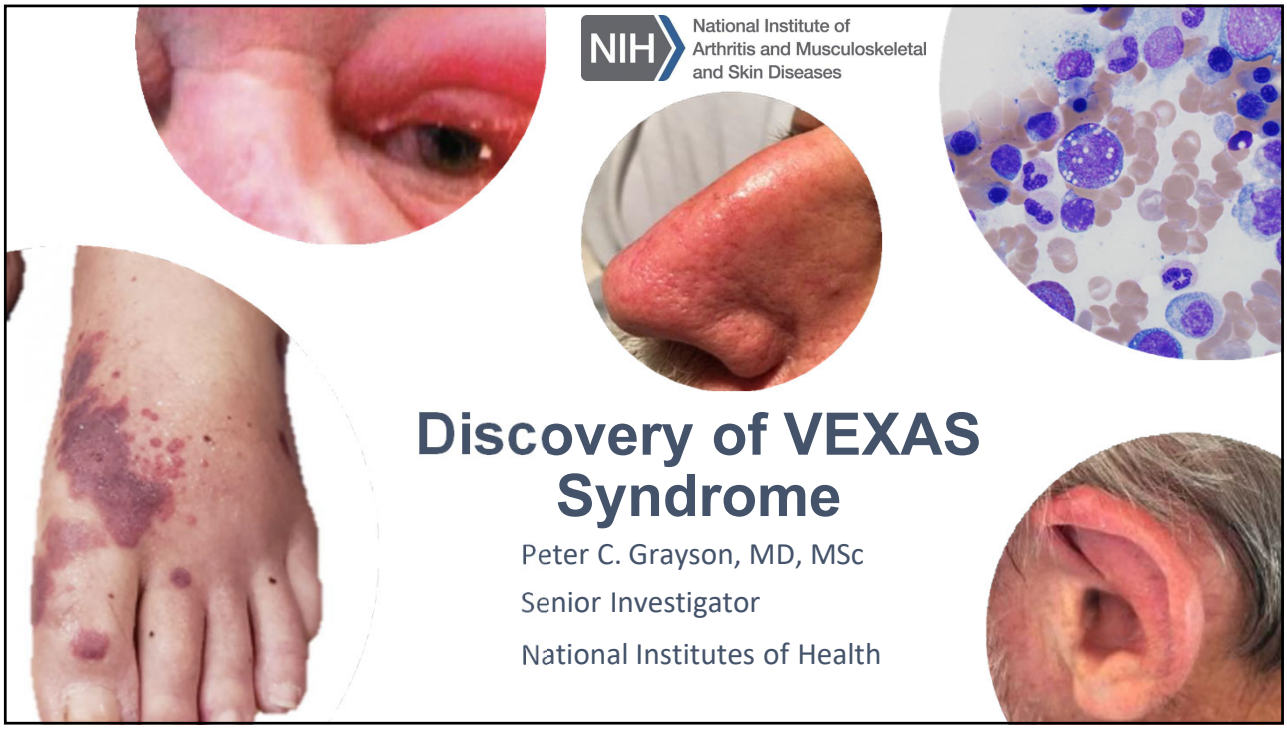
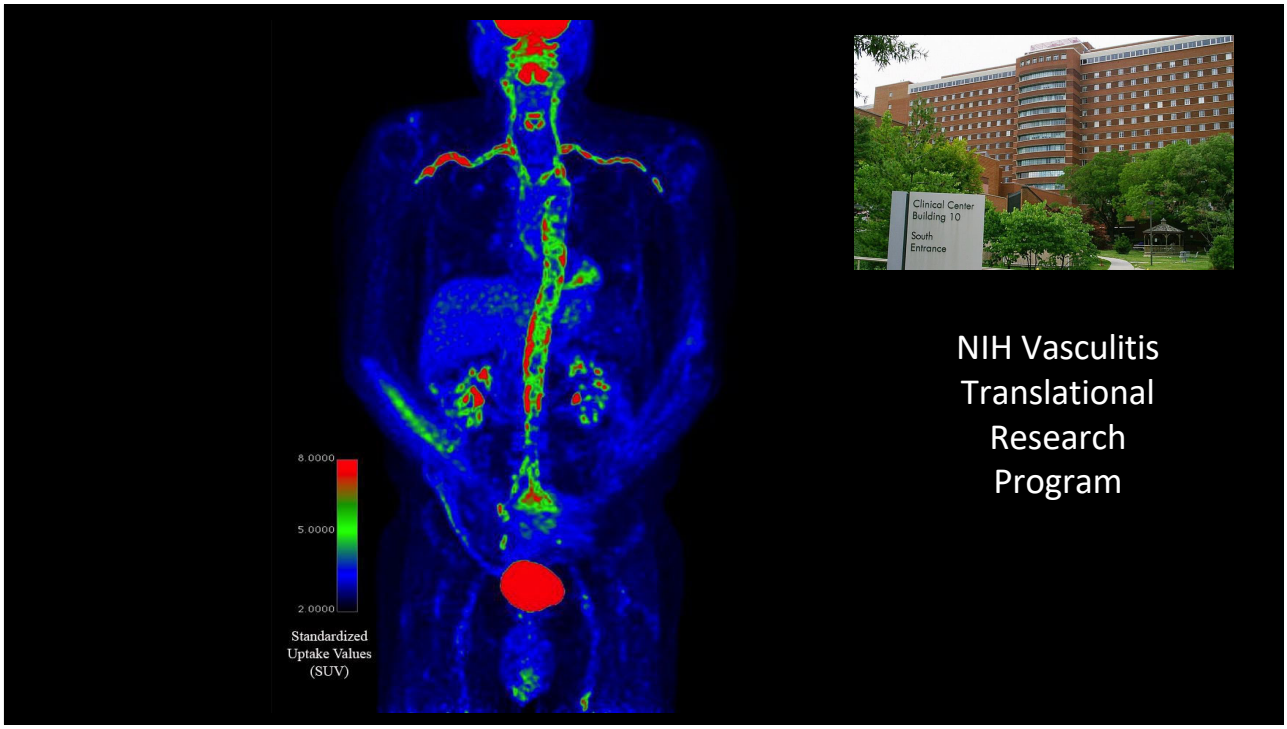


