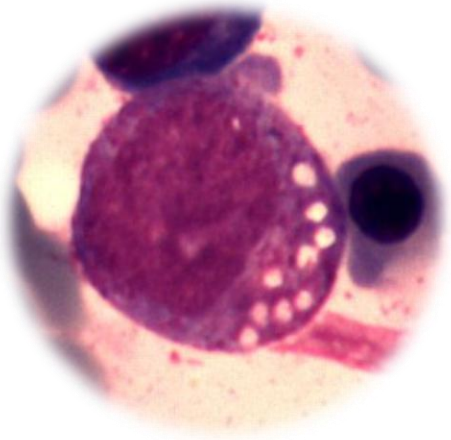
Université de Paris

CMR
CENTRE MALADIES RARES
VASCULARITES | SCLÉRODERMIES
GOUGEROT-SJÖGREN | LUPUS

HÔPITAUX UNIVERSITAIRES
PARIS CENTRE
Cochin • Port-Royal • Tarnier • Broca
La Collégiale • La Rochefoucauld • Hôtel-Dieu



VEXAS syndrome

Benjamin Terrier – Internal Medicine

Olivier Kosmider – Molecular Hematology

Cochin Hospital

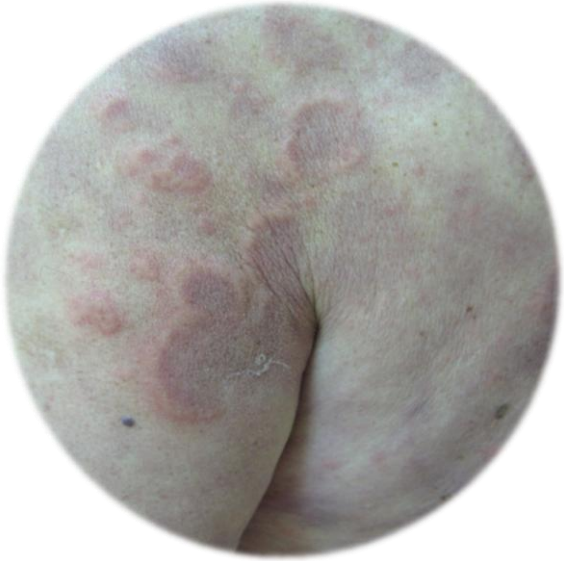
Clinical case

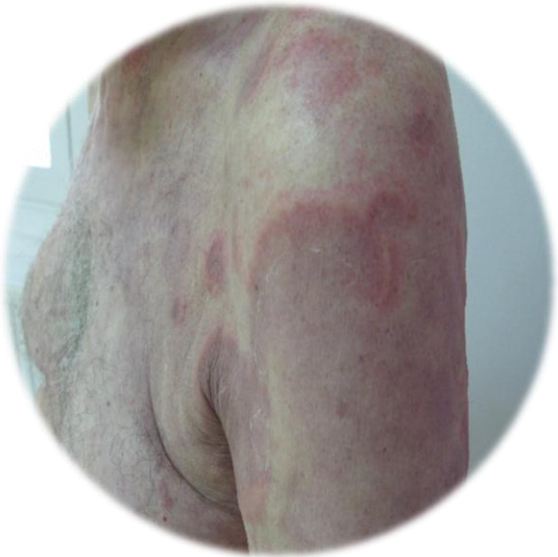
- **M. B. 76 years is referred in April 2013**

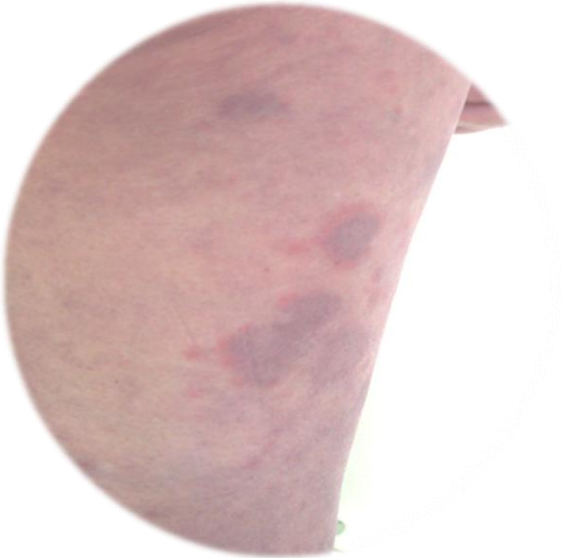
- **Personal medical history**
  - **Thombophilia with heterozygous factor V Leiden mutation complicated by deep venous thrombosis and pulmonary embolism**
  - **Cardiovascular risk factors**
  - **Essential tremor**

Clinical case

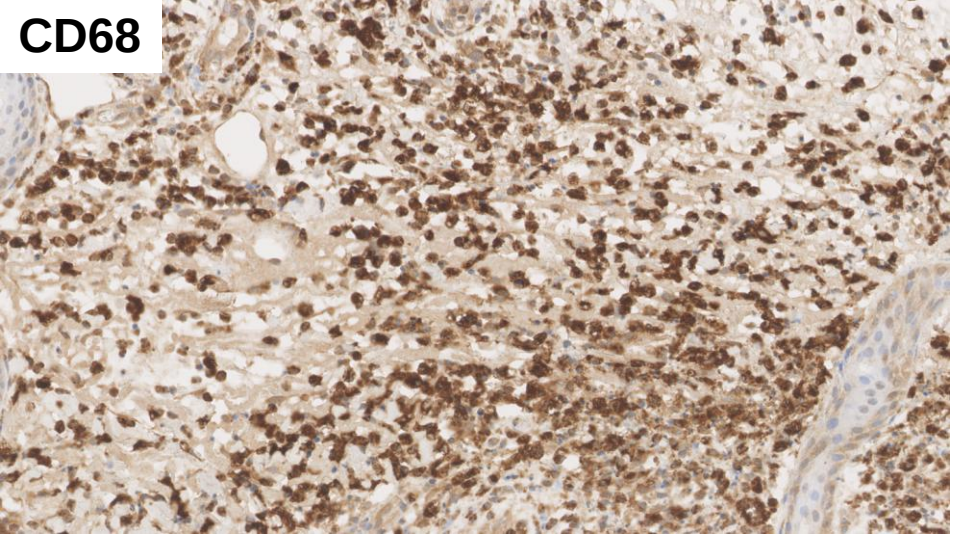
M. B. 76 years presenting since 2008 skin lesions suggestive of **neutrophilic dermatosis**

