EJCRIM
European Journal of Case Reports in Internal Medicine

VEXAS SYNDROME: A MULTISYSTEM CHALLENGE WITH SWEET SYNDROME AND MYELODYSPLASTIC SYNDROME

Ayla Kouli[1], Miriam Laflouf[1,2], Mahmoud Alhamadeh Alswij[1,2], Ammar Awad[1,2], Ahmad Al-Bitar[1], Mais Musleh[1,2], Heba Jumah[1,2]

[1] Faculty of Medicine, Damascus University, Damascus, Syrian Arab Republic
[2] Department of Haematology, National University Hospital, Faculty of Medicine, Damascus University, Damascus, Syrian Arab Republic

Corresponding author's e-mail: miriam1997.laflouf@damascusuniversity.edu.sy

Received: 08/07/2026
Accepted: 17/07/2026
Published: 24/08/2026

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: Written informed consent was obtained from the patient's family for publishing this report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.
This article is licensed under a CC Attribution-NonCommercial-NoDerivatives 4.0 License

How to cite this article: Kouli A, Laflouf M, Alswij MA, Awad A, Al-Bitar A, Musleh M, Jumah H. VEXAS syndrome: a multisystem challenge with sweet syndrome and myelodysplastic syndrome. EJCRIM 2026;13:doi:10.12890/2026_007318

ABSTRACT

Introduction: VEXAS (vacuoles, E1 enzyme, x-linked, autoinflammatory, somatic) syndrome, is a recently described autoinflammatory condition caused by *UBA1* gene mutations. It can present with both sweet syndrome (SS) and myelodysplastic syndrome (MDS). SS, or acute febrile neutrophilic dermatosis, is an inflammatory disorder characterised by fever, neutrophilia and painful erythematous plaques. MDS is a clonal haematopoietic stem cell disorder.

Case description: We present a case of a 43-year-old Arab male with a history of MDS. He presented with painful, non-pruritic, non-haemorrhagic skin lesions. The patient also reported having fever and chills, partially relieved by antipyretics. Bone marrow aspiration was done and revealed a 'dry tap' which was inadequate for evaluation. Immunophenotyping of bone marrow biopsy was consistent with MDS. A skin biopsy of the lesions was performed and confirmed sweet syndrome. The patient was treated with methylprednisolone 500 mg daily for five days, with a significant improvement in clinical symptoms. After stabilisation, treatment for MDS was started with 200 mg IV azacitidine daily for seven days.

Conclusion: Given the patient's age, gender, MDS diagnosis and atypical presentation of sweet syndrome, VEXAS syndrome is a strong possibility. Further investigation, including genetic testing for a *UBA1* mutation, is warranted. A diagnosis of VEXAS syndrome would significantly impact long-term management and prognosis, as it was determined to be important in reducing the recurrence rate of sweet syndrome.

KEYWORDS

Sweet syndrome (SS), myelodysplastic syndrome (MDS), VEXAS syndrome, *UBA1* mutation

LEARNING POINTS

- Features such as steroid-dependent skin lesions, cytopenias and MDS raise suspicion for VEXAS syndrome – a systemic autoinflammatory disorder linked to *UBA1* mutations and clonal haematopoiesis. Despite lacking genetic confirmation, the patient responded to high-dose steroids and azacitidine, underscoring the need for *UBA1* testing to guide management and prognosis in overlapping MDS-inflammatory syndromes.
- Sweet syndrome is not always just cutaneous; when it clusters with MDS and systemic inflammation, VEXAS becomes an important diagnostic consideration.

