Vasculitis in autoinflammatory diseases

Emilie Bohbot and Eldad Ben-Chetrit

Purpose of review
This review aims to explore the relationship between autoinflammatory diseases (AIDs) and vasculitis, with a focus on recently identified syndromes and newly published data since 2016.

Recent findings
While the connection between innate immune dysregulation and systemic inflammation is well established in AIDs, the occurrence of vasculitis in these disorders remains underrecognized and often misclassified. We discuss vasculitic manifestations in a wide range of AIDs, including familial Mediterranean fever, DADA2, HA20, VEXAS, CAPS, TRAPS, HIDS/MKD, Blau syndrome, and others. Each condition presents a unique pattern of vascular involvement, ranging from incidental cutaneous findings to life-threatening systemic vasculitis. The underlying mechanisms often involve overactivation of inflammatory pathways such as IL-1β, or NF-κB, and in some cases, novel genetic mutations affecting non-inflammatory pathways such as purine metabolism. The histologic, clinical, and genetic features often differ from classic vasculitic syndromes.

Summary
Recognizing vasculitis in the context of AIDs is critical for early diagnosis, especially in pediatric patients or those with treatment-resistant or atypical presentations. Genetic testing should be considered in such cases. Understanding these distinct disease patterns allows physicians to tailor management strategies, including biologic therapies or hematopoietic stem cell transplantation, improving outcomes in these complex and often severe disorders.

Keywords
autoinflammatory diseases, deficiency of adenosine deaminase 2, familial Mediterranean fever, vasculitis, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome

INTRODUCTION

The term autoinflammatory disease (AID) has been used since 1999 to describe a group of disorders of the innate immune system characterized by recurrent episodes of inflammation. In contrast to autoimmune diseases, in AIDs, there is no primary role for specific autoreactive T- or B-lymphocytes or autoantibodies in their pathogenesis [1,2]. Some of these diseases, such as familial Mediterranean fever (FMF), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), cryopyrin-associated periodic syndromes (CAPS), and hyper-immunoglobulin D syndrome/mevalonate kinase deficiency (HIDS/MKD), are monogenic in origin and lead to hereditary periodic fever syndromes [3]. Others may have polygenic or multifactorial etiologies, such as periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA), or Behcet's syndrome (BD).

Vasculitis refers to inflammation of blood vessel walls with subsequent damage to organs and tissues. It may be a dominant feature of some autoinflammatory disorders, such as adenosine deaminase 2 deficiency (DADA2) and haploinsufficiency of A20 (H20) [4]. In other autoinflammatory disorders, the association between vasculitis and autoinflammation is not always obvious.

In this review, we describe the prevalence and types of vasculitis in some AIDs, focusing on new diseases and recent evidence published since our last review in 2016 [5▪].

VASCULITIS IN AIDs

Familial Mediterranean fever

FMF is the most common AID, presenting with recurrent episodes of fever, serositis, and rash lasting

Rheumatology Unit, Division of Medicine, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

Correspondence to Eldad Ben-Chetrit, MD, Professor of Medicine (Rheumatology), Rheumatology Unit, Hadassah-Hebrew University Medical Center, POB: 12000, Jerusalem, Israel. Tel: +972 2 6777111; e-mail: eldadbc2912@gmail.com

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KEY POINTS

- Vasculitis is a key feature in several autoinflammatory diseases (AIDs) such as familial Mediterranean fever, deficiency of adenosine deaminase 2 (DADA2), HA20, and vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome (VEXAS), and may be underrecognized or misclassified in clinical practice.
- The patterns of vasculitis in AIDs often differ from classical forms, with distinct clinical features, histopathology, and genetic backgrounds, requiring tailored diagnostic approaches.
- Genetic testing should be considered in patients with early-onset, atypical, or treatment-refractory vasculitis, especially when associated with systemic inflammation or family history.
- Targeted therapies, including interleukin-1 and tumor necrosis factor inhibitors, JAK inhibitors, and hematopoietic stem cell transplantation, may be necessary and effective in managing vasculitic manifestations in AIDs.
- Raising clinical awareness of vasculitis within AIDs can enhance diagnostic accuracy and patient outcomes, especially in pediatric groups and complex multisystem inflammatory cases.