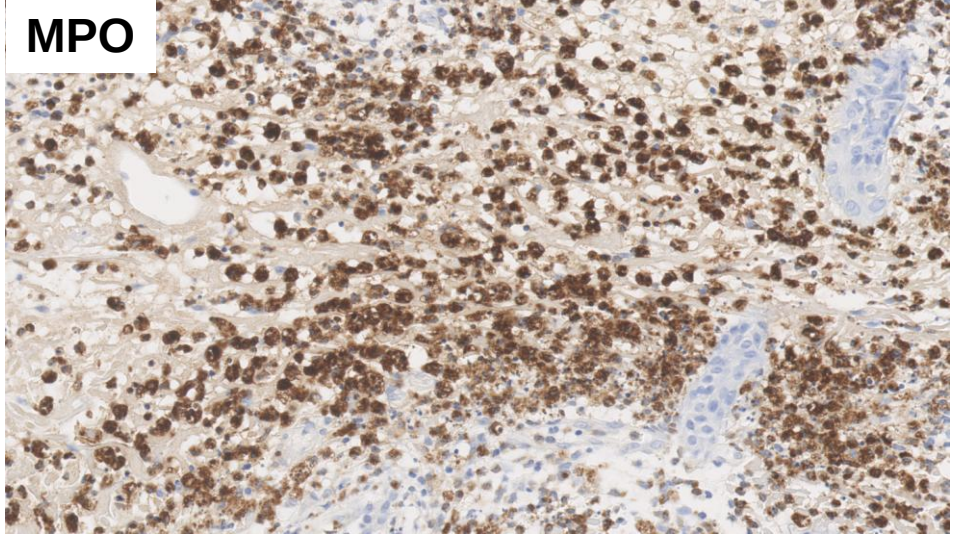




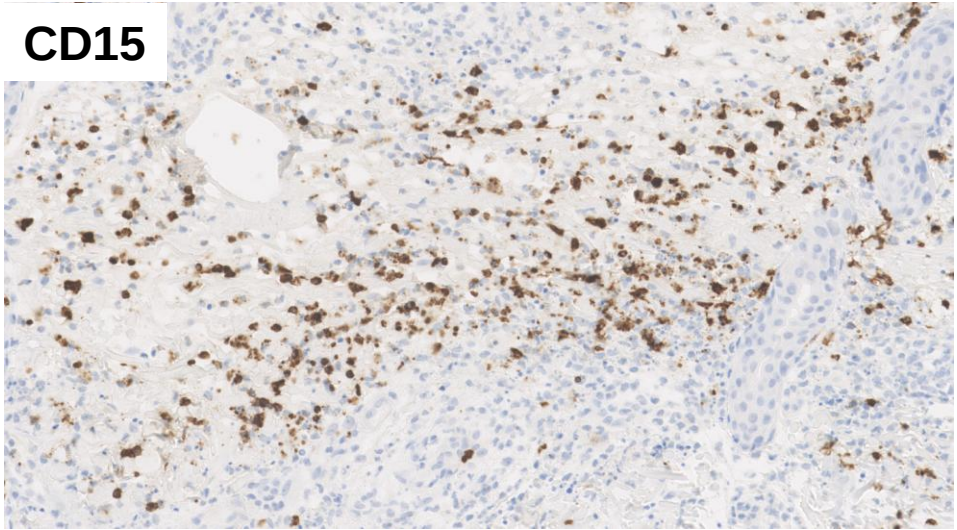


Pictures : Prof. Selim Aractingi

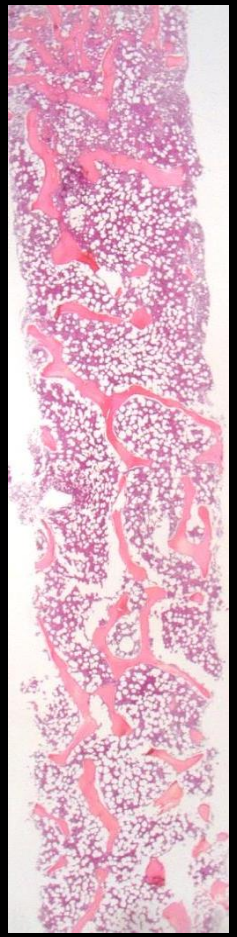


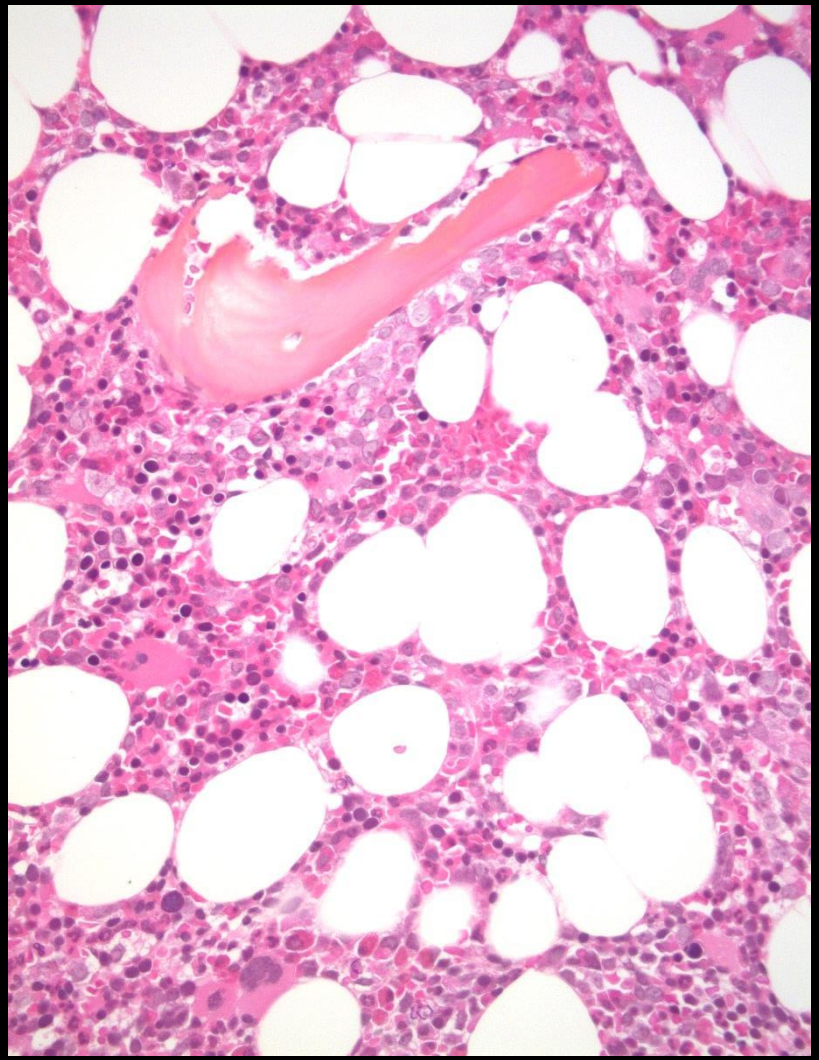


Skin biopsy: perivascular and peri-annexal infiltrate predominantly of mononuclear cells with monocytic differentiation, expressing MPO, which could be part of either **cutaneous localization of a myelodysplastic syndrome or histiocytotic Sweet syndrome**



BM





Screening for myelodysplastic syndrome: no MDS

Normal myelogram with normal karyotype (46 XY)
Bone marrow biopsy: **overrepresentation of granulocytic cell lines with many mature and immature forms**

Clinical case

- **April 2013:** headaches, deterioration of general health status and CRP level at 61 mg/L : suspicion of giant cell arteritis, GCs
- **November 2013:** relapse of deterioration of general health status, skin lesions and increased CRP with prednisone 15 mg/d
- Initiation of anakinra (IL-1RA) subcutaneously to treat potential MDS-related systemic manifestations with poor tolerance of anakinra
- Initiation of cDMARDs with GCs-dependency at 7.5 mg/d
- Death few months later from lower respiratory infection

Clinical case

- **November 2020:** less than a week after the description of a new entity in the ***N Engl J Med*** issue on October 27th, Sanger sequencing of *UBA1* gene is set up in Cochin

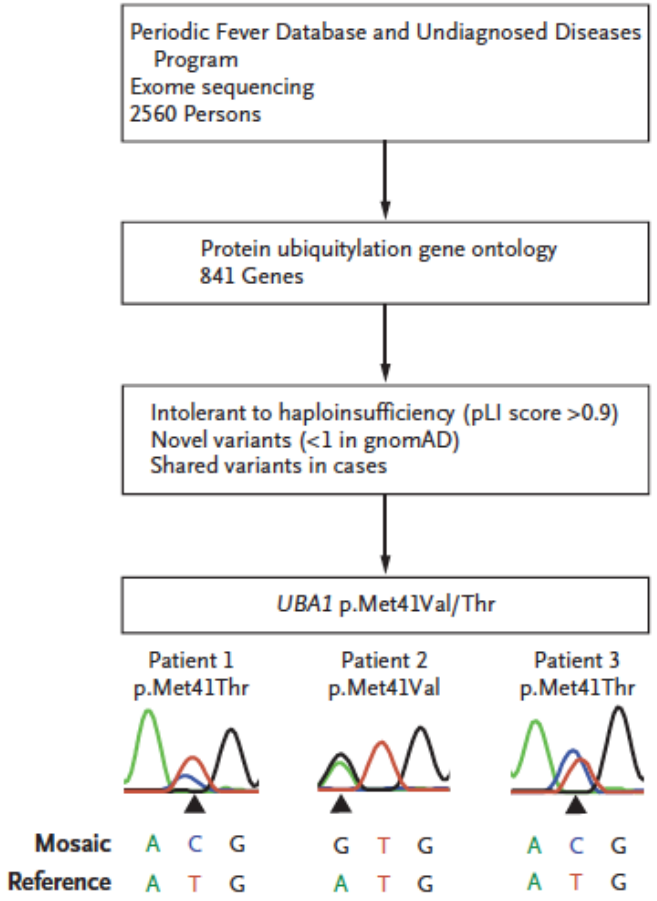
- Retrospective diagnosis of **VEXAS syndrome** is made

Unexplained chronic inflammatory diseases in adults

1477 patients with recurrent fever
+
1083 patients with atypical inflammatory diseases

