Putting on your VEXAS goggles:

Seeing what's in plain sight

Sobi-sponsored satellite symposium at EULAR 2025
Fira de Barcelona
Friday, 13 June 2025
17:30 – 18:45

NP-42384
Date of preparation: June 2025

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Welcome

Sophie Georgin-Lavialle

Disclosures

Speaker's fees	Sobi, Novartis, Amgen
Scientific advisory board	Sobi, Novartis

Disclaimer & **important information**

- This presentation serves educational purposes and is intended to provide information and stimulate discussion on selected topics in VEXAS syndrome.
- The intent of this symposium is not to provide medical or any other type of advice.
- All treatment decisions should be up to the discretion of the healthcare provider and the patient, as each patients' situation may vary.
- This scientific event is a non-promotional activity sponsored by Sobi and the speakers are being compensated for their involvement.
- The content, discussion, and answers reflect the personal opinion of the speaker and may not represent those of Sobi.
- No identifiable patient-specific information is included.

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Introducing the faculty

Sophie Georgin-Lavialle

French National Reference Center for Autoinflammatory Diseases and AA Amyloidosis
Tenon hospital, Paris, France

Thibault Mahévas

Paris Cité University
Saint-Louis hospital
Paris, France

Sara Bindoli

University of Padova
Department of Medicine,
Rheumatology Unit
Padova, Italy

Lachelle D. Weeks

Dana-Farber Cancer Institute
Department of Medical Oncology
Boston, Unites States

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We want you to participate!

Q&A and evaluation

Please **submit questions** throughout the symposium **via the EULAR App**

Questions will be addressed in the **live Q&A session**

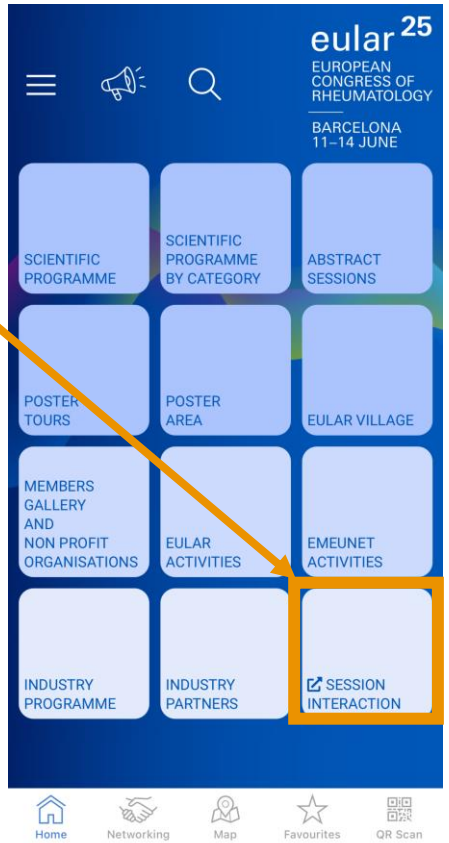
1 **Select** **Session Interaction** in the EULAR App

2 **Select the session**

Putting on your VEXAS goggles: Seeing what's in plain sight
Room B4

3 **Select** what you want to do

- **Q&A**
- **Voting**
- **Evaluation**



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Symposium objectives

Please **open the EULAR App** to be ready to vote in the poll

Disease awareness - educate on VEXAS disease manifestations to allow timely diagnosis and management

Provide guidance on specific disease manifestations across the medical specialties that are most typical for VEXAS and indicate who should be tested for a confirmed diagnosis

Provide opportunity for expert Q&A session

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Putting on your VEXAS goggles: **Seeing what's in plain sight**

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Agenda

17:30	**Welcome | Sophie Georgin-Lavialle (Chair)**
17:35	**Putting on your goggles - An introduction to VEXAS | Sophie Georgin-Lavialle**
17:45	**External presentation - Dermatologic features of VEXAS | Thibault Mahévas**
18:00	**Under the skin - Rheumatologic features of VEXAS | Sara Bindoli**
18:15	**Deep, into the marrow - Haematologic features of VEXAS | Lachelle D. Weeks**
18:30	**Panel discussion and Q&A | All Faculty**

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What's your opinion?

How would you rate your current knowledge of VEXAS syndrome?

A. Expert

B. Intermediate

C. Beginner

D. Unfamiliar

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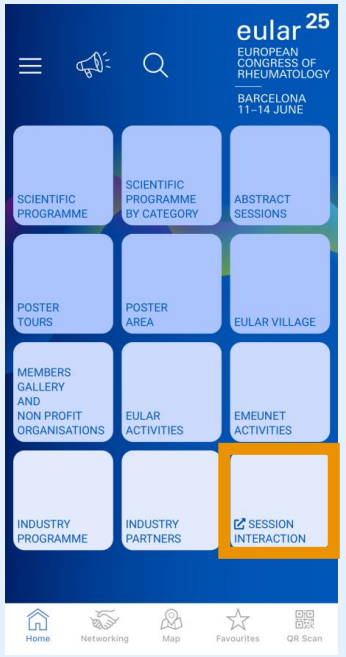

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Putting on your goggles – An introduction to VEXAS

Sophie Georgin-Lavialle

French National Reference Center for Autoinflammatory Diseases and AA Amyloidosis

Tenon hospital, Paris, France

French VEXAS Study Group

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VEXAS is a newly described disease[1]

V acuoles

E 1-enzyme

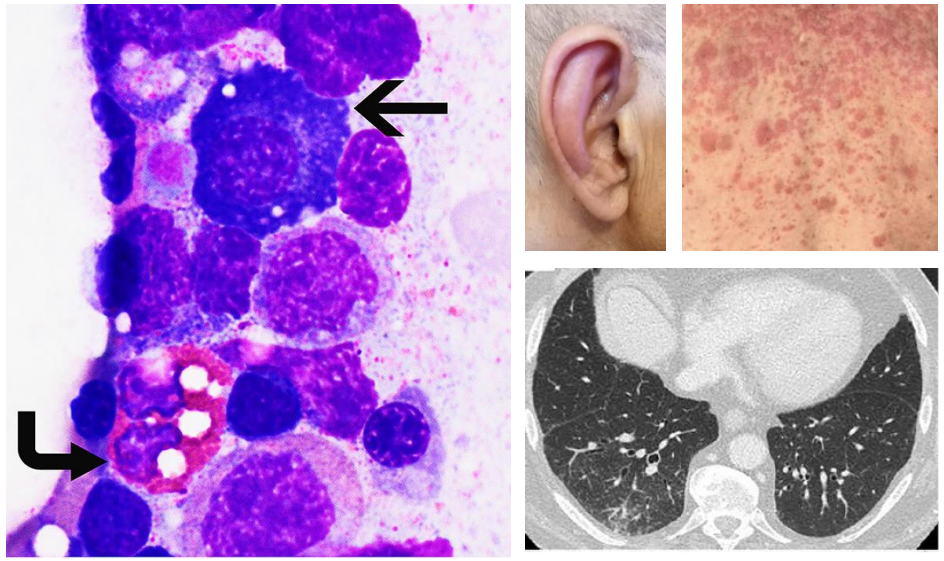
X -linked

A utoinflammatory

S omatic

Discovered in 2020

Somatic Mutations in UBA1 and
Severe Adult-Onset Autoinflammatory Disease
Beck DB, Ferrada KA, Sikora AK, et al.



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1. Beck et al. *N Engl J Med* 2020;383:2628-38.
Images (left) from Haines et al. *Int J Lab Hematol* 2024 (CC BY 4.0) © 2024 The Authors. International Journal of Laboratory Hematology published by John Wiley & Sons Ltd.; (middle) courtesy of Dr. Bindoli; (top right) courtesy of Dr Mahévas, Saint Louis hospital collection; (bottom) used with permission of American College of Chest Physicians, from Pleuropulmonary Manifestations of Vacuoles, E1 Enzyme, X-Linked, Autoinflammatory, Somatic (VEXAS) Syndrome. Borie et al. *Chest* 2023;163:575-85; permission conveyed through Copyright Clearance Center, Inc.

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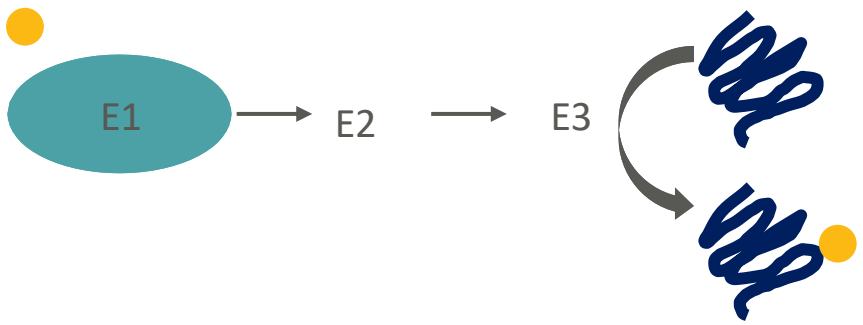
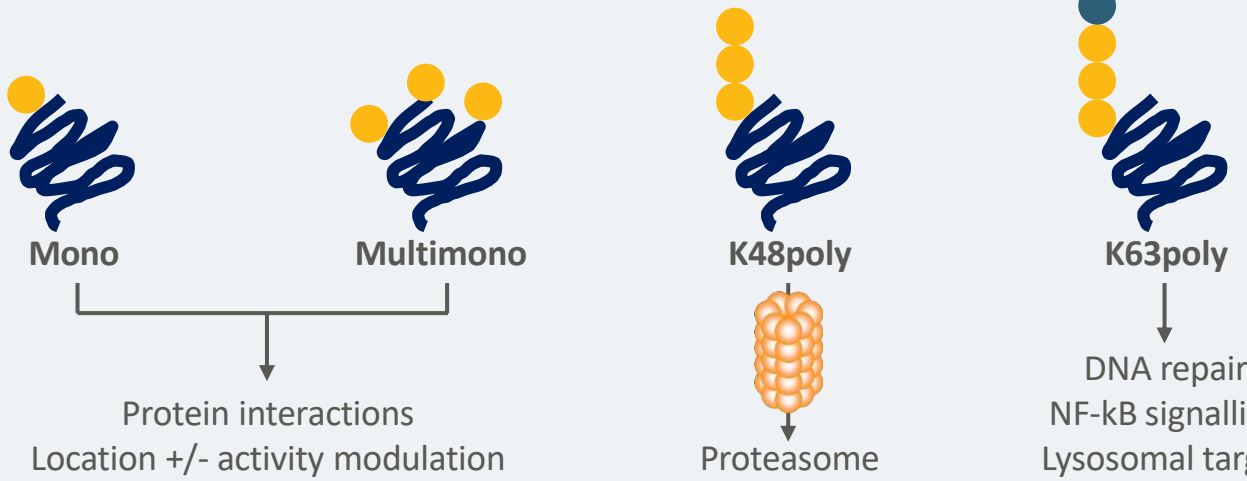
VEXAS: **Pathophysiology**



Different chain architecture: Different functions



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VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic. Content based on speaker experience. Image courtesy Prof. Georgin-Lavialle.