EFIM European Federation of Internal Medicine

Publisher smc media srl

INTRODUCTION

Myelodysplastic syndrome (MDS) is a clonal disorder of haematopoietic stem cells, which results in dysplasia and ineffective haematopoiesis within the bone marrow. This condition often leads to anaemia, leukopenia or thrombocytopenia[1]. Sweet syndrome is a rare disease and is characterised by an acute onset of tender erythematous plaques with dense neutrophilic infiltrate in the dermis[2]. VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome is a severe, progressive and potentially fatal autoinflammatory syndrome caused by somatic mutations in the *UBA1* gene. It typically affects men over 40 and is characterised by both haematologic and inflammatory manifestations[2]. This case highlights the complex presentation of a patient with SS and MDS, raising the possibility of underlying VEXAS syndrome.

CASE DESCRIPTION

A 43-year-old male with a history of MDS, diagnosed four months previously, was admitted to the haematology department in October 2024, due to the development of painful, non-pruritic, non-haemorrhagic skin lesions three days prior. His vital signs were within normal limits except for a 39-degree fever. On physical examination, pallor was noted in addition to numerous skin lesions. These lesions varied in size and were distributed across the upper and lower extremities, trunk, face, scalp and oral and nasal mucosa; lesions did not follow a specific dermatomal pattern *(Fig. 1)*. Hyperpigmentation was noted at sites of previous skin lesions on the lower abdomen and right buttock. No lymphadenopathy was detected, and the remainder of the physical examination was normal. The patient denied any loss of appetite or weight loss but reported generalised fatigue.

Four months before admission, the patient experienced generalised fatigue and exertional dyspnoea (Grade I). One month prior to admission, he developed three similar skin lesions on the lower abdomen and right buttock without any systemic symptoms. He was treated with prednisolone 60 mg, which was gradually reduced to 10 mg, weekly. The lesions resolved within one week of initiating treatment.

A peripheral blood smear revealed pancytopenia; laboratory and urine analysis results are shown in *Table 1*. Bone marrow aspiration was performed, resulting in a 'dry tap' that was inadequate for evaluation. Immunophenotyping was consistent with MDS, and



Figure 1. *The lesion on admission.*

Laboratory test	Result
Anti-hepatitis C virus (Anti-HCV)	Neg.
Activated partial thromboplastin time (aPTT) (sec)	28
Albumin (ALB) (g/dl)	3.5
Alkaline phosphatase (ALP) (U/l)	69
Aspartate aminotransferase (AST) (U/l)	20
Alanine aminotransferase (ALT) (U/l)	29
Calcium (Ca) (mg/dl)	8
Corrected calcium (Corrected Ca) (mg/dl)	8.4
Creatine kinase (CK) (U/l)	64
Creatinine (Crea) (mg/dl)	0.68
C-reactive protein (CRP) (mg/l)	40
Direct bilirubin (DB) (mg/l)	0.4
Erythrocyte sedimentation rate (ESR) (mm/hr)	92
Hemoglobin (Hb) (g/dl)	6
Glucose (GLU) (mg/dl)	115
Hepatitis B surface antigen (HBs Ag)	Neg.
Hematocrit (Ht) (%)	18
International normalized ratio (INR)	1.32
Potassium (K) (mmol/l)	4.1
Lactate dehydrogenase (LDH) (U/l)	670
Lymphocytes/neutrophils (L/N) (%)	31/60
Mean corpuscular hemoglobin (MCH) (pg)	30
Mean corpuscular volume (MCV) (fl)	90
Sodium (Na) (mmol/l)	132
Procalcitonin (PCT) (ng/ml)	9
Platelets (PLT) (× 10^3/µl)	45
Prothrombin time (PT) (%)	67
Phosphorus (P) (mg/dl)	3.5
Red blood cells (RBC) (× 106/µl)	2
Reticulocyte count (RET) (%)	1.2
Total bilirubin (TB) (mg/dl)	0.6
Total protein (TP) (g/dl)	5.9
Thyroid-stimulating hormone (TSH) (mIU/l)	2.19
Uric acid (UA) (mg/dl)	2.1
Urea (mg/dl) (mg/dl)	38
White blood cells (WBC) (× 10^3/µl)	1.9