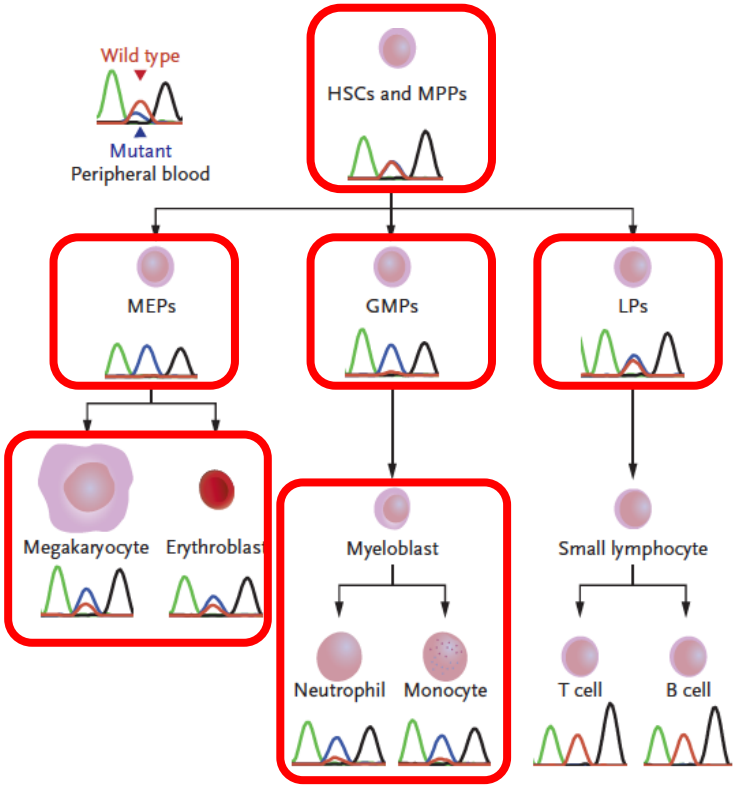
→ Exome sequencing

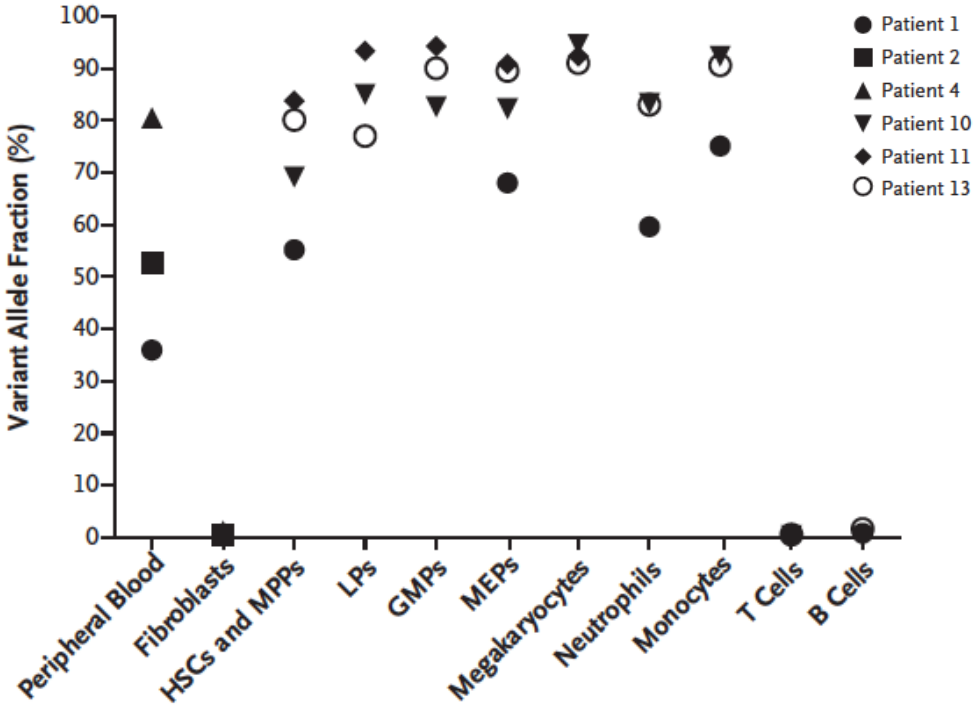
→ Identification of 3 men with the same *UBA1* gene mutation



Beck, N Engl J Med, 2020

Unexplained chronic inflammatory diseases in adults





Beck, N Engl J Med, 2020

Clinico-biological presentation of UBA1mut

Characteristic	Participants (N=25)
Demographic characteristics	
Male sex — no. (%)	25 (100)
Median age at onset (range) — yr	64 (45–80)
Died before the current study — no. (%)	10 (40)
Genetic characteristics	
Somatic *UBA1* (NM_003334.3) variant (p.Met41) — no. (%)	25 (100)
p.Met41Thr (c.122T→C)	15 (60)
p.Met41Val (c.121A→G)	5 (20)
p.Met41Leu (c.121A→C)	5 (20)
Key clinical features	
Fever — no. (%)	23 (92)
Skin involvement — no. (%)†	22 (88)
Pulmonary infiltrate — no. (%)	18 (72)
Ear and nose chondritis — no. (%)	16 (64)
Venous thromboembolism — no. (%)	11 (44)
Macrocytic anemia — no. (%)	24 (96)
Bone marrow vacuoles — no./total no. (%)	18/18 (100)
Laboratory findings	
Median C-reactive protein (IQR) — mg/liter	73 (18–128)
Median ESR (IQR) — mm/hr	97 (64–124)
Current or past treatment	
Glucocorticoids — no. (%)	25 (100)
Median no. of synthetic DMARDs (IQR)	2 (1–3)
Median no. of biologic or target synthetic DMARDs (IQR)	2 (0.5–3)
Diagnostic or classification criteria that were met — no. (%)	
Relapsing polychondritis	15 (60)
Sweet's syndrome	8 (32)
Myelodysplastic syndrome	6 (24)
Multiple myeloma or monoclonal gammopathy of undetermined significance	5 (20)
Polyarteritis nodosa	3 (12)
Giant-cell arteritis	1 (4)

Beck, N Engl J Med, 2020

Description of a new illness

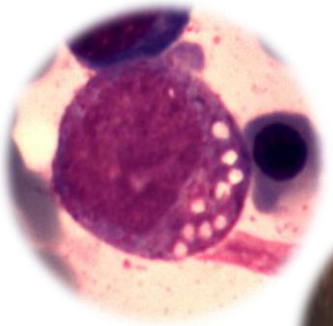
Vacuoles

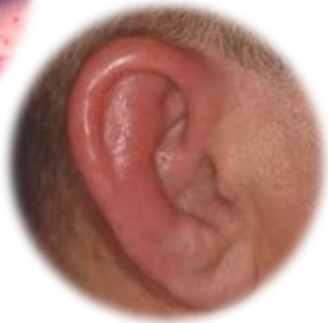
E1 enzyme

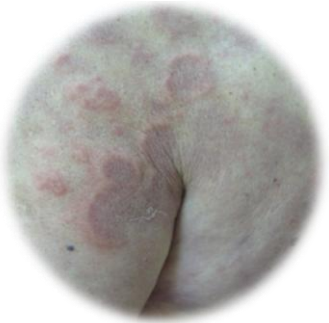
X-linked

Autoinflammatory

Somatic mutations





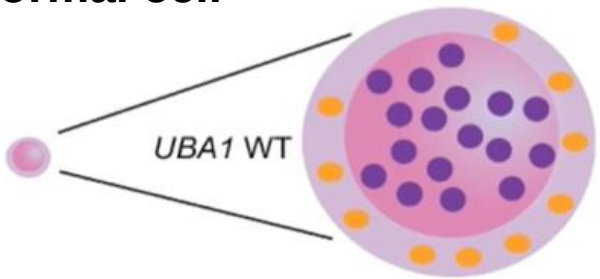


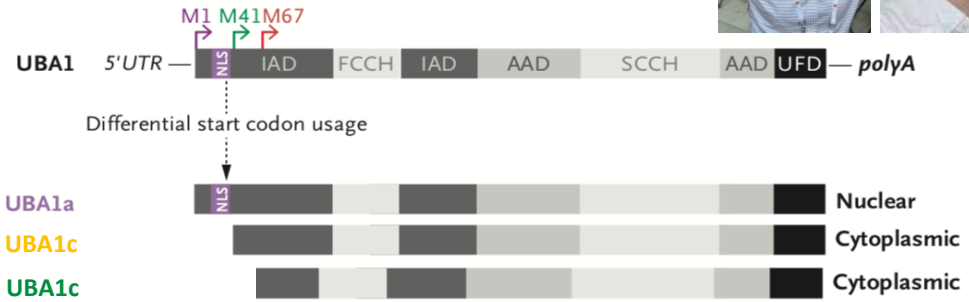
Other causes
Alcohol
Cupper deficiency, zinc toxicity
Myeloid hemopathies

Beck, N Engl J Med, 2020

Consequences of M41 abnormalities... A short isoform of UBA1

Normal cell

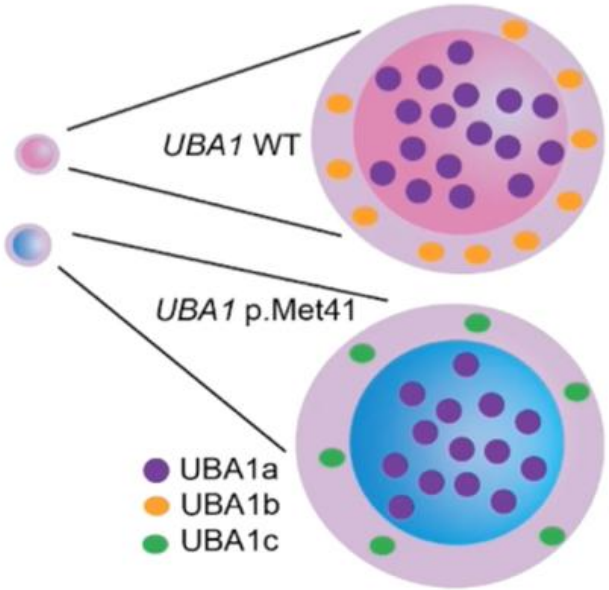




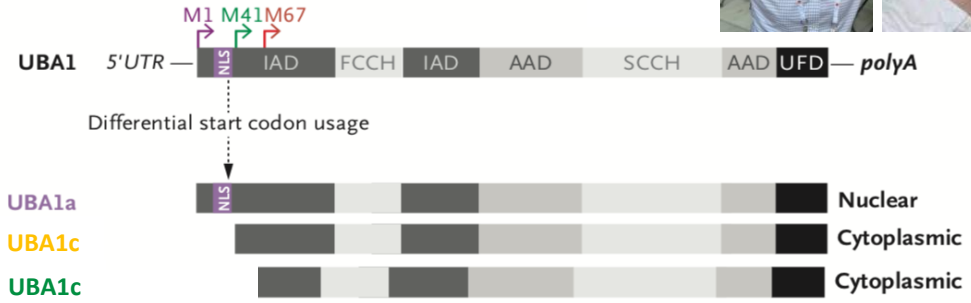
Beck, N Engl J Med, 2020

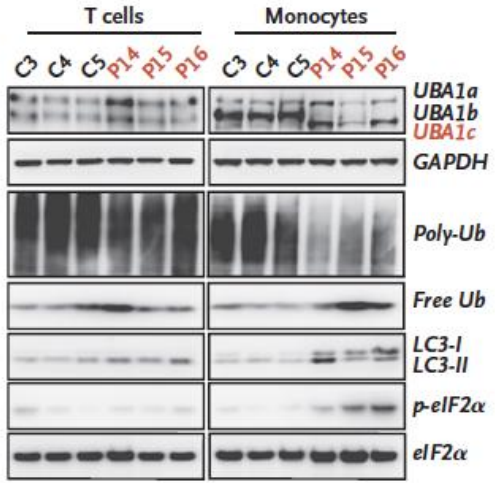
Consequences of M41 abnormalities... A short isoform of UBA1