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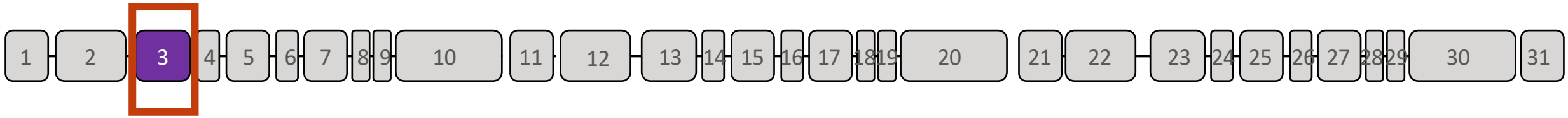
VEXAS is associated with **mutation in *UBA1***

Mainly in exon 3[1]

Hot spot



Most common mutation in methionine 41 of exon 3[1]

c.122T → C (p.Met41Thr)	45%
c.121A→G (p.Met41Val)	30%
c.121A → C (p.Met41Leu)	18%

Splice motif mutation 7%

The specific **mutational subtype impacts clinical manifestations and clinical outcome[2]**

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VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

1. Templé et al. *Diagnostics* 2022;12:1590 **2.** Ferrada et al. *Blood* 2022;140:1496–506.

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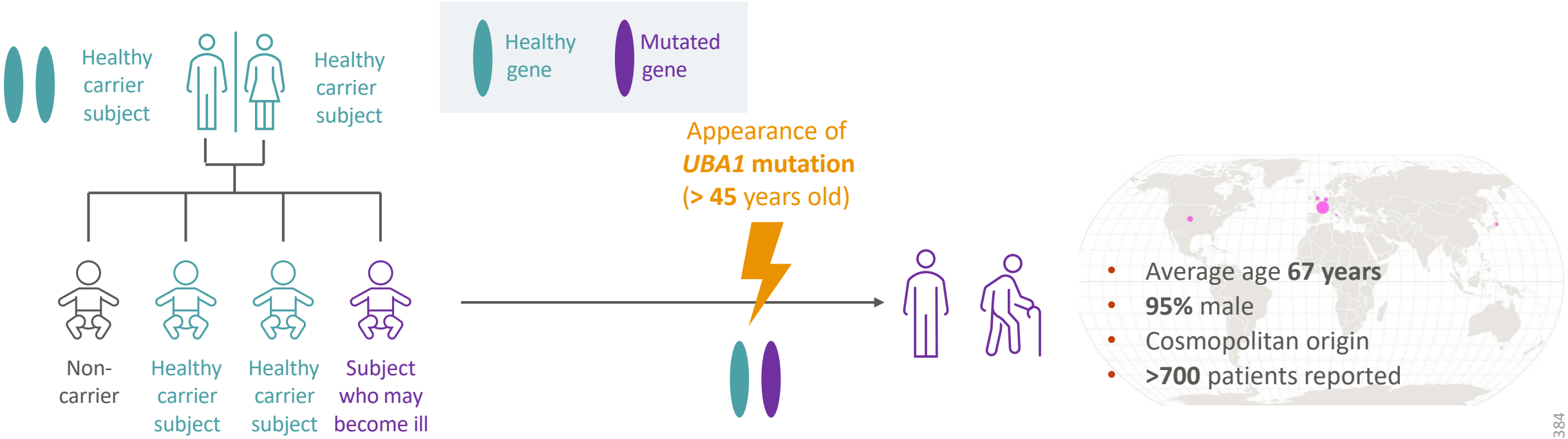
VEXAS appears **later in life, usually in men** and is the result of an **acquired mutation on the X chromosome**



Estimated prevalence 1/14000 (and **1/4000 in men > 50 years**)*[1]

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VEXAS was also reported in **young men**[2] and **women**[3]
Adults with clinical presentations of VEXAS syndrome **must be tested for *UBA1* mutations, regardless of age**

* Values rounded (estimated prevalence 1/13591 and 1/4269 in men >50 years). VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.
1. Beck et al. *JAMA* 2023;329:318-4 **2.** Sánchez-Hernández et al. *Rheumatology* 2024;63:e99-100 **3.** Barba et al. *Rheumatology* 2021;60:e402-3.
Image courtesy Prof. Georgin-Lavialle. Content based on speaker experience.

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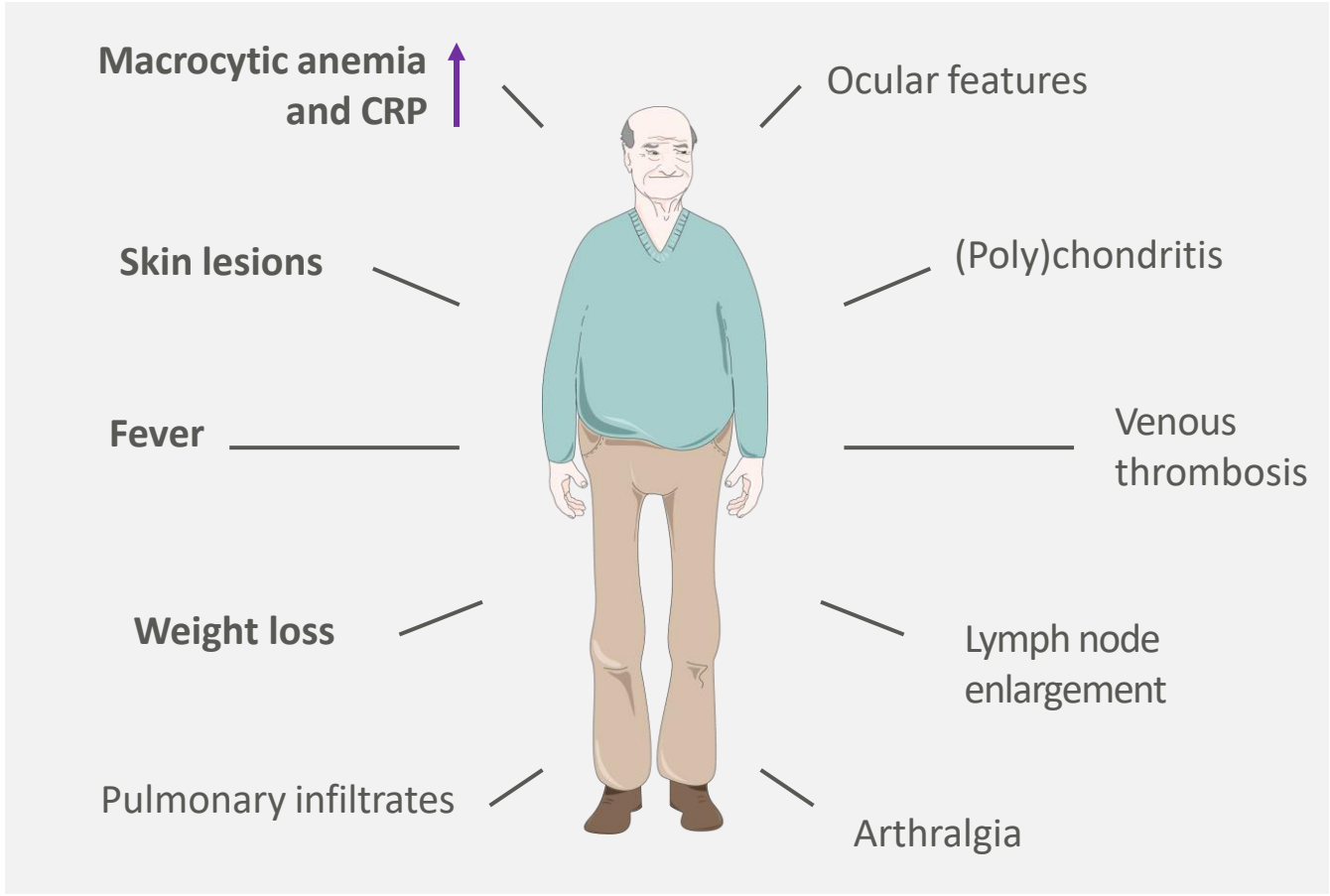
VEXAS is a **heterogeneous disease**

Delayed diagnosis & misdiagnosis[1]

5 years

Most frequent considered diagnosis prior to VEXAS syndrome

- Seronegative arthritis
- Relapsing polychondritis
- Sweet's syndrome
- Polymyalgia rheumatica
- Systemic lupus erythematosus
- Medium vessel vasculitis



Diagnosis is confirmed by **genetic testing for *UBA1* mutation**

CRP, C-reactive protein; VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.
1. Garcia-Escudero et al. *Rheumatology* 2025;64:3747-55.
Image on the right courtesy Prof. Georgin-Lavialle. Content based on speaker experience.

Key messages

Please **open the EULAR App** to be ready to vote in the poll

- VEXAS is an **inflammatory syndrome** primarily affecting **men >45 years of age**
- VEXAS is a **heterogeneous disease**
- Depending on clinical manifestations, patients are seen by **dermatologists**, **rheumatologists** or **haematologists**
- **Understanding clinical manifestations in other medical specialties** is critical for differential diagnosis, triggering a confirmatory genetic testing
- VEXAS can be diagnosed by **sequencing *UBA1*** (Sanger exon 3 or panel)

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VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

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What's your opinion?

What is the most frequent dermatologic manifestation suggestive of VEXAS syndrome?

A. Annular papules

B. Periorbital oedema

C. Livedo reticularis

D. Sweet's syndrome

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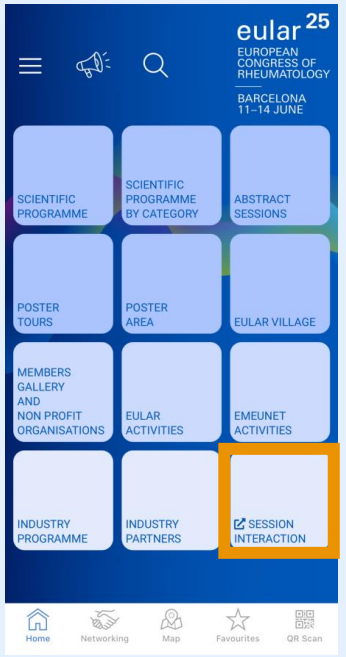

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External presentation - Dermatologic features of VEXAS

Thibault Mahévas

Dermatology Department
Hôpital Saint-Louis
Paris, France

Disclosures

Speaker's fees	Almirall, Janssen, Leo Pharma, Novartis, Sanofi
Scientific advisory board	Novartis, Sanofi

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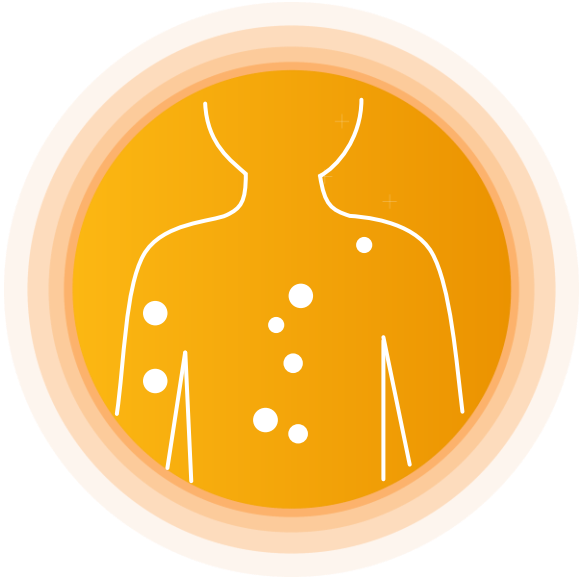
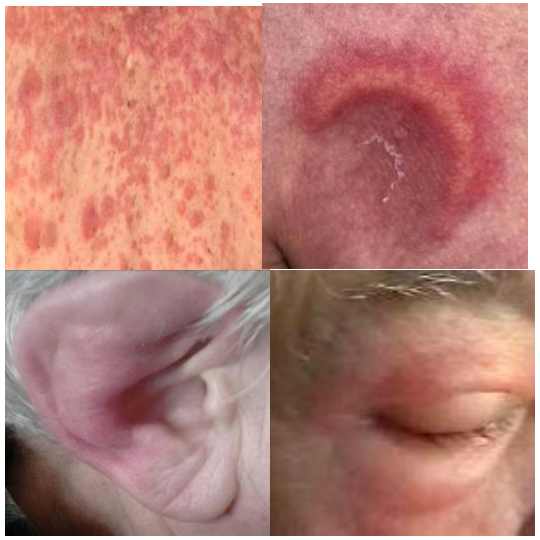
VEXAS syndrome from a dermatologist's perspective[1]



Cutaneous involvement is the **most frequent clinical sign** in VEXAS patients[1-7]

- **Up to 89%** of patients report cutaneous manifestations[2,5-7]
  - **First clinical symptom** in **up to 63%** of patients[4,7]
- Clonal neutrophilic dermatitis - **most frequent**[6]
- **Various cutaneous signs**[4-7]
  - Sweet's syndrome-like lesions (papules, nodules)
  - Pustules
  - Chondritis
  - Livedo
  - Periorbital oedema
- High frequency of **association between skin findings and systemic Inflammation** (fever, weight loss)[2,6,7]



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VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

1. Francès et al. *Medicine* 2001;80:173-9 **2.** Beck et al. *N Engl J Med* 2020;383:2628-38 **3.** Zakine et al. *JAMA Dermatol* 2021;157:1349-54 **4.** Zakine et al. *J Am Acad Dermatol* 2023;88:917-20
5. Sterling et al. *J Am Acad Dermatol* 2023;89:1209-14 **6.** Georgin-Lavialle et al. *Br J Dermatol* 2022;189:564-74 **7.** Tan et al. *JAMA Dermatol* 2024;160:822-9.

Images courtesy of Dr Mahévas, Saint Louis hospital collection. Image on the top right used with permission of the American Academy of Dermatology, Inc., from Clinical and Pathological Features of Cutaneous Manifestations in VEXAS syndrome: A Multicenter Retrospective Study of 59 Cases. Zakine et al. *J Am Acad Dermatol* 2023;88:917-20; permission conveyed through Copyright Clearance Center, Inc.