Table 1. *Laboratory and urine analysis.*

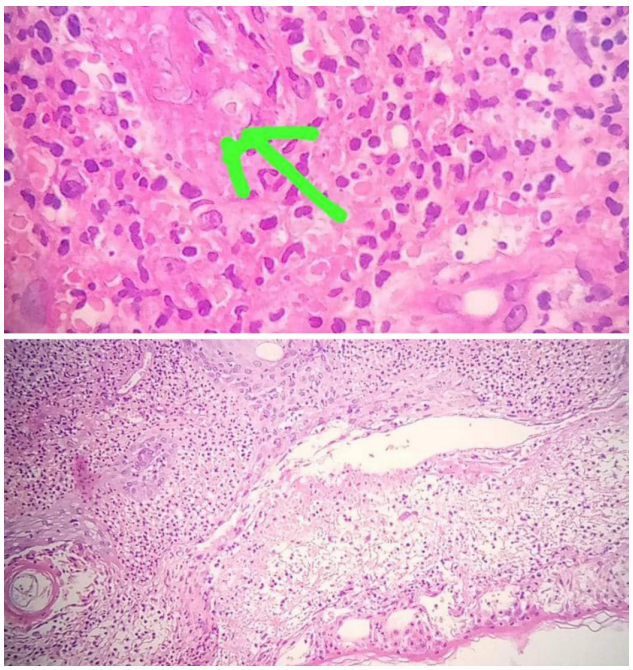


Figure 2. *Skin biopsy reveals marked neutrophilic infiltrate with nuclear fragmentation involving peri-vessels, skin adnexa and overlying squamous epithelium.*

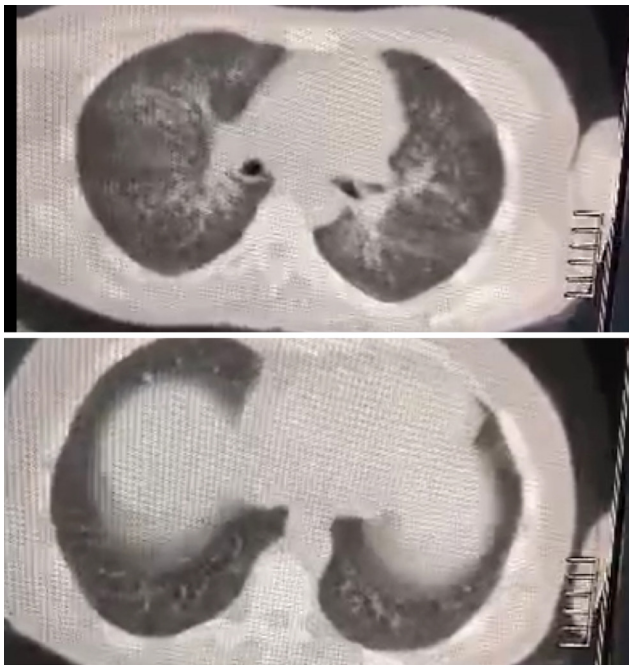


Figure 3. *CT-CX showing the lesion.*

cytogenetic analysis results showed 46,XY *(Table 2)*. A skin biopsy was obtained, and the tuberculin skin test was negative. Abdominal ultrasound indicated an increase in liver echogenicity with regular borders; skin biopsy revealed a marked neutrophilic infiltrate *(Fig. 2)*. No parasites, granulomas or neoplastic changes were found. These changes were consistent with acute febrile neutrophilic dermatosis, favouring SS.

Three days after admission, the patient developed worsening exertional dyspnoea (Grade III), accompanied by a dry cough and decreased oxygen saturation to 87%. He also experienced watery diarrhoea (approximately seven times daily), associated with abdominal pain unrelated to food intake or body position.

Chest CT without contrast showed diffuse infiltrates in both lung fields, bilateral pleural effusion and non-specific millimetric nodules in addition to progressive scleral icterus *(Fig. 3)*.