24–72 h [6]. It is associated with pathogenic mutations in the *MEFV* gene, which encodes pyrin. The characteristic skin rash of FMF, erysipelas-like erythema, is not vasculitic. However, protracted febrile myalgia (PFM), a severe form of disabling myalgia with high fever in FMF patients, may have a vasculitic etiology. Previous skin and muscle biopsies failed to show vasculitis, but a recent study revealed vasculitis involving the fasciae and myofascial areas, with minimal muscle involvement [7,8].

The most common vasculitides described in FMF are Henoch–Schonlein purpura (HSP)/immunoglobulin A vasculitis (IgAV) and polyarteritis nodosa (PAN), with a prevalence of 2.7–7% and 1%, respectively [9]. In a large pediatric FMF cohort including 1687 patients, IgAV was the second most common comorbid condition, after juvenile idiopathic arthritis [10]. *MEFV* mutations have also been found to be more common among IgA vasculitis patients [11▪]. IgA-associated vasculitis in the context of FMF often follows an atypical course, characterized by a younger age of onset, frequent recurrences, and rashes that may appear in uncommon locations such as the face and trunk [12]. Compared to patients with IgAV alone, IgAV-FMF patients had significantly higher gastrointestinal and renal involvement, a higher median pediatric vasculitis activity score, and a greater need for steroids, cyclophosphamide, IVIG, and plasma exchange therapy [13]. Furthermore, the IgAV-FMF patients seem to have an increased prevalence of intussusception [14]. It seems that *MEFV* variants, on exon 10, trigger a more severe form of IgAV [13,15▪]. In cases where skin biopsy was performed, histological examination revealed leukocytoclastic vasculitis without IgA deposition. This raised the hypothesis that HSP-like vasculitis may represent a distinct manifestation of FMF itself [12] (Table 1).

As for PAN, FMF-PAN patients have an earlier onset of disease, increased male-to-female ratio, more abdominal pain, more frequent perirenal hematomas, glomerular and central nervous system involvement compared to PAN alone [14,16]. Overall, it has a more favorable prognosis. Due to these distinctive features, it is not clear if these patients suffer from classical PAN or if these clinical findings represent a unique vasculitis specific to FMF [14] (Table 2).

Large vessel vasculitides such as Takayasu arteritis (TAK) or Cogan syndrome have been rarely described to co-occur with FMF [9]. There are 5 case reports of FMF together with TAK; most patients carried pathogenic variants of p.M694V. A recent report describes a 29-year-old man treated with tocilizumab, controlling both diseases [17].

Additionally, Behcet's syndrome (BS) may co-occur with FMF, which may be partially explained by the common ethnic and geographic distribution of these diseases. In these patients, cutaneous, gastrointestinal, and central nervous system involvement is more frequent than in isolated Behcet's. Interestingly, in cohorts of BS, FMF is more common than in the general population of the same region [9].

Finally, although FMF is a relapsing disease, most reports of vasculitis in FMF patients describe single episodes with good response to immunosuppressive therapy [18].

Cryopyrin-associated periodic syndromes

Cryopyrin-associated periodic syndromes (CAPS) encompasses a group of disorders historically divided into familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS), and neonatal onset multisystem inflammatory disease/chronic infantile neurological cutaneous articular syndrome (NOMID/CINCA). All three disorders are associated with mutations in the *NLRP3* gene, coding for the NLRP3 protein, or cryopyrin [5▪]. These syndromes are characterized by periodic fever, urticarial rash, arthritis, conjunctivitis, and neurological involvement, including hearing loss and aseptic meningitis [11▪]. The typical skin lesion is a neutrophilic urticarial

