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VEXAS syndrome: a Swiss national retrospective cohort study

Louis Wolff[a*], Leo Caratsch[b*], Fabian Lötscher[cd], Luca Seitz[c], Pascal Seitz[c], Yann Coattrenec[e], Jörg Seebach[e], Oliver Vilinovszki[f], Stefan Balabanov[f], Jakob Nilsson[g], Aylin Canbek[h], Aurélie Clottu[a], Rolf Bruecker[i], Anna Efthymiou[j], Dena Regli[k], Manolaraki Chrysoula[l], Andrea Amstad[l], Nicolas Bonadies[m], Sabine Blum[n], Mariana Chitic[o], Cornelia Schreiber[p], Denis Comte[b]

[a] Division of Immunology and Allergy, Department of Medicine, Lausanne University Hospital (CHUV), Lausanne, Switzerland
[b] Division of Internal Medicine, Department of Medicine, Lausanne University Hospital (CHUV), Lausanne, Switzerland
[c] Department of Rheumatology and Immunology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
[d] Upper Valais Hospital Centre Visp (SZO), Rheumatology, Hôpital du Valais, Visp, Switzerland
[e] Division of Immunology and Allergy, Geneva University Hospitals, Geneva, Switzerland
[f] Department of Medical Oncology and Hematology, University Hospital Zurich, Zurich, Switzerland
[g] Department of Immunology, University Hospital Zurich, Zurich, Switzerland
[h] Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland
[i] Rheumatology, Hirslanden Klinik St. Anna, Lucerne, Switzerland
[j] Department of Hemato-Oncology, HFR Hôpital Fribourgeois, Fribourg, Switzerland
[k] Department of Internal Medicine, HFR Hôpital Fribourgeois, Fribourg, Switzerland
[l] Department of Rheumatology, University Hospital Basel and University of Basel, Basel
[m] Oncology and Hematology Private Practice, Solothurn, Switzerland
[n] Division of Hematology and Hematology Central Laboratory, Lausanne University Hospital (CHUV), Lausanne, Switzerland
[o] Department of Medicine, Limattal Hospital, Schlieren, Switzerland
[p] Department of Oncology and Hematology, Limattal Hospital, Schlieren, Switzerland
[*] These authors equally contributed as first authors.

Summary

STUDY AIMS: VEXAS syndrome is a recently discovered monogenic auto-inflammatory disease caused by a somatic mutation in the *UBA1* gene that manifests with rheumatologic and haematologic features. In this report, we present the first Swiss cohort, detailing its manifestations and treatment outcomes among Swiss patients.

METHODS: Data were retrospectively collected from nine hospitals across Switzerland, representing a broad geographic distribution. Treating physicians completed a standardised case report form for each patient. The principal investigator and the co-investigators collected and analysed all case report forms.

RESULTS: We identified 23 patients between July 2022 and 2023, of which 17 are described. All were male. They presented with skin manifestations (88%), general symptoms (82%), venous thromboembolism (59%), ocular manifestation (59%), lung infiltrates (59%) and articular manifestations (47%). Central nervous system and kidney manifestations were very rare, and heart and digestive manifestations were absent. Macrocytic anaemia was present in all patients throughout the disease progression but only in two-thirds of patients (12/17, 71%) at the time of diagnosis. Clinical response was reached in all cases treated with ruxolitinib (4/4, 100%), upadacitinib (1/1, 100%), azacytidine (5/5, 100%) and haematopoietic stem cell transplantation (2/2, 100%). All deaths were attributed to infections (5/5, 100%).

CONCLUSION: This study corroborates the clinical spectrum of VEXAS syndrome described in other cohorts. It suggests that VEXAS syndrome is not limited to patients with macrocytic anaemia. In this study, azacytidine has been used effectively among patients with myelodysplastic syndrome. In addition, Janus kinase (JAK) inhibitors, particularly ruxolitinib, have been successfully used even in those without myelodysplastic syndrome. We report two successful treatments by haematopoietic stem cell transplantation.