Initially, the patient received prednisolone 80 mg daily with gradual tapering. He was then treated with 500 mg methylprednisolone daily for five days *(Fig. 4)*. Following treatment with high-dose methylprednisolone, he demonstrated significant clinical improvement; skin lesions regressed, and systemic symptoms (including fever, fatigue, GI symptoms) resolved. Regular skin examinations were performed to detect sweet syndrome (SS) recurrence, alongside routine blood tests.

After stabilisation, treatment for MDS was started with IV azacitidine of 200 mg daily for seven days *(Table 3)*. Azacitidine cycles (seven days/month) were continued to avoid disease progression and reduce SS flares. However, after his second cycle the patient developed severe febrile neutropenia, which unfortunately led to his death.

DISCUSSION

The patient's presentation of acute febrile neutrophilic dermatosis fulfils the histopathological criteria for sweet syndrome (SS)[1,2]. However, several features diverge significantly from the classic form of the disease, prompting consideration of an alternative underlying diagnosis. Classic SS typically affects middle-aged women (30–50 years), often following an upper respiratory or gastrointestinal infection or in association with inflammatory bowel disease or pregnancy[3-5]. This patient is a 43-year-old male whose dermatosis is directly associated with an underlying haematologic malignancy.

While malignancy-associated SS is a well-recognised



Figure 4. *After administering methyl prednisone.*

Feature	Classic sweet syndrome (SS)	VEXAS syndrome	This case
Demographics	Typically middle-aged females (30–50 years)	Almost exclusively males, >40 years	43-year-old male
Cutaneous lesions	Abrupt onset, tender erythematous plaques/nodules	Neutrophilic dermatosis resembling SS; papules, plaques, nodules	Painful erythematous plaques and nodules
Associated conditions	Idiopathic, post-infectious, inflammatory bowel disease, pregnancy	Myelodysplastic Syndrome (MDS) (~36%), other haematologic disorders	Diagnosed MDS
Systemic symptoms	Fever (>38°C), malaise, arthralgia	Recurrent fever, fatigue, weight loss, pulmonary infiltrates, GI symptoms	Fever (39°C), fatigue, pulmonary infiltrates, diarrhoea
Key lab findings	Neutrophilic leucocytosis, elevated ESR/CRP	Macrocytic anaemia (MCV >100 fl), thrombocytopenia, progressive cytopenias	Pancytopenia, macrocytic anaemia (MCV 90 fl)
Bone marrow	Typically reactive neutrophilia	Hypercellular, dysplasia, vacuolisation of myeloid/erythroid precursors	'Dry tap' on aspiration; biopsy consistent with MDS
Response to therapy	Excellent, often curative response to corticosteroids	Steroid-dependent or refractory; requires high doses or other targeted agents	Recurrent; required escalation to high-dose pulse methylprednisolone for control
Genetic marker	None	Somatic *UBA1* mutation	46 XY

Table 2. *Comparison of clinical and laboratory features: classic sweet syndrome, VEXAS syndrome, and this case.*

Therapeutic class	Examples	Reported efficacy in VEXAS	Rationale/mechanism
Glucocorticoids	Prednisone, methylprednisolone	High initial response rates, but disease is typically steroid-dependent or refractory	Broad, potent anti-inflammatory and immunosuppressive effects.
IL-1 Inhibitors	Anakinra, canakinumab	Partial responses in ~47%; steroid-sparing but rarely induces remission as monotherapy	Blocks IL-1, a key cytokine in innate immune activation.
IL-6 Inhibitors	Tocilizumab	Partial responses in ~70%; can reduce inflammatory markers and steroid dose	Blocks IL-6 receptor, targeting a major downstream inflammatory pathway.
JAK Inhibitors	Ruxolitinib	Good response rates (Ruxolitinib CR ~42%); rapid onset, steroid-sparing	Inhibits JAK/STAT signalling, which is downstream of multiple inflammatory cytokines.
Hypomethylating agents (HMAs)	Azacitidine, decitabine	Good response rates (CR ~73% in one series); can improve both inflammatory and haematologic features	Targets the underlying *UBA1*-mutant haematopoietic clone, reducing its burden and addressing the root cause.
Allogeneic HSCT	N/A	Potentially curative; high remission rates (~86%) but with significant morbidity and mortality	Eradicates the mutant haematopoietic stem cell clone and replaces it with a healthy donor system.

