Journal of Translational Autoimmunity 3 (2020) 100071

Contents lists available at ScienceDirect

Journal of Translational Autoimmunity

journal homepage: www.journals.elsevier.com/journal-of-translational-autoimmunity/

Ancient friends, revisited: Systematic review and case report of pyoderma gangrenosum-associated autoinflammatory syndromes

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ARTICLE INFO

Keywords:
PASS -syndrome
Ankylosing spondylitis
Autoinflammatory syndrome
Hidradenitis suppurativa
Pyoderma gangrenosum
Adalimumab

ABSTRACT

In the last decade, new scientific findings significantly improved our understanding of the molecular pathogenesis of autoinflammation and have resulted in the identification and definition of several pyoderma gangrenosum-associated autoinflammatory syndromes (PGAAIS) as new and distinct clinical entities. These different clinical entities include PAPA (pyogenic arthritis, pyoderma gangrenosum and acne conglobata), PASH (pyoderma gangrenosum, acne and suppurative hidradenitis), PAPASH (pyoderma gangrenosum, acne, suppurative hidradenitis and pyogenic arthritis), PsAPASH (pyoderma gangrenosum, acne, suppurative hidradenitis and psoriatic arthritis), PASS (pyoderma gangrenosum, acne conglobata, suppurative hidradenitis, and axial spondyloarthritis) and PAC (pyoderma gangrenosum, acne and ulcerative colitis), which can be distinguished by their clinical presentation and the presence or absence of mutations in several genes, such as the genes encoding proline-serine-threonine phosphatase-interacting protein 1 (PSTPIP1), nicastrin (NCSTN), Mediterranean fever (MEFV) and nucleotide-binding oligomerization domain-containing protein (NOD). In this systematic review, we summarize the present knowledge of this rapidly developing hot topic and provide a guide to enable the easy diagnosis of these syndromes in everyday clinical practice. Moreover, we report a rare case of PASS syndrome demonstrating successful treatment with adalimumab and another case of a previously unreported combination of symptoms, including psoriatic arthritis, pyoderma gangrenosum, suppurative hidradenitis and Crohn's disease (newly coined PsAPSC), as examples. Because of the identification of similar genetic and pathogenic mechanisms of PGAAIS, we think the wide variety of seemingly different syndromes may represent distinct phenotypes of one disease.

1. Introduction

Because of their often dismal clinical outcomes and the lack of effective therapies, the management of pyoderma gangrenosum (PG) and its associated autoinflammatory syndromes is still a great challenge today. During the last decade, however, knowledge about the molecular mechanism of autoinflammation has greatly expanded, opening new avenues for effective therapies. Several PG-associated inflammatory disorders have been coined as distinct PG-associated autoinflammatory syndromes, leading to a vast system of acronyms such as PAPA, PASH, PAPASH, PsAPASH, PASS and PAC. All of these syndromes are considered hereditary and thus associated with mutations in various genes, including genes encoding proline-serine-threonine phosphatase interacting protein 1 (PSTPIP1), nicastrin (NCSTN), nucleotide-binding oligomerization domain-containing protein (NOD) and Mediterranean fever (MEFV). In this systematic review, we summarize the current knowledge of this rapidly developing hot topic and provide, for the first time, a guide that was developed to enable the easy diagnosis of theses disease in clinical practice.

1.1. Methods

Relevant publications in MEDLINE (from 1946) and ISI Web of Science (from 1945) were searched independently by two authors (RS and JR) using the following key terms: "pyoderma gangrenosum", "pyoderma gangrenosum-associated autoinflammatory syndrome", "PAPA", "PASH", "PAPASH", "PsAPASH", "PASS", and "PAC". The articles identified, including reviews, were cross-referenced to find articles missed in the database search. The following two criteria were used for inclusion: studies/reports published to January 15, 2019 and reports on a clinical outcome and/or molecular basis of PGAAIS. There were no language restrictions. The exclusion criteria were defined accordingly.

As examples of how to use this new guide in clinical practice, we

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https://doi.org/10.1016/j.jtauto.2020.100071
Received 28 October 2020; Received in revised form 15 November 2020; Accepted 16 November 2020

