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A clinical phenotype of VEXAS syndrome with pleural effusion, infiltrates, and systemic inflammation in a 76-year-old patient: a case report

Melanie Berger[1*], Falk Schumacher[2,3], Maximilian Wollsching-Strobel[1], Doreen Kroppen[1], Sarah B. Stanzel[1], Daniel S. Majorski[1], Kathrin Fricke[1], Ilka Plath[1], Wolfram Windisch[1] and Maximilian Zimmermann[1]

Abstract

Introduction VEXAS syndrome, characterized by a UBA1 gene mutation, is a rare and severe systemic inflammatory disease predominantly affecting men. Since its initial description in 2020, it has been noted for its broad clinical phenotype and frequent misdiagnosis.

Case Presentation A 76-year-old Caucasian male patient diagnosed with VEXAS syndrome is presented in this case report. He presented with typical symptoms including pulmonary manifestations (infiltrates and effusions), systemic inflammation, and haematological abnormalities. The diagnosis was challenging due to the disease's heterogeneous presentation, often resembling autoimmune or haematological diseases. This patient's case featured ground-glass opacities and pleural effusions, underlining the significant pulmonary involvement seen in 50–67% of VEXAS patients. His condition was further complicated by recurrent fever and systemic inflammation affecting multiple organs.

Conclusion VEXAS syndrome demands an aggressive treatment approach due to its high mortality rate and refractory nature. This case underscores the importance of including VEXAS syndrome in differential diagnoses, particularly for patients with systemic inflammation and pulmonary symptoms, and calls for multidisciplinary management and extensive research to understand its full range of clinical phenotypes.

Established facts and novel insights

1 VEXAS syndrome is a rare systemic inflammatory disease with UBA1 gene mutation.
2 VEXAS syndrome involves various UBA 1 gene mutations, including the p.splice c.118-1G > C.
3 It mainly affects men, often misdiagnosed due to its broad clinical phenotype.

*Correspondence:
Melanie Berger
bergerme@kliniken-koeln.de
Full list of author information is available at the end of the article

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Novel insights

1 Significant pulmonary involvement in VEXAS, including ground-glass opacities and pleural effusions.
2 Patients with the same mutation exhibit a broad range of disease phenotypes
3 A specific UBA1 mutation as the p.splice c.118-1G > C cannot be directly linked to a distinct disease phenotype
4 Need for aggressive treatment strategies targeting the mutated clone and cytokine storms

Keywords VEXAS syndrome, Systemic disease, Pulmonary involvement, UBA1 gene

Introduction

VEXAS Syndrome (vacuoles, E1-ubiquitin-activating enzyme, X-linked, autoinflammatory, somatic), first described in 2020, is a severe systemic inflammatory disease with a mutation in the UBA1 gene on the X chromosome in haemopoietic stem cells and is restricted to myeloid and erythroid cells in the periphery [1]. In a recently published study, blood analysis using DNA screening detected UBA1 mutation in 12 men and estimated a prevalence of 1:4269 men over the age of 50, which is higher than some other autoimmune and inflammatory diseases [2].

The UBA1 gen encodes for the E1 enzyme that is necessary for the initiation of most cellular ubiquitylation. This mutation is limited to myeloid cells. Ubiquitylation is essential for an effective immune response orchestrating the balance between a sufficient but not exuberant response of the innate immune system. Disbalance leads to a wide range of clinical features, from autoinflammation and myeloproliferation to tumorigenesis [3]. Defects in genes that regulate the innate immune system are a part of systemic autoinflammatory diseases (SAIDs) [4]. Over 30 different autoinflammatory disorders have been detected over the past years differing from autoimmune diseases in the lack of high titre antibodies and an immune dysregulation of the innate immune system where as autoimmune diseases have a malfunction of the adaptive immune system [5, 6].

VEXAS syndrome has been described mostly in men in the 5th decade of life and for women suffering from Turner Syndrome or having heterozygous variants with clinical manifestations [2, 7]. The diagnosis of VEXAS syndrome is challenging due to the heterogeneous phenotypes with a wide range of corresponding diseases affecting multiple organ systems such as dermatological diseases such as Sweet syndrome, vasculitis such as polyarteritis nodosa and giant cell arteritis, nephritis, haematological abnormalities such as hemophagocytic lymphohistiocytosis, multiple myeloma and myelodysplastic syndrome [1].