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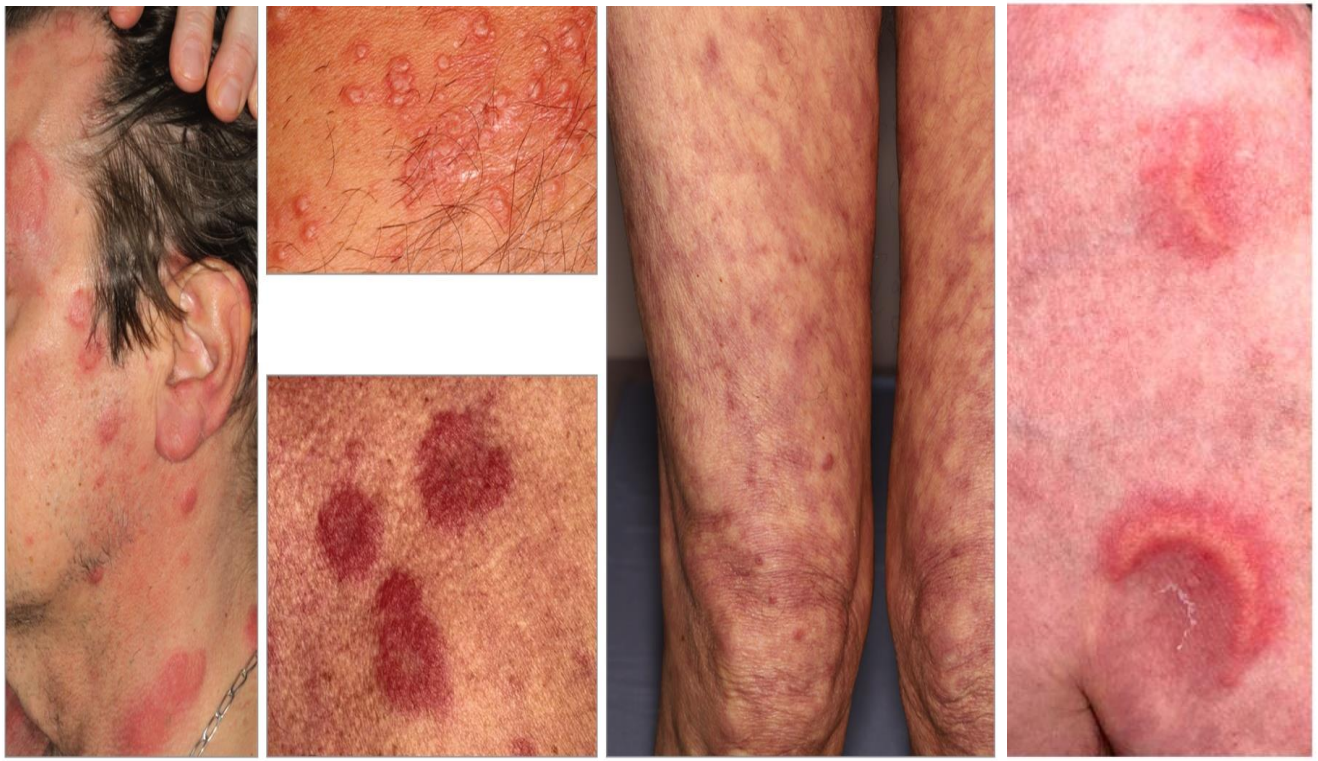
Cutaneous features:
Important for diagnosis of VEXAS syndrome[1,2]



Same loss-of-function *UBA1* mutation in bone marrow and skin lesions[1]

Clinical characteristics of skin involvement (N=37)[2]	
Lesion description	
Lesion type	
Maculopapules and nodules	37 (100%)
Pustules	5 (13%)
Vesicles/bullae	4 (11%)
Livedo	6 (16%)
Reticularis	3 (8%)
Racemosa	3 (8%)
Thickness of pattern < 1 cm	3 (8%)
Lesion shape	
Round/nummular	36 (97%)
Arcuate/annular	12 (32%)
Lesion colour	
Pink	28 (76%)
Red	27 (73%)
Violaceous/purpuric	18 (49%)
Lesion size	
< 1 cm	29 (78%)
≥ 1 cm	29 (78%)
Both	21 (57%)
Number of lesions	
≥ 10	33 (89%)
< 10	4 (11%)
Localisation	
Trunk	30 (81%)
Arms	32 (86%)
Legs	31 (84%)
Face	11 (30%)
Pathergy	5 (13%)
Cutaneous symptoms	
Pain	13 (35%)
Pruritus	9 (24%)
Evolution of skin lesions	
Flare/remission periods	30 (81%)
Frequency of flare-ups (times/year, median [IQR])	6 [2-12]
Duration of flare-ups (days, median [IQR])	9.8 [7-10]
Permanent	4 (11%)

IQR, interquartile range; VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

1. Zakine et al. *JAMA Dermatol* 2021;157:1349-54 **2.** Zakine et al. *J Am Acad Dermatol* 2023;88:917-20.

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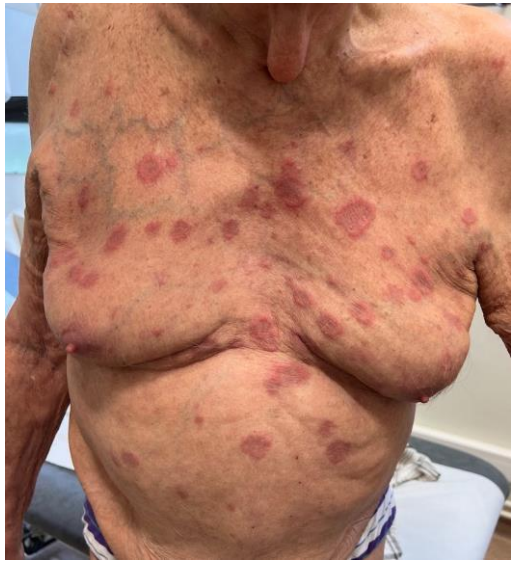
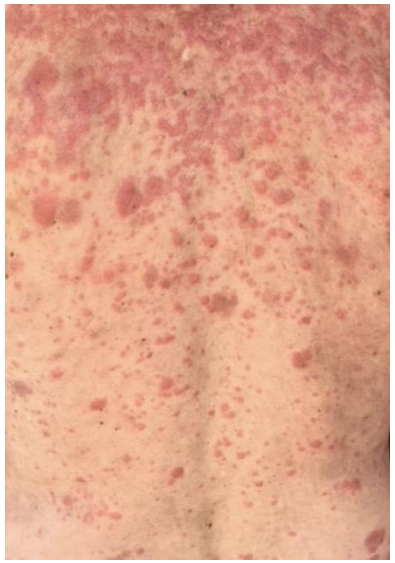
Papules and nodules:
A common sign in VEXAS patients

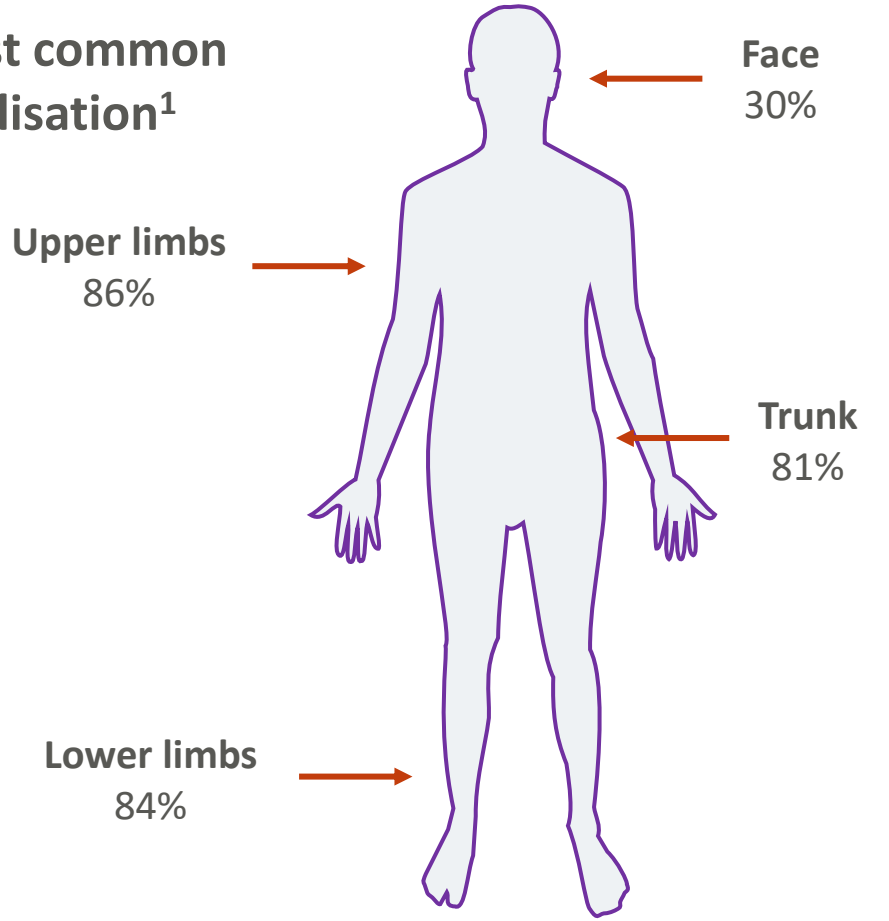
Papules and nodules

- **Inflammatory** in 100% of cases
- **Multiple** (≥10 in 89% of cases)[1]
- **Variable** in size and colour[1]





Most common localisation[1]



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VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

1. Zakine et al. *J Am Acad Dermatol* 2023;88:917-20. Images courtesy of Dr Mahévas, Saint Louis hospital collection.

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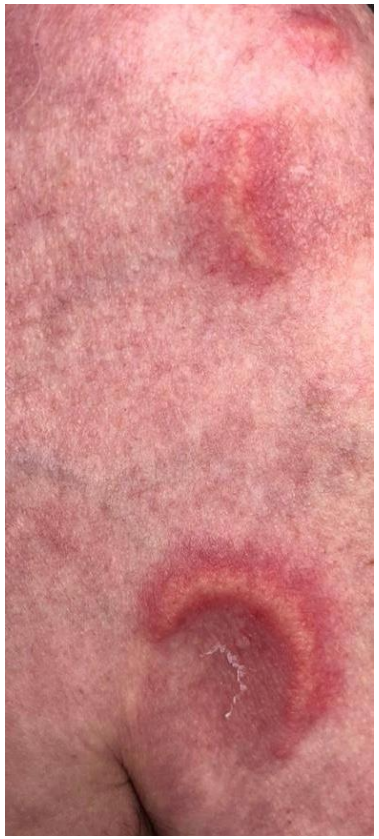
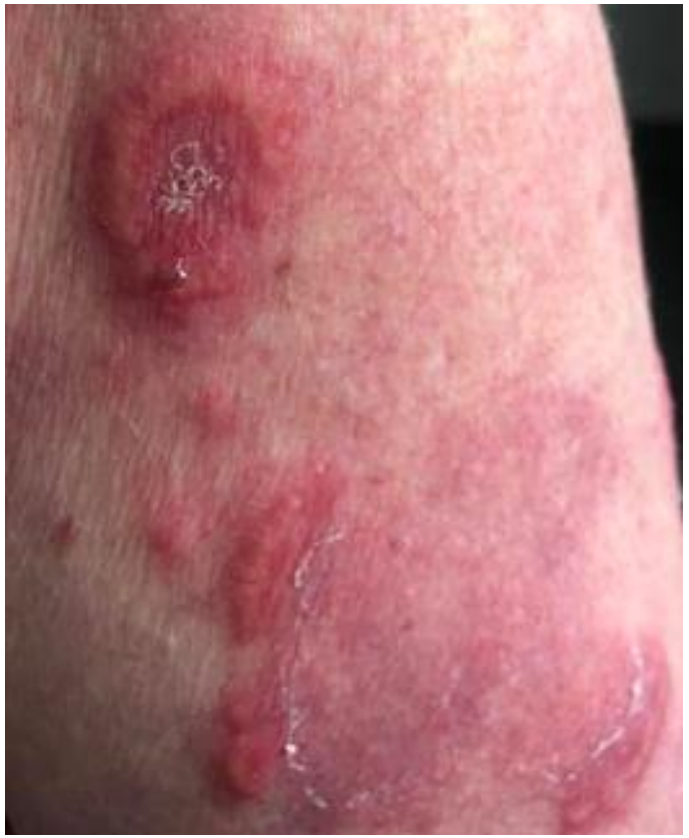
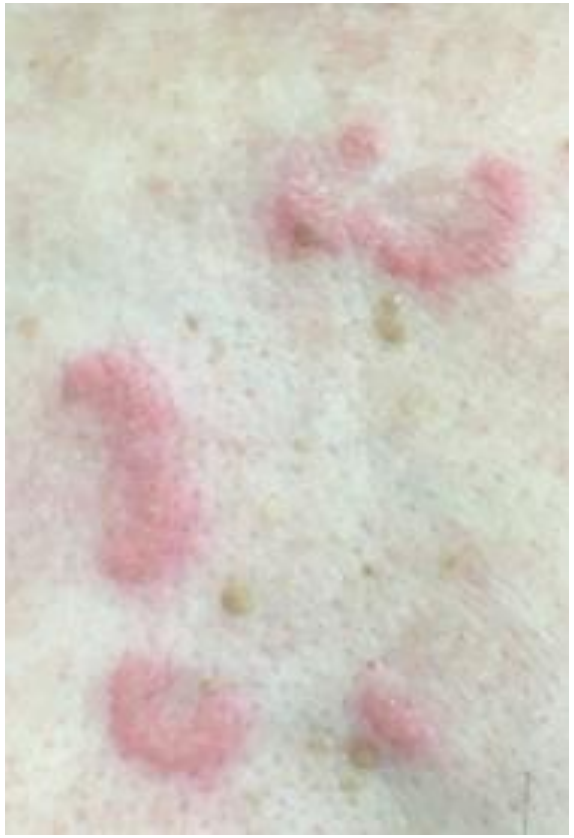
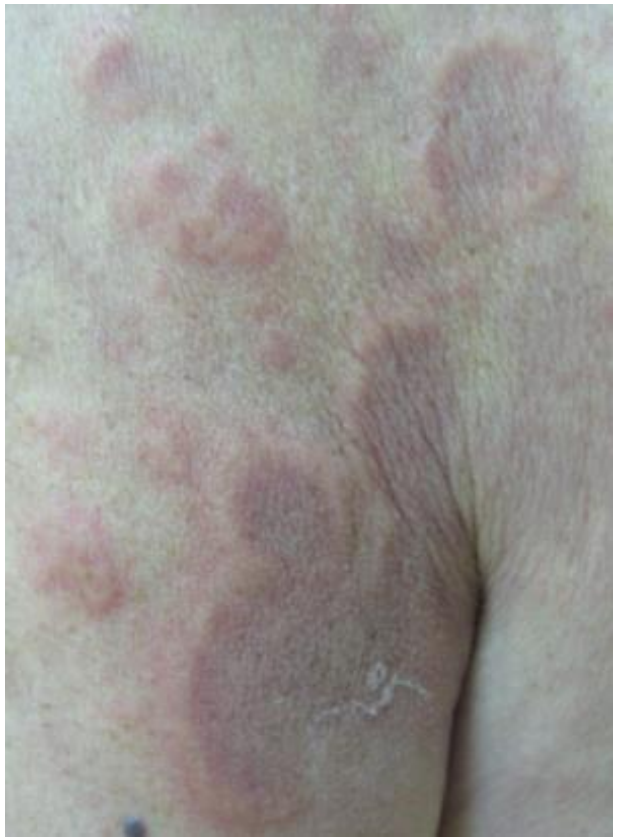
Papular lesions:
A common sign in VEXAS patients