Louis Wolff
Division of Immunology and Allergy
Department of Medicine
Lausanne University Hospital (CHUV)
CH-1005 Lausanne
louis.wolff[at]ulb.be

Introduction

Identified in 2020, VEXAS syndrome (Vacuoles, E1 Enzyme, X-linked, Auto-inflammatory, Somatic) is a unique monogenic auto-inflammatory disease that emerges predominantly in the later stages of life. It is caused by a somatic mutation in the ubiquitin-like modifier activating enzyme 1 (*UBA1*) gene, predominantly impacting myeloid precursor cells. Current scientific understanding suggests that *UBA1* mutation reduces ubiquitylation, leading to heightened oxidative stress and the accumulation of unfolded proteins, resulting in inflammation [1, 2]. The clinical features of VEXAS syndrome include general symp-

ABBREVIATIONS

JAK:	Janus kinase
UBA1:	ubiquitin-like modifier activating enzyme 1
VEXAS:	Vacuoles, E1 Enzyme, X-linked, Auto-inflammatory, Somatic

toms (fever, weight loss and sweats), musculoskeletal complaints, pulmonary infiltrates, skin manifestations (e.g. neutrophilic dermatosis), eye involvement and thromboembolism [3]. Interestingly, VEXAS syndrome has specific features that distinguish it from other immune-mediated inflammatory diseases: it is highly associated with myelodysplastic syndromes and is more resistant to immunosuppressive drugs [3].

Currently, our understanding of the management of VEXAS syndrome remains nascent. The therapeutic approach varies according to the presence or absence of myelodysplastic syndrome. When myelodysplastic syndrome is present, targeting clonal haematopoiesis with a hypomethylating agent, such as azacytidine, is suggested as first-line therapy. Conversely, when myelodysplastic syndrome is absent, the treatment aims to mitigate inflammation. Here, immunosuppressants such as ruxolitinib or tocilizumab have shown promise [4, 5]. Haematopoietic stem cell transplantation emerges as a potential curative treatment not only for those with myelodysplastic syndrome but also for some cases without myelodysplastic syndrome. Those patients usually suffer severe autoinflammatory manifestations and are refractory to immunosuppressants [5, 6].

Given the emerging nature of VEXAS syndrome and the diversity of therapeutic approaches, there is an urgent need to consolidate data and experience. This study was designed as a national retrospective cohort study involving nine major hospitals across Switzerland, spanning multiple regions. Our primary objective is to analyse the phenotypic aspects of VEXAS syndrome and investigate the various treatments used in Switzerland.

Materials and methods

We performed a retrospective study across nine major hospitals in Switzerland from July 2022 to July 2023, including institutions in Bern, Zurich, Geneva, Fribourg, Sion, Lausanne, Lucerne, Neuchâtel and Basel. These hospitals represent both university centres and regional medical facilities, ensuring a broad geographic distribution and diverse representation of the Swiss population. Physicians from relevant specialities, including internal medicine, rheumatology, haematology, and immunology, were contacted to identify potential patients. The patient could be included if he or she was diagnosed with a mutation in the *UBA1* gene, independent of the sequencing method. The treating physician completed a case report form for each patient in a Microsoft Excel spreadsheet (version 16.73). The case report form encompassed the patient's demographics, epidemiological data, detailed clinical presentation, laboratory results – including *UBA1* mutation analysis – bone marrow examination, treatment modalities and clinical response. Two authors (LW and LC) compiled the case report forms, with a team of three authors (LW, LC and DC) conducting subsequent analyses. This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [7]. Quantitative variables are presented as the median (interquartile range [IQR]), and categorical variables are presented as the number (percentage). The clinical response was defined as the induction of a state without relapse and no need to transition to an alternative immunosuppressor. The laboratory results were recorded at the time of diagnosis, which was defined as the discovery of the mutation.

This study was approved by the Ethics Committee of the Canton of Vaud (CER-VD 2022-01365) and performed according to the Declaration of Helsinki, as revised in 2013, and written informed consent was obtained from all participating patients.

Results

Epidemiology

Of the 23 patients identified as suffering from VEXAS syndrome, 17 were included in our study: two refused to participate, and four were excluded due to incomplete data. All included patients were male. The median age at symptom onset and diagnosis were 67.5 (58–75) and 70.3 (59–77) years, respectively. The youngest recorded age for disease onset and diagnosis were 49 and 52 years, respectively. By the end of the study period, 29% (5/17) of the patients had died (table 1).

Clinical manifestations

Most patients exhibited general symptoms: fever (11/17, 64%), night sweats or weight loss (14/17, 82%). Skin manifestations were the most commonly reported (15/17, 86%), including neutrophilic dermatosis (6/17, 35%), leukocytoclastic vasculitis (5/17, 29%), spongiotic dermatitis (3/17, 18%) and unspecified panniculitis (2/17, 12%). Chondritis was observed in four patients (4/17, 24%), primarily affecting the ear, nose, costal cartilage and upper airways.