Abbreviations

A	acne
ANAs	Antinuclear antibodies
AS	ankylosing spondylitis
ASC	adaptor apoptosis-associated speck-like protein containing a CARD
ASCA	anti-Saccharomyces cerevisiae antibodies
C	ulcerative colitis
c-Abl	c-Abelson tyrosine kinase
c-ANCAs	antineutrophil cytoplasmic antibodies
CAPS	cryopyrin-associated periodic syndromes
CARD	caspase activation and recruitment domain
CD	Crohn's disease
CD2	cluster of differentiation 2
CD2BP1	CD2-binding protein 1, in murine also known as PSTPIP1
CINCA	chronic infantile neurological cutaneous and articular syndrome
DAMPs	damage-associated molecular patterns
FASL	Fas ligand
FCAS	familial cold urticarial syndrome
FCH	Fes/CIP4 homology
FMF	familial Mediterranean fever
FRA	familial recurrent arthritis
H/PSC	autoimmunhepatitis and primary sclerosing cholangitis
HIDS	hyper-IgD syndrome, hypergammaglobulinemia D, mevalonate kinase deficiency
HPFS	hereditary periodic fever syndrome
Hz/Hc	hypercalprotectinemia and hyperzincemia
IL-1β	interleukin 1β
IL-18	interleukin 18
IL1RN	interleukin 1 receptor antagonist
JAK	Janus kinase
LRR	leucine-rich repeat
MEFV	Mediterranean fever
MHC	major histocompatibility complex
MRP8	myeloid-related protein 8 (S100A8)
MRP14	myeloid-related protein 14 (S100A9)
MWS	Muckle-Wells syndrome
NBD	nucleotide-binding domain
NCSTN	nicastrin
NF-kB	nuclear factor 'kappa-light-chain-enhancer' of activated B-cells
NLR	nucleotide-binding oligomerization domain-like receptor
NOD	nucleotide-binding oligomerization domain-containing protein
PA	pyogenic arthritis
PAASCH/PSC	pyogenic arthritis, acne, suppurative hidradenitis ulcerative colitis, autoimmunhepatitis and primary sclerosing cholangitis
PGAAIS	pyoderma gangrenosum-associated autoinflammatory syndromes
PG or P	pyoderma gangrenosum
PAC	pyoderma gangrenosum, acne and ulcerative colitis
PAMI	PSTPIP1-associated myeloid-related proteinemia inflammatory syndrome
PAMPs	pathogen-associated molecular patterns
PAPA	pyogenic arthritis, pyoderma gangrenosum and acne conglobata
PAPASC	pyogenic arthritis, pyoderma gangrenosum, acne, suppurative hidradenitis and ulcerative colitis
PAPASH	pyoderma gangrenosum, acne, suppurative hidradenitis and pyogenic arthritis
PASC	pyoderma gangrenosum, acne, suppurative hidradenitis and ulcerative colitis
PASCD	pyoderma gangrenosum, acne, suppurative hidradenitis and Crohn's disease
PASH	pyoderma gangrenosum, acne and suppurative hidradenitis
PASS	pyoderma gangrenosum, acne conglobata, suppurative hidradenitis and axial spondyloarthritis
pMHC	peptides bound to major histocompatibility complex (MHC)
PsA	psoriatic arthritis
PsAPASH	pyoderma gangrenosum, acne, suppurative hidradenitis and psoriatic arthritis
PsAPSC	psoriatic arthritis, pyoderma gangrenosum, suppurative hidradenitis and Crohn's disease
PSMB8	proteasome [prosome, macropain] subunit beta type 8
PSTPIP1	proline-serine-threonine phosphatase-interacting protein 1, also known as CD2BP1
PTP-PEST	protein tyrosine phosphatases - proline, glutamic acid, serine and threonine-rich region
PYHIN	Pyrin and hematopoietic interferon-inducible nuclear antigens with 200 amino-acid repeats domain-containing protein
PYD	pyrin domain
S	spondyloarthritis
SAPHO	synovitis, acne, pustulosis, hyperostosis and osteitis syndrome
SH or S	suppurative hidradenitis
SH3	Src-homology 3
TLR	Toll-like receptor
TNF	necrosis factor alpha
TRAPS	tumor necrosis factor receptor-associated periodic syndrome
V	leukocytoclastic vasculitis
VPASH	leukocytoclastic vasculitis, pyoderma gangrenosum, acne and suppurative hidradenitis
WASP	Wiskott–Aldrich Syndrome protein

report a rare case of PASS syndrome demonstrating successful treatment with adalimumab and another case report of a previously unreported combination of symptoms, including psoriatic arthritis, pyoderma gangrenosum, suppurative hidradenitis and Crohn's disease. We therefore propose the term PsAPSC.

1.2. Unraveling hidden secrets: the molecular basis of pyoderma gangrenosum-associated autoinflammation

PG is a rare neutrophilic dermatosis characterized both by aseptic neutrophilic infiltration, destruction of the skin and systemic inflammation [1–3]. A multifactorial pathogenesis of pyoderma gangrenosum which include neutrophilic dysfunction, inflammatory mediators, and genetic predisposition has been described [3,4]. Clinically, PG lesions are painful ulcers with sharply circumscribed and demarcated, frequently undermined, livid borders and a necrotic base [2]. Notably, a complex reaction pattern in all areas of neutrophil activity has been described for PG [rev. in 1]. Although the histological examination of the skin lesions indicates normal-looking and mature neutrophils in the dermis, several investigations have reported dysfunctions in these cells, including the elevated expression and dysregulated signaling of integrins [rev. in 1]. It has been established that PG is a type of neutrophilic dermatitis. In combination with other symptoms, including pyogenic arthritis (PA), acne (A) or suppurative hidradenitis (SH), PG can be a symptom of

distinct autoinflammatory syndromes [5].

Another group of autoinflammatory diseases not associated with PG includes cryopyrin-associated periodic syndromes (CAPS), familial Mediterranean fever (FMF), hyper-IgD syndrome (hyper-gammaglobulinemia D and HIDS, also known as mevalonate kinase deficiency), tumor necrosis factor receptor-associated periodic syndrome (TRAPS) and Schnitzler's syndrome (urticarial vasculitis) [5,6]. CAPS, FMF, HIDS and TRAPS are distinct entities of hereditary periodic fever syndrome (HPFS), usually seen in children [6]. CAPS comprise familial cold urticarial syndrome (FCAS), Muckle-Wells syndrome (MWS) and chronic infantile neurological cutaneous and articular syndrome (CINCA) [6].

The basic shared pathomechanism of autoinflammatory syndromes is the dysfunction of inflammasomes [5].

Inflammasomes comprise protein complexes located within the cytosol that are in a group involved in the production of important proinflammatory cytokines such as interleukin-1β (IL-1β) and IL-18 via caspase 1 activation [5,7]. Inflammasomes also play key roles in recognizing conserved pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) [5,7].

In general, two families of core inflammasome components can be distinguished: the NLR (nucleotide-binding oligomerization domain (NOD)-like receptor) family and the PYHIN (Pyrin and hematopoietic interferon-inducible nuclear antigens with 200 amino-acid repeats domain-containing protein) family [7]. An example for a possible domain organization and its activation of the inflammasome is shown in [Fig. 1].

