition generally ascribed to mutations that affect apoptosis (Fas/FasL) [3,12,19,27]. The inflammatory phenotype seems to be at the forefront of the clinical picture, and refractoriness to treatment is the rule. The changes in phenotype throughout life raises management challenges and support a personalized medicine strategy [4,6,12].

10.2. Otulipenia

The long-term outcomes of otulipenia are unknown. TNFα antagonist or IL-1 antagonist therapy seems effective in restoring normal growth and controlling the inflammatory process. Otulipenia is not responsible for immune deficiencies. The cases of infection reported to date have been ascribed to the immunosuppressants used to treat the condition [4,7,9].

11. Conclusion

This description of a new pathway responsible for autoinflammatory disease constitutes further evidence of the well-known limitations of purely clinical medicine, by raising new issues about entities such as Behçet's syndrome, PFAPA syndrome, and juvenile idiopathic arthritis. It also highlights the tight interrelations between autoinflammation and autoimmunity (involving the innate and adaptive immune systems), as the same abnormality in the same individual seems capable of causing a sequence of PFAPA syndrome, Behçet's disease, and even autoimmune lymphoproliferative syndrome. The extraordinary variability of the phenotypes of the patients, some of whom carry the same mutation, suggests that personalized medicine may be the best approach for understanding the underlying pathophysiological mechanisms, which probably involve other modifying genes, and for identifying the optimal treatment targets.

Disclosure of interest

IKP, SGL, and VH declare that they have no competing interest, but have received honoraria for expert assessments of conferences from Novartis and Sobi.

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