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Adult-onset autoinflammation caused by somatic mutations in *UBA1*: A Dutch case series of patients with VEXAS

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Background: A novel autoinflammatory syndrome was recently described in male patients who harbored somatic mutations in the X-chromosomal *UBA1* gene. These patients were characterized by adult-onset, treatment-refractory inflammation with fever, cytopenia, dysplastic bone marrow, vacuoles in myeloid and erythroid progenitor cells, cutaneous and pulmonary inflammation, chondritis, and vasculitis, which is abbreviated as VEXAS.

Objective: This study aimed to (retrospectively) diagnose VEXAS in patients who had previously been registered as having unclassified autoinflammation. We furthermore aimed to describe clinical experiences with this multifaceted, complex disease.

Methods: A systematic reanalysis of whole-exome sequencing data from a cohort of undiagnosed patients with autoinflammation from academic hospitals in The Netherlands was performed. When no sequencing data were available, targeted Sanger sequencing was applied in cases with high clinical suspicion of VEXAS.

Results: A total of 12 male patients who carried mutations in *UBA1* were identified. These patients presented with adult-onset (mean age 67 years, range 47-79 years) autoinflammation with systemic symptoms, elevated inflammatory parameters, and multiorgan involvement, most typically involving the skin and bone marrow. Novel features of VEXAS included interstitial nephritis, cardiac involvement, stroke, and intestinal perforation related to treatment with tocilizumab. Although many types of treatment were initiated, most patients became treatment-refractory, with a high mortality rate of 50%.

Conclusion: VEXAS should be considered in the differential diagnosis of males with adult-onset autoinflammation characterized by systemic symptoms and multiorgan involvement. Early diagnosis can prevent unnecessary diagnostic procedures and provide better prognostic information and more suitable treatment options, including stem cell transplantation. (J Allergy Clin Immunol 2022;149:432-9.)

Key words: *UBA1, VEXAS, autoinflammation, somatic variants*

INTRODUCTION

Autoinflammatory diseases are characterized by recurrent inflammatory episodes driven by dysregulated innate immune responses; they stand separate from autoimmune diseases, which are characterized by autoreactive T and B cells and accompanying autoantibodies. Many patients with these diseases have underlying germline mutations and present early in life. Adult-onset Still's disease and Schnitzler syndrome are exceptions, with an average age of onset of 36 years[1] and 55 years,[2] respectively. Autoinflammatory diseases can have distinct clinicopathologic substrates resulting from disrupted inflammasome assembly and functioning, impaired interferon and/or nuclear factor-κB signalling, protein misfolding, and cellular stress.[3] Several

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Abbreviations used
CT: Computed tomography
IEI: Inborn error of immunity
IQR: Interquartile range
MDS: Myelodysplastic syndrome
PET: Positron emission tomography
VAF: Variant allele fraction
VEXAS: Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome

autoinflammatory syndromes have been associated with impaired ubiquitination (ie, *TNFAIP3* haploinsufficiency, *RBCK1* [*HOIL1*], *RNF31* [*HOIP*], and *OTULIN* deficiency), thereby predominantly unleashing nuclear factor-κB signaling.[4-6] Recently, a novel adult-onset X-linked autoinflammatory disorder was described in male patients exhibiting treatment-resistant autoinflammation with episodes of fever, cytopenias, dysplastic bone marrow, characteristic vacuoles in myeloid and erythroid cells, neutrophilic cutaneous and pulmonary inlfmmation, (poly)chondritis and vasculitis.[7] Somatic mutations affecting the methionine at amino acid position 41 in *UBA1*, coding for 1 of the 2 known E1 ubiquitylation enzymes, were shown to cause this disorder, which the authors named the VEXAS syndrome.[7] Most recently, others have identified novel somatic variants in *UBA1*.[8-10] In this study, we characterize a small cohort of patients with VEXAS syndrome. We discuss novel clinical observations and strategies to improve diagnosis and treatment of VEXAS.

RESULTS AND DISCUSSION

The patients included in this study were diagnosed retrospectively after systematic reanalysis of existing whole-exome sequencing data from a cohort of undiagnosed patients with inborn errors of immunity (IEIs) from the Dutch academic hospitals in Nijmegen, Maastricht, Groningen, Utrecht, Rotterdam, and Amsterdam. When no sequencing data were available, targeted Sanger sequencing was performed. Male patients were selected for reanalysis based on the clinical profile of VEXAS, encompassing a reported suspicion of an unclassified autoinflammatory syndrome with multiorgan involvement, systemic vasculitis (including polyarteriitis nodosa) without autoantibodies or relapsing polychondritis with pulmonary involvement. A total of 12 male patients were identified that carried somatic mutations at p.Met41 in *UBA1* (Table I). No somatic mutations were identified at the recently described novel positions in *UBA1* (Table I). Detailed genetic and clinical information on the individual cases can be viewed in Table I or accessed in the full case descriptions in this article's Online Repository [available at www.jacionline.org].

All 12 patients were males with adult-onset (mean age of onset of 67 years, range 47-79) autoinflammation characterized by constitutional symptoms and multiorgan involvement, including bone marrow (12 of 12 patients [100%]), skin (10 of 12 patients [83.3%]), lungs (8 of 12 patients [66.7%]), lymph nodes (with lymphadenopathy affecting 7 of 12 patients [58.3%]), heart and vasculature (6 of 12 patients [50%]), cartilage (6 of 12 patients [50%]), joints (4 of 12 patients [33.3%]), nervous system (4 of 12 patients [33.3%]), urogenital tract (4 of 12 patients [33.3%]), gastrointestinal tract (3 of 12 patients [25%]), eyes (3 of 12 patients [25%]), and kidneys (2 of 12 patients [16.7%]). The patients presented with elevated inflammatory parameters and macrocytic anemia (patient I developed macrocytosis later). Initial presentations additionally included chondritis of the ear or nose (patients B and D, and later patients F and L), oligoarthritis (patients B, C, G, and H), and pulmonary or systemic vasculitis (patients A, F, J, K, and L) (Table I, Fig 1). Histopathologic examination of the bone marrow revealed hypercellularity and signs of bone marrow dysplasia with vacuoles in the myeloid progenitor cells in most patients, although only in 4 cases (patients C, G, H, and J) the IPSS-R criteria for myelodysplastic syndrome (MDS) were met. In patients D and E the bone marrow furthermore showed signs of hemophagocytosis. Moreover, the patients presented with a wide range of skin lesions, which were hallmarked by leukocytoclastic vasculitis with variable infiltrates of neutrophils, monocytes, lymphocytes, and eosinophils (Table I). Pulmonary involvement was also common and included infiltrates and idiopathic interstitial pneumonia (cryptogenic organizing pneumonia [patient G], nonspecific interstitial pneumonia (patient I), and bronchiolitis obliterans (patients D, E, and H). The patients had no disease-specific autoantibodies.