Normal cell



***UBA1*-mutated cell**

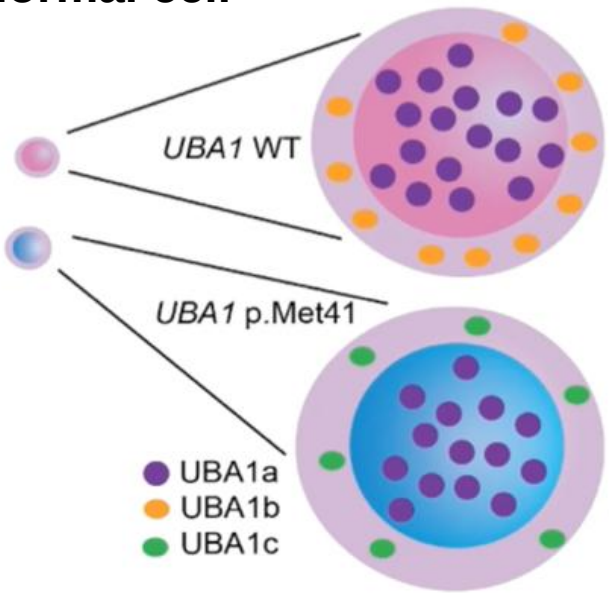




Beck, N Engl J Med, 2020

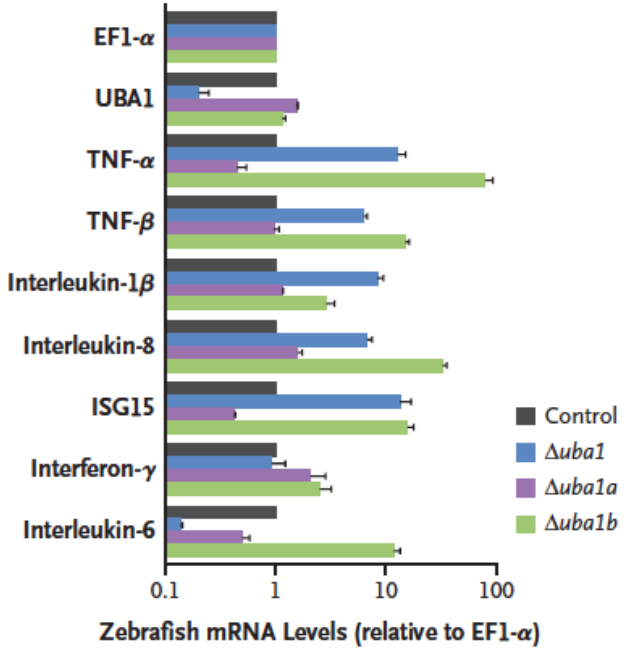
Consequences of M41 abnormalities... A short isoform of UBA1

Normal cell



***UBA1*-mutated cell**

Functional analysis in Zebrafish

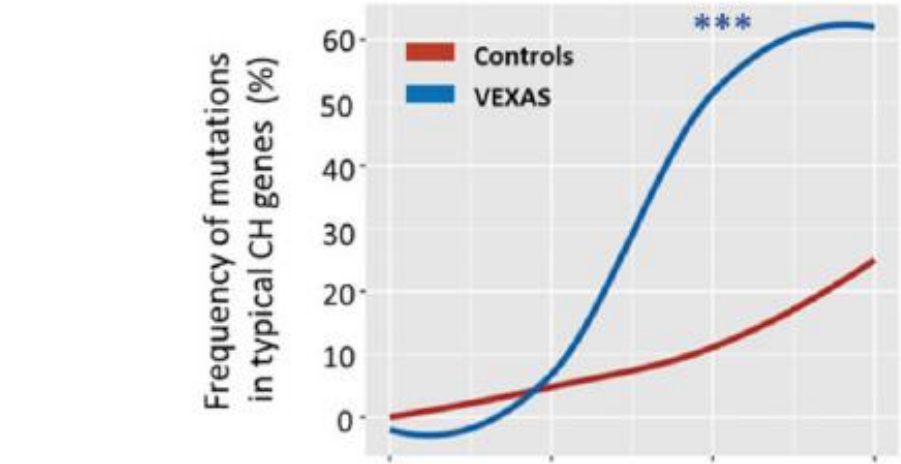


Beck, N Engl J Med, 2020

Spectrum of clonal hematopoiesis in VEXAS

Typical clonal hematopoiesis mutations co-occurr with UBA1mut in 60% of patients, more commonly than in controls

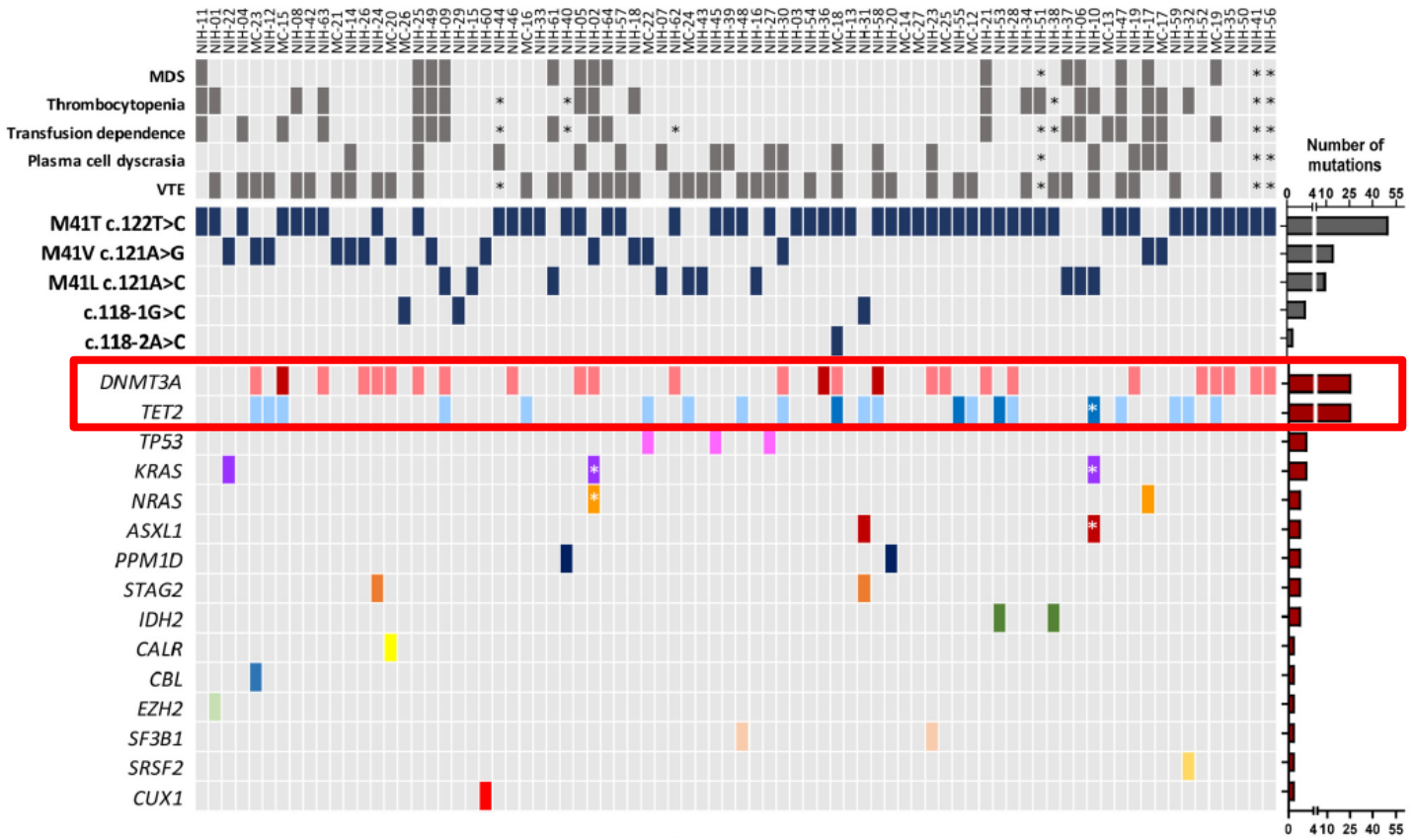
CH mutations are not associated with inflammatory or hematologic manifestations



Age range	0-20	21-40	41-60	60>
n of mutated patients (total)	0/0	0/0	7 (12)	39 (65)
n of mutated controls (total)	0 (17)	1 (21)	2 (18)	8 (28)