Musculoskeletal involvement was present in nearly half of the patients, presenting as arthralgias (8/17, 47%) and arthritis (6/17, 35%). The affected joints included the small joints (7/17, 41%), such as the metacarpophalangeal (MCP), proximal interphalangeal (PIP) and distal interphalangeal (DIP), as well as large joints (6/17, 35%), such as the knees, wrists, ankles and elbows. Moreover, sacroiliitis was present in one patient.

Ophthalmologic manifestations were present in more than half of the patients (10/17, 59%) and manifested as orbital inflammation (4/17, 24%), scleritis (2/17, 12%), episcleritis (3/17, 18%), ocular venous thrombosis (1/17, 6%), anterior uveitis (2/17, 12%) and anterior ischaemic optic neuropathy (1/17, 6%). Venous thromboembolism was observed in ten patients (10/17, 59%), with deep vein thrombosis (6/17, 35%) and pulmonary embolism (3/17, 18%) being the most common forms. Confounding factors such as anticoagulant use or specific triggers were not investigated. Vasculitis was found in seven patients (7/17, 41%), including leukocytoclastic vasculitis (4/17, 24%), aortitis (2/17, 12%) and renal artery aneurysms in one case. Lung involvement was present in ten patients (10/17, 59%), including cryptogenic organising pneumonia (4/17, 23%), usual interstitial pneumonia (2/17, 12%), micro and macro nodules (2/17, 12%) and nonspecific interstitial pneumonia (1/17, 6%). One patient presented pleuritis with lymphohistiocytic reactions. Lymphadenopathies were observed in eight patients (8/17, 41%), predominantly in the mediastinal, cervical, axillary and inguinal chains, with biop-

Table 1:
Epidemiology and manifestations: characteristics at diagnosis.

Age (years), median (IQR)			74 (59–77)
Male sex, number (%)			17/17 (100)
Death, number (%)			5/17 (29)
General symptoms, number (%)			14/17 (82)
	Fever, number (%)		11/17 (65)
	Weight loss, number (%)		7/17 (41)
	Sudation, number (%)		7/17 (41)
Skin manifestations, number (%)			15/17 (86)
	Neutrophilic dermatosis, number (%)		5/17 (29)
	Dermatitis spongiotic, number (%)		3/17 (18)
	Panniculitis, number (%)		2/17 (12)
	Atopic dermatitis, number (%)		1/17 (6)
Pulmonary manifestations, number (%)			10/17 (59)
	Cryptogenic organising pneumonia (COP), number (%)		4/17 (23)
	Nodules, number (%)		2/17 (12)
	Usual interstitial pneumonia (UIP), number (%)		2/17 (12)
	Nonspecific interstitial pneumonia (NSIP), number (%)		1/17 (6)
	Pleural effusion, number (%)		1/17 (6)
Chondritis, number (%)			4/17 (24)
	Auricular, number (%)		2/17 (12)
Nasal, number (%)			2/17 (12)
	Costal, number (%)		1/17 (6)
	Tracheal, number (%)		1/17 (6)
Conductive hearing loss, number (%)			1/17(6)
Adenopathy, number (%)			8/17 (47)
	Mediastinal, number (%)		5/17 (29)
	Paraoeosphageal, number (%)		1/17 (6)
	Inguinal, number (%)		2/17 (12)
	Axillary, number (%)		2/17 (12)
	Cervical, number (%)		4/17 (24)
Polyarthralgia, number (%)			8/17 (47)
	Polyarthritis, number (%)		6/17 (35)
	Peripheral, number (%)		8/17 (47)
		Small articulations, number (%)	7/17 (41)
		Large articulations, number (%)	8/17 (47)
		Axial, number (%)	1/17 (6)
Ocular manifestations, number (%)			10/17 (50)
	Orbital inflammation, number (%)		4/17 (24)
	Scleritis, number (%)		2/17 (12)
	Episcleritis, number (%)		3/17 (18)
	Anterior uveitis, number (%)		2/17 (12)
	Ocular veinous thrombosis, number (%)		1/17 (6)
	Anterior ischaemic optic neuropathy, number (%)		1/17 (6)
Digestive, number (%)			0/17 (0)
Central nervous system, number (%)			1/17 (6)
Peripheral nervous system, number (%)			2/17 (12)
Orchitis, number (%)			1/17 (6)
Heart, number (%)			0/17 (0)
Vasculitis, number (%)			7/17 (41)
	Leukocytoclastic vasculitis, number (%)		5/17 (29)
	Aortitis, number (%)		1/17 (6)
	Aneurysm of renal arteries, number (%)		1/17 (6)
Acute renal insufficiency, number (%)			1/17 (6)
Venous thromboembolism, number (%)			10/17 (59)
	Deep vein thrombosis, number (%)		6/17 (35)
	Pulmonary embolism, number (%)		3/17 (18)
Haematological manifestations, number (%)			15/17 (86)
	Myelodysplastic syndrome, number (%)		12/17 (71)
	Lymphoproliferative disease, number (%)		1/17 (6)
	Monoclonal gammopathy of undetermined significance (MGUS), number (%)		3/17 (18)