Although the clinical symptoms and distribution of organ involvement broadly resembled the findings of previous studies,[7,8,10] several observations are complementary. First, patient B presented without episodic fever but did have progressive renal insufficiency with marked proteinuria and dysmorphic erythrocyturia. A renal biopsy revealed a homogeneous interstitial infiltrate, with myeloperoxidase-positive and $CD68^+$ myeloid cells without the presence of eosinophils, lymphocytes, or plasma cells (Fig 1, *E*) and endothelitis with intermediate-vessel vasculitis. The occurrence of interstitial nephritis as part of VEXAS has not been reported in the first cohort or in the most recent publications.[7,8,10] Interestingly, histopathologic examination of the bone marrow also showed a similar population of myeloperoxidase-positive and $CD68^+$ myeloid cells, with accompanying signs of myelodysplasia and vacuoles in myeloid precursor cells. Furthermore, 4 cases (patients B, E, H, and J) presented with evidence of cardiac involvement. Patients B and E had signs of a myocarditis, whereas patient F showed nonspecific FDG-avidity in the left ventricle and patient J had a reduced LVEF of unknown cause. In the first study, this cardiac involvement was less prominent, as only 1 of 25 patients was diagnosed with a myocarditis.[7]

Third, 3 patients (A, F, and H) developed either a minor stroke or cerebrovascular accident. These events might be related to the VEXAS syndrome, as both venous thromboembolisms, which also occurred in patient E, as well as an arterial pulmonary embolism were reported in the original cohort.[7]

Moreover, another 3 patients (D, E, and G) had signs of gastrointestinal involvement, a clinical feature that has been reported in patients with VEXAS syndrome and appeared in 2 patients with small bowel inflammation. Patient G displayed signs of gastrointestinal ulceration within the colon. The patient temporarily received antibiotics for a secondary gram-negative bacteremia. Patients D and E both died of the consequences of a perforation of the jejunum and ileum, respectively. Patient D developed the jejunal perforation 1 month after starting treatment with tocilizumab. Histopathological examination of the surgically resected intestine revealed signs of extensive inflammation with abscess formation, indicating that the perforation was most

TABLE I. Demographic and clinical characteristics of patients diagnosed with VEXAS

Patient	A	B	C	D	E	F	G	H	I	J	K	L
Demographics												
Sex	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male
Race	European	European	European	European	European	European	European	European	Middle Eastern	European	European	European
Age of onset (y)	55	69	76	79	78	74	70	66	47	62	76	56
Follow-up (y)	8	3	4	1	3	0,5	4	5	4	8	5	2
Status (alive/deceased)	Alive	Alive	Deceased	Deceased	Deceased	Alive	Deceased	Deceased	Alive	Deceased	Alive	Alive
Age at death (y)	—	—	80	80	81	—	74	71	—	70	—	—
Genetics												
UBA1 (NM_0003334.3) somatic variant	c.121A>G, p.(Met41Val), VAF 73%	c.122T>C, p.(Met41Thr), VAF 63%	c.122T>C, p.(Met41Thr), VAF 17%	c.121A>G, p.(Met41Val), VAF 63%	c.121A>G, p.(Met41Val), VAF 66%	c.122T>C, p.(Met41Thr), VAF 73%	c.122T>C, p.(Met41Thr), VAF 83%	c.121A>C, p.(Met41Leu), VAF 81%	122T>C, p.(Met41Thr), VAF 43%	c122T>C p.(Met41Thr), VAF 70-80% (Sanger)	c.121A>G, p.(Met41Val), VAF 85%	c.122T>C, p.(Met41Thr), VAF 58%
Clinical features (stratified by organ system)												
Systemic symptoms	Fever	Fatigue, no fever	Fatigue, fever, weight loss	Fatigue, fever, weight loss, night sweats	Fatigue, fever, weight loss, night sweats	Fatigue, fever, night sweats, weight loss	Fever, night sweats	Fever	Fever, weight loss, night sweats	Fever, weight loss, night sweats	Muscle ache, no fever	Fever, night sweats, headache
Bone marrow	Macrocytic anemia, thrombocytopenia, no convincing signs of MDS	Macrocytic anemia, vacuoles of myeloid progenitor cells in bone marrow aspirate, dysplasia	Macrocytic anemia, trilinear dysplasia suggestive of MDS, vacuolization	Pancytopenia, with hypercellular bone marrow and granulopoiesis, limited hemophagocytosis, vacuolization present	Macrocytic anemia, dysplastic myelopoiesis and megakaryopoiesis with hemophagocytosis, vacuolization	Macrocytic anemia, thrombocytopenia, no convincing signs of MDS	Macrocytic anemia, lymphopenia, eosinophilia, trilinear dysplasia compatible with MDS. Additional *DNMT3a* mutation (c.2727delT (p.Phe909Leufs*13)	MDS, IPSS-R 1, mild macrocytic anemia	Monocytopenia, neutropenia, absent NK cell function, bone marrow examination mild dyserythropoiesis	MDS	Macrocytic anemia. No convincing signs of MDS, vacuolization	Macrocytic anemia, no signs of MDS, vacuolization
Skin	Nodules/erythema nodosum. Skin biopsy: leukocytoclastic vasculitis	Erythematous plaque and red-purple papules. Skin biopsy: leucocytoclastic vasculitis small/medium vessels with a monocytic and neutrophilic infiltrate	Erythematous plaque and red-purple papules. Skin biopsy: possible lymphocytic vasculitis, urticaria	Erythematous papules. Multiple skin biopsies: lymphocytic dermatitis and eosinophilic vasculitis	Erythematous subcutaneous nodules, exanthema. Skin biopsy: mixed infiltration with lymphocytes, neutrophils, and eosinophils	Erythema nodosum, erythematous plaque and papules. Skin biopsy: leukocytoclastic vasculitis	Erythema nodosum, maculopapular exanthema upper legs, compatible with Sweet syndrome, periorbital edema, vasculitis fingers	Erythema exudativum multiforme, Sweet syndrome	Erythema nodosum	Erythema nodosum	—	—
Lungs	Pulmonary infiltrates with ground glass opacities, thickening of the intralobular septa and lymphadenopathy. Lung biopsy: lymphohistioplasmocellular vasculitis of the larger arterioles	—	—	Pulmonary fibrosis with diffuse alveolar confusing densities with signs of bronchiolitis obliterans in between	Predominant peripheral tree-in-bud signs with reticular infiltration in the lower fields, matching with a bronchiolitis with mediastinal and hilar lymphadenopathy	—	Cryptogenic organizing pneumonia (histopathological diagnosis), pleuritis	Bronchiolitis obliterans, organizing pneumonia	NSIP	Pathologically proven vasculitis of the pulmonary vasculature with eosinophilia	Cavitating lesion right upper lobe	—
Lymphadenopathy	—	—	—	Hilar and mediastinal	Hilar and mediastinal	—	Cervical lymphadenopathy	—	Paraaortic lymphadenopathy	Paraaortic, axillary	Hilar	Cervical

(Continued)