Clinical symptoms and signs include persisting and recurrent fever, elevated acute-phase proteins, haematological changes with cytopenia and dysplastic bone marrow with vacuolisation of myeloid and erythroid precursor cells and systemic inflammation of the skin, lung, cartilage and vascular vessels. Arthralgia or arthritic symptoms are also described [8]. Novel findings include interstitial nephritis and cardiac manifestations with myocarditis [9]. Laboratory findings include elevated C-reactive protein, macrocytic anaemia, elevated sIL2 receptor, ferritin and elevated IL-6.

Pulmonary involvement occurs in up to 50–67% of patients [1]. The most common findings on chest computed tomography are ground-glass opacities and consolidations. Pleural effusions are seen in 43% of the cases [10, 11]. Interstitial lung diseases has also been reported with organising pneumonia, non-specific interstitial pneumonia and bronchiolitis obliterans [9].

There are no standardised diagnostic criteria for VEXAS syndrome according to leading scientific societies such as the American Haematological Society, the European Haematological Association and the European Rheumatological Society. VEXAS is often confused with autoimmune or haematological disorders. The most common diagnostic sequence, adapted from Beck et al. is to identify a systemic inflammatory disease characterised by late onset and refractory symptoms. Histopathological examination reveals vacuolization in myeloid and erythroid progenitor cells, and a definitive diagnosis is confirmed by identification of a mutation in the UBA1 gene [3].

Treatment

Due to the high mortality rate of over 50%, VEXAS syndrome requires an aggressive treatment strategy [9]. There are currently two established strategies.

The first strategy is to reduce the activity of the mutated clone, employing therapies as hypomethylating agents (e.g. azacytidine) or allogeneic stem cell transplantation. Azacytidine is already established in the treatment of steroid-dependent autoimmune diseases associated with MDS or CML and has shown success in a French registry study involving five VEXAS syndrome patients with MDS [12, 13].

The second strategy aims to inhibit the cytokine storm using treatments such as glucocorticoids or Janus kinase inhibitors. A retrospective series of 19 patients revealed the use of corticosteroids as first-line treatment, supplemented with various disease-modifying-anti-rheumatic drugs (DMARDS) like methotrexate, anti-TNF-alpha (adalimumab), anti-interleukin-6 (tocilizumab), calcineurin-inhibitors (cyclosporine), JAK inhibitors (ruxolitinib, tofacitinib). Although randomised controlled trials are not available for these treatments, it can be hypothesised that cyclosporine and azacytidine may result in longer remission periods; however, relapse is also common [8]. In addition to these two strategic approaches, symptomatic therapy with blood transfusions and infection prophylaxis is also used.

Furthermore, symptomatic therapy, encompassing blood transfusions and infection prophylaxis, is employed in conjunction with the previously described strategies. Given the refractory nature and high mortality of VEXAS syndrome, future studies are essential to explore advanced treatments like allogenic stem cell transplantation and CART-cell therapy, which could target the myeloid progenitor cell clones to disable the clonal spread.

Case presentation

A 76-year-old Caucasian male patient with a past medical history of a myelodysplastic syndrome and a perichondritis of the right auricle was transferred to our hospital with the chief complaint of dyspnoea in June 2023. Clinical assessment revealed recurrent pulmonary infiltrates refractory to antibiotic treatment, fever, fatigue, malaise, chills and elevated acute-phase-proteins including CRP and procalcitonin in the previous 8 weeks. Broad-spectrum antibiotics, including piperacillin/tazobactam, meropenem in combination with vancomycin and linezolid in combination with fluconazole, had been administered for the previous 6 weeks without any relevant clinical and radiological improvement. The patient had a right traumatic pertrochanteric femur fracture which had been scheduled for surgery seven days prior to the onset of this episode.

Since 2017, he had been treated for an indeterminate systemic lung disease with peribronchial thickening, basal consolidations on CT scan with a working hypothesis of sarcoidosis without histological evidence at an outpatient rheumatology clinic. In 2019 he was diagnosed with chondritis of the right ear. Following a COVID 19 vaccination with an mRNA vaccine in March 2021, he developed a complicated infection on the side of the puncture leading to a severe wound healing disorder (Fig. 1). He was treated with prednisolone 5 mg/day and azathioprine until August 2022. The patient was diagnosed with myelodysplastic syndrome (MDS) in September 2019.