IQR: interquartile range.

sies showing follicular and interfollicular hyperplasia and haemophagocytic lymphohistiocytosis in one patient. Orchitis was reported in one patient, central nervous system involvement (stroke) in another patient, and peripheral nervous system involvement was observed in two patients (2/17, 12%), described as distal symmetric sensory polyneuropathy. One patienthad progressive chronic renal insufficiency of unknown origin (figure 1).

Laboratory work-up at diagnosis

At the time of diagnosis, macrocytic anaemia was present in 12 patients (12/17, 71%), with all patients eventually developing macrocytosis. The mean corpuscular volume (MCV) was 101 fl (range: 100–108), and the mean haemoglobin level was 84 g/l (range: 80–100). Platelet level was found at 169 × 10^9/l (range: 97–261), with thrombopenia observed in seven patients (7/17, 41%). Notably, all patients with thrombopenia also exhibited anaemia.

The mean total white blood cell count was 3.9 × 10^9/l (range: 3.2–4.9), with lymphocyte and neutrophile counts of 0.65 × 10^9/l (range: 0.38–0.88) and 2.8 × 10^9/l (range: 2.2–3.6), respectively. Eosinophilia was noted in only one patient (1.44 × 10^9/l). Inflammatory markers showed elevated C-reactive protein (CRP) of 103 mg/l (range: 49–130) and an erythrocyte sedimentation rate (ESR) of 95 mm/h (range: 78–103). The mean creatinine was 75 mmol/l (range: 68–108). The coagulation profile included a mean INR of 1.1 (range: 1.05–1.2) and activated partial thromboplastin time (aPTT) of 30 s (range: 26–33). The antinuclear antibody titers (ANA) were equal to or greater than 1/160 in five patients (5/17, 29%), with titers of 1/160 in three patients and 1/640 in two patients. Complement components C3 and C4 were within normal limits in all seven patients tested (table 2).