Annular papules and arcuate lesions in **32% of cases**[1]

VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic. **1.** Zakine et al. *J Am Acad Dermatol* 2023;88:917-20.

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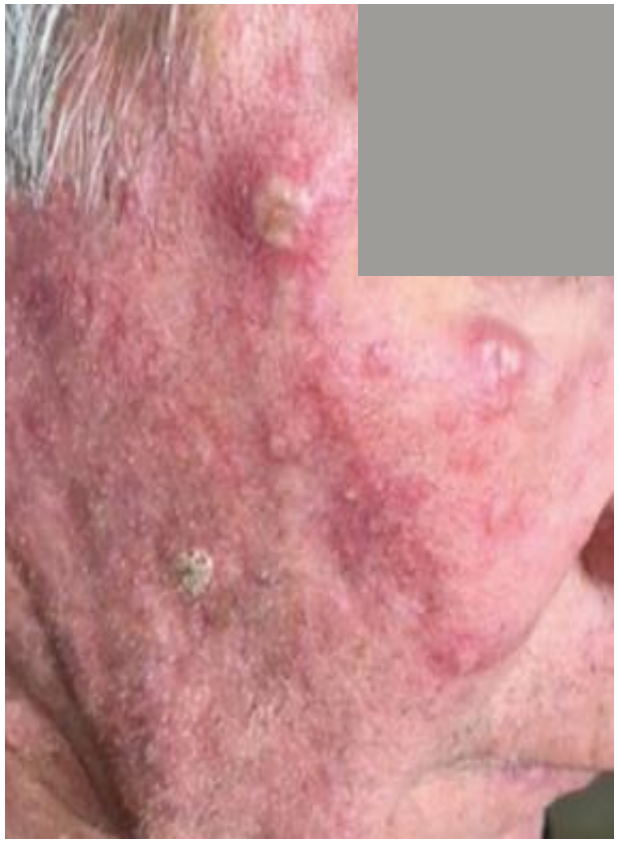
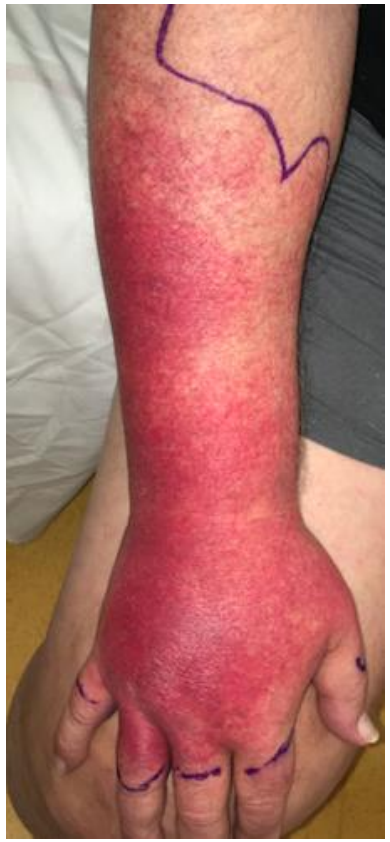
Rare cutaneous features in VEXAS patients

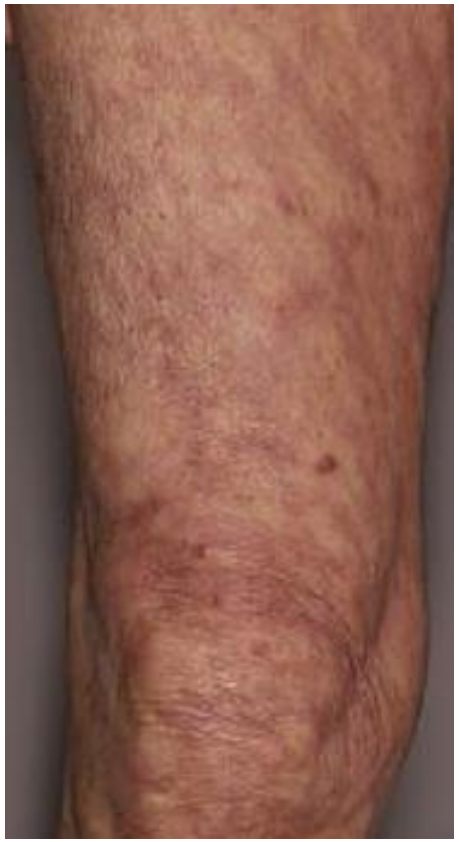
Pustules 13%[1]



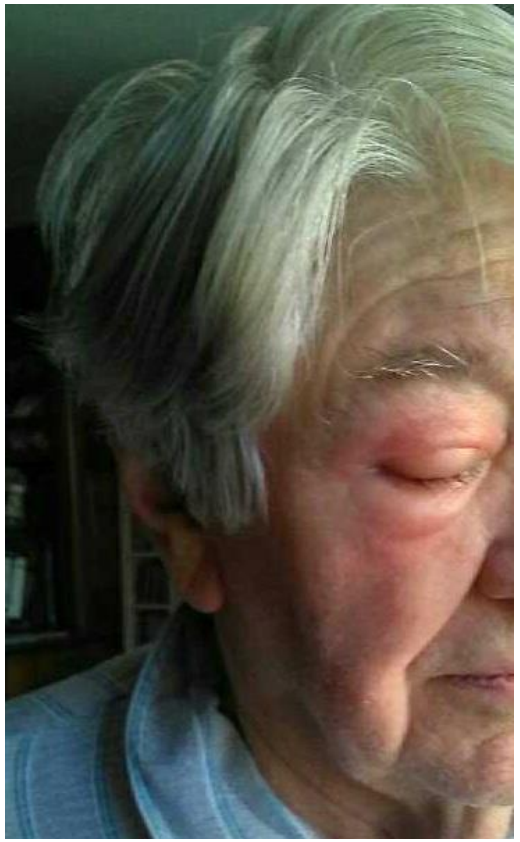
Pseudocellulitis



Livedo 16%[1]



Periorbital oedema



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VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

1. Zakine et al. *J Am Acad Dermatol* 2023;88:917-20. Images courtesy of Dr Mahévas, Saint Louis hospital collection.

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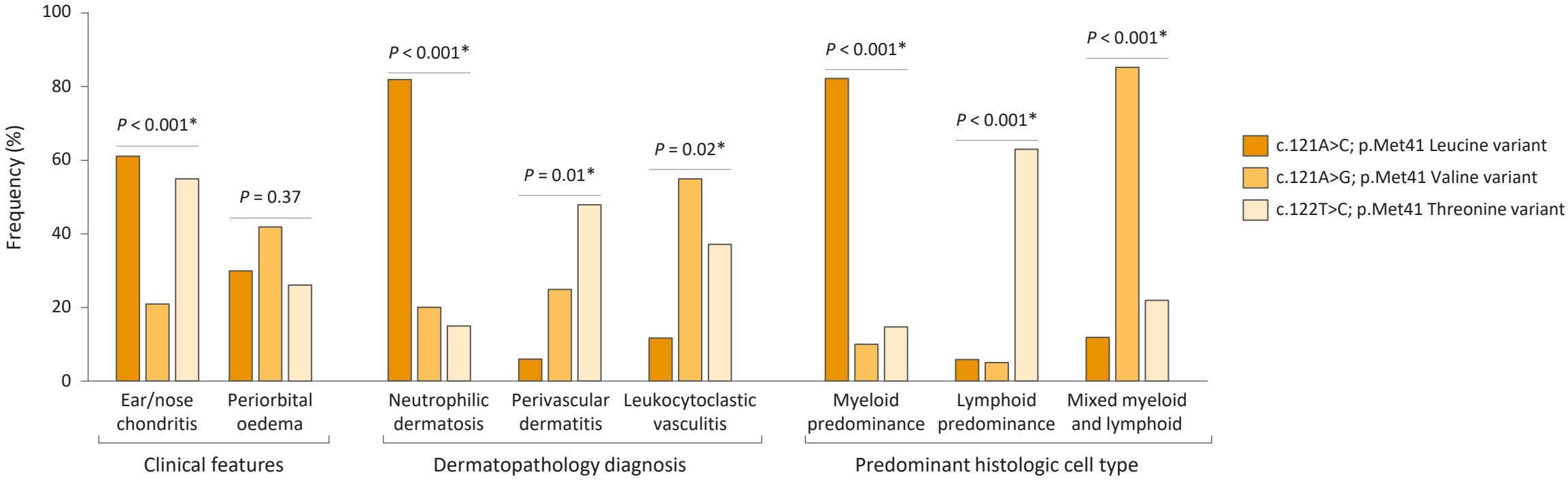
Skin manifestations of VEXAS syndrome and associated genotypes

Association of genotype with clinical and histopathologic findings[1]



*Statistically significant comparison ($p < 0.05$).
VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic. **1.** Tan et al. *JAMA Dermatol* 2024;160:822-9.
Figure adapted from Skin Manifestations of VEXAS Syndrome and Associated Genotypes. Tan et al. *JAMA Dermatol* 2024;160:822-9. Reused with permission of the American Medical Association; permission conveyed through Copyright Clearance Center, Inc.