Gutierrez-Rodrigues, Blood, 2023

Spectrum of clonal hematopoiesis in VEXAS

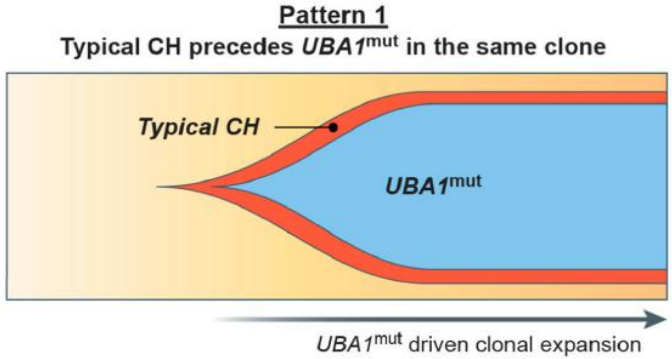


Gutierrez-Rodrigues, Blood, 2023

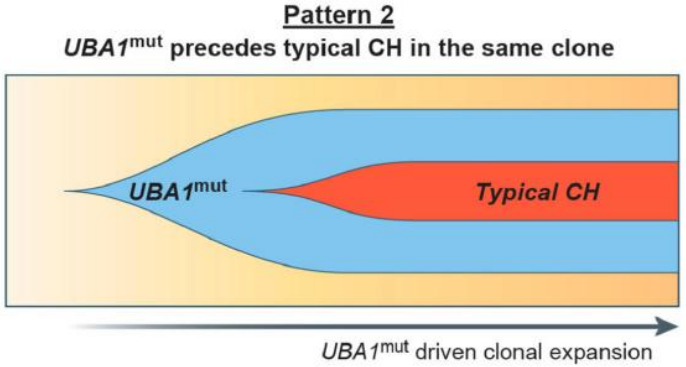
Clonal dynamics in VEXAS syndrome

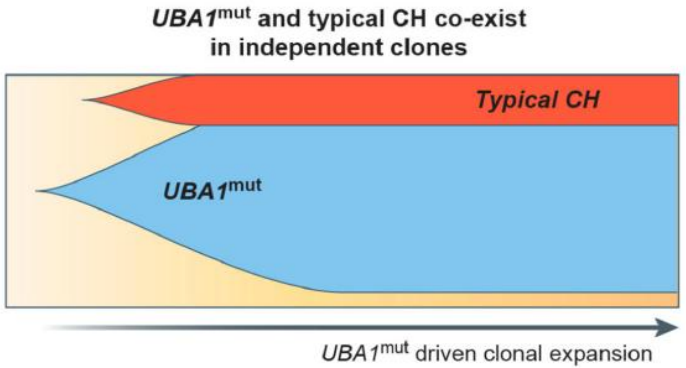
Clonality in VEXAS follows two major patterns:

- Typical CH preceding UBA1mut selection in a clone (**Pattern 1**)



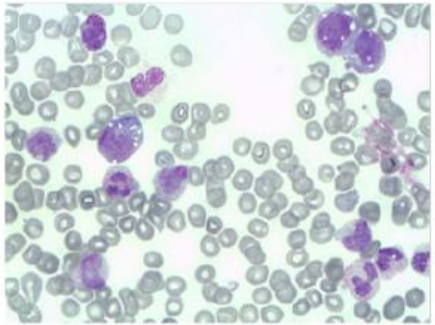
- Typical CH occurring as an UBA1mut subclone or in independent clones (**Pattern 2**)

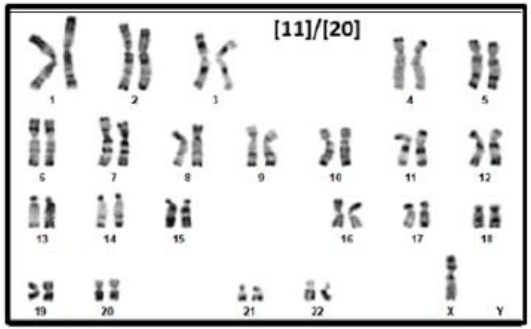


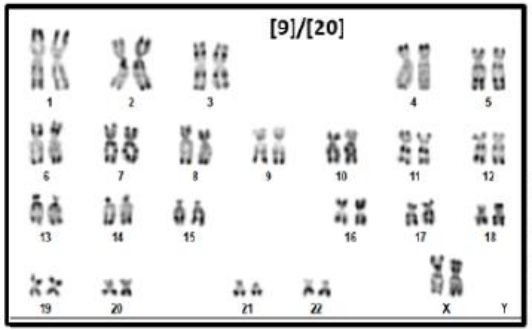


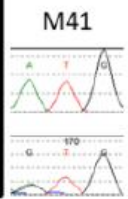
Gutierrez-Rodrigues, Blood, 2023

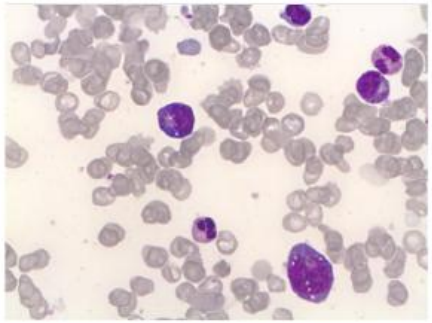
An "almost" exclusively male disease

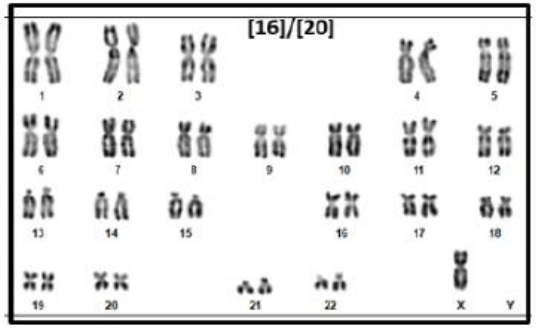


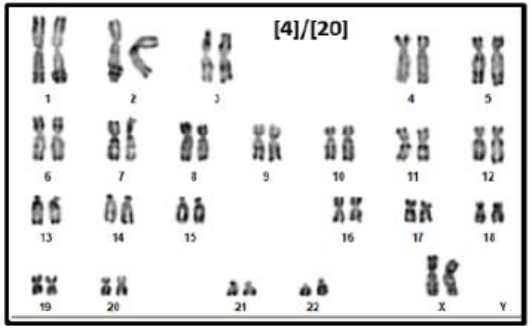


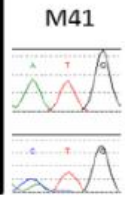












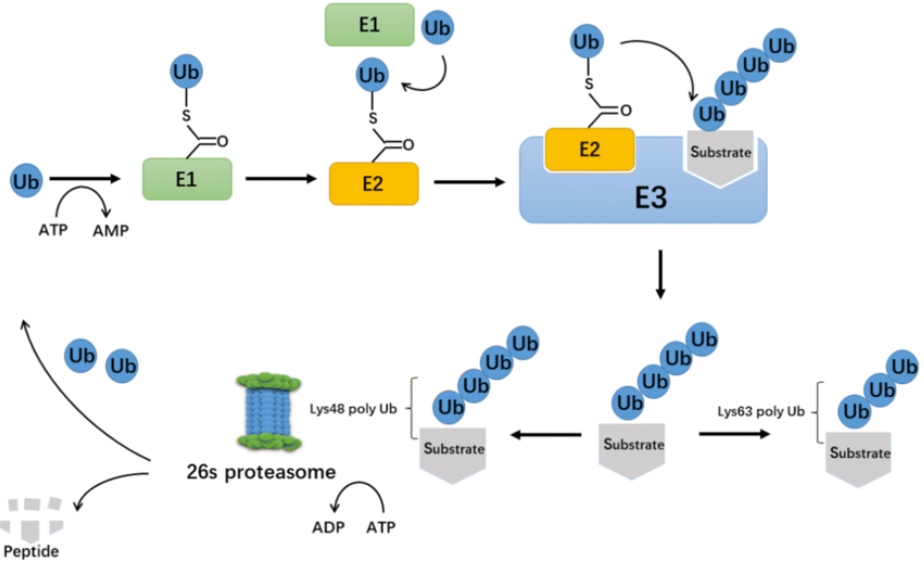
Arlet, Terrier, Kosmider, N Engl J Med, 2021

Novel UBA1 variants

Description of multiple putative novel UBA1$^{non\text{-}M41}$ variants in patients with various hematological malignancies expanding the genomic spectrum of VEXAS syndrome

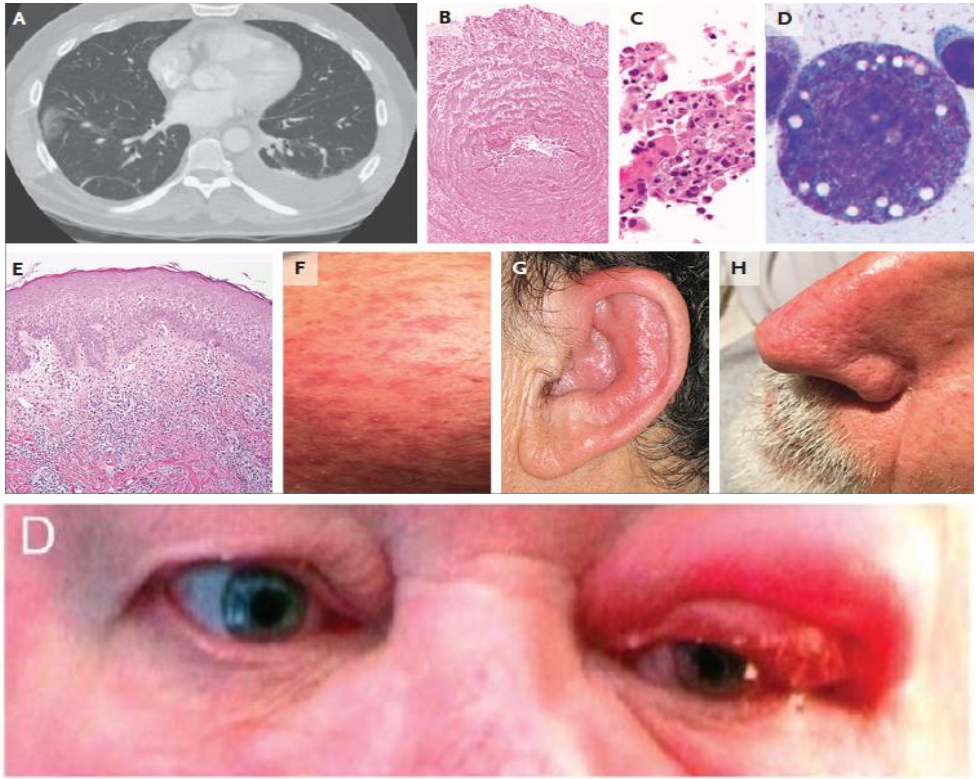
Identification of new non-canonical VEXAS-causing mutations associated with deficient ubiquitylation in cells (especially in **loss of cytoplasmic E2 transfer**)