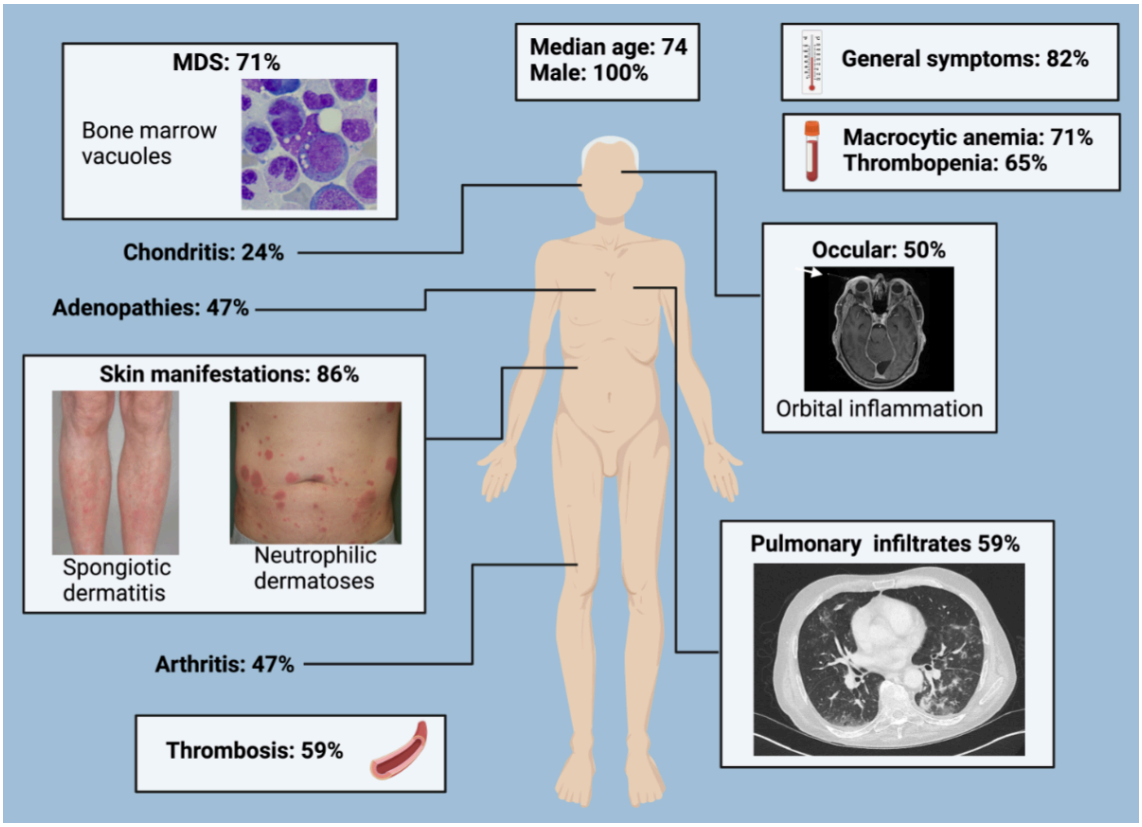
Haematological manifestations

Haematological manifestations were present in 13 patients (13/17, 75%), with 12 showing myelodysplastic syndrome (12/17, 71%). Transfusion dependence was reported in two patients (2/17, 12%). One case of small cell lymphocytic lymphoma and three cases of monoclonal gammopathy of undetermined significance were reported. Bone marrow analysis revealed vacuoles in 16 patients (16/17, 94%) and dysplasia in 12 patients, with all cases of myelodysplastic syndrome showing multilineage dysplasia. Bone marrow fibrosis was observed in three patients (3/17, 18%). Somatic mutations in *UBA1* were identified in all patients. Canonical mutations were the most common: Met41Thr (65%, 11/17), Met41Val (12%, 2/17) and Met41Leu (12%, 2/17). Splicing site mutations were less common: c.118–1G>C (6%, 1/17) and c.118–2A>C (6%, 1/17). The variant allele frequency (VAF) was available for four patients and averaged 57% (range: 47–83).

Treatments responses

All patients required glucocorticoids and various lines of immunosuppressants. Janus kinase inhibitors induced clinical remission in five of the treated patients (5/6, 83%). Specifically, ruxolitinib achieved clinical remission in all

Figure 1: Illustrations of the signs and symptoms of VEXAS syndrome. The images are from patients within our cohort and illustrate the wide range of clinical manifestations of VEXAS syndrome. MDS: myelodysplastic syndrome.



treated patients (4/4, 100%) and was well-tolerated. Upadacitinib also resulted in a clinical remission in the only treated patient (1/1, 100%). Tofacitinib, used in two cases, did not induce a clinical remission as a standalone treatment (0/1, 0%) but, when combined with cyclosporine, led to a clinical remission in another patient (1/1, 100%) (table 3).

Tocilizumab, an interleukin-6 receptor (IL-6R) blocker, induced a clinical remission in three treated patients (3/8, 37%), with adverse events reported in two treated patients (2/8, 25%), including cytopenia and anaphylaxis. Combining tocilizumab with methotrexate failed to induce a clinical remission in two patients (0/2, 0%) and was discontinued in one patient due to neutropenia (1/2, 50%).

Regarding tumour necrosis factor (TNF)-alpha blockers, adalimumab led to a clinical remission in one patient, but infliximab did not result in a clinical remission in any treated patient (0/3, 0%). Combining infliximab with methotrexate did not achieve a clinical remission and caused pancytopenia. Cyclosporine alone led to a clinical remission in both treated patients. All patients treated with anakinra exhibited reactions at the injection site, necessitating treatment interruption. Six patients were treated, but no clinical remission was observed, even among those treated for more than a month. While it did not lead to cutaneous intolerance, canakinumab did not lead to a clinical remission in two patients. Even in combination with mycophenolate mofetil, rituximab failed to induce a clinical remission. Other treatments that failed to induce a clinical remission included cyclophosphamide, colchicine, hydroxychloroquine, methotrexate, mycophenolate mofetil, azathioprine, dapsone, abatacept and intravenous immunoglobulin.

Treatments for myelodysplastic syndrome

In patients with myelodysplastic syndrome, treatment with azacytidine achieved a clinical remission in all cases (5/5, 100%) and was well-tolerated. Lenalidomide was used in one patient and did not lead to a clinical remission (0/1, 0%). Haematopoietic stem cell transplantation led to a clinical remission in two patients (2/2, 100%), both of whom are currently in remission after one year and one month, respectively.