A member of the cytosolic NLR family is NOD2 that activates the downstream pro-inflammatory pathway mediated by NF-kB [8]. Mutations in the NOD2 gene are associated with susceptibility to Crohn's disease, ulcerative colitis, psoriatic arthritis and sarcoidosis [9].

Another important mechanism of the adaptive immune system is the recognition of foreign peptides bound to major histocompatibility complex (MHC) molecules (pMHC) via the specific binding by T cell receptors [10]. Since this bond is weak, additional molecules are necessary to stimulate the efficiency of the T cell activation process. One of these costimulatory molecules is cluster of differentiation 2 (CD2), a transmembrane cell surface glycoprotein expressed on T cells, thymocytes, and NK cells that act as an effector of T cell activation and adhesion [10,11].

In mature T cells, CD2BP1 (CD2-binding protein 1, also known as PSTPIP1 (Proline-serine-threonine phosphatase-interacting protein 1)) is involved in recruiting PTP-PEST (protein tyrosine phosphatases - proline, glutamic acid, serine and threonine-rich region) to the cytoplasmic tail of CD2, resulting in the downregulation of the adhesion process by regulating the dephosphorylation of relevant substrates [11–13]. Mutations in the PSTPIP1 gene influence the ability of PSTPIP1 to phosphorylate proinflammatory pyrin domains [13–15] [Fig. 2]. This downregulation leads to the accumulation, activation and reduced inhibition of the inflammasome, release of IL-1β and IL-18, and activation of caspase 1 [1,14,15]. This may alter T-cell activity, resulting in an influx of neutrophils to inflammatory sites which leads to an exaggeration of the signal for proliferation and infiltration of inflammatory initiator cells, modifying apoptotic pathways and inhibiting cell clearance [12]. These mechanisms may explain one possible pathogenetic pathway of PGAAIS.

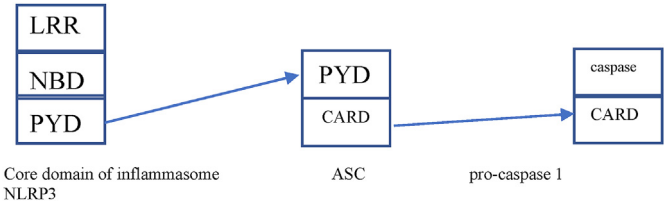

Fig. 1. Example of domain organization and activation of the inflammasome, containing the core domain NLRP3 (left), ASC (middle) and pro-caspase 1 (right) is shown.
Left: Each member of the NLR family contains a LRR (carboxy-terminal leucine-rich repeat) and a NBD (nucleotide-binding domain). Additionally, they contain a PYD (pyrin domain) or a CARD (caspase activation and recruitment domain). Middle: Another key player in the activation of caspase 1 is the adaptor apoptosis-associated speck-like protein containing a CARD (ASC), which contains a PYD and a CARD. Upon activation, NLRP3 first interacts with ASC via the PYD. The CARD domain of ASC recruits the CARD domain of pro-caspase-1 (right). These proteins form the NLRP3–ASC–pro-caspase-1 complex (also known as NLRP3 inflammasome). Activated caspase 1 converts the cytokine precursors pro-IL-1β and pro-IL-18 into IL-1β and IL-18 [7,58].

It has been shown that the location of the mutation site within the PSTPIP1 protein varies [see Table 1].

The rare autoinflammatory diseases hypercalprotectinemia and hyperzincemia (Hz/Hc) have also been reported to be linked to mutations in the PSTPIP1 gene [16]. Hz/Hc is characterized by severe systemic and cutaneous inflammation, hepatosplenomegaly, arthritis, pancytopenia, failure to thrive and extremely high myeloid-related protein 8 (MRP8, S100A8) and 14 (MRP14, S100A9) serum levels [16]. MRP8 and MRP14 are endogenous ligands of Toll-like receptor (TLR) 4 [16]. The term PSTPIP1-associated myeloid-related proteinemia inflammatory syndrome (PAMI syndrome) has been proposed for this condition [16].

As described above, mutated PSTPIP1 shows increased binding to pyrin [12,15]. Pyrin is encoded by the MEFV gene in inflammatory cells and is part of the inflammasome [7,17]. Mutations in the MEFV gene are associated with typical symptoms of recessive familial Mediterranean fever [9,15]. FCAS, MWS and neonatal-onset multisystem inflammatory disease are autoinflammatory syndromes caused by mutations in the CIAS1 gene, which encodes cryopyrin (NLRP3) [15]. These syndromes are summarized as a cryopyrin-associated periodic syndrome (CAPS) [rev. in 14].

Nicastrin is part of the gamma secretase protein complex, one of the proteases involved in processing amyloid precursor protein to amyloid beta, which plays a pathogenic role in Alzheimer's disease [18]. Gamma-secretase is a multicomponent protein complex serving as an aspartyl protease with intramembrane domain-cleaving activity [18].

Mutations in the above mentioned genes are reported to be associated with PGAAIS. These syndromes include PAPA, PASH, PAPASH, PsA-PASH, PASS and PAC and other subsets of PGAAI symptoms. The clinical and molecular findings of the established syndromes are presented below.

2. Pyoderma gangrenosum-associated autoinflammatory syndromes: clinical and molecular findings

The clinical phenotypes PGAAIS are ill-defined [19].

2.1. PAPA (pyogenic arthritis, pyoderma gangrenosum and acne conglobata) syndrome

The autosomal-dominantly inherited PAPA syndrome was first described by Lindor in 1997 [20].

Clinically, PAPA syndrome is characterized by the presence of pyogenic arthritis, pyoderma gangrenosum and acne conglobata [21]. The severity of individual symptoms may vary [20], leading to the term PAPA-like syndrome in which cutaneous manifestations, such as pyoderma gangrenosum and acne fulminans, predominate [22].