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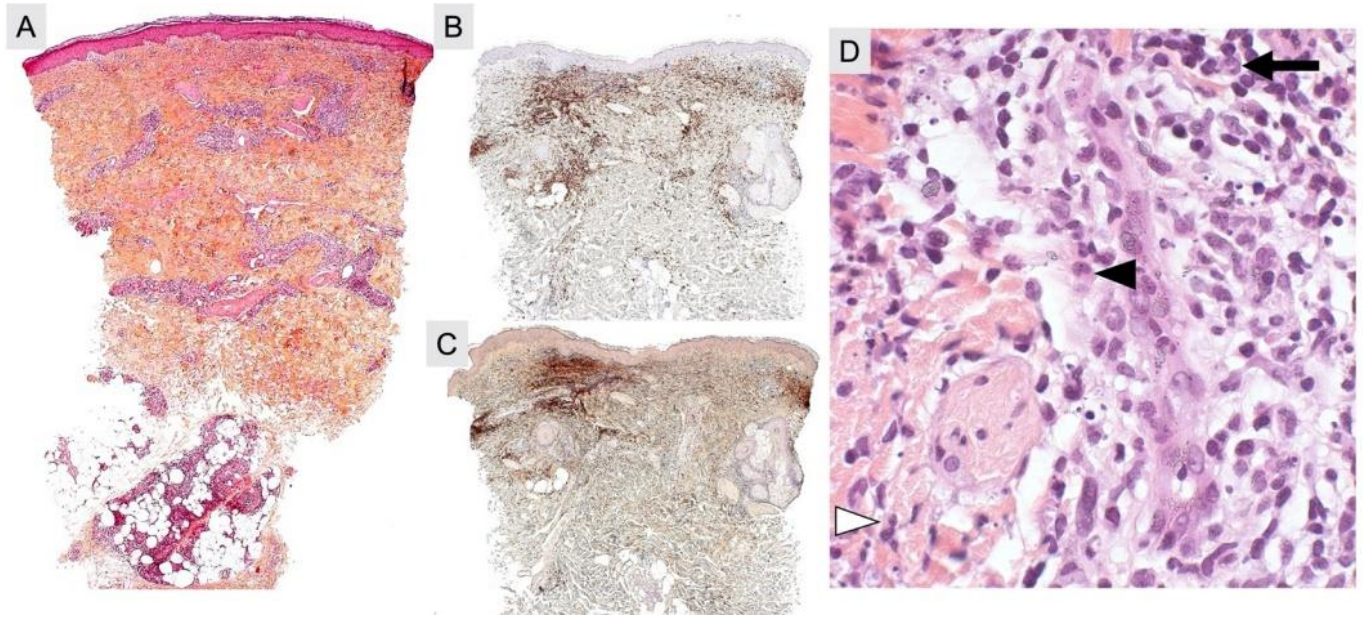
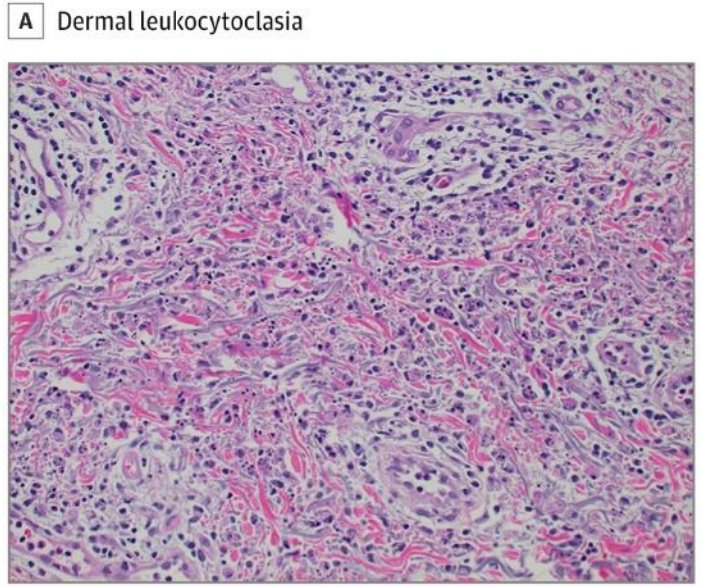
VEXAS histology[1,2]





- **High frequency** of **neutrophilic dermal infiltrate**, histiocytoid Sweet's syndrome (CD68, MPO positive)
- **Leukocytoclasia** with or without vasculitis (controversial)
- **Perieccrine lymphocytic** and **neutrophilic infiltrate with leukocytoclasia**
- **Polyarteritis nodosa** aspect

MPO, myeloperoxidase; VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic. **1.** Zakine et al. *J Am Acad Dermatol* 2023;88:917-20 **2.** Tan et al. *JAMA Dermatol* 2024;160:822-9.
Image (left) used with permission of the American Academy of Dermatology, Inc., from Clinical and Pathological Features of Cutaneous Manifestations in VEXAS syndrome: A Multicenter Retrospective Study of 59 Cases. Zakine et al. *J Am Acad Dermatol* 2023;88:917-20; (right) used with permission of American Medical Association, from Skin Manifestations of VEXAS Syndrome and Associated Genotypes. Tan et al. *JAMA Dermatol* 2024;160:822-9; permissions conveyed through Copyright Clearance Center, Inc.

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Dermatology: **Key messages**

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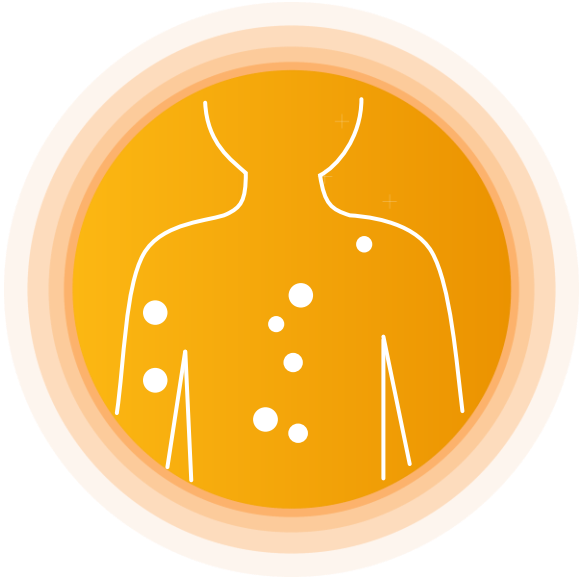

- **VEXAS syndrome: Haemato-auto-inflammatory syndrome**, associated with clonal haematopoiesis and myelodysplasia cutis concept
- **Skin involvement: Frequent** (up to 89%) and often **first sign** of VEXAS (up to 63%)
- **Skin features in VEXAS syndrome:** Papules, nodules, plaques, **arcuate lesions**, peri-orbital oedema
- **Myelodysplasia cutis:** Neutrophilic dermal infiltrate, histiocytoid Sweet's syndrome with clonal UBA1 cell

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VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

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What's your opinion?

What is the most frequent rheumatological manifestation suggestive of VEXAS syndrome?

A. **Musculoskeletal**
(arthritis/arthralgia, myalgia/myositis-like symptoms)

B. **Vasculitis-like manifestations** (leukocytoclastic vasculitis, erythema nodosum, livedo reticularis etc.)

C. **Chondritis**

D. **Organ involvement**
[pleuritis, (myo) pericarditis, pneumonia]

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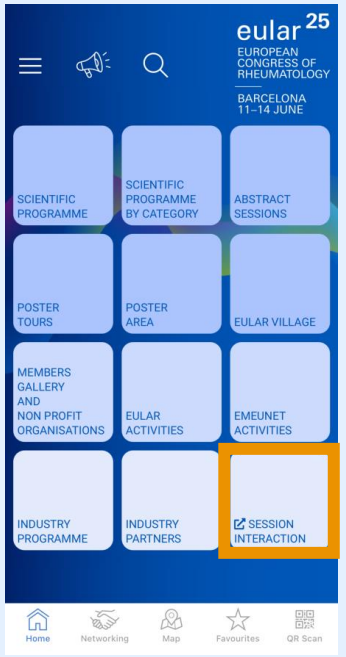
1. Select **Session Interaction**
2. Select the **session**
3. Select **voting**



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Under the skin - Rheumatologic features of VEXAS

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Disclosures

Speaker's fees	**Sobi**
Scientific advisory board	**Novartis, Sobi**

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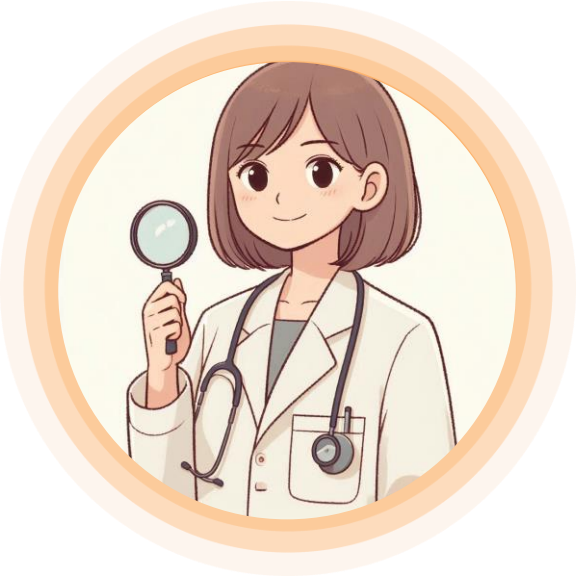
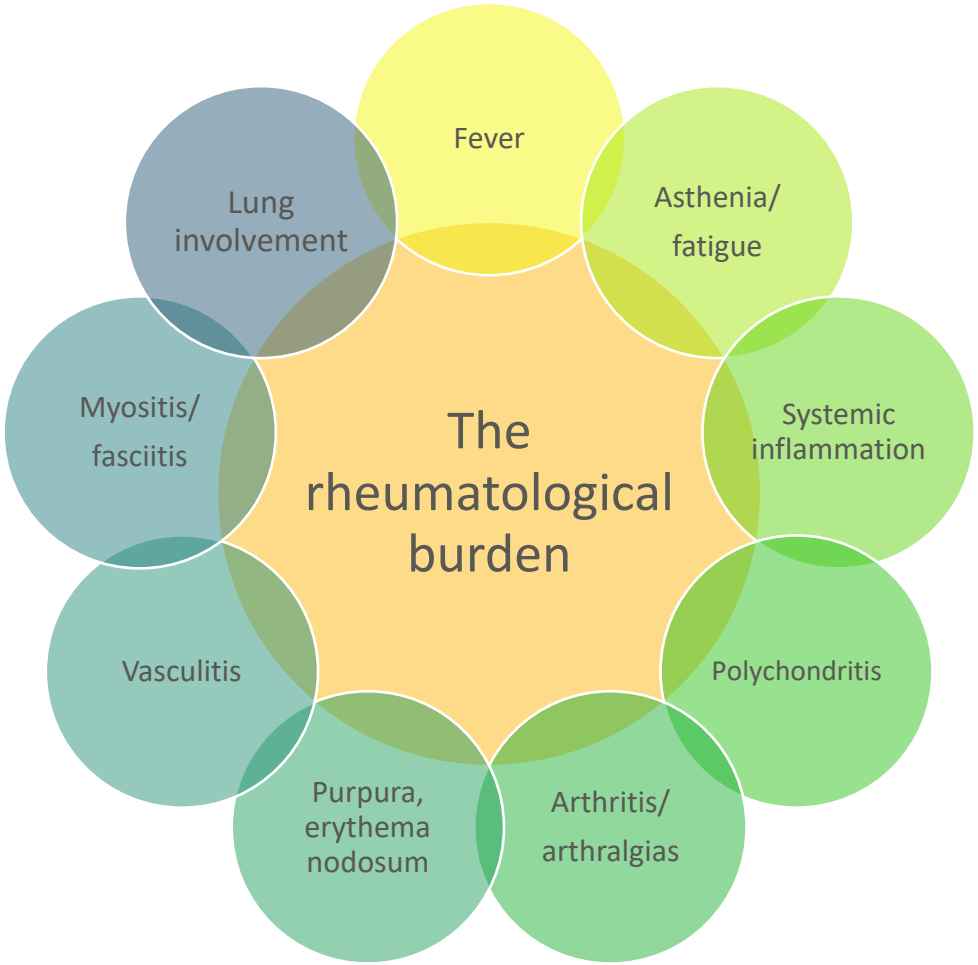
VEXAS syndrome from a rheumatologist's perspective

In medicine, as in life, we often see what we are looking for





Due to the **broad inflammatory and systemic nature of the condition** and **prevalence of musculoskeletal symptoms**, rheumatologists will frequently see potential VEXAS patients

VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.
Image generated with Microsoft Copilot. Content based on speaker experience.