Prognosis

All five deaths in the study were attributed to infectious complications. One patient with the Met41Val mutation (1/2, 50%) died at the age of 75 years, five years after diagnosis. Four patients with the Met41Thr or Met41Leu mutations had died by the time of this study (4/15, 27%).

Discussion

We present the first Swiss cohort of patients diagnosed with VEXAS syndrome. Epidemiologically, their ages at presentation and diagnosis align with those reported in oth-

Table 2:
Additional work up: characteristics at diagnosis.

Laboratory parameter		
Macrocytic anaemia, number (%)		12/17 (71)
Thrombopenia, number (%)		11/17 (65)
Haemoglobin (g/l), median (IQR)		84 (80–100)
MCV (fl), median (IQR)		101 (100–108)
Leucocytes (10^9/l), median (IQR)		3.9 (3.2–4.9)
	Lymphocytes (10^9/l), median (IQR)	0.66 (0.38–0.88)
	Neutrophils (10^9/l), median (IQR)	2.9 (2.2–3.6)
	Eosinophils (10^9/l), median (IQR)	0.01 (0–0.1)
Platelets (10^9/l), median (IQR)		169 (97–261)
CRP (mg/l), median (IQR)		103 (49–130)
ESR (mm/h), median (IQR)		95 (78–103)
Creatinine (µmol/l), median (IQR)		78 (68–108)
INR (number), median (IQR)		1.1 (1.05–1.2)
aPTT (s), median (IQR)		30 (26–33)
Anti-nuclear antibodies (≥1/160), number (%)		5/17 (29)
Identified antinuclear antibodies, number (%)		0/17 (0)
Bone marrow		
Vacuoles, number (%)		16/17 (94)
Dysplasia, number (%)		12/17 (71)
	Trilinear dysplasia, number (%)	5/17 (29)
	Bilinear dysplasia, number (%)	5/17 (29)
Presence of blasts, number (%)		0/17 (0)
Fibrosis, number (%)		3/17 (18)
Genetic mutations		
c.122T>C (p.Met41Thr), number (%)		11/17 (65)
c.121A>G (p.Met41Val), number (%)		2/17 (12)
c.121A>C (p.Met41Leu), number (%)		2/17 (12)
c.118-1G>C, number (%)		1/17 (6)
c.118-2A>C, number (%)		1/17 (6)

aPTT: activated partial thromboplastin time; CRP: c-reactive protein; ESR: erythrocyte sedimentation rate; INR : international normalised ratio; IQR: interquartile range; MCV: mean corpuscular volume.

er case series [2, 3, 8]. Our cohort consisted exclusively of males, a characteristic similar to most reported series [2, 8]. Notably, the prevalence of VEXAS is approximately 23 in 100,000 for males aged >50 years, compared to 4 in 100,000 for females [9]. The lower prevalence in females is mainly due to its X-linked nature, with cases in females typically attributed to constitutive monosomy [10]. While the sample size of our cohort is limited due to the rarity of VEXAS syndrome, the inclusion of cases from nine hospitals across Switzerland strengthens the generalisability of our findings within the Swiss population and underscores the national scope of our study. This multi-centre approach provides valuable insights into the clinical characteristics and treatment responses in a real-world setting, highlighting the importance of collaboration in rare disease research.

In our cohort, patients presented with general symptoms (82%) and skin manifestations (88%), similar to findings in other cohorts. However, despite its limited size and important risk of random variability, our cohort showed a tendency toward higher rates of venous thromboembolism (59%), ocular manifestations (59%), pulmonary infiltrates (59%) and articular manifestations (47%), which were more common compared to previous studies [2, 3, 8]. Consistent with other cohorts, the arthritis observed was non-erosive, and cases of chondritis did not progress to saddle nose deformity. Moreover, the involvement of the central nervous system, kidneys, heart, and digestive tract was rare in our cohort, aligning with other reports [3, 11].