However, a homozygous PSTPIP1 mutation, which may define a novel form of a recessively inherited PAPA-like syndrome, has been reported [22].

Mutations in the CD2BP1/PSTPIP1 gene have been shown to be linked with PAPA syndrome [Table 2] [12,13,16,22–29]. Hong et al. reported a case without mutation in the CD2BP1/PSTPIP1 gene [30].

Treatment with the tumor necrosis factor (TNF)-alpha antagonists infliximab, etanercept or adalimumab has been effective [23–25,31–34]. Other options include the IL-1 receptor antagonist anakinra and the

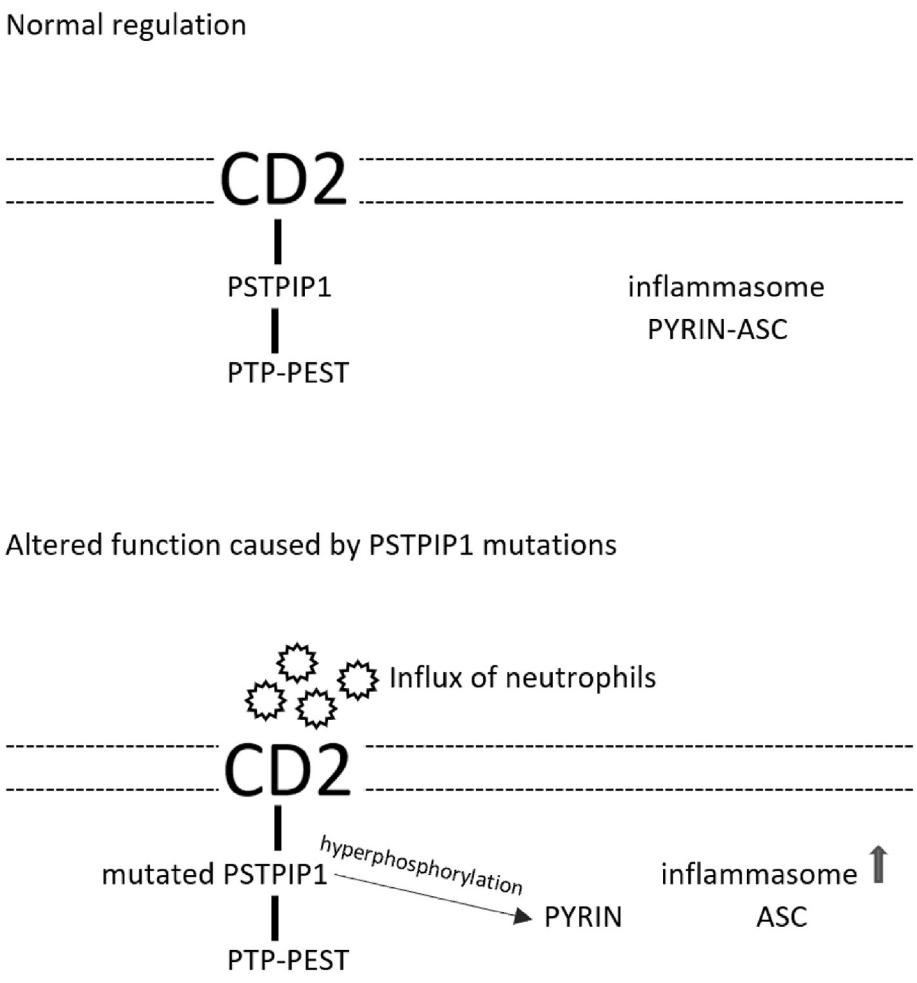

Fig. 2. T-cell membrane is shown. CD2BP1/PSTPIP1 is involved in recruiting PTP-PEST to the cytoplasmic tail of CD2, resulting in the downregulation of the adhesion process by regulating the dephosphorylation of relevant substrates [11,12]. Mutations in the PSTPIP1 gene influence the ability of PSTPIP1 to phosphorylate proinflammatory pyrin domains. This downregulation leads to the accumulation, activation and reduced inhibition of the inflammasome, release of IL-1β and IL-18, and activation of caspase 1 [rev. in 1,14,15]. This may alter T-cell activity, resulting in an influx of neutrophils to inflammatory sites which leads to an exaggeration of the signal for proliferation and infiltration of inflammatory initiator cells, modifying apoptotic pathways and inhibiting cell clearance [12]. These mechanisms may explain one possible pathogenetic pathway of PGAAIS.

anti–interleukin 1 monoclonal antibody canakinumab [22,24,35,36] as well as less targeted drugs like corticosteroids, tacrolimus, methotrexate, isotretinoin, mycophenolate and antibiotics (such as dapsone or minocycline).

2.2. PASH (pyoderma gangrenosum, acne, and suppurative hidradenitis) syndrome

The present of pyoderma gangrenosum, acne, suppurative hidradenitis has been described as PASH syndrome [Table 3] [37–40].

Mutations in the NLRP3, PSTPIP1 (CD2BP1), NOD2, MEFV and/or NCSTN genes have been shown to be associated with PASH syndrome [Table 2] [40–43].

Reported successful treatment includes infliximab, anakinra, prednisolone, azathioprine, cyclosporine and prolonged targeted antibiotic therapy, eg. dapsone for 20 months [37,41,44–46].

2.3. PAPASH (pyoderma gangrenosum, acne, suppurative hidradenitis and pyogenic arthritis) syndrome

Clinically, PAPASH syndrome is characterized by the presence of pyoderma gangrenosum, acne, suppurative hidradenitis and pyogenic arthritis [9]. Associations with mutations in PSTPIP1, IL1RN (interleukin 1 receptor antagonist) and MEFV genes have been reported [Table 2] [9,41].