Table 1. Comparison of IgA vasculitis (HSP) with and without FMF

Features	IgA vasculitis (HSP) only	IgA vasculitis + FMF
Age of onset	Typical childhood onset	Younger than usual
Clinical course	Generally self-limited	Atypical, recurrent episodes
Distribution of rash	Buttocks, lower extremities	Includes face and trunk (atypical)
Gastrointestinal involvement	Common	More frequent and severe
Intussusception	Rare	Increased prevalence
PVAS (Pediatric Vasculitis Activity Score)	Lower median	Higher median
CRP (C-reactive protein)	Lower median	Higher median
Treatment requirements	Less intensive (steroids may suffice)	More intensive: steroids, cyclophosphamide, IVIG, plasma exchange
Histology on skin biopsy	Leukocytoclastic vasculitis with IgA deposition	Leukocytoclastic vasculitis without IgA deposition
MEFV mutations	Absent or incidental	Common, especially exon 10 variants
Possible interpretation	Classic IgAV	May represent FMF-related vasculitis, possibly distinct from classic IgAV

IgA, immunoglobulin A; IgAV, immunoglobulin A vasculitis.

dermatosis without vasculitis. There are case reports of CAPS patients with small-vessel vasculitis of the skin and testis [5▪], retinal vasculitis [19,20], and one report of a young CINCA patient with pauci-immune crescentic glomerulonephritis [21]. A recent review described a Muckle–Wells patient who developed recurrent fever and severe vasculitis with intestinal perforations shortly after birth and died at age 15 from alveolar hemorrhage [22]. Consequently, vasculitis is not considered a primary feature of CAPS but may occur as a coincidental or coexisting condition.

Hyper-immunoglobulin D syndrome/ mevalonate kinase deficiency

Hyper-immunoglobulin D syndrome/mevalonate kinase deficiency (HIDS/MKD) is characterized by recurrent fever, rash, lymphadenopathy, and gastrointestinal manifestations; in severe forms, it results in Mevalonic aciduria, causing neurological, ocular, and auditory disorders [4,18]. The most common types of rash are erythematous macules, papules, nodules, and urticarial lesions [5▪,11▪]. In a cohort of 44 patients, 10 underwent skin biopsy, which

Table 2. Comparison of PAN with and without FMF

Feature	Isolated PAN (classical PAN)	PAN associated with FMF (FMF-PAN)
Age of onset	Later onset	Earlier onset
Sex ratio (male:female)	Balanced or slight male predominance	Increased male-to-female ratio
Abdominal pain	Present in some cases	More frequent and prominent
Perirenal hematomas	Rare	More frequent
Glomerular involvement	Uncommon (PAN usually spares glomeruli)	More frequent glomerular involvement
Central nervous system Involvement	Variable	More frequent CNS involvement
Prognosis	Variable, can be severe	More favorable prognosis overall
Nosological status	Recognized systemic medium-vessel vasculitis	Unclear: may represent a unique FMF-related vasculitis

CNS, central nervous system; FMF, familial Mediterranean fever; PAN, polyarteritis nodosa; TNF, tumor necrosis factor.

showed mild features of vasculitis [23]. There are additional case reports of HIDS patients with vasculitis in skin biopsies, strengthening the theory that cutaneous vasculitis may be a component of the disease [11▪]. Omoyinmi *et al.* recently published the case of a 2-year-old boy presenting with high fever, abdominal pain, diarrhea, rectal bleeding, and extensive purpuric and necrotic lesions predominantly in the lower limbs. Next-generation sequencing revealed compound heterozygous mutations in the *MVK* gene. The patient had a rapid and complete recovery with IL-1 blockade [24]. IgA vasculitis, Kawasaki-like, and Behcet-like syndromes were rarely described in MKD [15▪]. Taken together, these findings suggest that cutaneous vasculitis may represent one of the clinical manifestations of MKD, although its occurrence appears variable.

Tumor necrosis factor receptor-associated periodic syndrome

Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is an autosomal dominant disease associated with mutations in the *TNFRSF1A* gene. It presents as recurrent fever, serositis, periorbital edema, and myalgia with an overlying migratory rash [5▪,11▪]. Most skin biopsies do not show evidence of vasculitis. There is a case report of a 66-year-old female with TRAPS whose skin biopsy demonstrated small vessel vasculitis and panniculitis; she was positive for anti neutrophilic cytoplasmic antibody (ANCA) against neutrophil elastase [25]. There is also a report of a 4-year-old child with TRAPS who presented with a clinical syndrome consistent with IgA vasculitis [26]. In a review of adult patients diagnosed with autoinflammatory disease, one out of six TRAPS patients had leukocytoclastic vasculitis [27]. An additional autopsy report of a 26-year-old patient with TRAPS showed pronounced intimal thickening and medial hypertrophy of medium and small vessel walls without inflammatory cell involvement, suggesting a systemic vasculopathy [28]. These observations suggest that, although not a defining feature, vasculitic manifestations and systemic vasculopathy may occur in TRAPS patients.