TABLE I. *(Continued)*

Patient	A	B	C	D	E	F	G	H	I	J	K	L
Heart and vasculature	ANCA-negative vasculitis	Cardiomyopathy LVEF 20%, recovery after start of anti-inflammatory treatment	—	—	Possible myocarditis	Signs of vasculitis (orchitis, epistaxis with crust formation), FDG avidity of left ventricles atypical for myocarditis, normal echocardiography findings and cardiac enzyme levels	—	—	—	LVEF 29%, elevated right ventricular pressure	—	—
Cartilage	Ulcerative lesions in the nose, likely related to the vasculitis	Chondritis of the left ear	—	—	—	Chondritis of the ears, nose, and possibly the sternum. Also, epistaxis and crust formation of the nose	—	Chondritis of the ears	Chondritis	—	—	Chondritis of the ears
Joints	—	Oligoarthritis	Possible arthritis of the left knee	—	—	—	Periarthritis of the ankles	Polyarthritis, myalgia	—	Myalgia	Myalgia	—
Nervous system	Cerebrovascular accident	—	Possible polyneuropathy with numbness, pins, and needles in forearms (electromyography not performed)		Axonal polyneuropathy	Minor stroke posterior area, followed by vestibular neuritis (CT brain: no abnormalities; MRI with vessel wall imaging: no abnormalities)		—	Aseptic meningitis	Headache, no abnormalities on MRI or in analysis of spinal fluid	—	—
Urogenital system	—	—	—	Epididymitis	—	Orchitis (possible PAN)	—	—	—	Prostatitis, epididymitis	—	Epididymitis
Gastrointestinal tract	—	—	—	Perforation of the jejunum during treatment with tocilizumab	Perforation of the ileum during treatment with tocilizumab	—	Ulcerative lesions in colon and caecum	—	Lesion in pancreas with increased FDG uptake on PET imaging, parotitis	No abnormalities via endoscopy, PET uptake	—	—
Eyes	—	Blepharitis left eyelid	—	Bilateral anterior uveitis and exophthalmos caused by periorbital and intraorbital panniculitis	—	Uveitis anterior	—	—	Blepharitis	—	—	Posterior scleritis
Kidneys	—	Progressive renal insufficiency, proteinuria, dysmorphic erythrocyturia. Renal biopsy: homogeneous interstitial infiltrate with MPO-positive and $CD68^{+}$ myeloid cells, no eosinophils, lymphocytes, or plasma cells	—	—	—	—	—	—	Proteinuria, later erythrocyturia (biopsy: no vasculitis)	—	—	—

(Continued)

TABLE I. *(Continued)*

Patient	A	B	C	D	E	F	G	H	I	J	K	L
Laboratory findings (at presentation/ before start of treatment)												
Hemoglobulin (g/dL)	6.8	10.9	10.3	10.96	9.67	9.35	11.8	10.15	10.7	10,8	NA	NA
Mean corpuscular volume (fL)	106	102-107	105	92	102	107-111	96	91	82	88	NA	NA
Platelets (10^9/L	126	239	328	95	220	80-200	351	326	306	180	NA	NA
White blood cell count (10^9/L)	2.9	9.7	3.5	3.5	6.8	4.9	8.9	8.1	4.3	6,8	NA	NA
Absolute neutrophil count (10^9/L)	2.09	8.0	2.9	3.4	6.01	3.8	NA	5.6	2.9	NA	NA	NA
Absolute monocyte count (10^9/L)	0.08	0.77	0.07	0.4	0.12	0.24	NA	0.69	0.08	NA	NA	NA
Absolute lymphocyte count)(10^9/L)	0.67	0.87	0.56	1	0,55	0.74	NA	1.2	1.3	NA	NA	NA
Absolute eosinophil count (10^9/L)	NA	NA	NA	NA	NA	0.59	NA	0.9	0.03	NA	NA	NA
C-reactive protein (mg/L)	153	230	166	351	407	130-300	61	226	112	190	NA	NA
Procalcitonin (mg/L)	NA	NA	NA	NA	NA	NA	NA	0.59	NA	NA	NA	NA
Serum amyloid A (mg/L)	198	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Ferritin (ug/L)	875	1108	1873	2564	2711	1083	1200	NA	761	NA	NA	NA
ESR/BSE (mm/h)	71	101	78	NA	111	130	105	102	94	97	NA	NA
sIL2 receptor (pg/mL)	17933	380	21700	10831	4443	759	21500	NA	NA	NA	NA	NA
Neopterin (ng/mL)	NA	NA	17,6	NA	NA	NA	NA	NA	NA	NA	NA	NA
IL-6 (pg/mL)	492	38 (measured in 2019)	NA	858 (measured 1 y after disease onset)	NA	NA	3.9	NA	NA	NA	NA	NA
IL-18 (pg/mL)	NA	NA	NA	NA	213	NA	NA	NA	NA	NA	NA	NA
Vitamin B12 (pmol/L)	304	247	>1000 (supplementation)	717 (measured 5 mo after disease onset)	196	406	NA	NA	NA	484	NA	NA
Treatment												
Glucocorticoids	Prednisone, 60 mg/d, tapering schedule. Methylprednisolone pulse therapy during pulmonary vasculitis flares (3 days, 1000 mg iv)	Methylprednisolone pulse therapy (3 days, 1000 mg iv), tapered to 7,5 mg/d of oral prednisone at best	Prednisone, 60 mg/d, tapering schedule	Prednisone 60 mg/d, tapered to 20 mg/d at best	Prednisone, 60 mg/d, tapered to 5 mg/d at best	Prednisone, 30 mg/d, tapering schedule	Prednisone, 60 mg/d, after tapering multiple flares for which methylprednisolone pulse therapy (3 days, 1000 mg iv)	Prednisone, 60 mg/d, tapering schedule	Prednisone, 60 mg/d, tapering schedule	Prednisolone, 60 mg/d, tapering schedule	Prednisolone, 60 mg/d, tapering schedule	Prednisolone, 60 mg/d, tapering schedule
Methotrexate	—	15 mg/wk, add-on to tocilizumab	—	—	10 mg/wk, discontinued because of side effects	—	15 mg/wk, steroid-sparing agent	25 mg/wk, steroid-sparing agent	—	—	20 mg/wk, steroid-sparing agent	20 mg/wk, steroid-sparing agent
Mycophenolate	—	2 × 1000 mg/d, no response	—	—	—	—	—	—	—	2 × 1000 mg/d	—	—

(Continued)