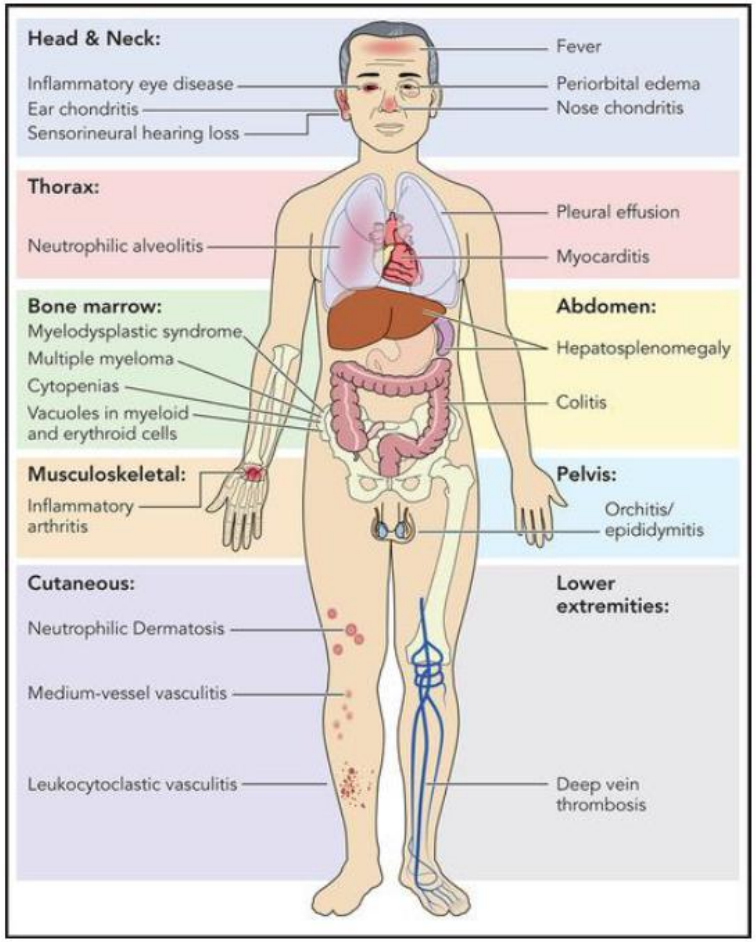
Beck, unpublished data



Sakuma, Leukemia, 2023
Bhogaraju, Nature, 2016

Clinico-biological spectrum of VEXAS





Grayson, Blood, 2021
Beck, N Engl J Med, 2020

Clinico-biological spectrum of VEXAS

Retrospective study from the French VEXAS group
116 patients

- Male (96%)
- Skin lesions (84%)
- Fever (64%)
- Weight loss (62%)
- Lung involvement (50%)
- Ocular involvement (39%)
- Chondritis (36%)
- VTE (35%)
- **Renal involvement (9.5%)**

MDS in 50%

VEXAS-MDS showing:

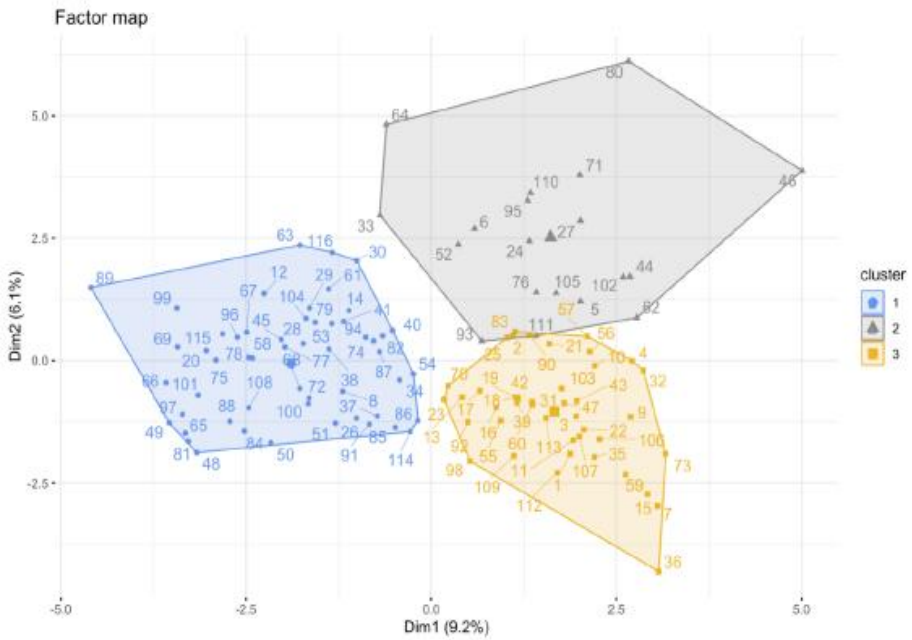
- More fever (76 vs 55%)
- More GI involvement (22 vs 5%)
- More lung infiltrates (54 vs 29%)
- More arthralgia (40 vs 17%)

Georgin-Lavialle, Br J Dermatol, 2022

Clinico-biological spectrum of VEXAS

Unsupervised analysis:

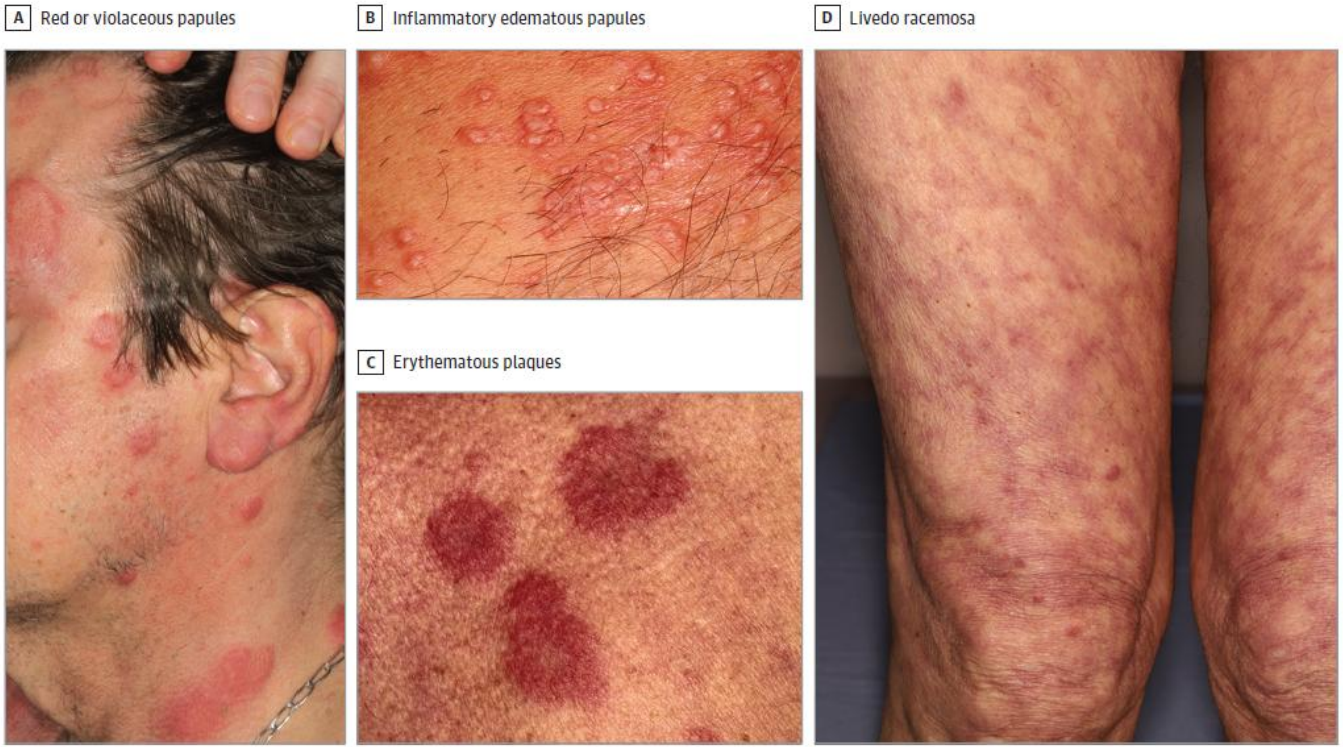
- **Cluster 1 (47%) : mild-to-moderate disease, p.M41Leu mutation**
- **Cluster 2 (16%) : chondritis, lung involvement, MDS +++, increased mortality**
- **Cluster 3 (37%) : deterioration of general health +++, skin vasculitis, increased CRP**



