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VEXAS syndrome: A Swiss National Retrospective Cohort Study

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Abstract

Aims of the study: VEXAS syndrome is a recently discovered monogenic auto-inflammatory disease due to a somatic mutation in UBA1 gene that manifests with rheumatologic and hematologic features. In this report, we present the first Swiss cohort, detailing its manifestations and treatment outcomes among Swiss patients.

Methods: Nine Swiss hospitals were contacted. Data was retrospectively filled by each treating physician in a case report form (CRF). All CRFs were collected and analyzed by the principal investigator and its co-investigators.

Results: We identified 23 patients and described 17 of them between July 2022 and 2023. All were males. 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 whereas heart and digestive manifestations were absent. Macrocytic anemia was present in all patients throughout the disease progression but only in 2/3 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 (AZA, 5/5, 100%) and hematopoietic stem cell transplantation (HSCT 2/2, 100%). All deaths were attributed to infections (5/5, 100%).

Conclusion: This study corroborates the clinical spectrum of VEXAS syndrome as described in other cohorts. It suggests that VEXAS syndrome isn't limited to macrocytic anemia patients. Azacytidine seems to be the appropriate first-line treatment in case of myelodysplastic syndrome (MDS). Conversely, JAK inhibitors, especially ruxolitinib, seem to be the best option in absence of MDS. For refractory cases, HSCT seems to be the only curative treatment.

Introduction

VEXAS syndrome (Vacuoles, E1 Enzyme, X-linked, Auto-inflammatory, Somatic), identified in 2020, is a unique monogenic auto-inflammatory disease that emerges predominantly in later stages of life. This syndrome originates from 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 leads to reduced ubiquitylation, leading to heightened oxidative stress and accumulation of unfolded proteins, which results in inflammation [1,2]. Clinical features of VEXAS syndrome include general symptoms (fever, weight loss, sweats), musculoskeletal complaints, pulmonary infiltrates, skin manifestations such as neutrophilic dermatosis, eye involvement and thrombo-embolism [3]. Interestingly, VEXAS syndrome has specific features that distinguish it from other immune-mediated inflammatory diseases: it is highly associated with myelodysplastic syndromes (MDS) and more resistant to immunosuppressive drugs [3]. As of now, our understanding of the management for VEXAS syndrome remains nascent. The therapeutic approach varies according to the presence or absence of MDS. In scenarios where MDS is present, targeting clonal hematopoiesis with a hypomethylating agent such as Azacytidine (AZA) is suggested as first-line therapy. Conversely, in the absence of MDS, the treatment aims at mitigating the inflammation. Here, immunosuppressants such as Ruxolitinib or Tocilizumab (TCZ) have shown promises [4,5]. Hematopoietic stem cell transplantation (HSCT) emerges as a potential curative treatment not just for those with MDS but also for certain cases without MDS. Those patients usually suffer severe autoinflammatory manifestations and are refractory to immunosuppressant medication [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 aims to fill this gap through a Swiss national retrospective cohort study. Our primary objective is to analyze the phenotypic aspects of VEXAS syndrome and discern the differential effectiveness of the various treatments.

Materials and Methods

We performed a retrospective study across 9 major hospitals in Switzerland (Bern, Zurich, Geneva, Fribourg, Sion, Lausanne, Lucerne, Neuchâtel and Basel) from July 2022 to July 2023. The treating physician filled out a case report form (CRF) for each patient on an Excel sheet (Microsoft Excel version 16.73). The CRF encompassed patient demographics,

epidemiological data, detailed clinical presentation, laboratory results including UBA1 mutation analysis, bone marrow examination, treatment modalities, and clinical response. Two authors (L. W. and L. C.) compiled the CRFs, with a team of three authors (L. W., L. C. and D. C.) conducting subsequent analysis. This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [7]. Quantitative variables were expressed as medians (interquartile range, IQR) and categorical variables as number (percentage). Clinical response was defined as the induction of a state without relapse and no necessity to transition to an alternative immunosuppressor. Laboratory results were recorded at the time of diagnosis, defined by the discovery of the mutation.

The project was approved by the Ethics Committee of the Canton of Vaud (CER-VD 2022-01365) in accordance with the Helsinky Declaration as revised in 2013, and written 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 males. The median ages 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 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%), leucocytoclastic vasculitis (5/17, 29%), spongiotic dermatitis (3/17, 18%) and unspecified panniculitis (2/17, 12%). Chondritis was observed in 4 patients (4/17, 24%), primarily affecting the ear, nose, costal cartilage, and upper airways.