TABLE I. *(Continued)*

Patient	A	B	C	D	E	F	G	H	I	J	K	L
Azathioprine	—	—	—	—	—		150 mg/d	—	2 mg/kg, initial good response but soon ineffective	150 mg/d	—	—
Cyclo-phosphamide	150 mg/d, partial response	150 mg/d, good response	—	25 mg/d, low dose because of leukopenia	—	—	—	—	—	150 mg/d, 4 mo	—	—
Cyclosporine	—	—	100 mg bid, in combination with steroids partial response	—	5 mg/kg/d, discontinued because of renal toxicity	—	—	—	—	100 mg bid	—	—
Anti–IL-1 therapy	Anakinra, 2 × 100 mg/d sc, lowered to 1 d 100 mg sc owing to neutropenia, good response	Anakinra, 100 mg/d sc, stopped owing to severe local reaction	Anakinra, 100 mg/d sc "on demand"; later 100 mg/d, good response	Anakinra, 100 mg/d sc, discontinued because of disease recurrence	Anakinra, 100 mg/d sc, discontinued owing to subcutaneous infiltrates at injection site. Switch to canakinumab, 300, mg/mo sc; stopped because of disease recurrence	—	Anakinra, 100 mg/d, discontinued owing to persisting skin infiltrates at injection sites, switch to canakinumab, 150 mg/4 wk sc	—	Anakinra, 100 mg/d, discontinue owing to severe skin infiltrates at the injection site, switch to canakinumab, 150 mg/4 wk; reduced to 150 mg/3 wk; variable to good response	—	—	—
Anti–IL-6 therapy	—	Tocilizumab 162 mg/wk sc, partial response	—	Tocilizumab 162 mg/wk sc, response unknown	Tocilizumab 162 mg/wk sc and later iv 8 mg/kg once a mo, partial response	—	—	—	—	Tocilizumab 8 mg/kg/mo iv	Tocilizumab 162mg/wk sc, partial response	Tocilizumab 162mg/wk sc, good response
TNF-α inhibitors	—	—	—	—	—	—	Infliximab	Adalimumab 40 mg/2 wk sc; in combination with methotrexate partial to good response	—	Infliximab	—	—
Rituximab	Initially 1000 mg iv 3×/y, later 100 mg/y with good response	—	—	Initially 2 × 1000 mg iv, repeated after 6 mo	—	—	—	—	Initially 2 × 1000 mg followed by third infusion iv of 500 mg, followed by disease flare	2 × 1000 mg iv and follow-up treatment	—	—
Azacitidine	—	—	—	—	—	—	1 cycle	—	—	—	—	—
Dapsone	—	—	—	—	—	—	—	100 mg/d, intolerance	—	—	—	—

ANCA, Antineutrophil cytoplasmic antibody; *bid*, twice daily; *EMG*, electromyography; *FDG*, F-fluorodeoxyglucose; *IPSS-R,* Revised International Prognostic Scoring System; *iv*, intravenous; *LVEF*, left ventricular ejection fraction; *MPO*, myeloperoxidase; *MRI*, magnetic resonance imaging; *NA*, not available; *NK*, natural killer; *NSIP*, nonspecific interstitial pneumonia; *PAN*, polyarteriitis nodosa; *sc*, subcutaneous.

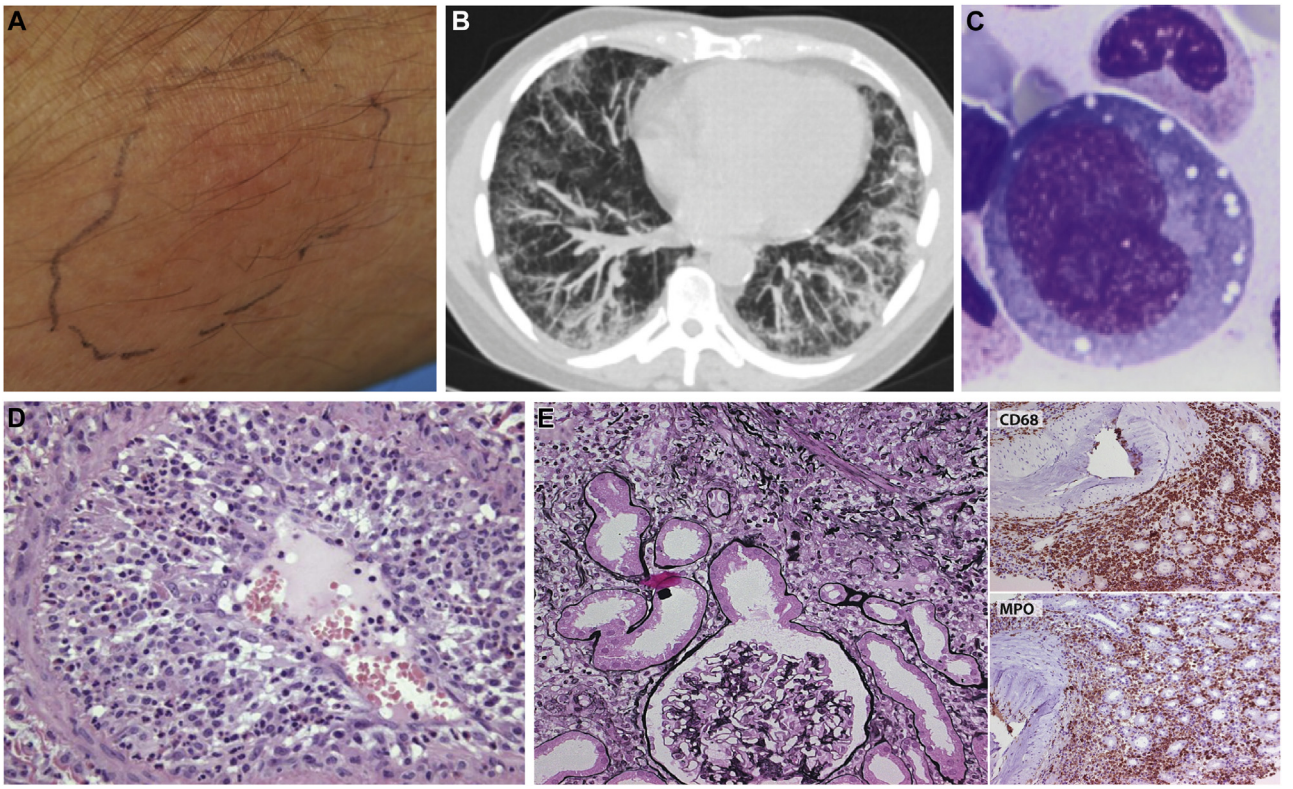

FIG 1. Clinicopathologic signs of VEXAS. **A,** An erythematous, painful, palpable nodule on the lower arm consistent with erythema nodosum caused by medium-vessel vasculitis. **B,** An example of the pulmonary involvement in our patients, which included various forms of interstitial lung disease. Most patients displayed vacuolization in myeloid progenitor cells from bone marrow aspirates on retrospective analysis. **C,** Wright-Giemsa staining. **D,** A skin biopsy specimen with inflammation of the medium- and smaller-size arteries and venules, focal necrosis, and eosinophilic infiltrates, supporting the diagnosis of polyarteritis nodosa. **E,** A kidney biopsy specimen with extensive interstitial infiltrates of $CD68^{+}$ and myeloperoxidase-positive myeloid and monocytic cells. **D** and **E**, Staining with hematoxylin and eosin.