Overall survival at 5 years : 84.2% in cluster 1, 50.5% in cluster 2, 89.6% in cluster 3

Georgin-Lavialle, Br J Dermatol, 2022

Cutaneous infiltration by mutated cells



8 patients
Neutrophilic and myeloid cell infiltrate positive for MPO and CD163
Presence of *UBA1* mutation in the skin

Zakine, JAMA Dermatol, 2021

Renal involvement in VEXAS

72-yr-old patient who presented with acute kidney injury

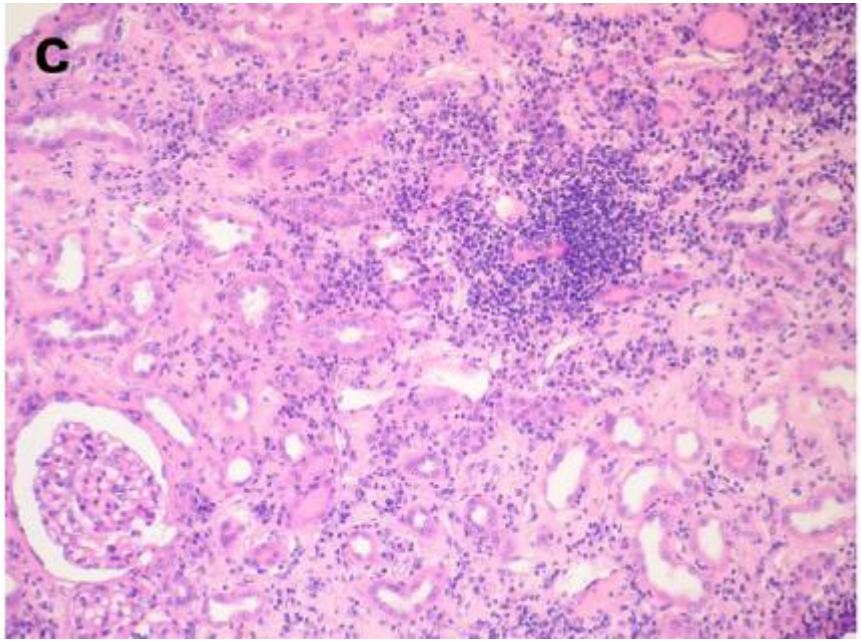
Initial presentation

- Papulonodular rash on the trunk and lower limbs
- Laboratory data : Hb 6.2 g/dL, MCV 106 fl, platelet count 79 G/L
- Elevated serum creatinine 1338 umol/L
- Urine analysis : proteinuria 1.8 g/g, leukocyturia and hematuria

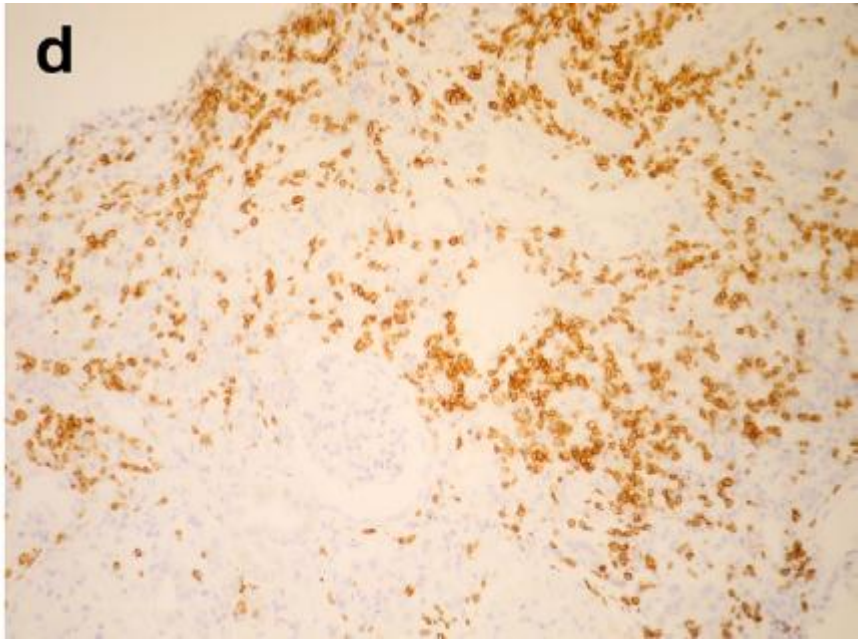
Initiation of dialysis

Ronsin, Kidney Int, 2022

Renal involvement in VEXAS



Lymphocytic and plasmocytic interstitial infiltrate, tubular atrophy, and 1 normal glomerulus



Kidney immunochemistry showing predominance of CD3+ lymphocytic interstitial infiltrate

Ronsin, Kidney Int, 2022

Renal involvement in VEXAS

72-yr-old patient who presented with acute kidney injury

Initiation of dialysis

Kidney biopsy

Treatment with GCs 1 mg/kg/d, with improvement of serum creatinin to 228 umol/L

Ronsin, Kidney Int, 2022

Renal involvement in VEXAS
French cohort


Initial cohort

116 patients, including 9.5% with "renal involvement"
Older patients (mean age 71 yrs) with frequent comorbidities

Current cohort

220 patients, including 8 patients with renal biopsy
Mean age 70.8 yrs, only male, myelodysplastic syndrome in 50%
Renal presentation
AKI in 4/8, mean serum creatinine 388 µmol/L, leucocyturia in 5/7, hematuria in 5/7, nephrotic syndrome in 3/7
Monoclonal IgM component in 4/8

M. Mathurin, K. El Karoui, D. Buob

Renal involvement in VEXAS French cohort


7/8 renal biopsy before VEXAS diagnosis

Centralized review

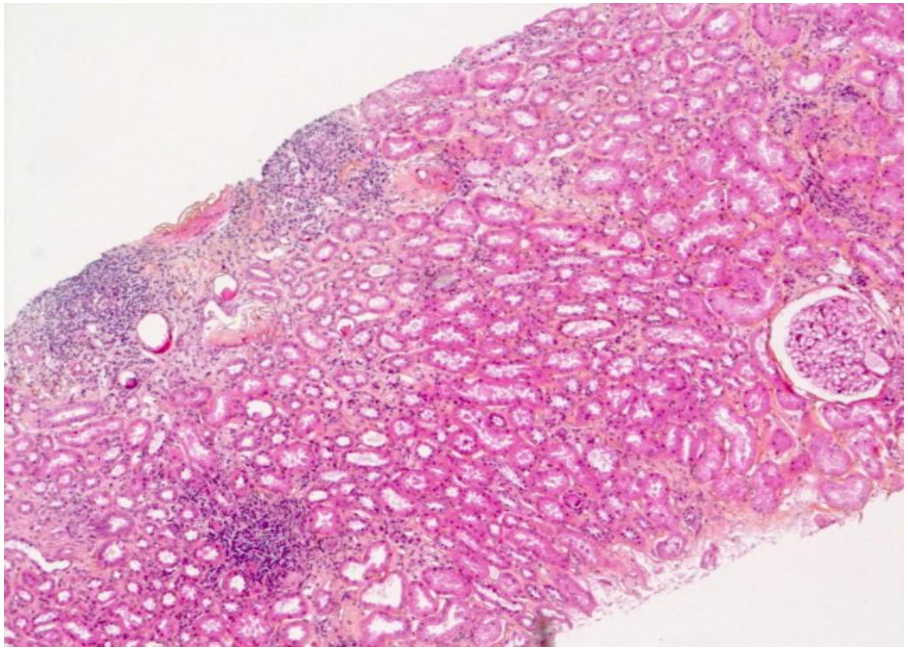
- Interstitial nephritis with mononuclear cells infiltrate and neutrophils in 3 cases
- Non-proliferative IgA nephropathy on two cases
- ANCA-negative pauci-immune vasculitis in one case
- Diabetic and vascular nephropathy in one case
- Acute tubular necrosis in septic context in one case
- AA amyloidosis in one case

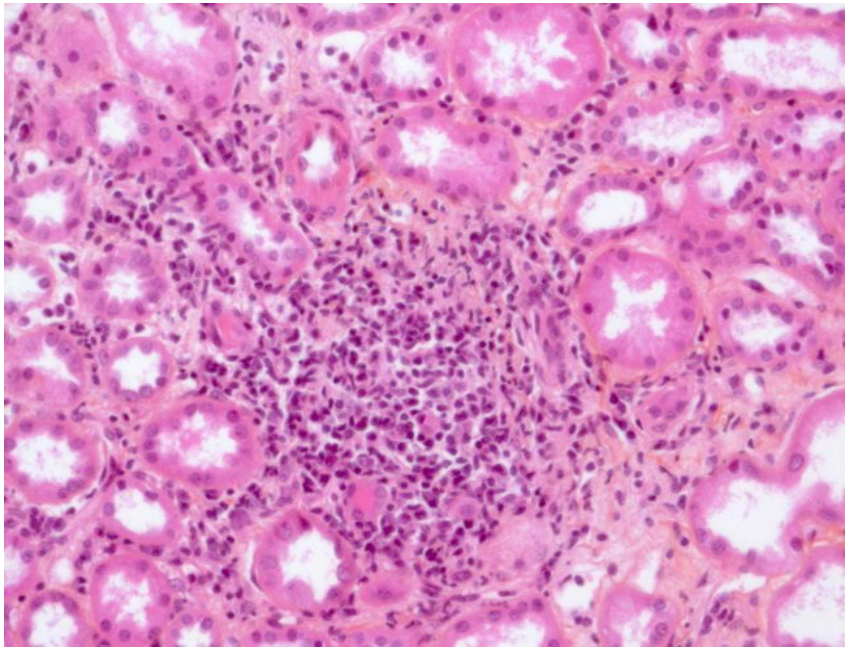
Renal localization of clonal hematopoiesis ?