On clinical admission, the patient was tachycardic and with type 1 respiratory failure requiring 2 L oxygen per minute at rest, and he presented with fever and malaise (Table 1). A rheumatic disorder was excluded by our consulting rheumatologists since clinical symptoms

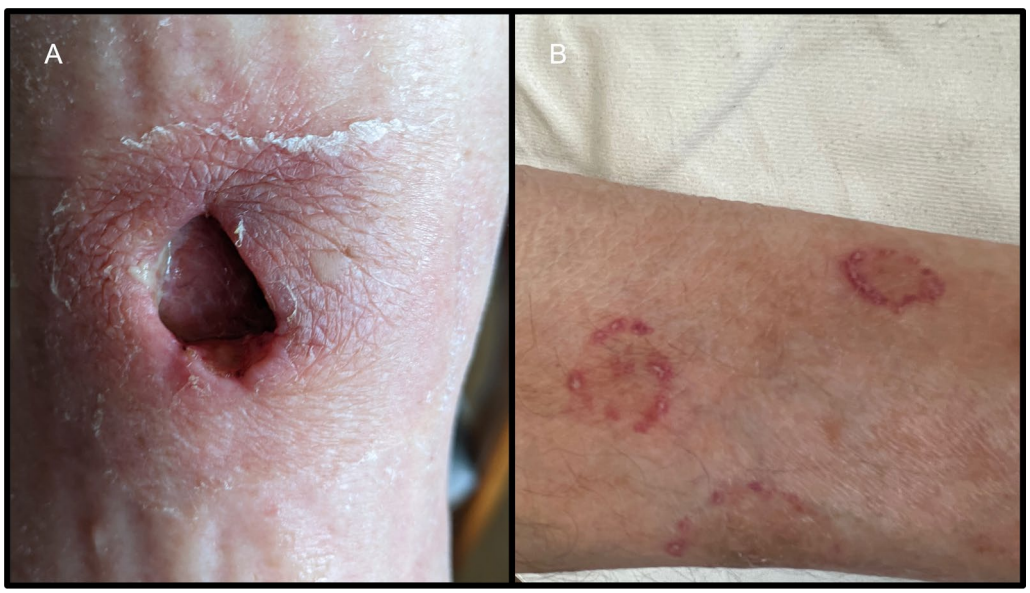

Fig. 1 Clinical findings: **A** Severe epidermal wound healing disorder following mRNA vaccination against Covid-19. **B** Non-purulent cutaneous eruptions on the ventral right calf

Table 1 Relevant clinical and diagnostic features at the time of admission to the pulmonary clinic

Relevant clinical and diagnostic features at admission	
Physical exam	Temperature of 39.9 °C, heart rate 112 bpm, respiratory rate 26, BP 110/60, HT 170 cm, WT 72 kg, BMI 24.9 kg/m^2, O_2 Saturation 89% on room air
Constitutional	Undernourished and acutely ill-appearing male with signs of exsiccosis
Pulmonary/Chest	Tachycardic, regular rhythm and normal heart sound with no murmur, Tachypnoea present, wheezing and bilateral rhonchi
CT scan of the lung	Signs of interstitial pneumonia, pleural effusions on both sides
PFTs	Restrictive pattern: FEV1 1.4 l/45%; FEV1/FVCex 99%; FVCex 1.5 l/40%, TLC 3.3 l/52% Reduced diffusion capacity: Dlco 28%, Kco 71%
Echocardiography	Global impression: normal ejection fraction, no pericardial effusion no signs of elevated RF pressure
Capillary blood gas	pH 7.54, $PaCO_2$ 37 mmHg, PaO_2 60 mmHg, O_2 Saturation 93% with 2 l oxygen/min
Laboratory findings on admission	haemoglobin 6.7 g/dl, platelets 67/nl, MCV 100 fl, ferritin 6559.9 ng/ml, CRP 34 mg/l, PCT 1.3 ng/ml, sIL-2 1233 U/ml
Bronchoalveolar lavage	Complete cell count: 70 mio/l; macrophages 44%, lymphocytes 41%, T4/T8 1.3%, neutrophils 14%, eosinophils 1%; mild pulmonary alveolar haemorrhage,
Microbiological diagnostic:	Influenza A and B and COVID 19 negative, sequential blood cultures negative, bronchoalveolar lavage with no growth of bacteria and negative respiratory virus panel