Musculoskeletal involvement concerned nearly half of the patients, presenting as arthralgias (8/17, 47%) and arthritis (6/17, 35%). The affected joints included small joints (7/17, 41%) – such as metacarpophalangeal (MCP), proximal interphalangeal (PIP) and distal interphalangeal

(DIP) – as well as large joints (6/17, 35%) like the knees, wrists, ankles and elbows. Moreover, sacroiliitis was present in one patient.

Ophthalmologic manifestations concerned 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 ischemic optic neuropathy (AION, 1/17, 6%). Venous thrombo-embolism (VTE) was observed in 59% of patients (10/17), with deep vein thrombosis (6/17, 35%) and pulmonary embolism (3/17, 18%) being the most common. Confounding factors such as anticoagulant use or specific triggers were not investigated. Vasculitis was found in 41% of the patients (7/17), including leukocytoclastic vasculitis (4/17, 24%), aortitis (2/17, 12%) and renal artery aneurysms in one case. Lung involvement was present in 59% of patients (10/17), including cryptogenic organizing pneumonia (COP, 4/17, 23%), usual interstitial pneumonia (UIP, 2/17, 12%), micro and macro nodules (2/17, 12%) and non-specific interstitial pneumonia (NSIP, 1/17, 6%). One patient presented pleuritis with lymphohistiocytic reactions. Lymphadenopathies were observed in 41% of patients (8/17), predominantly in mediastinal, cervical, axillary and inguinal chains, with biopsies showing follicular and interfollicular hyperplasia and hemophagocytic lymphohistiocytosis in one patient. Orchitis was reported in one patient, central nervous system involvement in another one (stroke), and two patients showed peripheral nervous system involvement (2/17, 12%), described as distal symmetric sensory polyneuropathy. One patient had progressive chronic renal insufficiency of unknown origin (Figure 1).

Laboratory work-up at diagnosis

At the time of diagnosis, macrocytic anemia was present in 71% of patients (12/17), with all patients eventually developing macrocytosis. The mean corpuscular volume (MCV) averaged 101 fL (range 100–108), and the mean hemoglobin level was 84 g/L (range 80–100). Platelet level was found at 169 $\cdot 10^9$/L (range 97–261), with thrombopenia observed in 41% of the patients (7/17). Notably, all patients with thrombopenia also exhibited anemia.

The total white blood cell count averaged 3.9 $\cdot 10^9$ /L (range 3.2–4.9), with lymphocyte and neutrophile counts at 0.65 $\cdot 10^9$ /L (0.38–0.88) and 2.8 $\cdot 10^9$ /L (range 2.2–3.6), respectively. Eosinophilia was noted in only one patient (1.44 $\cdot 10^9$ /L). Inflammatory markers showed elevated C-reactive protein (CRP) at 103 mg/l (range 49–130) and erythrocyte sedimentation rate (ESR) at 95 mm/h (range 78–103). Average creatinine was 75 µmol/l (68-108).

Coagulation profile, including INR and activated Partial Thromboplastin Time (aPTT), were INR 1.1 (range 1.05–1.2) and 30 s (range 26–33), respectively. Antinuclear antibodies titers (ANA) were equal to or greater than 1/160 in 29% of patients (5/17), with titers of 1/160 in 3 patients and 1/640 in 2. Complement components C3 and C4 were within normal limits in all seven patients tested (Table 2).

Hematological manifestations

Hematological manifestations were present in 75% of patients (13/17), with 71% showing MDS (12/17). Transfusion dependence was reported in 12% of patients (2/17). One case of small cell lymphocytic lymphoma and 18% of monoclonal gammopathy of undetermined significance (MGUS) were reported. Bone marrow analysis revealed vacuoles in 94% and dysplasia in 71% of patients, with all MDS cases showing multilineage dysplasia. Bone marrow fibrosis was observed in a 18% of patients (3/17). UBA1 somatic mutations were identified in all patients, with MET41Thr (65%, 11/17), MET41Val (12%, 2/17) and MET41Leu (12%, 2/17). Less prevalent mutations included splicing sites c.118–1G>C (6%, 1/17) and c.118–2A>C (6%, 1/17). Variant allele frequency (VAF) was available for four patients and averaged 57% (range 47–83).

Treatments Responses

All patients required glucocorticoids (GC) and various lines of immunosuppressants. Janus Kinase inhibitors (JAKi) were effective in inducing clinical remission (CR) in 83% of the cases (5/6). Specifically, ruxolitinib achieved CR in all treated patients (4/4, 100%) and was well-tolerated. Upadacitinib also resulted in a CR in the one patient it was administered to (1/1, 100%). Tofacitinib, used in two cases, was not effective as standalone treatment (0/1, 0%) but, when combined with cyclosporine, led to CR in another patient (1/1, 100%). (Table 3).