Orbital inflammation was observed more frequently in our cohort than in others. Notably, our study is the first to describe a case of anterior ischaemic optical neuropathy as a manifestation of VEXAS syndrome. Ocular manifestation in VEXAS syndrome can affect any structure within the eye and orbit, with approximately 12% of reported cases experiencing orbital or periorbital inflammation [12–14]. This type of inflammation is typically associated with granulomatosis with polyangiitis and immunoglobulin G4 (IgG4)-related disease but is rare in relapsing polychondritis and other autoinflammatory disease (except for tumour necrosis factor receptor-associated periodic fever syndrome [TRAPS]) [15–18]. In cases of polychondritis or autoinflammatory diseases, the presence of orbital inflammation may suggest VEXAS syndrome. However, the specific mechanisms leading to the development of orbital inflammation in VEXAS syndrome remain to be elucidated.

Like the French cohort, lung involvement in our cohort was often characterised by consolidations compatible with cryptogenic organising pneumonia, nodules or interstitial involvement (usual interstitial pneumonia or nonspecific

Table 3:
Treatments.

Medication			Clinical response	Intolerance
Janus kinase inhibitors	Ruxolitinib, number (%)		4/4 (100)	0/4 (0)
	Upadacitinib, number (%)		1/1 (100)	0/1 (0)
	Tofacitinib, number (%)		0/1 (0)	0/1 (0)
	Tofacitinib with cyclosporine, number (%)		1/1 (100)	0/1 (0)
IL-6R blockers	Tocilizumab, number (%)		3/8 (37)	2/8 (25): Cytopenia and anaphylaxis
	Tocilizumab with methotrexate, number (%)		0/2 (0)	1/2 (50): Neutropenia
IL-1 blockers	Anakinra, number (%)		0/5 (0)	5/5 (100): Reactions at the injection site
	Canakinumab, number (%)		0/2 (0)	0/2 (0)
TNF-alpha blockers	Adalimumab, number (%)		1/3 (33)	0/3 (0)
	Infliximab, number (%)		0/3 (0)	0/3 (0)
	Infliximab with methotrexate, number (%)		0/1 (0)	1/1 (100): Pancytopenia
Other treatments	Cyclosporine, number (%)		2/2 (100)	0/2 (0)
	Rituximab, number (%)		0/2 (0)	0/2 (0)
	Rituximab with mycophenolate mofetil, number (%)			
	Cyclophosphamide, number (%)		0/2 (0)	0/2 (0)
	Methotrexate, number (%)		0/6 (0)	1/6 (17): Pancytopenia
	Hydroxychloroquine, number (%)		0/2 (0)	0/2 (0)
	Mycophenolate mofetil, number (%)		0/2 (0)	0/2 (0)
	Colchicine, number (%)		0/5 (0)	0/5 (0)
	Azathioprine, number (%)		0/3 (0)	0/3 (0)
	Intravenous immunoglobulin, number (%)		0/1 (0)	0/1 (0)
		Abatacept, number (%)	0/1 (0)	0/1 (0)
		Dapsone, number (%)	0/1 (0)	0/1 (0)
Treatments for myelodysplastic syndrome	Azacytidine, number (%)		2/2 (100)	0/2 (0)
	Azacytidine with anakinra, number (%)		1/1 (100)	1/1 (100): Reaction at the injection site
	Azacytidine with canakinumab, number (%)		1/1 (100)	0/1 (0)
	Azacytidine with tocilizumab, number (%)		1/1 (100)	0/1 (0)
	Lenalidomide, number (%)		0/1 (0)	0/1 (0)
	Haematopoietic stem cell transplantation, number (%)		2/2 (0)	0/2 (0)

IL-6R: interleukin-6 receptor; IL-1: interleukin-1; TNF: tumour necrosis factor.

interstitial pneumonia). However, pleural effusion was present in only one patient, contrasting with the French cohort, where 53% of the patients with pulmonary involvement had pleural effusions [19]. These effusions were predominantly small in volume. Given our study's focus on the complete clinical picture of VEXAS syndrome rather than solely on its pulmonary manifestations, small effusions, which are common in the elderly, may have been overlooked.

The predilection site of chondritis in VEXAS syndrome is controversial. While two studies reported that VEXAS syndrome never affects upper airways and costal cartilage [18, 19], others found these sites to be affected, albeit less frequently [17, 20]. In our cohort, 50% of the patients with chondritis had costochondritis (one patient) or upper-airway chondritis (one patient). We conclude that the presence of costochondritis or upper-airway chondritis should not rule out VEXAS syndrome as a differential diagnosis of relapsing polychondritis.

Interestingly, we report one patient with sensorineural hearing loss without chondritis. Initially absent in the description by Beck et al., sensorineural hearing loss was later described in patients with VEXAS-related polychondritis [17, 18]. Its occurrence in relapsing polychondritis is well documented, although its development mechanism is largely unknown [21]. Our findings suggest that sensorineural hearing loss in VEXAS syndrome can occur independently of chondritis. Therefore, further studies are needed to investigate the relationship between VEXAS syndrome, chondritis and sensorineural hearing loss.