BP: blood pressure; bpm: beats per minute; BMI: body mass index; CT: computer tomography; PFTs: pulmonary function tests; FEV1: forced expiratory volume in 1 s; FVCex: forced expiration capacity; TLC: total lung capacity; DLco: diffusion capacity of the lung for carbon monoxide; Kco: carbon monoxide transfer coefficient; MCV: mean corpuscular volume; PCT: procalcitonin, sIL-2: soluble interleukin 2

and missing typical pattern of antibody profiles were negative. The diagnosis of MDS was established prior in September 20219 including a bone marrow aspiration explaining the blood count changes and connected to the strong inflammatory reaction and pulmonary symptoms and past medical history of a perichondritis VEXAS syndrome was the suspected diagnosis in favour. Sanger sequencing analysis was used to genetically test peripheral blood for a somatic variant of a UBA1 gene mutation. Codon Met41 showed a p.splice c.118-1G>C mutation with 94% allele and a diagnosis of VEXAS syndrome was established.

By mid-July 2023, the patient commenced oral steroids at a dose of 100 mg prednisolone, administered for three days and subsequently tapered to 1 mg per kilogram of body weight. Within 48 h, the patient improved markedly, and the prednisolone was tapered. At the prednisolone dose of 10 mg/day, symptoms recurred, leading to hospital readmission by the end of September 2023. He developed non-purulent cutaneous eruptions on the ventral right calf (Fig. 1) and the CT scan showed pulmonary infiltrates (Fig. 2), while laboratory findings were consistent with previous admission. The prednisolone dose was restarted at 100 mg/day for 3 days and then tapered. After haematological consultation in September 2023, the patient was started on azacytidine with standard dose [every 4 weeks 7 day cycle with 75 mg/m^2 BSA (body surface area) = 130.67 mg s.c.]. Despite azacytidine therapy, the patient was readmitted twice in the following 6 months with flares, always when the prednisolone dose was reduced below 15 mg/day. Future approaches are being discussed with a multidisciplinary team including general medicine, rheumatology, oncology and pulmonology. The gene variation of our patient, the p.splice

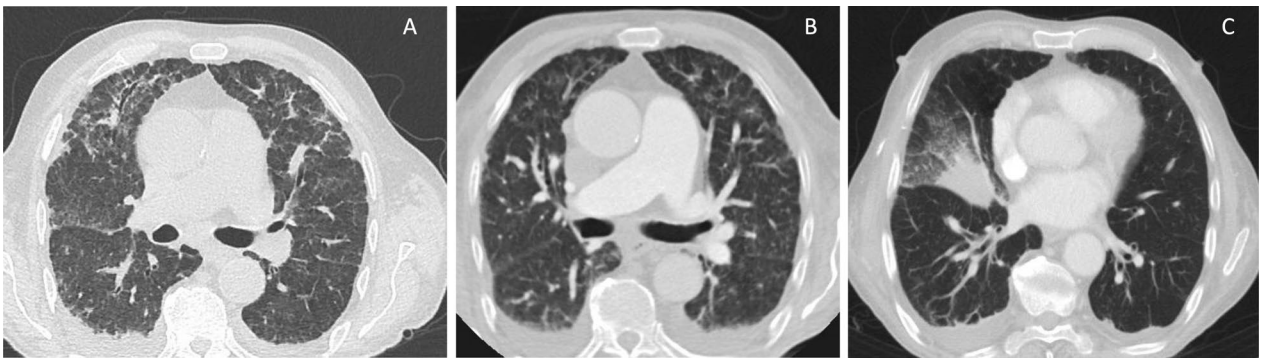

Fig. 2 **A** CT scan 4 weeks before initial admission, **B** CT scan on admission, **C** CT scan on readmission after 10 weeks with flare and right upper lobe infiltrate

c.118-1G>C mutation, was previously discovered and first described in a case series in 2021 [14]. Subsequently, in another retrospective study of 77 patients, this mutation was found in 3 patients, in a Spanish cohort in 2 out of 30 VEXAS patients and in a recently published cohort of Beck et al. in one out of 11 VEXAS patients [2, 11, 15].

The characteristics of these 8 VEXAS patients with the same genetic mutation are summarized in Table 2. We were able to compare eight VEXAS patients with a c.118-1G>C mutation, who seem to have a common general presentation with systemic symptoms of fever, fatigue and weight loss, as well as skin involvement. There was inter-individual variation in organ manifestations. In a case cohort study by Poulter et al. eight of ten patients were described as carrying the original mutation [14]. General symptoms such as fever and weight loss as well as laboratory findings such as elevated inflammatory enzymes, skin and haematological changes affected most of them. Organ manifestations such as interstitial nephritis, pulmonary infiltrates and chondritis were limited to 1/8, 2/8 and 4/8 patients, respectively. A recent Spanish cohort of 30 with confirmed VEXAS syndrome and four different types of mutations showed the same picture of disease [11].