probably caused by a perforating diverticulitis. Patient E also had therapy-refractory VEXAS and developed an ileal perforation 2 months after the reintroduction of tocilizumab. The patient was treated conservatively and no *post mortem* obduction was performed. Intestinal perforation is a rare and feared complication of tocilizumab, and it could be hypothesized that treatment with anti–IL6-blockade carries an increased risk of bowel perforation in patients with VEXAS who might have underlying gastrointestinal involvement.[11] This relationship between small bowel inflammation and treatment with tocilizumab was not established in the previous cohorts.[7,8,10]

Multiple lines of treatment (mean of 4, IQR 3.5-5) were initiated in our patients, similar to previous studies.[7,8,10] There was a significant interindividual variation in treatment efficacy. For example, treatment with the IL-1 blocker anakinra proved effective and led to stable disease for at least 1.5-2 years in patients A and C, in patient D the effect was absent and in 4 patients (B, E, F, and I) the effect could not be evaluated owing to severe local reactions at the subcutaneous injection site. Interestingly, 62% of the 13 patients in the original study also developed local severe reactions during treatment with anakinra, analogous to those developed by other patients with autoinflammatory syndromes such as cryopyrin-associated periodic fever syndrome.[7] Local reactions at the injection site with anakinra are well known (owing to the additives and pH of the preparation rather than to the recombinant IL-1 receptor antagonist),[12] and it is therefore conceivable that patients with VEXAS would experience a stronger local inflammatory reaction. It could therefore be proposed to treat patients with VEXAS with anakinra administered intravenously for induction therapy to overcome this treatment-limiting side effect, or desensitization therapy can be considered.[13] Nevertheless, most if not all patients with VEXAS become therapy-refractory during the years of follow-up and have a high mortality rate. In our study, this rate was 50% (6 of 12) during an average of 3.96 years of follow-up (range 0.5-8 years). Treatments that eliminate the clonal process, such as allogenic stem cell transplantation or future gene-editing therapies, should therefore be considered.[7] Consequently, it is important to minimize the time between symptom onset and genetic diagnosis of the VEXAS syndrome, so that allogenic bone marrow transplantation can be considered during early disease.

It has long been recognized that somatic mutations leading to somatic mosaicism in immune cells can be causative of immunodeficiency and/or autoinflammation, as has been shown for somatic mutations in *NLRP3*,[14] *NLRC4*,[15] *TNFRSF1A*,[16] and *NOD2*.[17] Conversely, somatic mutations can (partly) rescue pathogenic germline mutations through revertant mosaicism, which was shown first in 1994 and thereafter for multiple other IEIs.[18,19] The mutations in *UBA1* form a striking example of disease-causing somatic mosaicism, with VEXAS constituting

the first IEI that is not a phenocopy of a germline disease. Interestingly, germline mutations in *UBA1* underlie a very distinct neuromuscular disease, namely, X-linked infantile spinal muscular atrophy.[20] This discovery further underscores the importance of specifically evaluating somatic variants during exome analysis, as normal variant filtering can wrongly eliminate these variants if the variant allele fraction (VAF) is below the threshold, such as in patient C (with a VAF of only 17%). Similar to what has been demonstrated in patients with cryopyrin-associated periodic fever syndrome,[14] somatic variation might therefore explain a larger portion of unexplained autoinflammatory syndromes. We therefore propose to implement the evaluation of somatic *UBA1* variants in the routine molecular genetic investigation of the bone marrow in patients with suspected MDS, which is an important feature of VEXAS syndrome. Furthermore, it should be investigated whether the VAF of the causative *UBA1* variants in the myeloid lineage might correlate with disease severity and prognosis, although with the current data, including that of our study, it is unclear whether this could be used as a prognostic factor and whether it should be determined at the level of the peripheral blood or at the bone marrow. Moreover, the age of onset might be a prognostic factor, because it is known that if a somatic mutation occurs earlier during development, it usually acquires a higher VAF.[21] Conversely, the presence of a variant with a relatively low VAF in a younger patient already expressing full-blown VEXAS syndrome, such as patient J, could be a negative prognostic factor. Lastly, the significance of the co-occurrence of other myeloid mutations should be further elucidated, which has been described in patient G (*DNMT3A*) and several patients from other cohorts, to gain insight into clone development and trajectory over time.

In conclusion, this study supports the consideration of the VEXAS syndrome in the differential diagnosis of men after their fourth decade of life exhibiting signs of adult-onset autoinflammation with multiorgan involvement, typically including skin inflammation and MDS-like features in peripheral blood, and including patients with systemic autoantibody-negative vasculitis and relapsing polychondritis with pulmonary involvement. Furthermore, we describe novel features of VEXAS, which include interstitial nephritis, more prominent cardiac involvement, stroke, and intestinal perforation related to treatment with tocilizumab. In line with previous reports, patients are often treatment-refractory despite multiple lines of treatment. However, early diagnosis could prevent unnecessary diagnostic procedures and could provide better prognostic information and more suitable treatment options. Clinicians should consider allogenic stem cell transplantation at an early stage to prevent progression of organ damage that would render these patients ineligible. In such patients, treatment with IL-1 or IL-6 blockade could be considered.

Clinical implications: This study expands the clinical spectrum of VEXAS and advocates its consideration in the differential diagnosis of men older than 40 years who are presenting with adult-onset autoinflammation and multiorgan involvement.

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FULL CASE DESCRIPTIONS

Patient A

The patient was a 55-year-old male with an unremarkable medical history who presented in 2013 with symptoms of fever, coughing, dyspnea, and leukocytoclastic vasculitis, as well as erythema nodosum of the extremities. Further investigations indicated increased inflammatory parameters, macrocytic anemia, and mild thrombocytopenia (see Table I in the print text). A chest computed tomography (CT) scan displayed ground glass opacities and interstitial markings suggestive of interstitial lung disease. Histopathologic evaluation of the bone marrow showed nonspecific alterations in the maturation of hematopoietic cells without signs of vacuolization in myeloid progenitor cells. Despite initial treatment with high-dose corticosteroids (60 mg/kg body weight), the inflammatory and pulmonary symptoms persisted. Subsequently (in 2013), anakinra was added to the treatment regimen at a dose of 200 mg per day with a good clinical effect. Nevertheless, after almost 2 years, the patient was rehospitalized because of progressive dyspnea and hypoxemia. A high-resolution CT scan and lung biopsy then showed interstitial inflammation with lymphohistioplasmocellular vasculitis of the larger arterioles, together with crust formation in the nose, leading to diagnosis of antineutrophil cytoplasmic antibody–negative vasculitis. Over the next months, the vasculitis flared up with episodes of fever and respiratory insufficiency and proved resistant to treatment with methylprednisolone pulses (1000 mg per day intravenously for 3 days), cyclophosphamide (150 mg per day), intravenous immunoglobulins, plasmapheresis, and a long-lasting high dose of oral corticosteroids. Thereafter, it was decided to treat the patient with rituximab (1000 mg/infusion) in 2015, leading to a good clinical and biochemical response. After both 1 and 2 years, the patient experienced a relapse of pulmonary symptoms, and a cerebrovascular accident occurred. Both relapses were treated with additional infusions of rituximab and high-dose corticosteroids. Over the following 3 years, it became possible to discontinue the corticosteroids and maintain a complete remission with rituximab once a year.