Blau syndrome

Blau syndrome is a rare autoinflammatory disease associated with mutations in the *NOD2* (*CARD15*) gene, which causes autoactivation of the NF-κB pathway. The disorder presents with granulomatous dermatitis, arthritis, and uveitis, typically with onset before the age of four years [29▪,30]. A recent retrospective study of 47 Chinese patients with Blau syndrome demonstrated an incidence of vasculitis in 28% of patients, mostly with medium and large vessel involvement, such as the abdominal aorta, common carotid, and renal arteries [29▪]. In another series of 44 patients, 34% had cardiovascular involvement, which included Takayasu-like arteritis and/or cardiopathy. These patients had a higher incidence of recurrent fever and were treated more frequently with anti-TNFα agents [31]. Because of the insidious onset of vasculitis in Blau syndrome, clinicians should maintain a high level of suspicion for this complication [30]. Thus, Blau syndrome does have features of vasculitis, especially of large arteries.

Otulipenia/Otulin-related autoinflammatory syndrome

Otulipenia/OTULIN-related autoinflammatory syndrome (ORAS) is an autosomal recessive disease associated with mutations in the *FAM105B* gene, which encodes Otulin, a de-ubiquitinase acting as a down-regulator of the NF-κB signaling pathway. It was first described in 2016 by two separate groups [32,33]. Patients present with early-onset prolonged episodes of fever, failure-to-thrive, erythematous skin rash with nodules, lipodystrophy, arthralgia, abdominal pain, diarrhea, and lymphadenopathy [32–34]. The flares are prolonged and do not resolve without treatment [35]. Skin biopsies usually show different types of panniculitis and neutrophilic dermatoses, but small- and medium-sized vessel vasculitis has also been reported [32,34]. The disease seems to respond well to TNF inhibition [33,36].

Haploinsufficiency of A20

Haploinsufficiency of A20 (H20), is associated with heterozygous loss-of-function mutations in the *TNFAIP3* gene (coding for TNFα-induced protein 3, or A20). It was first described as a monogenic form of Behcet's syndrome, presenting with oral and genital ulcers, uveitis, skin, joint, and gastrointestinal inflammation [37]. H20 is also associated with autoimmunity (such as thyroiditis or systemic lupus erythematosus) [38,39▪,40] and lymphoproliferation [15▪,39▪]. As in BS, it may be accompanied by a variable vessel vasculitis with a preference for the venous side of the vasculature [15▪]. A review of 16 H20 patients revealed retinal vasculitis in one patient, CNS vasculitis in another, and CNS vasculitis together with pulmonary artery emboli in a third [38]. Another review of 45 patients compares H20 patients to classical BS, highlighting the differences between the two diseases; in H20, there is a reversal of the male-to-female ratio to 1 : 2, early appearance of symptoms with a median age of 5.5 years, recurrent fever, lower prevalence of HLA-B51, more

Table 3. Comparison: Behçet's syndrome vs. haploinsufficiency of A20 (HA20)

Feature	Behçets syndrome	HA20 (haploinsufficiency of A20)
Genetic basis	Polygenic; no single associated gene	Monogenic: heterozygous TNFAIP3 loss-of-function mutations
Pathogenic mechanism	Aberrant immune regulation; unclear etiology	Dysregulated NF-κB signaling due to defective ubiquitin-editing enzyme (A20)
Disease classification	Variable-vessel vasculitis, autoinflammatory/ autoimmune overlap	Monogenic autoinflammatory disease (AID), mimicking variable-vessel vasculitis
Age of onset	Typically, adolescence or early adulthood	Early-onset, often in childhood
Oral ulcers	Recurrent	Recurrent, typically early and prominent
Genital ulcers	Common	Common
Gastrointestinal symptoms	Present in some cases	Frequent
Fever	Not a consistent feature	Periodic fevers common
Arthritis/arthralgia	Often present	Polyarthralgia or arthritis is common
Skin involvement	Erythema nodosum, pseudofolliculitis, etc.	Cutaneous involvement common
Eye involvement	Uveitis, retinal vasculitis	Retinal vasculitis has been reported in some patients
CNS involvement	May occur	CNS vasculitis was documented in several patients
Thrombosis	Common (venous > arterial)	Pulmonary artery emboli reported; possible thromboembolic risk