Reported successful treatment include infliximab, methotrexate, adalimumab and anakinra [9,19,41,47].

2.4. PsAPASH (pyoderma gangrenosum, acne, suppurative hidradenitis and psoriatic arthritis) syndrome

Clinically, PsAPASH syndrome is characterized by the presence of pyoderma gangrenosum, acne, suppurative hidradenitis and psoriatic arthritis [39]. To date, no mutations have been reported to be linked with PsAPASH syndrome [48]. It has been speculated that mutations in PSTPIP1 gene could cause PsAPAH [48]. Successful treatment with adalimumab and methotrexate has been reported [19,39,48].

2.5. PASS (pyoderma gangrenosum, acne conglobata, suppurative hidradenitis and axial spondyloarthritis) syndrome

In 2012, Bruzzese et al. presented a case of pyoderma gangrenosum, acne conglobata, suppurative hidradenitis and axial spondyloarthritis and termed this combination of symptoms PASS syndrome [49]. However, a link between PASS syndrome and PSTPIP mutations has not yet been found [49]. Reported successful treatment include adalimumab with sirolimus or methotrexate, anakinra, infliximab, periodic antibiotic and/or steroid treatment [19,49,50].

2.6. PAC (pyoderma gangrenosum, acne and ulcerative colitis) syndrome

Clinically, PAC syndrome is characterized by the presence of pyoderma gangrenosum, acne and ulcerative colitis [51]. A mutation in the PSTPIP1 gene has been described [Table 2] [51].

Successful treatment with 100 mg of anakinra taken daily, 10 mg of prednisone taken every other day and 40 mg of isotretinoin taken three times a week has been reported [51].

Table 1
Protein structure of PTSTPIP1.

amino acid	schematic protein structure	Binding location of downstream interaction proteins	reported location site of mutation
1-122 123-288 320-340 359-416	N FCH CDC15-like PEST SH3 C	PTP-PEST; Pyrin c-Abl; WASP; CD2; Pyrin; FASL	**PAPA** (p.A230T; p.D246N; p.E250Q; p.E256G;p.D266N) **PAMI** (p.E250K;p.E257K) **PAPASH** (p.E277D) **PAPA-like** (p.G258A homozygous) **PG** (p.G258A heterozygous) **PAC** (p.G403R) **PASH** (p.R405C)

The protein structure of PTSTPIP1 with its corresponding amino acid sites, the binding location of downstream interaction proteins and reported location site of mutation within the protein are shown.
c-Abl: c-Abelson tyrosine kinase; CD2: cluster of differentiation 2; FASL: Fas ligand; FCH: Fes/CIP4 homology; PEST: proline, glutamic acid, serine and threonine rich region; PTP-PEST: protein-tyrosine phosphatase with C-terminal rich in proline, glutamic acid, serine, and threonine residues)-type motif; SH3: Src-homology 3, WASP: Wiskott–Aldrich Syndrome protein.
Modified from Ref. [56,57].

2.7. Overlap and undefined syndromes

In addition to the syndromes mentioned above, some alternative subsets of symptoms have been described. In a recent article, Schäffler et al. presented a family whose members had a confirmed mutation in the PSTP1P gene [52]. A female from this family suffered from ulcerative colitis, pyogenic arthritis, acne, suppurative hidradenitis and an overlap syndrome of autoimmune hepatitis and primary sclerosing cholangitis. One of her sons had pyogenic arthritis and acne. Another son suffered from Crohn's disease and PA [52]. However, based only on the proof of mutation in the PSTP1P gene, the authors concluded that this family exhibited PAPA syndrome, although none of the family members were described as having PG [52].

Ursani et al. presented a patient with acne, suppurative hidradenitis, pyoderma gangrenosum and arthritis, corresponding to PAPASH syndrome but also with ulcerative colitis and the presence of cANCA [53].

Niv et al. described a case of PG, acne, and SH corresponding to PASH syndrome with recurrent leukocytoclastic vasculitis. However, they found no mutation in the PSTP1P gene [54].

Marzano et al. presented a patient with PASH syndrome and Crohn's disease who attained partial remission with adalimumab [41]. They also described a patient with acne, PG, SH, spondyloarthritis (corresponding to PASS syndrome) and osteitis who attained partial remission with infliximab [41]. However, they classified this combination of symptoms as an overlap syndrome of PASH and SAPHO syndrome [41]. They found a mutation in the PSMB8 (proteasome [prosome, macropain] subunit beta type 8) gene in this patient [41]. SAPHO syndrome was described in the 1970s, and its symptoms include synovitis, acne, pustulosis, hyperostosis and osteitis [37–41].

Murphy et al. presented a patient with PASH syndrome and ulcerative colitis who was successfully treated with adalimumab [55]. Rarer subsets of the common autoinflammatory phenomena can be named accordingly [Table 3].

Table 2
Reported mutations in genes involved in the pathomechanism in PGAAIS with the corresponding protein alteration and associated distinct PGAAIS syndromes are shown.