Patient B

The patient presented in 2017, at 69 years of age, with fatigue, persisting vasculitic skin lesions, left-sided chondritis of the ear and blepharitis, and oligoarthritis. The patient's medical history included hypertension and atrial fibrillation. Serologic investigations showed high inflammatory parameters, macrocytic anemia, and the absence of autoantibodies (Table I). Moreover, the patient exhibited a progressive renal insufficiency with marked proteinuria and dysmorphic erythrocyturia. A subsequently performed renal biopsy revealed unusual and extensive interstitial infiltrates consisting of myeloid and monocytic cells, without eosinophils, lymphocytes, or plasma cells, and endothelitis with intermediate-vessel vasculitis. There was no peripheral monocytosis. Histopathologic examination of the bone marrow showed myelodysplasia, a myeloperoxidase-positive and $CD68^+$ myeloid cell infiltrate, and vacuoles. Lastly, a skin biopsy indicated a leukocytoclastic vasculitis with monocytic and neutrophilic infiltrate. The patient was initially treated with methylprednisolone and oral cyclophosphamide, 2 mg/kg body weight, after which all symptoms (including renal function) recovered. However, after tapering of the prednisone dosage to less than 10 mg per day, the vasculitis, arthralgias, and elevated inflammatory parameters recurred. Treatment with mycophenolate mofetil was not effective. Because the patient's symptoms were, at the time, regarded as a novel autoinflammatory disorder of unknown cause, clinicians decided to start treatment with anakinra, 100 mg per day. Although this led to an excellent clinical response, the patient decided to discontinue taking anakinra on account of severe reactions at the site of injection. Presently, the patient is being treated with tocilizumab, a low dose of methotrexate, and prednisone (7.5 mg per day) (Table I). With this regimen, his renal status is stable, but he still experiences arthralgia and a macrocytic anemia.

Patient C

The patient presented in 2016 at the age of 76 years with progressive macular lesions on the legs, arms, and abdomen; weight loss; fever; and painful edema of the forearms and hands. In addition, the patient complained of chronic cough and recurrent chest pains. His medical history included myocardial infarction, stroke, atrial fibrillation, hypertension, and obesity. Laboratory investigation revealed a macrocytic anemia and marked elevation of inflammatory markers (Table I). A chest CT scan showed no abnormalities. The patient was hospitalized, and a bone marrow examination was performed. The bone marrow examination revealed hypocellularity with trilinear dysplasia without an excess of blasts or signs of hemophagocytosis and was therefore suggestive of MDS. A biopsy of the skin lesions showed signs of perivascular lymphocytic infiltrate with some eosinophils, which was compatible with urticaria/urticarial vasculitis. At the time, the patient was diagnosed with "an inflammatory disease due to an undefined bone marrow disease." He was treated with high-dose prednisone and cyclosporine. Initially, the patient responded favorably to treatment; however, in subsequent years after tapering of the prednisone, he was recurrently admitted to the hospital with episodes of fever that was sometimes accompanied by urticaria. The patient also regularly presented with complicated urinary tract infections involving sepsis with gram-negative bacteria, requiring antibiotic treatment. As these fever episodes with urticaria were suggestive of an autoinflammatory syndrome, the patient began receiving treatment with anakinra, leading to complete remission of the autoinflammatory symptoms. In addition, the recurrences of urosepsis also declined. However, the patient died 2 years later as a result of his vascular disease.

Patient D

The patient was a 79-year-old male with a medical history of hypertension and polyposis nasi. His disease course started in 2019 with an epididymitis that responded well to antibiotics. One month later he developed exophthalmos on the right side, with periorbital and intraorbital swelling and soft tissue infiltration. Histopathologic evaluation showed adipose tissue with reactive changes and panniculitis. Subsequently, he developed symptoms of fever, malaise, weight loss, and a skin rash that was histologically characterized by an eosinophilic vasculitis with perivascular dermatitis. His laboratory results showed increased inflammatory parameters, including hyperferritinemia. A chest CT scan showed mediastinal lymphadenopathy and mild nonspecific interstitial pulmonary abnormalities with mild unilateral pleural effusion. Pleural puncture was then performed and showed a transudate, with negative microbiologic cultures. An

additional positron emission tomography (PET) scan showed reactive mediastinal and hilar lymphadenopathy and diffuse activity at the bone marrow, spleen, and thyroid gland. Initial treatment was started with corticosteroids (60 mg per day), with complete resolution of inflammation.

When the corticosteroids were tapered to less than 30 mg per day in the next few months, the patient's symptoms of fever, night sweats, and malaise returned. As the diagnosis remained unclear, the steroids were further tapered to 0 mg per day. At that time, the patient developed high fever spikes (as high as 40°C), weight loss, Raynaud syndrome, bilateral anterior uveitis (on the left side with cotton wool spots), elevated inflammatory parameters, and macrocytic anemia. A high-resolution chest CT scan showed signs of beginning fibrosis with diffuse alveolar confusing densities and signs of bronchiolitis obliterans. A pulmonary function test indicated a normal diffusion capacity without signs of obstruction but with a slight restrictive dysfunction. In the meantime, the patient had developed pancytopenia, and histopathologic examination of the bone marrow showed hypercellularity with increased granulopoiesis, as well as minimal signs of hemophagocytosis. At that point, treatment was started again with corticosteroids, 60 mg per day, and rituximab (2×1000 mg intravenously).

The corticosteroids could not be tapered to less than 30 mg per day owing to disease recurrences. Additionally, treatment with anakinra (100 mg per day) was initiated, after which the symptoms and inflammatory markers normalized within several days. However, 1 month later patient developed a deep vein thrombosis of the calf vein up to the distal iliac vein. The patient redeveloped a rash with erythematous papules on his neck and upper chest, arms, and legs, which showed nonspecific lymphocytic dermatitis on biopsy. There were no signs of vasculitis on immunofluorescence. Because of this new disease activity, anakinra was stopped and switched to cyclophosphamide (a low dose of 25 mg per day because of leukopenia). A second round of rituximab (2×1000 mg intravenously) was given, but despite this, inflammation recurred. Eventually, it was decided to start administration of tocilizumab, 162 mg per week subcutaneously. One month later, the patient was admitted to the hospital because of a perforation of the jejunum. Resection of this segment of the small intestine was performed 40 cm distal of the ligament of Treitz. Postsurgically, the patient's situation deteriorated rapidly and he died of the complications 1 year after onset of the disease. Pathohistologic examination of the resected intestine showed extensive inflammation with abscess formation, most probably caused by a perforating diverticulitis.