Discussion

VEXAS syndrome is a rare disease that can be easily missed and misdiagnosed due to its broad clinical phenotype. Pulmonary manifestations such as infiltrates, effusions or even interstitial lung disease may occur together with signs of systemic inflammation such as fever, arthralgias and concomitant haematologic disorders and a wide range of other organ manifestations.

Several mutations in the UBA1 gene have been identified and associated with VEXAS syndrome. The UBA1 mutation carried by our patient symbolises the heterogeneity of the disease, as several phenotypes of VEXAS syndrome have been described with these mutations. Clinical findings such as skin involvement, highlighted in our case by the wound healing defect after Covid-19 vaccination, are partly variable, like the inter-individual differenced in patients with other mutations in the UBA1 gene.

This highlights the complexity and the need for a multidisciplinary approach to the diagnosis of VEXAS syndrome. Once diagnosed, VEXAS syndrome requires urgent and highly aggressive treatment due to its severe and progressive course with involvement of multiple organ systems.

Table 2 Characteristics of 5 VEXAS patients with c.118-1G>C mutation

	Berger et al. *N*=1	**Poulter et al. *N*=1 [14]**	**Gutierrez et al. *N*=3 [15]**	**Beck et al. *N*=1 [2]**	**Mascaro et al. *N*=2 [11]**
Age of onset	70	67	62.8 (61.0; 71.3)	70–79	52/61
Gender	Male	Male	Male	Female	Male
CRP median mg/l	42	48	–	–	–
Thrombocytopenia ($<100\times10^3$/µl)	1	–	0	0	2
Ferritin ng/ml	Max: 6559	–	–	–	Mean: 1554/2058
Macrocytic anaemia	1	1	–	1	2
MDS	1	1	0	0	–
MGUS	0	1	1	1	–
Sweet syndrome	0	0	2	–	–
Systemic symptoms	1	1	3	1	2
Skin involvement	1	1	3	0	2
Arthritis	0	–	–	1	0
Stroke	0	–	–	1	0
Periorbital oedema	0	–	1	0	0
Inner ear involvement	0	–	2	1	0
Chondritis (ear/nose)	1	0	3		0
Cardiac manifestations	1	–	0		–
Pulmonary/pleura	1	0	0	1	0
musculoskeletal	1	–	2		0
Treatment	Steroids/Azacitidine	Steroids with pr	–	Steroids	Steroids cr

pr: partial response; cr: complete response; systemic symptoms: at least one of: fever, fatigue, unintentional weight loss

Conclusion

Our case report also highlights that there are many other clinical features associated with VEXAS syndrome that have not yet been described. Further studies and case reports are needed to highlight the wide range of clinical phenotypes of this relatively young disease.

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None.

Author contributions
MB, MZ, FS, WW made substantial contributions to conception and design. MB, MZ were responsible for the acquisition of data. MB, MZ, WW took part in drafting the article. MB, FS, MWS, DK, SBS, DSM, KF, IP, WW, MZ revised the article and proved it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published and agree to be accountable for all aspect of the work.

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Data availability
All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Declarations

Ethics approval and consent to participate
Ethical approval is not required for this study in accordance with the Ethic committee of the University Witten/Herdecke, Germany and national guidelines. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
MB: no conflict of interest in this field. FS: no conflict of interest in this field. MWS: no conflicts of interest in this field. DK: no conflicts of interest in this field. SBS: no conflicts of interest in this field. DSM: no conflicts of interest in this field. KF: no conflict of interests in this field. IP: no conflicts of interest in this field. WW no conflicts of interest in this field. MZ: no conflict of interest in this field.

Author details
[1]Department of Pneumology, Faculty of Health/School of Medicine, Cologne Merheim Hospital, Kliniken der Stadt Köln gGmbH, Witten/Herdecke University, Ostmerheimer Strasse 200, 51109 Cologne, Germany. [2]Department Humanmedizin, Universität Witten/Herdecke, Witten, Germany. [3]Klinik für Rheumatologie, Krankenhaus Porz am Rhein gGmbH, Cologne, Germany.

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