TCZ, an IL-6R blocker, induced CR in 37% of patients (3/8), with adverse events in 25% of patients (2/8). These included cytopenia and anaphylaxis. The combination of TCZ with MTX failed to induce CR in two patients (0/2, 0%) and was discontinued in one patient due to neutropenia (1/2, 50%).

Regarding TNF-alpha blockers, Adalimumab led to CR in one case, but Infliximab (IFX) did not result in CR in another case. IFX combined with MTX did not achieve CR and caused pancytopenia. Cyclosporine alone led to CR in both patients who received it. All patients treated with Anakinra exhibited reactions at the injection site, necessitating treatment interruption. 6 patients were treated but no CR were observed, even among patients treated

more than a month. Canakinumab, even though it did not lead to cutaneous intolerance, did not lead to CR in two patients. Rituximab, even in combination with MMF, failed to induce CR. Other ineffective treatments included cyclophosphamide, colchicine, hydroxychloroquine, methotrexate, mycophenolate mofetil (MMF), azathioprine, dapsone, abatacept and intravenous immunoglobulin.

Treatments of MDS

In patients with MDS, treatment with AZA achieved CR in all cases (5/5, 100%) and was well-tolerated. Lenalidomide was used in one patient and did not lead to CR (0/1, 0%). HSCT was successful in two patients (2/2, 100%), both of whom achieved CR and are currently in remission – one year for the first patient and one month for the second.

Prognosis

All five deaths in the study were attributed to infectious complications. Half of the patients with MET41Val mutation (1/2, 50%) passed away, one at the age of 75, 5 years after the diagnosis, five years post diagnosis. Among patients with MET41Thr or Leu mutations, 27% (4/15) died by the time of the study.

Discussion

We present the first Swiss cohort of patient diagnosed with VEXAS syndrome. Epidemiologically, the ages at presentation and diagnosis in our cohort align with those reported in other case series [2,3,8]. Our cohort consisted exclusively of male patients, a characteristic that is similar to most reported series [2,8]. Notably, the prevalence of VEXAS in males older than 50 years old is approximately 1 in 4269, compared to 1 in 26238 for females [9]. The lower prevalence in women is mainly due to the X-linked nature of the disease, with cases in women typically attributed to constitutive monosomy [10].

In our study, patients presented with general symptoms (82%) and skin manifestations (88%), similar to findings in other cohorts. However, our cohort, despite its limited size, showed a tendency toward higher rates of VTE (59%), ocular manifestations (59%), pulmonary infiltrates (59%) and articular manifestations (47%), which were more prevalent 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, involvement of

the central nervous system, kidneys, heart, and digestive tract involvement was rare in our cohort, aligning with other reports [3,11].

Orbital inflammation was observed more frequently in our cohort compared to others. Notably, this study is the first to describe a case of anterior ischemic optical neuropathy (AION) 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 [12,13]. This type of inflammation is typically associated with granulomatosis with polyangiitis and IgG4-related disease, but is rare in relapsing polychondritis and other autoinflammatory disease (except for TRAPS) [14–17]. In cases of polychondritis or autoinflammatory diseases, the presence of orbital inflammation may suggest VEXAS. The specific mechanisms leading to the development of orbital inflammation in VEXAS syndrome, however, remain to be elucidated.

Similar to the French cohort, lung involvement in our cohort was often characterized by consolidations compatible with COP, nodules or interstitial involvement (UIP or NSIP). However, pleural effusion was present in only one patient, contrasting with the French cohort where 53% of patient with pulmonary involvement had pleural effusions [18]. These effusions were predominantly small in volume. Given our study's focus on the complete clinical picture of VEXAS syndrome, rather than solely on 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 never affects upper airways and costal cartilage [18,19], others found these sites were affected, albeit less frequently [16,20]. In our cohort, 50% of patient with chondritis had costochondritis (one patient) or upper-airways chondritis (one patient). We conclude that 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 [16,19]. It’s occurrence in RP is well documented, though its development mechanism is largely unknown [21]. Our findings suggest that sensorineural hearing loss in VEXAS can occur independently of chondritis. Therefore, further studies are

needed to investigate the relationship between VEXAS, chondritis and sensorineural hearing loss.