Patient E

The patient was a 78-year-old male with an unremarkable medical history who presented for the first time in 2017 with fatigue, severe unilateral headache, diplopia, night sweats, fever, and elevated inflammation parameters. A diagnosis of arteritis temporalis was suspected and treatment was started with corticosteroids (60 mg per day). When prednisone was tapered to 5 to 10 mg per day, the patient developed fever and interstitial pulmonary abnormalities that included bronchiectasis. Methotrexate was started as a steroid-sparing agent but was stopped after several months because of side effects. For optimal diagnostic evaluation, the prednisone was tapered to 0 mg per day at the beginning of 2019. A PET/CT scan then showed diffuse activity at the bone marrow and spleen, a pulmonary nodus of the right upper lobe, and mediastinal lymphadenopathy. At that time, the patient had also developed axonal polyneuropathy, painful erythematous subcutaneous nodules, and macrocytic anemia (hemoglobin level 5.3 g/dL). Histopathologic examination of the bone marrow showed dysplastic myelokaryopoiesis and megakaryopoiesis with hemophagocytosis. In June 2019, administration of darbopoetin was started to treat the patient's anemia and he began receiving anakinra 100 mg per day subcutaneously. With anakinra, his symptoms improved and the levels of his inflammatory parameters, including C-reactive protein and ferritin, decreased. However, because of the development of neutropenia, the anakinra was discontinued.

The patient was referred for a second opinion, for which the corticosteroids were again tapered to 0 mg per day. The patient then developed fever, night sweats, weight loss, and a generalized erythematous lenticular rash with macules and papules. Skin biopsy showed mixed infiltration with lymphocytes, neutrophils, and eosinophils without signs of vasculitis. Further pulmonary evaluation showed predominant peripheral tree-in-bud signs with reticular infiltration in the lower fields, consistent with a bronchiolitis with mediastinal and hilar lymphadenopathy.

Because of the earlier good effect of anakinra (100 mg per day subcutaneously), it was reintroduced in November 2019. The patient responded well clinically and biochemically, and prednisone was tapered to 12.5 mg daily. However, the patient developed severe subcutaneous infiltrates caused by the anakinra injections. Anakinra had to be discontinued again, and subcutaneously administered tocilizumab, 162 mg weekly, was started in December 2019. Initially the patient responded well and the steroids were tapered to 15 mg per day. In February 2020 the patient's clinical situation deteriorated, and he experienced fever, fatigue, and the many side effects of the corticosteroids. We decided to switch treatment to cyclosporine with a target dose of 5 mg/kg body weight. Because of renal toxicity, after a few weeks the cyclosporine was subsequently replaced by canakinumab, 300 mg subcutaneously once monthly. There was improvement of his inflammation parameters, but clinically there was only mild improvement. The patient primarily complained of dyspnea. Further investigation showed improvement of pulmonary abnormalities, mild decreased left ventricular function, and a possible myocarditis that had been missed on cardiac magnetic resonance imaging. In June 2020 the patient again developed fever and elevation of inflammation markers after 2 months of canakinumab and prednisone 17.5 mg per day. We decided to try tocilizumab again, this time administered intravenously at a dose of 8 mg/kg body weight once a month starting in August 2020. Two months later the patient was admitted to the hospital because of an ileum perforation. In consideration of the patient's poor clinical condition at that time, a conservative treatment was chosen with intravenous antibiotics. The patient died in November 2020.

Patient F

The patient presented in November 2020 at the age of 74 years with recurrent constitutional symptoms (fever, night sweats, fatigue, and weight loss), highly elevated inflammatory markers, and pancytopenia with macrocytic red blood cells without folic acid or vitamin B12 deficiency. The findings of bone marrow investigation and PET/CT were unremarkable, and the results of extensive analysis for possible infectious diseases and

malignancy were negative. In the course of his illness he developed various signs of vasculitis. such as leukocytoclastic vasculitis, epididymoorchitis, and epistaxis with crust formation, all of which resolved spontaneously. Autoimmune serology results were negative. The patient also developed a mild uveitis anterior and symptoms consistent with chondritis of the nose, ears, and sternum that were subsequently followed by a minor stroke, vestibular neuritis, and non-ST elevation myocardial infarction. We started with a relatively modest prednisone dosage of 30 mg, which ameliorated his night sweats, improved his anemia, and normalized his C-reactive protein level to a value of 1 mg/L.

Patient G

The patient presented in 2014 at the age of 70 with episodic fever, night sweats, coarseness, periorbital edema, periarthritis of the ankles, cervical lymphadenopathy (level 2 left side [histopathology revealed a reactive lymph node]), subcutaneous nodules, and maculopapular exanthema on the upper legs. His medical history included COPD (Gold stage I) and surgical correction of an inguinal hernia. Laboratory investigations initially revealed elevated inflammatory marker levels, anemia, lymphopenia, eosinophilia, and significantly increased soluble IL-2 receptor. Initially there was no major organ involvement. Later that year, the patient developed pulmonary infiltrates and biopsies through video-assisted thoracoscopy showed cryptogenic organizing pneumonia. He was treated with prednisone, 60 mg per day, and azathioprine. During tapering he developed erythema nodosum and inflammatory flares. Azathioprine was switched to methotrexate. In 2015 he had ulcerative disease in his colon and was subsequently treated for secondary gram-negative bacteremia. Because of disease flare with lung disease, fever, and mild dysplasia on bone marrow examination with mild hemophagocytosis, he received methylprednisolone pulses, and methotrexate was replaced by anakinra, 100 mg per day. An unclassified autoinflammatory disease or adult-onset Still's disease was then suspected. Prednisone was tapered, yet owing to severe infiltrates at the injection site, anakinra was tapered, after which the disease flared up again. Because of repeated ulcerative gastrointestinal disease, the treatment regimen was switched to infliximab and methotrexate; yet shortly after in 2016, this was switched to canakinumab on account of a severe disease flare with inflammation of the skin, pleuritis, blue finger, pancytopenia, lung disease, skin vasculitis, acrocyanosis, and Raynaud syndrome). During this period he was also admitted to the intensive care unit because of pneumococcal sepsis. Despite this treatment, disease flares recurred, and in 2018 a revision of earlier bone marrow examination confirmed a MDS with a confirmed *DNMT3a* mutation. Azacitidine was initiated, but because of septic shock with respiratory failure and lactic acidosis and a very poor performance state, further diagnosis and treatment was stopped and the patient died within 24 hours.

Patient H

The patient presented in 2015 at the age of 66 years with fever and arthritis of a knee. He developed a bronchiolitis obliterans organizing pneumonia with a spontaneous pneumothorax and a parenchymal fistula, which was treated with segmental resection of the right lower lobe. He was treated with prednisone. His medical history reported exudative erythema multiforme, autoimmune hypothyroidism, a surgically cured stage I rectum carcinoma, hemorrhoids, and sliding diaphragmatic hernia. Fever episodes waxed and waned, and the patient also developed polyarthritis and Sweet syndrome. Bone marrow examination in 2018 revealed a mild MDS. The patient further developed chondritis of his ears. He was treated with dapson but developed fever, dyspnea, arthralgia, myalgia, skin rash, and unilateral swelling of the neck due to dapson allergy within 3 weeks of therapy. Treatment was switched to methotrexate, and because of persistent skin disease and polyarthritis, adalimumab was added. The corticosteroids were tapered. He was admitted and treated for *Pneumocystis jirovecii* pneumonia in 2019. Despite continuation of anti-inflammatory therapy, stable lung disease, and only relatively mild relapsing and remitting skin and joint inflammation, the patient died unexpectedly in 2020, most likely as a result of a cardiovascular event.