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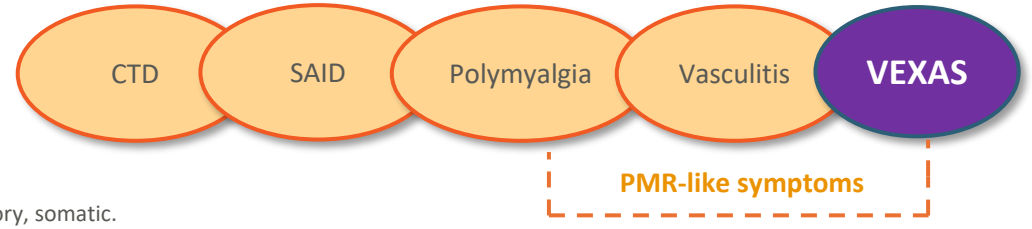
Chronic, steroid-dependent inflammation with severe fatigue (asthenia) in VEXAS syndrome

Persistent inflammation:
VEXAS syndrome is a chronic progressive autoinflammatory disease with a high unmet need[1,2]

Constitutional symptoms, such as **fatigue**, fever, night sweats and weight loss, **affect almost all patients**[2-4]

- Anaemia may worsen **fatigue** contributing to physical weakness
- **Cytokine release** (mainly IL-6, TNF-alpha, IL-1) directly induces fatigue and malaise
- Recurrent or persistent **low- to high-grade fever** may occur daily or intermittently
- Inflammatory manifestations of VEXAS generally **require management with corticosteroid**[3]



CTD, connective tissue disease; PMR, polymyalgia rheumatica;
SAID, systemic autoinflammatory disease; VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.
Content based on speaker experience. **1.** Uchino et al. *Int J Hematol* 2022;116:463–4 **2.** Al-Hakim and Savic. *Expert Rev Clin Immunol* 2023;19:203-15
3. Beck et al. *N Engl J Med* 31;383:2628-38 **4.** Lee et al. *Aus J Gen Pract* 2025;54:219-21.

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Inflammatory arthritis and arthromyalgias in VEXAS syndrome

Inflammatory arthritis is a frequent manifestation in

up to 80%

of VEXAS patients[1-3]

- **Articular involvement** in VEXAS is variable
- Patients typically present with **joint pain and swelling**
- Mostly **large and medium joints** are affected, with no specific distribution pattern[4]
- Symptoms **may resemble rheumatoid arthritis** or **other autoimmune arthropathies like seronegative arthritis[2]**

Arthritis in VEXAS syndrome can affect multiple joints, leading to **increased discomfort and functional limitations impacting daily life**

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VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

Content based on speaker experience. **1.** Ferrada et al. *Blood* 2022;140:1496-1506 **2.** Georgin-Lavialle et al. *Br J Dermatol* 2022;186:564-74 **3.** Garcia-Escudero et al. *Rheumatology* 2025;64:3747-55 **4.** Kucharz et al. *Reumatologia* 2023;61:123–9.

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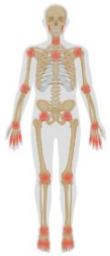
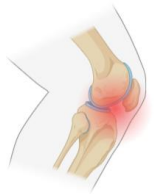
Joints and beyond: Articular involvement, myalgias and myositis in VEXAS syndrome

Arthralgias



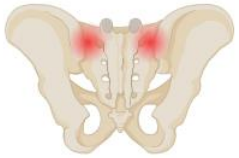
FRENVEX ~36%[1]
Cohort: 299 patients

Inflammatory arthritis



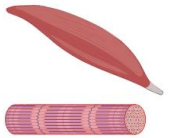
Spanish cohort ~82%[2]
Cohort: 39 patients
Swiss cohort ~ 35%[3]
Cohort: 17 patients

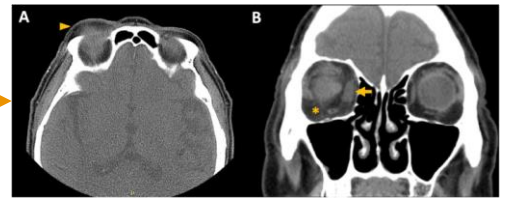
Sacroiliitis and SpA pattern (HLA-B27)



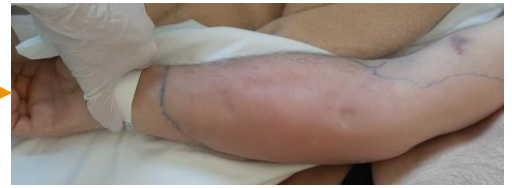
Case reports[2,3,4]

Muscular and peri-muscular involvement

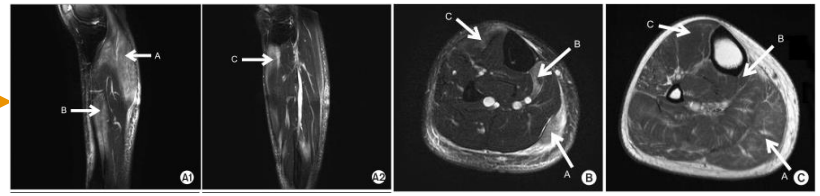




CT scan showing medial rectus enlargement **(orbital myositis)**[5]



Arm fasciitis



Focal myositis[6]

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CT, computer tomography; SpA, spondyloarthritis; VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

1. Georgin-Lavialle et al. *Arthritis Rheumatol* 2024;76(suppl 9):1886 **2.** Garcia-Escudero et al. *Rheumatology* 2025;64:3747-55 **3.**Wolff et al. *Swiss Med Wkly* 2025;155:3879
4. Magnol et al. *Rheumatology* 2021;60:e314-5 **5.** Vitale et al. *Semin Arthritis Rheum* 2024;66:152430 **6.** Jun et al. *Ann Rehabil Med* 2011;35:944-8.

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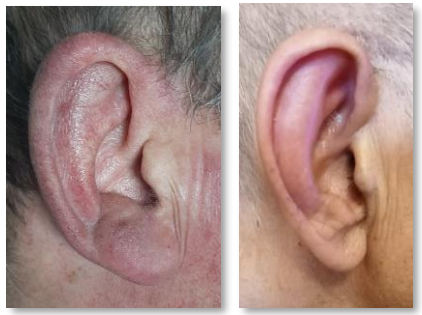
Relapsing polychondritis (RP) in VEXAS syndrome

Polychondritis or localised chondritis is **one of the most common features of VEXAS syndrome**[1]

Auricular or nasal chondritis reported

in up to 60% of patients[2,3]



Prediction of VEXAS syndrome in patients with RP:
Coexisiting male sex, macrocytosis, and a platelet count <200×10^3/µl[4,5]

- **Recurrent inflammation of cartilage**, particularly in the ears, nose, and respiratory tract[5]
- In the majority of cases, chondritis in patients with VEXAS syndrome is **indistinguishable from RP**[1]

Differences between VEXAS-associated and idiopathic RP[5,6]

Patient %	VEXAS-associated RP	Idiopathic RP
Fever	60%	10%
Skin lesions	82%	20%
Ocular involvement	57%	28%
Lung infiltrates	46%	0%
Higher median CRP	64 mg/L	10 mg/L

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CRP, C-reactive protein; RP, relapsing polychondritis; VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.
1. Kucharz. *Reumatologia* 2023;61:123–9 **2.** Watanabe et al. *Front Med* 2022;9:983939 **3.** Georgin-Lavialle et al. *Br J Dermatol* 2022;186:564-74 **4.** Ferrada et al. *Arthritis Rheumatol* 2021;73:1886–95
5. Al-Hakim and Savic. *Expert Rev Clin Immunol* 2023;19:203-15 **6.** Khitri et al. *RMD Open* 2022;8:e002255. Images courtesy of Dr. Bindoli.

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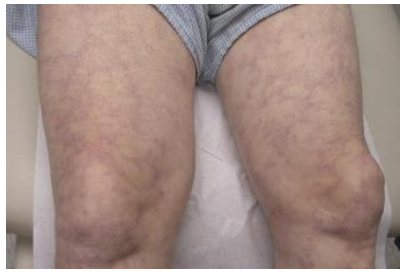
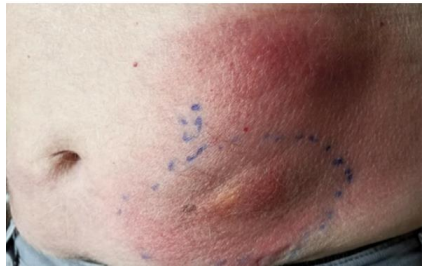
Vasculitis-like manifestations in VEXAS syndrome

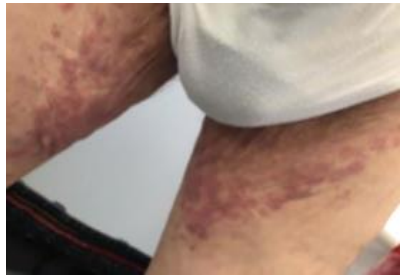
Be aware of vasculitis features in VEXAS



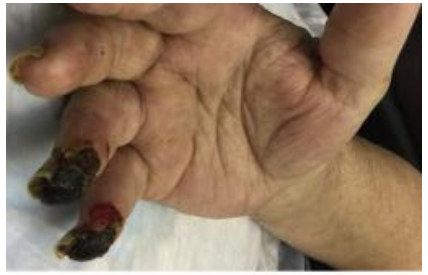
Livedo reticularis



Panniculitis (EN-like)



Purpuric rash



Cryoglobulinemia (Type III)

- **~20% of VEXAS patients** had **evidence of vasculitis** in a cohort of 89 patients[1]
- Prevalence of **small (19%,** n=89)[1], **medium (up to 18%,** n=39)[1,2] and **large vessel vasculitis (up to 23%,** n=35)[1,3]
  - **Leukocytoclastic vasculitis:** Small vessel vasculitis, most common vasculitis reported in VEXAS, typically manifests as palpable purpura[4,5]
  - **Polyarteritis nodosa:** Medium-vessel vasculitis with widespread clinical manifestations including renal disease, hypertension, cutaneous lesions and cardiovascular injury[4]
- **86% of vasculitis patients with cutaneous manifestations** (purpuric rashes, ulcers, or subcutaneous nodules)[1]

Is VEXAS a form of «variable» vessel vasculitis?

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EN, erythema nodosum; VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

1. Sullivan et al. *Rheumatology* 2025;64:3889-94 **2.** Garcia-Escudero et al. *Rheumatology* 2025;64:3747-55 **3**. Bixio et al. *Intern Emerg Med* 2024;19:2331-45
4. Al-Hakim and Savic. *Expert Rev Clin Immunol* 2023;19:203-15 **5.** Watanabe et al. *Front Med* 2022;9:983939. Image top left used with permission of Excerpta Medica Inc., from Web of confusion. Gunderson et al. *Am J Med* 2011;124:501-4; permission conveyed through Copyright Clearance Center, Inc.; top right from Argobi et al. *Dermatol Reports* 2022;14:9414, used with permission (CC BY 4.0) © 2022 The Authors, published by PAGEPress; bottom left from Pereira da Costa et al. *Front Immunol* 2024;15:1403808, used with permission (CC BY 4.0) © 2021 The Authors, published by Frontiers Media S.A.; bottom right used with permission of Mayo Foundation for Medical Education and Research, from Clinical Heterogeneity of the VEXAS Syndrome: A Case Series. Koster et al. *Mayo Clin Proc* 2021;96:2653-9; permission conveyed through Copyright Clearance Center, Inc.

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How to search for VEXAS **starting from vasculitis**[1]

147 vasculitis patients
(LVV, ANCA, PAN, Behçet, IgA vasculitis, relapsing polychondritis)

7 patients with VEXAS features

3/5 (60%) had ***UBA1 mutations*** confirming VEXAS

A **clinically oriented**, **phenotype-first** approach is central to enhancing the diagnosis of undiagnosed VEXAS syndrome cases

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ANCA, antineutrophil cytoplasmic antibody; LVV, large vessel vasculitis; PAN, polyarteritis nodosa; VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

1. Muratore et al. *Arthritis Rheumatol* 2022;74:665-70.

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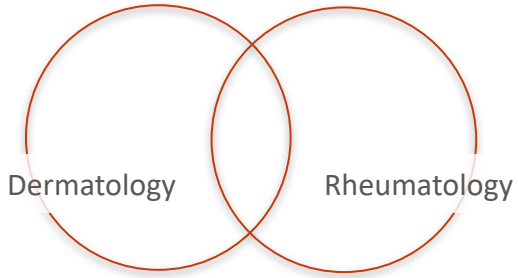
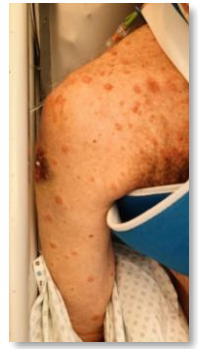
Sweet's syndrome (neutrophilic dermatosis) in VEXAS syndrome

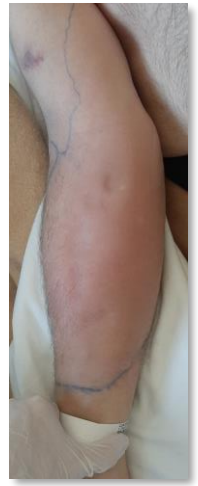
Important clinical clue for healthcare professionals during the diagnostic process

Highlighting the need for multidisciplinary management



- Manifests with painful skin lesions (tender erythematous papules, nodules or plaques) often accompanied by systemic symptoms such as fever and neutrophilia[1,2]
- Several inflammatory and autoimmune diseases can present in a similar way to Sweet's syndrome[3]
  - Eosinophilic dermatosis
  - RAS-associated autoimmune leukoproliferative disease
  - Rheumatoid neutrophilic dermatosis
  - Rosacea-like dermatitis
  - Synovitis acne pustulosis hyperostosis syndrome





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VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.
1. Al-Hakim and Savic. *Expert Rev Clin Immunol* 2023;19:203-15 **2.** Cohen. *Orphanet J Rare Dis* 2007;2:34 **3.** Joshi et al. Am J Clin Derma 2022;23:301-18.
Images courtesy of Dr. Bindoli.