One patient in our cohort presented with genital involvement and renal artery aneurysms, initially leading to a diagnose of polyarteritis nodosa (PAN). Post-mortem bone marrow analysis revealed UBA1 mutation, confirming VEXAS syndrome. While orchi-epididimytis is 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, which is consistent with previous description of VEXAS patients [23].

The classical hematologic manifestations of VEXAS syndrome are macrocytic anemia and thrombopenia [3,19]. However, in our cohort at the time of diagnosis, only 71% of patients exhibited macrocytic anemia, and thrombopenia was present in 65%. Therefore, their absence should not preclude a diagnosis of VEXAS syndrome if the clinical presentation is suggestive. Notably, the proportion of macrocytosis varies significantly across different cohorts (Table 4), with the lowest proportion perhaps indicating a more acutely presenting cohort [9]. Studies have shown that plasma cell dyscrasia is more prevalent in VEXAS than in the general population, particularly in the form of monoclonal gammopathy of undetermined significance (MGUS) [24,25] In our study, 18% of patients had MGUS, but none had multiple myeloma (MM). Most patients with myelodysplastic syndrome (MDS) displayed vacuoles and multilineage dysplasia without blasts. Remarkably, only one case of MDS progressing to acute myeloid leukemia has been reported in VEXAS [26]. Our cohort exhibited the three main mutations previously identified in VEXAS: p.MET41Thr, -Leu, and -Val, with Thr being the most common. Notably, patients with the MET41Val mutation appeared to have a shorter survival rate, as previously documented [3]. Additionally, the presence of lymphohistiocytic reactions in the bone marrow, adenopathy, and pleural fluid of three patients aligns with VEXAS syndrome's association with macrophage activation syndrome or similar features. This likely correlates with the high inflammatory state and monocyte dysregulation characteristic of the disease [27–29].

All patients in our study treated with ruxolitinib, upadacitinib, cyclosporine, AZA and HSCT achieved CR. These findings are consistent with previous retrospective studies on the efficacy

of JAKi, particularly ruxolitinib, in VEXAS syndrome [30,31]. Azacitydine was effective in managing cases of concomitant MDS [32]. The successful use of cyclosporine, including its combination with Tofacitinib, was already reported in previous case reports [33,34]. Therefore, Cyclosporine could be considered as a treatment option in case of limited access to biotherapies. We report here the successful use of HSCT in two patients, which remains to date the only curative therapy [6].

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

Our study has several limitations. First, as a retrospective cohort study with a relatively small population, the generalizability of our findings may be limited. Second, the case report forms were filled by treating physicians without a centralized and standardized review process by a dedicated investigator, potentially leading to variability in data reporting and interpretation.
In addition, our definition of CR is based on subjective parameters, specifically: the occurrence of relapse and the need for additional immunosuppression, neither of which are clearly defined.

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

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Potential competing interest

No potential conflict of interest related to the content of this manuscript was disclosed.

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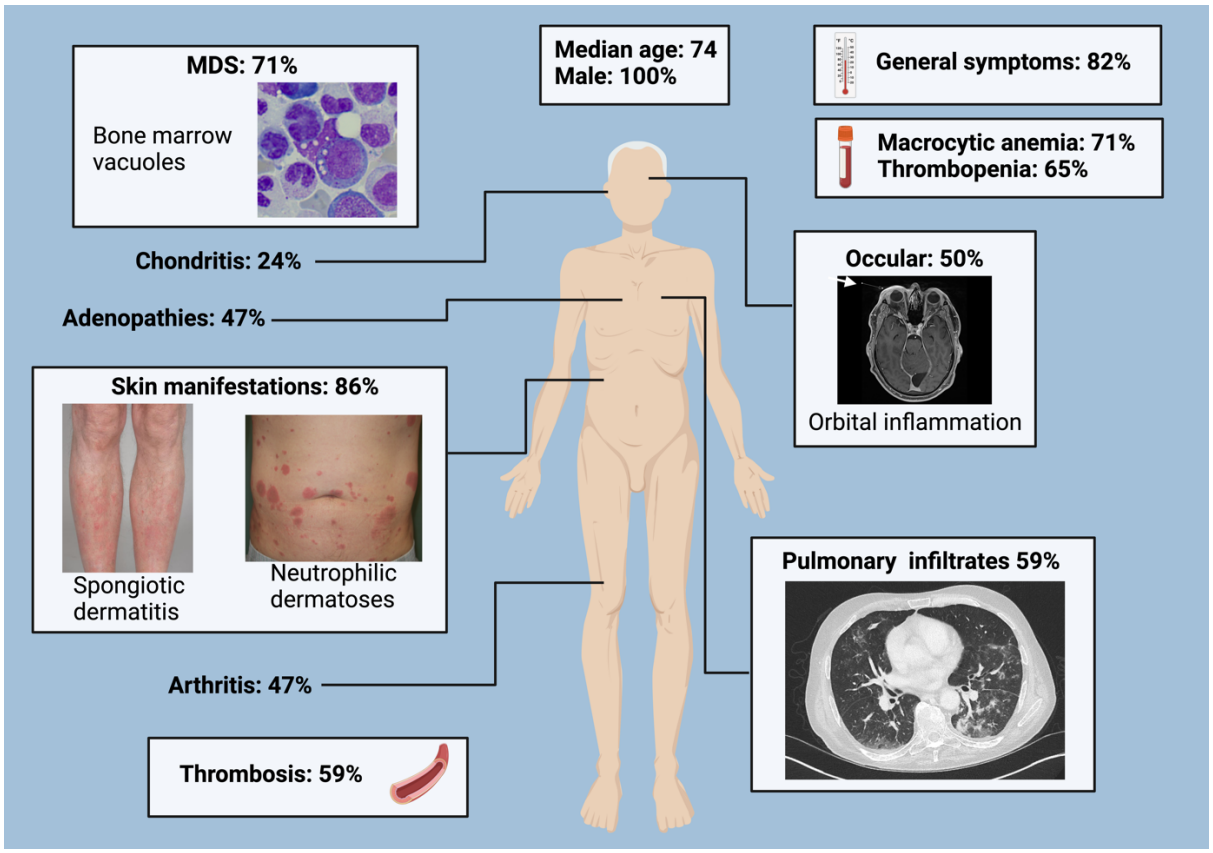
Figures