Gene	Mutation	Protein Change	PGAAIS	Reference
PTSPIP1/ CD2BP1	c.1034 A > G	p.Y345C	PASH	[43]
	c.1213C > T	p.R405C		[40]
	c.773G > C	p.G258A homozygous	PAPA-like	[22]
	c.904G > A	p.A230T	PAPA/FRA	[12,25,
	c.964G > C	p.E250Q		26]
	n/a	p.V344I	PAPA	[27]
	n/a	p.E256G		
	n/a	p.G904A		
	n/a	p.E256G		[16]
	n/a	p.D266 N		[28]
	c.736G > A	p.D246 N		[29]
	n/a	p.E250K		[13,23, 24]
	n/a	p.E250K	PAMI	[16]
	n/a	p.E257K		
	n/a	p.G258A heterozygous	PG	[4]
	c.1207G > C	p.G403R	PAC	[51]
	c.831G > T	p.E277D	PAPASH	[9]
NCSTN	c.344_351del	p.T115 N*20	PASH	[42]
MEFV	Chr16:3293880 A > G	p.I1591T	PASH	[41]
	chr16:3293407 T > C	p.M694V	PAPASH	
	chr16:3293310 A > G	p.V726A		
NOD2	Chr16:50745926C > T	p.R702W	PASH	
	Chr16:50756540G > C	p.G908R		
NLRP3	Chr1:247588858C > A	p.Q703K	PASH	
IL1RN	chr2:113890284G > A	p.A106T	PAPASH	
PSMB8	Chr6:32811752C > T	p.G8R	Overlap PASS/ SAPHO	

3. Introduction of a short guide for the easy identification of PGAAIS and demonstrations for its use in clinical practice using two case reports: a patient with PASS syndrome and a patient with an overlap syndrome

Because distinguishing individual PGAAIS may be challenging in clinical practice, we have developed a short guide for easy diagnosis [Fig. 3] and demonstrate its use using two case reports of two white females. This guide is based on a four-step questionnaire about the most frequent symptoms of possible PGAAIS. The first three criteria are met by presentation with symptoms of PG, acne and HS, and the fourth criterion is presentation with symptoms of axial spondyloarthritis, psoriatic arthritis, pyogenic arthritis, ulcerative colitis, Crohn's disease or leukocytoclastic vasculitis. We demonstrate the application of this new guide on two case reports.

The first patient was a female, born in 1988, who first presented to our dermatological outpatient clinic in 2009. She was diagnosed with suppurative hidradenitis, and most of the skin lesions, which were predominantly localized in both axillae and the genital area (Hurley stage III), were widely excised. Wound healing was attained without any complications. The patient was, at the time of initial treatment, a non-obese ex-smoker who used oral contraceptives with no other reported relevant risk or trigger factors for SH. In 2011, she was diagnosed with ankylosing spondylitis, which was successfully treated with etanercept for 5 months. The therapy was stopped due to an "infected wound". Shortly thereafter, the first skin ulceration appeared spontaneously around her right ankle. Considering the clinical presentation and because the histological and laboratory findings (including blood analysis for

Table 3
Overview of the different possible combinations of symptoms with abbreviations that define a specific PGAAIS syndrome are shown. The abbreviations PASH, PAPA, PAPASH, PsAPASH, PAC and PASS already accepted in the literature are shown on the left. On the right, acronyms were suggested for symptom constellations that have not been described as a syndrome so far.

	Accepted acronyms						*Proposed acronyms*					
Clinical symptoms with abbreviation	**PASH**	**PAPA**	**PAPASH**	**PsAPASH**	**PAC**	**PASS**	*PAPASC [53]*	*VPASH [54]*	*PASCD [41]*	*PASC [55]*	*PAASCH/PSC [53]*	*PsAPSC*
psoriatic arthritis (PsA)	-	-	-	✓	-	-	-	-	-	-	-	✓
pyogenic arthritis (PA)	-	✓	✓	-	-	-	✓	-	-	-	✓	-
pyoderma gangrenosum (P)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	-	✓
Acne (conglobate) (A)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	-
suppurative hidradenitis (SH or S)	✓	-	✓	✓	-	✓	✓	✓	✓	✓	✓	✓
Ulcerative Colitis (C)	-	-	-	-	✓	-	✓	-	-	✓	✓	-
Spondyloarthritis (S)	-	-	-	-	-	✓	-	-	-	-	-	-
leukocytoclastic vasculitis (V)	....	-	-	-	-	-	-	✓	-	-	-	-
Crohn´s disease (CD)	-	-	-	-	-	-	-	-	✓	-	-	✓
autoimmunhepatitis and primary sclerosing cholangitis (H/PSC)	-	-	-	-	-	-	-	-	-	-	✓	-

HIV, hepatitis, ANAs, ANCAs, paraprotein and lymphocyte subpopulations) did not reveal evidence of any other disease, pyoderma gangrenosum was diagnosed. Because she presented with no acne, PGAAIS were excluded as diagnoses.

In agreement with the generally accepted treatment recommendations for PG, we initiated an intravenous high-dose pulse treatment with methylprednisolone (250 mg/day for 3 days every four weeks) as the first-line therapy. Additionally, we prescribed oral treatment with cyclosporine A (200 mg/day) and methylprednisolone (16 mg/day between pulse treatments). For external therapy, antiseptic treatment was combined with tacrolimus ointment 0.1%. Because the symptoms of spondylitis showed little improvement, the oral treatment with cyclosporine was discontinued, and etanercept (50 mg s.c./week) was reintroduced. By 2015, the PG lesions had spread to both shanks, and the suppurative hidradenitis flared again in the axillary and groin areas. The patient presented seemingly ill, with two very painful inflamed and purulent ulcers, one on each shank, and with disseminated erythematous acne papules and scarring on both shoulders/axillae. The blood analysis revealed elevated C-reactive peptide (52.0 mg/dl; ref: 0–5), thrombocytosis (453 × 109/l; ref: 140–400) and leukocytosis (19.9 × 109/l; ref: 4.0–10.0), especially neutrophilia (72%; ref: 50–65) and lymphopenia (17%; ref: 25–45).