Patient I

The patient presented in 2017 at the age of 47 years with fever, weight loss, night sweats, and erythema nodosum. Laboratory investigation initially revealed inflammation, anemia of chronic disease, and monocytopenia. Imaging revealed waxing and waning nodules in the lungs, pancreas, and parotids and enhancement of fludeoxyglucose F 18 uptake by the bone marrow. Infectious causes were excluded, and despite repeated histology no diagnosis could be confirmed. Because of a concurring serum IgG4 level higher than 3.2 g/L (total serum IgG level 17.1 g/L) IgG4-related disease was suspected and the patient was initially treated with corticosteroids, followed by the addition of azathioprine, thereby rendering disease remission. Because of a disease flare that now also included chondritis (on histology no diagnosis could be made), azathioprine was replaced by rituximab. Over time, the patient developed temporary microscopic haematuria, parotitis, blepharitis, and interstitial lung disease compatible with nonspecific interstitial pneumonia. Because of recurrence of inflammation shortly after the third infusion of rituximab and later hospitalization with high fevers, high sIL-2R level, hyperferritinemia, acute respiratory distress syndrome, and absent natural killer cell function, adult-onset Still's disease was considered as an alternative diagnosis and additional treatment with anakinra was started. On bone marrow examination hemophagocytic lymphohistiocytosis could not be excluded or confirmed. Next-generation sequencing was subsequently performed, but no genetic cause for hemophagocytic lymphohistiocytosis or any other known monogenetic primary immunodeficiency was found. Because of very severe injection site infiltrates within the first 2 weeks, anakinra was switched to canakinumab, 150 mg subcutaneously every 4 weeks, with a favorable response. Because of recurrence of symptoms, the dosing interval was reduced to once every 3 weeks. A kidney biopsy specimen obtained because of repeated erythrocyturia did not reveal vasculitis or other abnormalities when examined by conventional, fluorescence, and electron microscopy. The patient was repeatedly hospitalized for draining of a pilonidal sinus with *Streptococcus pyogenes*, which was finally surgically removed. Once more, he was hospitalised on account of a

disease flare with fever and aseptic meningitis, for which he was treated with dexamethasone with slow tapering.

Patient J

The patient presented in 2008 with subcutaneous nodules, painful testicles, fever, malaise, night sweats, and weight loss. He had elevated inflammatory parameters, a normocytic anemia, and thrombocytopenia. No autoantibodies were present. The patient was diagnosed with polyarteritis nodosa and was treated initially with prednisolone, 30 mg per day, with a favorable response. However, during the course of his disease relapses occurred after tapering of the prednisolone dose. Mycophenolate mofetil was added as a corticosteroid-sparing agent, but because of lack of efficacy it was switched to methotrexate. The disease relapsed with vasculitis of the pulmonary vasculature, which was proved after an open lung biopsy. Treatment with cyclophosphamide and rituximab was then started, followed with azathioprine. The addition of infliximab and intravenous immunoglobulins did not improve the patient's clinical status. In 2011, it was decided to start tocilizumab next to a prednisolone dose of 12.5 mg per day, which resulted in a quiescent disease state for 1.5 years. The patient subsequently developed macrocytic anemia, after which it was decided to discontinue his cotrimoxazole prophylaxis, as this was a suggested cause. Intercurrently, the patient contracted a nosocomial pneumonia that responded to treatment with broad-spectrum antibiotics. However, in the months thereafter the patient developed a *P jirovecii* pneumonia, after which treatment with cotrimoxazole was reinstated. The patient remained stable during continued use of 15 mg of prednisolone per day and monthly injections of tocilizumab. However, he developed type 2 diabetes, squamous cell carcinoma at multiple sites, thrombotic complications, pulmonary infections, and recurrent phlebitis. Because of the numerous infectious episodes the clinicians decided to stop the tocilizumab treatment. Subsequently, further macrocytic anemia, thrombocytopenia, and leukopenia developed. A bone marrow examination revealed some abnormalities pointing toward MDS, type refractory cytopenia with multilineage dysplasia, with normal cytogenetics and a low-intermediate International Prostate Symptom Score. Erythropoietine and monthly blood transfusions were initiated. Additionally, cyclosporine was added without any benefit. The patient remained dependent on an intermediate dose of prednisolone and was treated preventively with cotrimoxazole and valaciclovir. Unfortunately, he developed progressive cardiac failure and died in 2016 as a result of a complicated urinary tract infection with respiratory failure.

Patient K

The patient presented in 2016 at the age of 76 with fever, back pain, elevated inflammatory parameters, and a macrocytic anemia. After extensive workup he was ultimately diagnosed with large-vessel vasculitis, although this diagnosis could not be confirmed by additional testing. He was treated with high-dose corticosteroids. Although his symptoms improved, the dose could not be tapered to acceptable levels. Methotrexate was then added, and subsequently, the patient was treated with tocilizumab for a limited time. During the course of his disease he developed several complications, including recurrent skin lesions and pulmonary infiltrates. Eventually he also developed a *Nocardia* infection for which long-lasting treatment was started. Because of the infectious complications, the corticosteroids were drastically tapered. Although the patient's fever did not recur, he continued to have markedly elevated inflammatory parameters and a macrocytic anemia. Bone marrow aspiration showed a hypercellular bone marrow without dysplastic features but with extensive vacuolization. After the diagnosis of VEXAS was made, tocilizumab was restarted. The patient still has many complaints of muscle ache and arthralgia. His anemia has improved, but his inflammatory parameters are still elevated.

Patient L

The patient presented in 2019 at 56 years of age with high fever and night sweats. He had elevated inflammatory parameters and a macrocytic anemia. Because he also complained of proximal muscle weakness, a presumptive diagnosis of large-vessel vasculitis was made, although this diagnosis could not be confirmed by additional testing. He began receiving high-dose corticosteroids (prednisone, 60 mg per day, and ultimately, because of nonresponse, 100 mg per day). During immunosuppressive treatment he developed a severe influenza pneumonia for which he was admitted to the intensive care unit. While his prednisone dose was being tapered, he developed inflammation of both the cartilage of his ear and the posterior sclera. It was concluded that he must be experiencing relapsing polychondritis, and methotrexate was added to his medications. During workup, a bone marrow aspiration was performed; it showed a hypercellular bone marrow but without dysplastic features. There were signs of hemophagocytosis and striking vacuolization. After the diagnosis of VEXAS was made, the patient began receiving a combination of corticosteroids in a tapering dose (currently 20 mg) and weekly tocilizumab. He is currently doing well. Both his inflammatory parameters and his anemia have improved.