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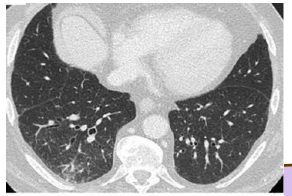
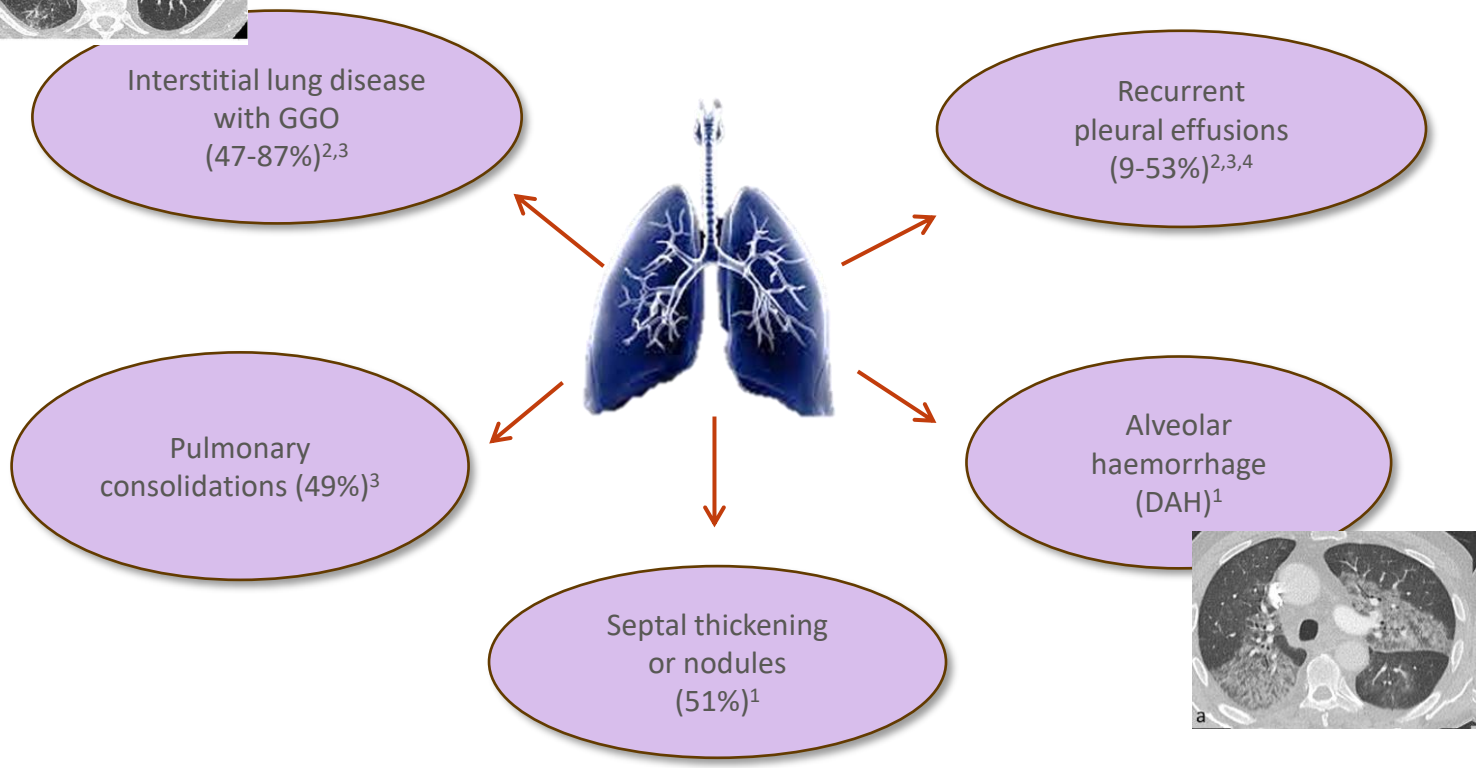
Lung involvement
in VEXAS syndrome



Variable disease involvement in 50 to 72% of patients[1]



- Be aware of the pulmonary **legionellosis risk** in VEXAS
- Differential diagnosis with **COVID-19 pneumonia** or and other types of **viral pneumonia** (e.g. HSV) is required

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DAH, diffuse alveolar haemorrhage; GGO, ground-glass opacity; HSV, herpes simplex virus; VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic. Content based on speaker experience.

1. Puseljic et al. *ARP Rheumatology* 2024;2:151-6 **2**. Casal Moura et al. *Respir Med* 2023;213:107245 **3.** Borie et al. *Chest* 2023;163:575-85 **4.** Bruno et al. *J Allergy Clin Immun*ol 2023;151:1204-14.

Images (top) used with permission of American College of Chest Physicians, from Pleuropulmonary Manifestations of Vacuoles, E1 Enzyme, X-Linked, Autoinflammatory, Somatic (VEXAS) Syndrome. Borie et al. *Chest* 2023;163:575-85; permission conveyed through Copyright Clearance Center, Inc., (bottom) from Puseljic et al. *ARP Rheumatology* 2024;2:151-6, used with permission (CC BY-NC-ND 4.0)

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Rheumatology: **Key messages**

Please **open the EULAR App** to be ready to vote in the poll

Rheumatologic features of VEXAS

- Consider **differential diagnosis** to exclude mimics
- Be alert, in particular to **vasculitis-like** manifestations and **chondritis**
- **Musculoskeletal symptoms** may be **non-specific**
- **Always investigate** for associated haematological and/or dermatological manifestations

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VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

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What's your opinion?

What is the most frequent haematologic manifestation suggestive of VEXAS syndrome?

A. Pancytopenia

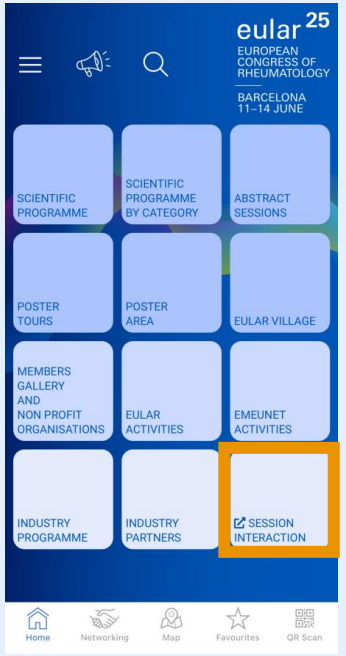
B. Macrocytic anaemia

C. Plasma cell dyscrasias (MGUS/SMM)

D. Myelodysplastic syndrome

Please **open the EULAR App** on your mobile device to **vote in the poll**

1. Select **Session Interaction**
2. Select the **session**
3. Select **voting**



MGUS, monoclonal gammopathy of undetermined significance; SMM, smouldering myeloma.

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Deep, into the marrow - Haematologic features of VEXAS

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Disclosures

Speaker's fees	Sobi
Scientific advisory board	Vertex, Sobi

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VEXAS syndrome is a rare autoinflammatory condition **with several haematological manifestations**

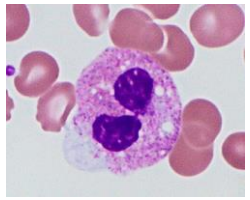
Peripheral blood and marrow findings

Cytopenias

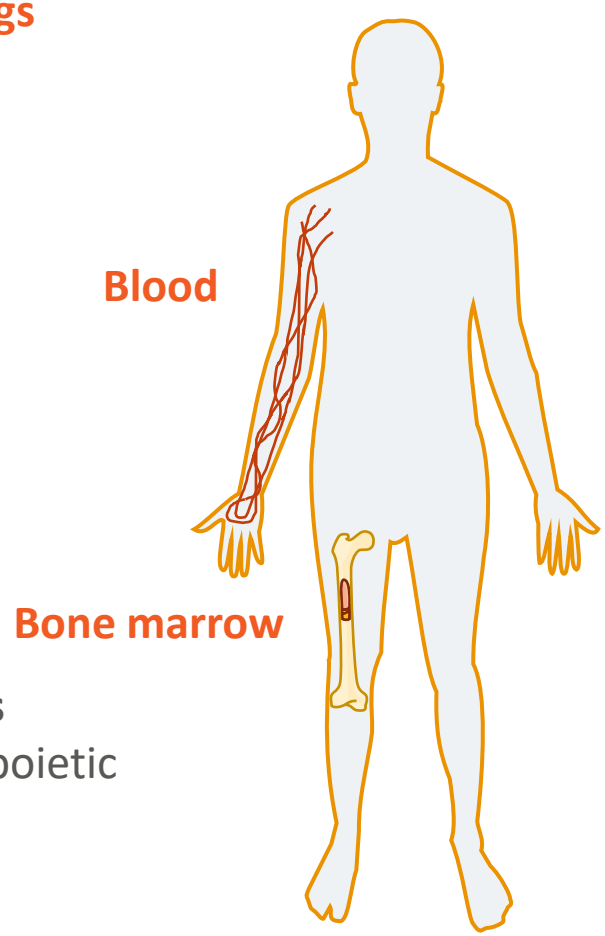
Macrocytic anaemia

Thrombocytopenia

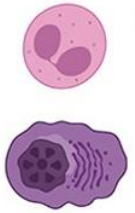
Neutropenia



Cytoplasmic vacuoles
Vacuoles in haematopoietic precursor cells



Haematologic malignancies

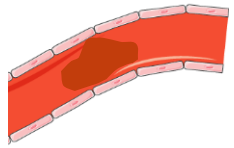


Myelodysplastic syndrome

MGUS

Multiple myeloma

Thrombosis



Venous thromboembolism

Transient ischaemic attack

Stroke

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MGUS, monoclonal gammopathy of undetermined significance. Figure adapted from Obiorah et al. *Blood Adv* 2021;5:3203-3215.
Image on the bottom left from Haines et al. *Int J Lab Hematol* 2024 (CC BY 4.0) © 2024 The Authors. International Journal of Laboratory Hematology published by John Wiley & Sons Ltd.

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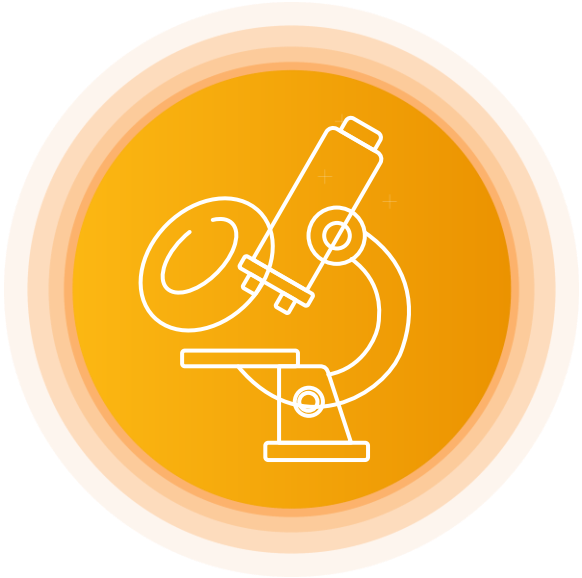
VEXAS syndrome from a haematologist's perspective[1]



From the start, VEXAS syndrome stood out as a **rheumatologic disease with clear haematologic overtone**

- **UBA1 mutations** are primarily **responsible for myeloid clonal expansion** and both the **inflammatory and haematologic phenotype** in VEXAS[1]
- Patients with VEXAS have an **enrichment of typical clonal haematopoiesis mutations**, particularly in DNMT3A and TET2[1]
- Although VEXAS presents symptomatically as a rheumatologic disease, **morbidity and mortality are associated with progression to haematologic disease**[2]

Understanding the unique haematological features of VEXAS syndrome is essential for accurate diagnosis and management

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VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

1. Gutierrez-Rodrigues et al. *Blood* 2023;142:244–259 **2.** Obiorah et al. *Blood Adv* 2021;5:3203-3215.

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Clonal haematopoiesis and haematologic malignancy:
Key aspects of VEXAS syndrome

Benign clonal haematopoiesis

- **Myeloid restricted somatic mutations in UBA1 are, by definition, a type of clonal haematopoiesis**
- **Co-occurrence of myeloid malignancy driver mutations that are common to MDS and CHIP**[1,2]

Myelodysplastic syndrome

- Often **low risk by IPSS-M**[3]
  - Involves **fewer mutations** which often **correlate with lower risk** of progression to AML
  - **Survival estimates** from IPSS-M are **unreliable for patients with VEXAS and MDS** due to the morbidity associated with the severe inflammatory manifestations
- **Frequent presentation of systemic inflammatory autoimmune disease symptoms** and diagnoses in MDS
  - **Case for screening for UBA1 in MDS**[4]

Plasma cell dyscrasias

- **MGUS and multiple myeloma**
  - **Mechanism** relating plasma cell dyscrasias to VEXAS is **not fully understood**

NP-42384

AML, acute myeloid leukaemia; CHIP, clonal haematopoiesis of indeterminate potential; IPSS-M, Molecular International Prognostic Scoring System; MDS, myelodysplastic syndrome; MGUS, monoclonal gammopathy of undetermined significance; VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic. **1.** Gutierrez-Rodrigues et al. *Blood* 2023;142:244–259 **2.** Sperling et al. *Nat Rev Cancer* 2017;17:5-19 **3.** Ferrada et al. *Blood* 2022;140:1496-1506 **3.** Sirenko et al *Blood* 2024;144:1221-1229. Content based on speaker experience.