Table 3. *Overview of therapeutic strategies in VEXAS syndrome.*

entity, the clinical course in this patient is particularly noteworthy. His skin lesions are recurrent and demonstrate a clear steroid-dependency, requiring escalation to high-dose pulse therapy for control. This pattern of refractoriness is a key feature of the inflammatory manifestations seen in VEXAS syndrome, which often respond poorly to standard immunosuppression and require high, sustained doses of corticosteroids[6,7]. Furthermore, the severity and nature of the systemic involvement – specifically the severe pulmonary infiltrates and gastrointestinal symptoms – are more characteristic of the profound, multisystem inflammation seen in VEXAS than is typical for classic SS[7]. A recent systematic review of 720 VEXAS patients found that respiratory disease affects over 61% of individuals, making it a core component of the syndrome's phenotype[8].

The constellation of this patient's clinical and haematologic features aligns remarkably well with the established phenotype of VEXAS syndrome. This syndrome, first described in 2020, provides a unifying diagnosis for patients with overlapping systemic inflammation and haematologic disorders[9,10]. The patient's demographics (male, age >40), cutaneous manifestation (neutrophilic dermatosis), and severe systemic inflammation (fever, pulmonary involvement) are all cardinal features of VEXAS[6,10].

However, the most compelling evidence lies in the haematologic abnormalities. The concurrent diagnosis of myelodysplastic syndrome (MDS) is a defining characteristic of VEXAS, present in approximately 36–40% of patients in large cohorts[9]. The presence of macrocytic anaemia is an even stronger clue, being an almost universal finding in VEXAS patients[6,7,10]. The combination of a severe, steroid-dependent autoinflammatory syndrome with underlying MDS and macrocytic anaemia in an adult male is the pathognomonic triad that should immediately raise a high index of suspicion for VEXAS syndrome[9].

Even the dry tap on bone marrow aspiration is a potential diagnostic clue. While it prevented cytological analysis of vacuolisation – a hallmark feature of VEXAS[6,9,10] – a dry tap often implies underlying marrow fibrosis. Chronic, unabated inflammation, as driven by the *UBA1*-mutant clone in VEXAS, can lead to a hypercellular marrow with dysplastic changes and reactive fibrosis, consistent with the biopsy findings of MDS and the technical difficulty of aspiration[10].

The therapeutic journey of this patient mirrors the typical challenges and emerging strategies in managing VEXAS syndrome. The initial reliance on and subsequent escalation of corticosteroids is a classic scenario. While effective for acute flares, VEXAS is notoriously steroid-dependent, and long-term control with steroids alone is fraught with toxicity and often proves insufficient[7,8].

The decision to initiate azacitidine is a critical and insightful therapeutic choice. While indicated for the patient's MDS, azacitidine is also a leading therapy for VEXAS syndrome itself[8]. Unlike purely immunosuppressive agents that target downstream inflammation (e.g. IL-1 or IL-6 inhibitors), hypomethylating agents (HMAs) like azacitidine are clone-directed therapies. They target the underlying *UBA1*-mutated hematopoietic stem cells, addressing the root cause of both the haematologic and inflammatory manifestations of the disease[8]. Recent studies and case series have shown that azacitidine can induce both clinical and haematologic responses in a significant proportion of VEXAS patients, often allowing for successful steroid tapering[8]. The use of azacitidine in this case, therefore, represents a modern, pathophysiology-driven approach to managing this complex haemato-inflammatory disorder.