MPO/CD68 staining + NGS on renal biopsy in progress

M. Mathurin, K. El Karoui, D. Buob

Renal involvement in VEXAS : French cohort





Interstitial nephritis with mononuclear cell infiltrate

Remerciements Dr DIJOUD, Anatomopathologie, Hospices Civiles de

When to think about VEXAS syndrome ?

- Clinical manifestations of relapsing polychondritis in 50% of VEXAS syndrome
- Cohort of 92 RP ➡ *UBA1* somatic mutation in 7.6%

PCA-VEXAS vs PCA

Male
≥45 years
Fever, ear chondritis, skin involvement, VTE, lung infiltrates
Less tracheal chondritis
Mortality +++ (27 vs 2%)

Decision-making algorithm in case of RP

- Male
- MCV >100 fL
- Platelets <200 G/L

Diagnosis of VEXAS-RP (Se 100%, Sp 96%)

Ferrada, Arthritis Rheumatol, 2021

Therapeutic strategies

Glucocorticoids — Effective at high dose
GC-dependency +++

cDMARDs — Ineffective +++

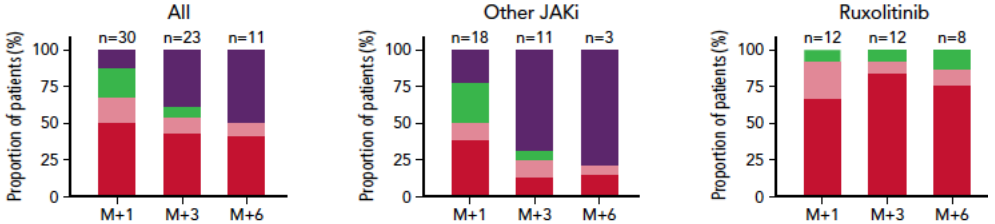
Biologics — Anti-TNF ineffective
Anti-IL-1/IL-6: variable efficacy

5-azacytidin, JAKi — Ruxolitinib : if no MDS
5-AZA : in case of MDS

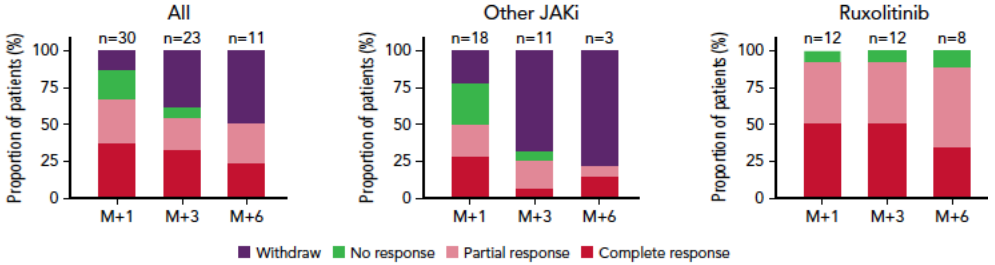
Allogeneic HSCT — Seems to be curative +++

JAK inhibitors

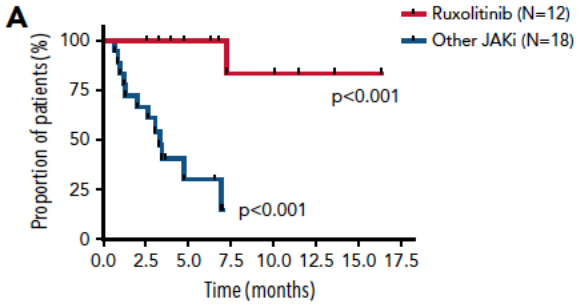
Clinical response

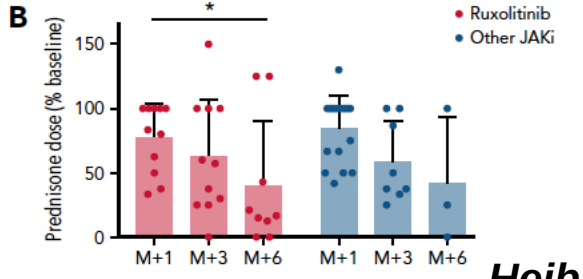


Biological response



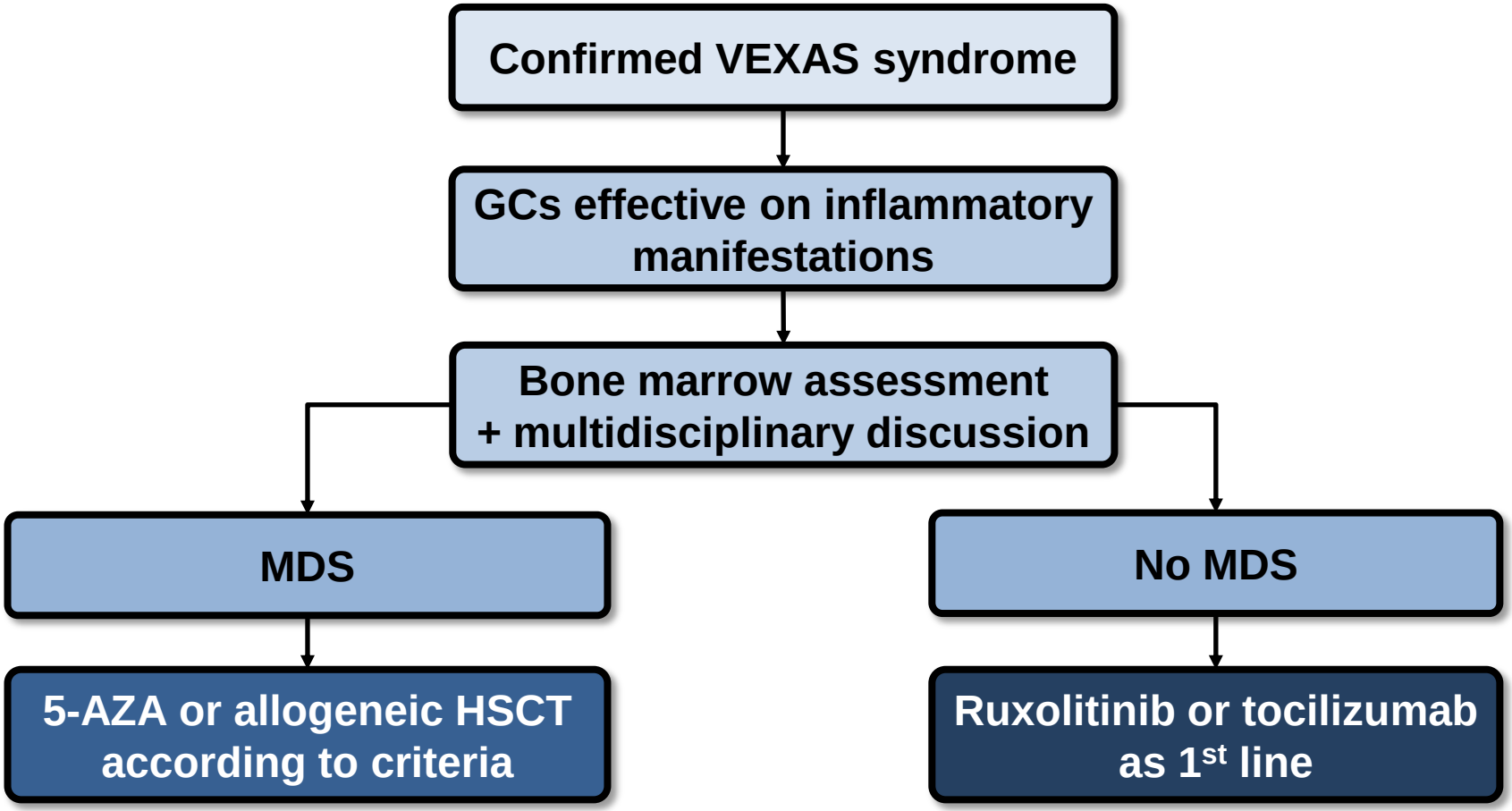
New treatment-free survival





Heiblig, Blood, 2022

Current therapeutic strategies



Take home messages

- **VEXAS = monogenic disease of adults linked to somatic mutations of the *UBA1* gene only in the myeloid lineage**
- **Prototype of a new group of disease**
- **Consider VEXAS in cases of: male gender, age >50 years, macrocytosis >100 fl, thrombocytopenia <200 G/L, treatment refractory disease**
- **Most encouraging strategies targeting the myeloid compartment: 5-azacytidin, ruxolitinib, or even HSC transplantation**

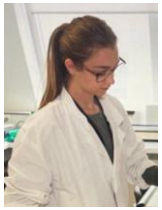
Acknowledgments

Cochin/PARCC local team

Olivier Kosmider

Marie Templé

Eugénie Duroyon



Léa Dionet

Paul Breillat

French VEXAS group

Sophie Georgin-Lavialle

Arsène Mekinian

International collaborators

David Beck

Peter Grayson

Institut Pasteur

Céline Posseme

Darragh Duffy

Institut Imagine

Francesco Carbone
Marine Lukas

Mickael Ménager