1

Objectives

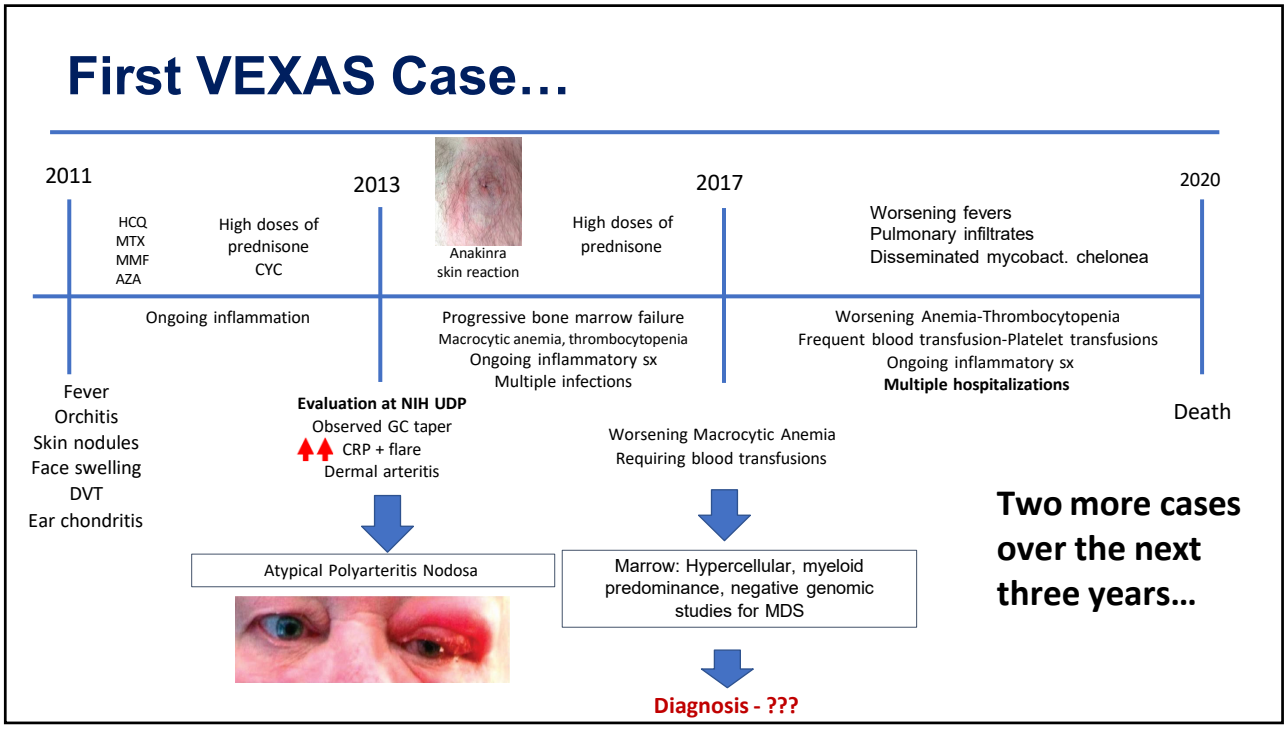
- Recognize and understand the VEXAS syndrome
- Review clonal hematopoiesis literature with respect to atherosclerosis and inflammatory diseases
- Unveil a brand new disease that causes coronary artery aneurysms in adults