The primary limitation of this report is the inability to perform *UBA1* genetic sequencing to definitively confirm the diagnosis of VEXAS syndrome. However, as argued, the clinical evidence is overwhelmingly supportive. This case highlights a critical issue in global medicine: the gap between the discovery of genetic diseases and the widespread availability of diagnostic testing[4]. It reinforces the need for clinicians to maintain a high index of suspicion based on recognisable clinical patterns[4,5].

Future efforts should focus on increasing awareness of the VEXAS phenotype and expanding access to *UBA1* testing for all patients with unexplained, overlapping inflammatory and haematologic syndromes[8,7]. Definitive diagnosis requires molecular confirmation of a somatic *UBA1* mutation[10]. Furthermore, as there is currently no standardised treatment algorithm, prospective clinical trials are urgently needed to evaluate the efficacy and safety of targeted therapies, including JAK inhibitors and HMAs, to establish a true standard of care for this severe and often fatal disease[7,9,10].

CONCLUSION

This case describes a 43-year-old male with MDS and an atypical, steroid-dependent neutrophilic dermatosis whose clinical and haematologic features strongly align with the VEXAS syndrome phenotype. The successful management with high-dose corticosteroids for the acute flare and the subsequent initiation of the clone-directed agent azacitidine highlights a modern therapeutic approach. This case emphasises that a high index of suspicion for VEXAS is crucial in patients with unexplained, overlapping haemato-inflammatory disorders, even when definitive genetic testing is not feasible.

REFERENCES

1. Nofal A, Abdelmaksoud A, Amer H, Nofal E, Yosef A, Gharib K, et al. Sweet's syndrome: diagnostic criteria revisited. J Dtsch Dermatol Ges 2017;15:1081-1088. doi: 10.1111/ddg.13350
2. Cohen PR. Sweet's syndrome--a comprehensive review of an acute febrile neutrophilic dermatosis. Orphanet J Rare Dis 2007;2:34. doi: 10.1186/1750-1172-2-34
3. Santos ML, Ferreira I, Embaló U, Alves G, Cotter J. Sweet's Syndrome: A Case of Fever and Painful Erythematous Nodules Following a Viral-Like Illness. Cureus 2026;18:e100701. doi: 10.7759/cureus.100701
4. Joshi TP, Friske SK, Hsiou DA, Duvic M. New Practical Aspects of Sweet Syndrome. Am J Clin Dermatol 2022;23:301-318. doi: 10.1007/s40257-022-00673-4
5. von den Driesch P. Sweet's syndrome (acute febrile neutrophilic dermatosis). J Am Acad Dermatol 1994;31:535-556; quiz 557-560. doi: 10.1016/s0190-9622(94)70215-2
6. Obiorah IE, Patel BA, Groarke EM, Wang W, Trick M, Ombrello AK, et al. Benign and malignant hematologic manifestations in patients with VEXAS syndrome due to somatic mutations in UBA1. Blood Adv 2021;5:3203-3215. doi: 10.1182/bloodadvances.2021004976
7. Loeza-Uribe MP, Hinojosa-Azaola A, Sánchez-Hernández BE, Crispín JC, Apodaca-Chávez E, Ferrada MA, et al. VEXAS syndrome: Clinical manifestations, diagnosis, and treatment. Reumatol Clin (Engl Ed) 2024;20:47-56. doi: 10.1016/j.reumae.2023.12.004
8. Boyadzhieva Z, Ruffer N, Kötter I, Krusche M. How to treat VEXAS syndrome: a systematic review on effectiveness and safety of current treatment strategies. Rheumatology (Oxford) 2023;62:3518-3525. doi: 10.1093/rheumatology/kead240
9. Wolff L, Caratsch L, Zhao LP, Blum S, Comte D. Understanding Myelodysplasia and Inflammation Through the Lense of VEXAS Syndrome: A Review. Cells 2024;13:1890. doi: 10.3390/cells13221890
10. Kucharz EJ. VEXAS syndrome: a newly discovered systemic rheumatic disorder. Reumatologia 2023;61:123-129. doi: 10.5114/reum/163090