One patient in our cohort presented with genital involvement and renal artery aneurysms, initially leading to a diagnosis of polyarteritis nodosa. Post-mortem bone marrow analysis revealed a *UBA1* mutation, confirming VEXAS syndrome. While orchiepididymitis was not reported in larger cohorts [2, 3], it was noted in two case series, with a prevalence of 33% in one study [8, 22]. This finding suggests that genital involvement could be a classical manifestation of VEXAS syndrome and should be further investigated. Additionally, two other patients in our cohort showed manifestations compatible with giant cell arteritis, consistent with a previous description of patients with VEXAS syndrome [23].

The classical haematologic manifestations of VEXAS syndrome are macrocytic anaemia and thrombopenia [3, 18]. However, in our cohort, only 71% of patients exhibited macrocytic anaemia at diagnosis, and 65% exhibited thrombopenia. Therefore, their absence should not preclude a diagnosis of VEXAS syndrome if the clinical presentation is suggestive. Notably, the proportion of patients with macrocytosis varies across cohorts, ranging from 91 to 96%, with the lowest proportions reported in more recent articles, perhaps indicating a more acutely presenting cohort [2, 9]. Studies have shown that plasma cell dyscrasia is more common in those with VEXAS syndrome than in the general population, particularly in the form of monoclonal gammopathy of undetermined significance [24, 25]. In our cohort, 18% of the patients had monoclonal gammopathy of undetermined significance, but none had multiple myeloma. Most patients with myelodysplastic syndrome exhibited vacuoles and multilineage dysplasia without blasts. Remarkably, only one case of myelodysplastic syndrome progressing to acute myeloid leukaemia has been reported in VEXAS syndrome [26]. Our cohort exhibited the three primary mutations previously identified in VEXAS syndrome: p.Met41Thr, p.Met41Leu, and p.Met41Val, with p.Met41Thr being the most common. Notably, patients with the Met41Val mutation appeared to have a lower survival rate, as previously documented [3]. Additionally, the lymphohistiocytic reactions in the bone marrow, adenopathy and pleural fluid observed in three patients align with VEXAS syndrome's association with macrophage activation syndrome or similar features, likely correlating with the high inflammatory state and monocyte dysregulation characteristic of the disease [27–29].

All patients in our cohort treated with ruxolitinib, upadacitinib, cyclosporine, azacytidine and haematopoietic stem cell transplantation achieved a clinical remission. These findings are consistent with previous retrospective studies on the efficacy of Janus kinase inhibitors, particularly ruxolitinib, in VEXAS syndrome [30, 31]. Azacytidine was effective in managing cases of concomitant myelodysplastic syndrome [32]. The successful use of cyclosporine, including in combination with tofacitinib, has already been reported in previous case reports [33, 34]. Therefore, cyclosporine could be considered a treatment option in case of limited access to biotherapies. We report the successful use of haematopoietic stem cell transplantation in two patients, which currently remains the only curative therapy [6].

Regarding outcomes, all patient deaths were attributed to infections, highlighting the importance of immunosuppression due to either the disease or the treatment. One patient received intravenous immunoglobulin for five months without improvement or reduced infection frequency.

Our study had several limitations. Firstly, as a retrospective cohort study with a relatively small cohort, the generalisability of our findings may be limited. Secondly, the case report forms were completed by treating physicians without a centralised and standardised review process by a dedicated investigator, potentially leading to variability in data reporting and interpretation. Thirdly, our definition of a clinical remission was based on the absence of relapse (recurrence or symptom worsening) and the absence of a need for additional or escalated immunosuppressive therapy, which are both based on subjective parameters and not clearly defined.

In conclusion, our cohort highlights the importance of considering VEXAS syndrome in the differential diagnosis of patients presenting with multiple symptoms that do not fit the typical profile of vasculitis or connective tissue disease. Therefore, the screening for *UBA1* mutations should not be limited to male patients with macrocytosis. While the optimal treatment approach warrants further investigation, existing data suggest the efficacy of Janus kinase inhibitors as a first therapeutic option. In addition, haematopoietic stem cell transplantation is currently the only curative treatment available for VEXAS syndrome.

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We used the ChatGPT 3.5 language model and Whisperit.ai to check the spelling and grammar in this medical article.

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