CNS, central nervous system.

abdominal symptoms and less response to colchicine [40] (Table 3). Next-generation genetic sequencing should be considered for the work-up of young patients with suspected BS, especially those with a positive family history, early disease onset, or atypical features [41].

Deficiency of adenosine deaminase 2

Deficiency of adenosine deaminase 2 (DADA2) is a monogenic disease resulting from biallelic loss-of-function mutations in the *ADA2* gene. It is unique in the AIDs as the gene associated with the disease is not involved in inflammatory pathways but rather affects purine metabolism and signaling [42]. DADA2 causes small- and medium-vessel necrotizing vasculitis, mimicking classical polyarteritis nodosa (PAN) [15▪,43] (Table 4). The onset of disease is usually in childhood, with 77% of patients presenting before the age of 10 years [44]. The clinical features include livedo racemosa, digital ischemia, renal or gastrointestinal infarcts, early-onset stroke (ischemic and hemorrhagic), and systemic vasculitis. Indeed, the predilection of DADA2 for central nervous system involvement (up to 50–77% of patients) is a distinguishing feature from classic PAN [15▪,39▪]. In addition to vasculitis, DADA2

Table 4. Vasculitis in DADA2 vs. classic polyarteritis nodosa

Feature	DADA2-associated vasculitis	Classic PAN
Age of onset	Early childhood or infancy	Mostly adulthood
Genetic cause	ADA2 mutations	Idiopathic, possibly HBV-related
Stroke	Frequent (ischemic and hemorrhagic)	Rare
Response to TNF inhibitors	Excellent	Variable
Immunodeficiency	Present in some patients	Absent
Hematologic involvement	Frequent (anemia, neutropenia)	Uncommon

DADA2, deficiency of adenosine deaminase 2; PAN, polyarteritis nodosa; TNF, tumor necrosis factor.

may cause hematological disorders, such as pure red cell aplasia, refractory thrombocytopenia, and even bone marrow failure [15▪,42]. Furthermore, immune dysregulation may present as autoimmune lymphoproliferative syndrome (ALPS), lymphoma, or common variable immunodeficiency [15▪]. The wide phenotypic variability is partly explained by specific mutations and by residual enzyme activity of *ADA2*, with higher levels presenting with a vasculitic phenotype and lower levels with prominent hematological disease [39▪,42]. Retrospective studies have demonstrated a clear beneficial role of TNF inhibitors, particularly for stroke prevention, although this strategy is less effective for controlling hematological manifestations. Allogeneic hematopoietic stem cell transplantation (HSCT) is reserved for patients with severe inflammatory and hematological disease who have not responded to conventional therapy [42,45▪].

Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome

VEXAS, first described in 2020, is a highly heterogeneous monogenic disease associated with somatic mutations in the *UBA1* gene located on the X chromosome, occurring almost exclusively in men over the age of 50 [46]. It is a life-threatening disease with a 5-year mortality rate of 30–40% [47]. There are rare reports of women with VEXAS, the majority of which have Turner syndrome or acquired monosomy X [48]. Typical features of the disease are fever, weight loss, relapsing polychondritis, various cutaneous manifestations (livedo racemosa, neutrophilic urticarial dermatosis, erythema nodosum, Sweet-syndrome-like eruptions), ocular and lung involvement, progressive bone marrow failure, and vasculitis [15▪,48,49] (Table 5). There are multiple forms of systemic vasculitis associated with VEXAS, including leukocytoclastic vasculitis, Polyarteritis nodosa, and Giant-cell arteritis. There is a high prevalence of thrombosis (35–45%), mostly unprovoked and recurrent venous thrombosis, as described in BS and H20 [15▪,48]. Macrocytic anemia and myelodysplastic syndrome are key features of VEXAS, which may help diagnose patients with unexplained, recurrent, or treatment-refractory inflammatory disorders [49]. Various treatments, including glucocorticoids, conventional disease-modifying antirheumatic drugs, biological agents, and JAK inhibitors (especially ruxolitinib) have been used with variable results [49–51]. Additional treatment options target the UBA1-mutant clone with hypomethylating agents such as azacytidine. Allogeneic HSCT is currently the only curative treatment for VEXAS, sometimes with considerable mortality and morbidity [48].