Due to the new clinical findings of acne lesions, we reconsidered the diagnosis and defined the clinical picture as PASS syndrome. To confirm the diagnosis, we recommended mutational analysis of genes linked to the pathogenesis of PGAAIS. However, the patient did not agree to perform this genetic examination. We then started therapy with adalimumab, which had been shown to be effective and safe for the treatment of both SH and PG (initial dose 160 mg s.c., followed by 80 mg and 40 mg for maintenance therapy). External therapy was conducted with 0.1% betamethasone valerate and 1% gentamicin containing ointments and various exudate-managing hydrocolloids, depending on the general wound condition. Along with this therapy, we observed the quick improvement of all clinical symptoms. When using the 4-step guide, the first 3 criteria (presence of pyoderma, acne and suppurative hidradenitis), which are the cardinal symptoms of PGAAIS, were met. The fourth criterion in this case was axial spondylarthritis. Following this guide led to the diagnosis of PASS syndrome. This example illustrates that PGAAIS are ill-defined clinical diagnoses. Genetic testing is not required for proper assessment and treatment.

The second patient was a female born in 1966 who first presented to our dermatological outpatient clinic in 2018. She had suffered from Crohn's disease since 1996. In 2004, she was diagnosed with severe SH at Hurley stage IV. In 2010, she underwent en bloc resection of a skin lesion in the left groin, which included the left labia majora. In 2017, a so-called LOOP thread inlay procedure was performed in the genital area.

In February 2018, therapy with a TNF-alpha inhibitor infliximab was initiated and replaced adalimumab due to initial adverse effects. Under treatment with adalimumab, the intestinal symptoms and skin lesions remained stable. After May 2018, weekly lAight therapy® (light and radiofrequency) of the SH area was performed. Unfortunately, under weekly doses of adalimumab, the known psoriasis vulgaris worsened, and she developed PG on both lower legs. For the treatment of PG, systemic steroid therapy was started, which ameliorated the PG lesions but worsened the SH areas.

When the patient first presented to our dermatological outpatient clinic in December 2018, she was a nonobese smoker. Due to joint pain in her left foot, we performed X-rays of both feet, which showed signs of psoriatic arthritis. After consultation with gastroenterologists, we recommended magnetic resonance imaging of both legs and the pelvis to determine the extent of the abscess and fistula. We also proposed systemic therapy with interleukin 12 and 23 inhibitor ustekinumab at a dosage established for Crohn's disease. The patient was undecided about accepting the treatment, and the course of the disease remains unclear because she did not return to our clinic.

To our knowledge, the second patient described represents the first case of a combination of symptoms that included psoriatic arthritis, PG, SH and Crohn's disease. We therefore propose the term PsAPSC [Table 3]. When using the 4-step guide, the first criterion (presence of a PG) was fulfilled. The second criterion (acne) was not present. Nevertheless, a PGAAIS was suspected due to the existing suppurative hidradenitis, psoriatic arthritis and Crohn's disease. The guide led specifically to the presence of a PsAPSC syndrome. This case illustrates that, even in the absence of a cardinal symptom (such as acne in this case), PGAAIS may still be present.

4. Outlook and discussion: challenge and promise - treatment and new perspectives for the management of pyoderma gangrenosum-associated autoinflammatory syndromes

In the last decade, new findings have significantly improved our understanding of the molecular pathogenesis of autoinflammation,