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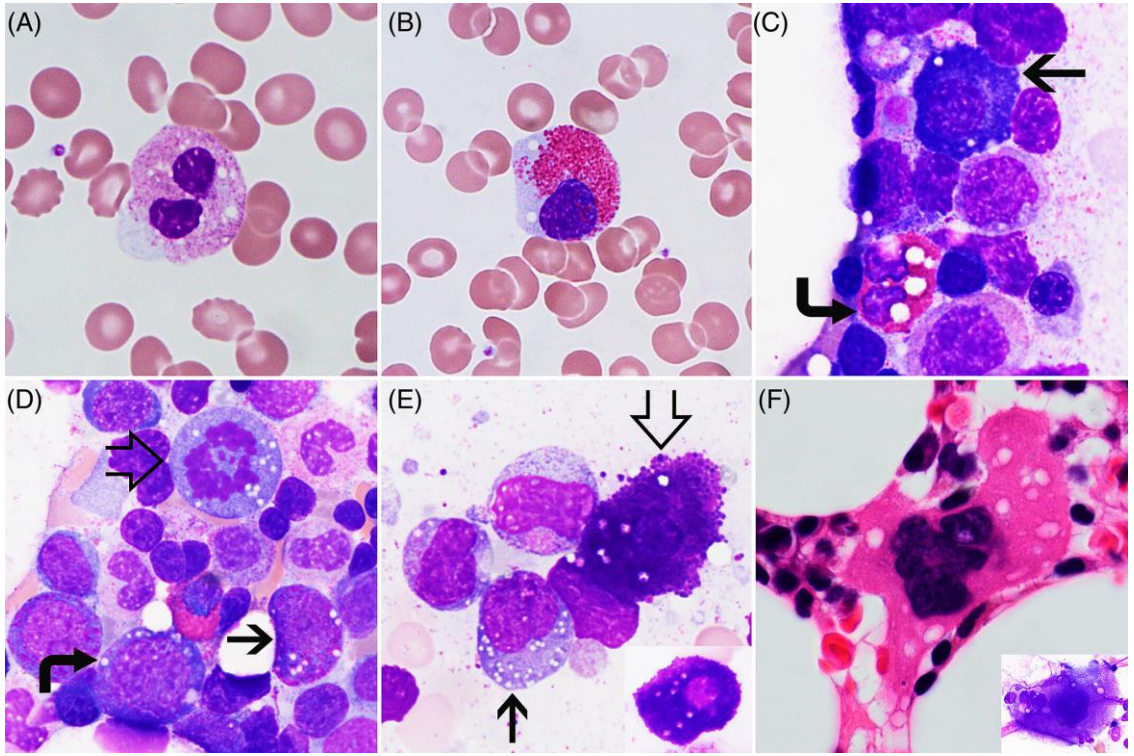
Haematopathologic features:
Important for diagnosis of VEXAS syndrome



VEXAS syndrome: Vacuoles in myeloid, erythroid, and lymphoid lineages[1]

Cytoplasmic vacuoles in haematopoietic cells are a key feature of VEXAS syndrome[1,2]

- Vacuoles predominantly in **marrow myeloid and erythroid precursor cells**
- **Not specific to VEXAS**[2]
  - Observed in MDS and other inflammatory conditions (e.g. infectious, autoimmune disease, nutrient deficiencies); monocyte vacuolization in other conditions
- **Intense marrow vacuolization highly specific** to VEXAS syndrome[2]

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MDS, myelodysplastic syndrome; VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.
1. Haines et al. *Int J Lab Hematol* 2024;46:8-9 **3.** Lacombe et al. *Am J Hematol* 2024; 99(2):E60-E62.

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Cytopenias:
A common manifestation in VEXAS syndrome

Macrocytic anaemia is present in

100%

of VEXAS patients[1]

Cytopenias

- **Macrocytic anaemia** - present **in all VEXAS patients[1]**
  - Anaemia is a **significant manifestation** of VEXAS syndrome, **affecting patient health and well-being**
- **Thrombocytopenia** - **more common** in patients with **MDS[1]**
  - Patients with thrombocytopenia face a **higher risk of bleeding**, which can **complicate medical procedures and daily activities**
- **Neutropenia** - **more common** in patients with **MDS[1]**
  - Patients have an **increased vulnerability to infections**

Bone marrow biopsy is essential to rule out MDS in patients with persistent and unexplained cytopenia

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MDS, myelodysplastic syndrome; VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

1. Obiorah et al. *Blood Adv* 2021;5:3203-3215.

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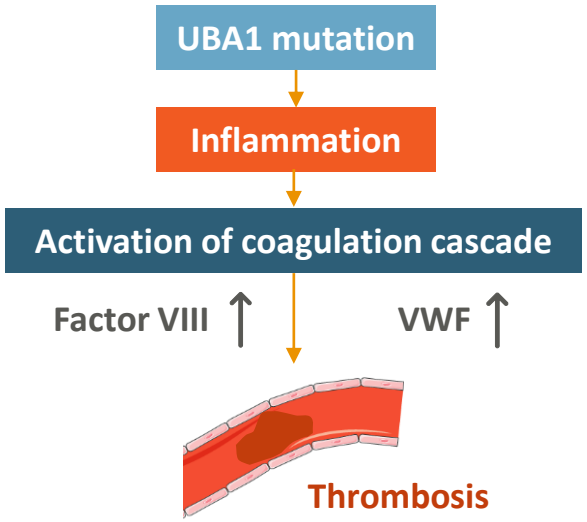
Thrombotic events:
A clinical concern in VEXAS syndrome

Thrombosis occurred in

49% of VEXAS patients[1]

Thrombosis pathophysiology[1]



- **High rates** of both **venous and arterial thrombosis** in VEXAS[1]
  - **Venous thromboembolism** was **most frequent** (up to 56%)[2]
  - Incidence of **arterial events** (e.g. transient ischaemic attack, stroke) **in up to 25%** of patients
- **Association with venous inflammation**[2]

Thrombotic events are common in VEXAS patients and treated as being a "provoked" event with inflammation as the provocation

Anticoagulation is indicated until provocation is resolved

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VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic; VWF, von Willebrand factor.
1. Kusne et al. *Blood* 2024;143:2109–2200 **2.** Karadeniz et al. *Rheumatology* 2023;62:e269–e270.
Figure adapted from Kusne et al. *Blood* 2024;143:2109–2200.

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Collaboration with Haematology:
Crucial for VEXAS diagnosis and management

Overlap between inflammatory disease manifestations and more serious haematologic diagnoses[1,2]

Bone marrow biopsy indicated in the workup of **unexplained and persistent cytopenias or cytoses**[1]

NGS panels containing UBA1

- Presence of **additional myeloid driver mutations** would be highly suggestive of co-occurrent MDS[1,3]

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MDS, myelodysplastic syndrome; NGS, next-generation sequencing; VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

1. Gutierrez-Rodrigues et al. *Blood* 2023;142:244–259 **2.** Obiorah et al. *Blood Adv* 2021;5:3203-3215 **3.** Sperling et al. *Nat Rev Cancer* 2017;17:5-19.

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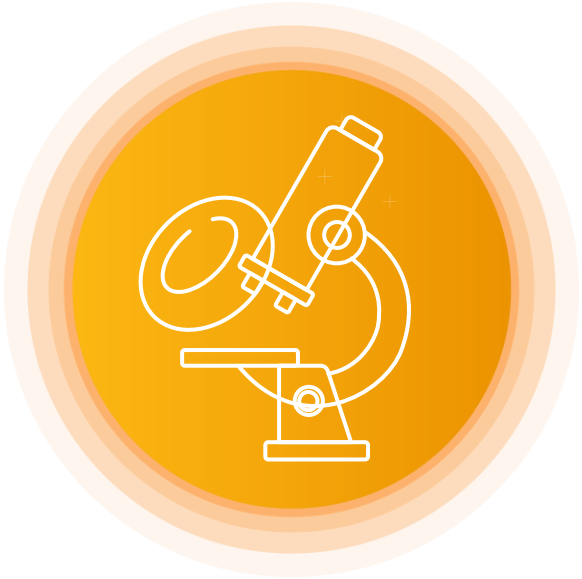
Haematology: **Key messages**

Please **open the EULAR App** to be ready to vote in the poll



VEXAS syndrome is a **haematologic disease** characterised by **association with myeloid and plasma cell neoplasia, cytoplasmic vacuoles**, **cytopenias**, and **risk of thrombosis**

- **Cytopenias require haematologic workup** to assess for malignancy
- **NGS containing UBA1** should be performed
- **Thrombotic events are common,** and venous/arterial thromboembolism are treated as being a "provoked" event with inflammation as the provocation
- **Partnership with Haematology** in clinical management of haematologic manifestations of VEXAS

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NGS, next-generation sequencing.

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What's your opinion?

How confident do you feel in being able to recognise common clinical characteristics/ features of VEXAS syndrome?

A. I am very confident

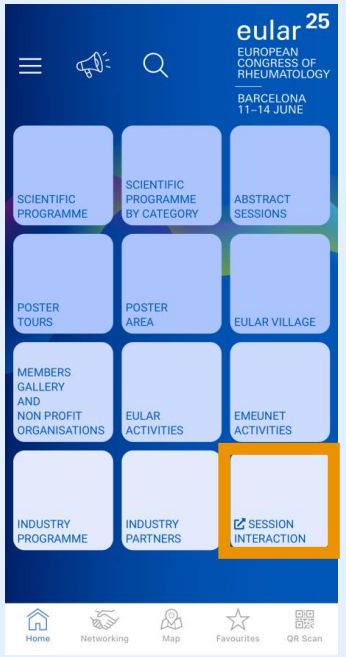
B. I am more confident

C. I need to learn more to be confident

D. I am not very confident

Please **open the EULAR App** on your mobile device to **vote in the poll**

1. Select **Session Interaction**
2. Select the **session**
3. Select **voting**



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Q&A

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Please submit questions via the EULAR App

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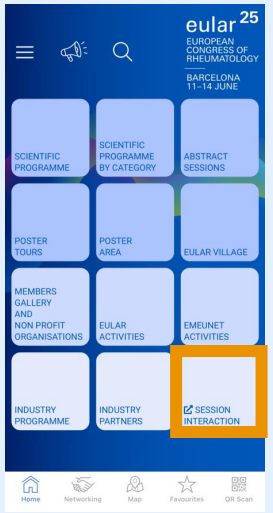

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Meeting close

Sophie Georgin-Lavialle

VEXAS syndrome: **Key messages**

An adult-onset haemato-inflammatory syndrome[1]

- Diagnosis by sequencing ***UBA1***
- Knowing the **key clinical manifestations** also in other medical specialties is **essential for timely diagnosis**
  - **Skin involvement is frequent** and often a **first sign** of VEXAS
  - **Be alert,** in particular to **vasculitis-like manifestations** and **chondritis**
  - VEXAS is characterised by **association with myeloid and plasma cell malignancies, cytoplasmic vacuoles**, **cytopenias**, and **risk of thrombosis**

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VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

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Your feedback is important to us!

Complete the evaluation here:

1. Select **Session Interaction**
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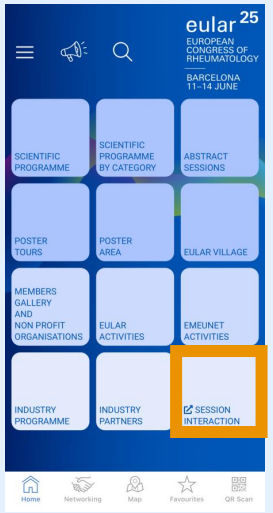

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Putting on your VEXAS goggles:

Seeing what's in plain sight

Many thanks for your participation

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