In summary, vasculitis in VEXAS spans a spectrum from skin-limited disease to systemic polyarteritis nodosa-like vasculitis and occasionally large-vessel arteritis. The syndrome challenges traditional classifications of vasculitis, requiring genetic confirmation of UBA1 mutations for diagnosis and consideration of targeted therapies beyond traditional immunosuppressants.

CONCLUSION

In this review, we explored the intersection between autoinflammatory diseases (AIDs) and vasculitis, focusing on emerging evidence since 2016. AIDs are disorders of the innate immune system, often driven by genetic mutations affecting inflammatory

Table 5. Vasculitis in VEXAS vs. classic vasculitic syndromes

Feature	VEXAS-associated vasculitis	Classic PAN/ANCA vasculitis
Age of onset	Late adulthood (>50 years)	Typically younger in PAN, variable in ANCA vasculitis
Gender predominance	Strong male predominance	No gender preference in PAN; slight male bias in GPA
Genetics	Somatic UBA1 mutations	Typically idiopathic or autoimmune
Hematologic features	Macrocytic anemia, thrombocytopenia	Uncommon
Bone marrow	Myeloid vacuoles	Normal
Response to immunosuppression	Often refractory to steroids alone	Variable
Treatment	Requires steroid-sparing agents, hypomethylating agents, and JAK inhibitors under study	Cyclophosphamide, rituximab, steroids

PAN, polyarteritis nodosa; VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome.

pathways, particularly inflammasomes, NF-κB signaling, or purine metabolism.

Vasculitis has emerged as a key and in some cases central feature of several monogenic autoinflammatory diseases, particularly FMF, DADA2, HA20, and VEXAS. The underlying mechanisms likely involve dysregulation of innate immunity, with central roles for IL-1β and NF-κB, resulting in endothelial dysfunction and vascular inflammation. Histopathologic and clinical features may differ from those of classic vasculitides, requiring a high index of suspicion and integration of clinical, genetic, and immunologic data.

Although vasculitis is not universally present in all AIDs, it is a prominent or recurrent feature in several conditions:

(1) FMF is often associated with IgA vasculitis and PAN, frequently presenting with atypical features and greater severity. Vasculitis-like manifestations may also occur during prolonged febrile myalgia.
(2) DADA2 is a prototypical monogenic vasculitis mimicking PAN, characterized by early-onset strokes and involvement of small- to medium-sized vessels.
(3) HA20, initially described as a Behçet-like syndrome, exhibits variable-vessel vasculitis and systemic inflammation, often starting in early childhood.
(4) CAPS, TRAPS, HIDS/MKD, and ORAS may present with vasculitic features in selected patients, although vasculitis is not their primary manifestation.
(5) VEXAS is notable for its severe, life-threatening inflammatory and vasculitic features, often necessitating hematologic monitoring and targeted treatment.

Genetic testing should be considered in young patients with vasculitis, especially in cases with early onset, systemic involvement, or poor response to standard immunosuppressive therapies. Targeted treatments – such as IL-1 or TNF inhibitors, JAK inhibitors, or hematopoietic stem cell transplantation – show promise in managing vasculitic features of AIDs, though treatment must be tailored to the individual's genotype, phenotype, and organ involvement. Some forms of vasculitis seen in AIDs do not align with current vasculitis classification systems, highlighting the need to reconsider existing diagnostic frameworks.

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Conflicts of interest

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