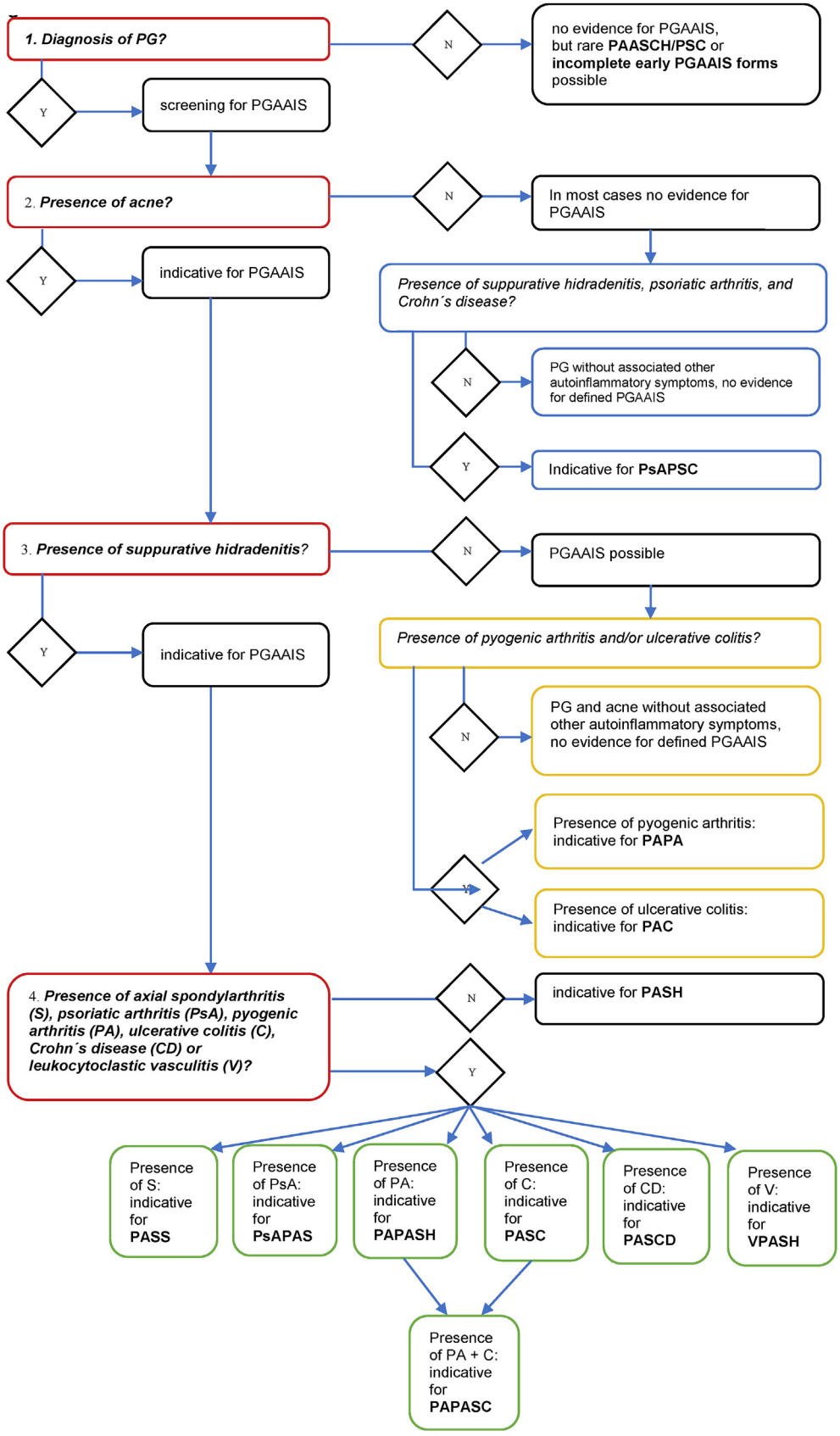

Fig. 3. Short guide (four-step algorithm) for the easy identification and definition of pyoderma gangrenosum-associated autoinflammatory syndromes in clinical practice. This guide is based on a four-step questionnaire about the most frequent symptoms of possible PGAAIS. Beginning with the presence of PG, presence of acne (A), suppurative hidradenitis (SH) and as fourth step, the presence of axial spondylarthritis (S), psoriatic arthritis (PsA), pyogenic arthritis (PA), colitis ulcerosa (C), Crohn's disease (CD) or leukocytoclastic vasculitis (V).

resulting in the identification and definition of several PGAAIS. Despite phenotypic heterogeneity of distinct PGAAIS entities, these syndromes seem to share similar underlying pathomechanisms. The improvement of our understanding of pathomechanisms and the identification of relevant genetic variants are preconditions for the development of therapeutic strategies.

Although great progress has been made in recent years in identifying several PGAAIS as distinct entities, in unraveling their underlying molecular mechanisms and in developing pathogenesis-oriented targeted therapies, their clinical management remains challenging. The current treatment focus is on a relatively unspecific immunosuppressive regimen. despite the combination of different immunosuppressants, some cases show no or little clinical improvement. The risk of serious infections must also be mentioned.

These aspects are particularly true with respect to individual symptoms, such as PSC. PSC has been described in several patients, but its pathogenesis remains largely unclear. None of the discussed genes have been proven to play a role. Similar to SAPHO syndrome, in which recurrent inflammation leads to chronic osteomyelitis, one hypothesis suggests that PSC plays a role through recurrent cholangitis and bacterial invasion.

The pathogenesis of Crohn's disease and ulcerative colitis is better known. In addition to complex barrier disease, NOD2 seems to be involved in inflammatory bowel disease, which also manifests several times in the course of PGAAIS.

There is a large variety of autoinflammatory, let alone autoimmune diseases. Two patients with the same diagnosis may experience very different courses of symptoms and treatment response. Additionally, these ailments tend to occur in multitudes in individual patients. This suggests an "inflammatory phenotype" that is on one hand genetically determined, on the other hand strongly influenced by a multitude of individual factors.

Interestingly, in a recent analysis of eight patients with PAPASH, PsAPASH or PASS made by Gottlieb et al. showed that seven out of eight patients had positive serological detection for anti-Saccharomyces cerevisiae antibodies (ASCA) as well as evidence of subclinical digestive tract inflammation and refractory course under immunosuppressive therapies [19]. The authors conclude that these facts could be explained by an underlying digestive dysbiosis [19].

To provide physicians of various disciplines with a convenient tool for easy assessment of individual PGAAIS in clinical practice, we have developed a short guide that is based on a four-step guide [Fig. 3]. Here, we demonstrate its use as a diagnostic tool in cases of PGAAIS. Treatment of PG and related PGAAIS can be difficult, as the therapeutic response to particular therapies varies greatly, and the outcome is not known in most cases. While some investigators, including Saraceno et al. [39], have previously reported successful treatment of PASS syndrome using treatment regimens primarily targeting SH (antibiotics, isotretinoin and dapsone), in our first patient, we focused on the latest on-label SH treatment with adalimumab, as this antibody may also effectively target spondyloarthritis. Interestingly, in contrast to the patient presented by Bruzzese et al. [49] who did not respond to etanercept therapy, a fusion protein predicted to bind free TNF and receptor-bound TNF was much less effective than adalimumab, which was developed based on the receptor-blocking principle. For instance, in terms of her psoriatic arthritis and plaque psoriasis, our first patient showed an impressive and fast remission of dermatological and rheumatological symptoms within a hospitalization period of only 14 days, rendering her quickly eligible for discharge and further full outpatient management. Hence, according to our experience and the published literature, TNF-alpha inhibitors, such as adalimumab are promising single agents for the effective and safe therapy of PG and at least of some symptoms of associated PGAAIS. Potential new molecular treatment regimens include IL-1 antagonists in combination with TNF-alpha antagonists, Janus kinase (JAK)- and methylenetetrahydrofolate-mediated signaling pathway inhibitors and IL-17 antagonists established for psoriasis therapy [rev. in 1,31]. However, the effects of these promising new molecule-targeting therapeutics for ameliorating PGAAIS remain to be evaluated in future studies.

It is still an open question whether different mutations, e.g., in the PSTPIP1 gene, are associated with clinically variable PGAAIS, which might require the use of a single first-line treatment or even diverse, if not individualized, strategies [9,13,41].

Conflict of interest:

The authors declare that there is no conflict of interest.

Acknowledgements

None.

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