Figure 1: Illustrations of signs and symptoms of VEXAS syndrome. Images are from patients within our cohort and illustrate the wide range of clinical manifestation in VEXAS syndrome.



Tables

Table 1: Epidemiology and manifestations (IQR: interquartile range)

Characteristics at diagnosis	
Median age, years (IQR)	74 (59–77)
Male sex, number (%)	17/17 (100)
Deaths, 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 organizing pneumonia, number (COP, %)	4/17 (23)
Nodules, number (%)	2/17 (12)
Usual interstitial pneumonia, number (UIP, %)	2/17 (12)
Nonspecific interstitial pneumonia, number (NSIP, %)	1/17 (6)
Pleural effusion	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 ischemic 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)
Hematological 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)

Table 2: Additional work up (MCV: Mean Corpuscular Volume, IQR: Interquartile Range)

Characteristics at diagnosis	
Laboratory values	
Macrocytic anemia, number (%)	12/17 (71)
Thrombopenia, number (%)	11/17 (65)
Hb, 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)
Neutrophiles, 10^9/L, median (IQR)	2.9 (2.2–3.6)
Eosinophiles, 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, umol/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 anti-nuclear 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 (18%)
Genetic	
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)

Table 3: Treatments (MDS: myelodysplastic syndrome, JAKi: Janus Kinase Inhibitors, MMF: mycophenolate mofetil, TCZ: Tocilizumab and AZA: Azacytidine)

Medication	Clinical response	Intolerance
JAKi		
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		
TCZ, number (%)	3/8 (37)	2/8 (25): Cytopenia and anaphylaxis
TCZ 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 MMF, 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)
MMF, 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 of MDS		
AZA, number (%)	2/2 (100)	0/2 (0)
AZA with Anakinra, number (%)	1/1 (100)	1/1 (100): Reaction at the injection site
AZA with Canakinumab, number (%)	1/1 (100)	0/1 (0)
AZA with TCZ, number (%)	1/1 (100)	0/1 (0)
Lenalidomide, number (%)	0/1 (0)	0/1 (0)
Hematopoietic stem cell transplantation, number (%)	2/2 (0)	0/2 (0)

Table 4: Comparison of gender, macrocytosis and MCV among the largest cohorts (MCV: Mean Corpuscular Volume).

Cohort	Beck et al. (2020)	Beck et al. (2023)	Georgin-Lavialle et al.	Ferrada et al.	Van der Made et al.	Wolff et al.
Male, number (%)	100	82	95.7	100	100	100
Macrocytosis at diagnosis, number (%)	96	91	NA	97	50	71
MCV, fL, median	NA	109	101	NA	99	101

Keywords:

VEXAS, UBA1, swiss, monogenic, ruxolitinib, JAKi, azacytidine, auto-inflammatory, vacuoles, myelodysplastic syndrome.

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