2



3

First VEXAS Case…



4

The NEW ENGLAND JOURNAL of MEDICINE

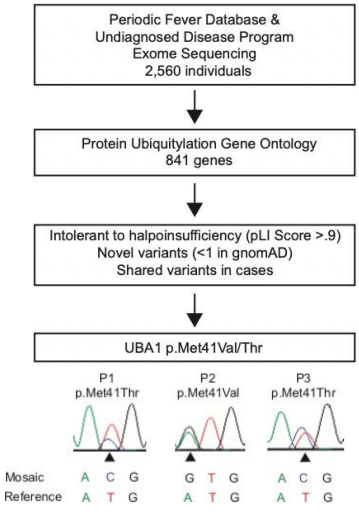
ORIGINAL ARTICLE

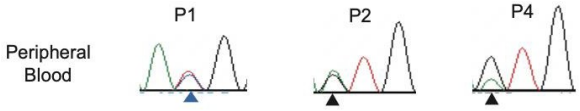
Somatic Mutations in *UBA1* and Severe Adult-Onset Autoinflammatory Disease

D.B. Beck, M.A. Ferrada, K.A. Sikora, A.K. Ombrello, J.C. Collins, W. Pei, N. Balanda, D.L. Ross, D. Ospina Cardona, Z. Wu, B. Patel, K. Manthiram, E.M. Groarke, F. Gutierrez-Rodrigues, P. Hoffmann, S. Rosenzweig, S. Nakabo, L.W. Dillon, C.S. Hourigan, W.L. Tsai, S. Gupta, C. Carmona-Rivera, A.J. Asmar, L. Xu, H. Oda, W. Goodspeed, K.S. Barron, M. Nehrebecky, A. Jones, R.S. Laird, N. Deuitch, D. Rowczenio, E. Rominger, K.V. Wells, C.-C.R. Lee, W. Wang, M. Trick, J. Mullikin, G. Wigerblad, S. Brooks, S. Dell'Orso, Z. Deng, J.J. Chae, A. Dulau-Florea, M.C.V. Malicdan, D. Novacic, R.A. Colbert, M.J. Kaplan, M. Gadina, S. Savic, H.J. Lachmann, M. Abu-Asab, B.D. Solomon, K. Retterer, W.A. Gahl, S.M. Burgess, I. Aksentijevich, N.S. Young, K.R. Calvo, A. Werner, D.L. Kastner, and P.C. Grayson

5

Somatic Mutations in a Single Residue of UBA1 are Associated with a Severe Adult-Onset Autoinflammatory Disease

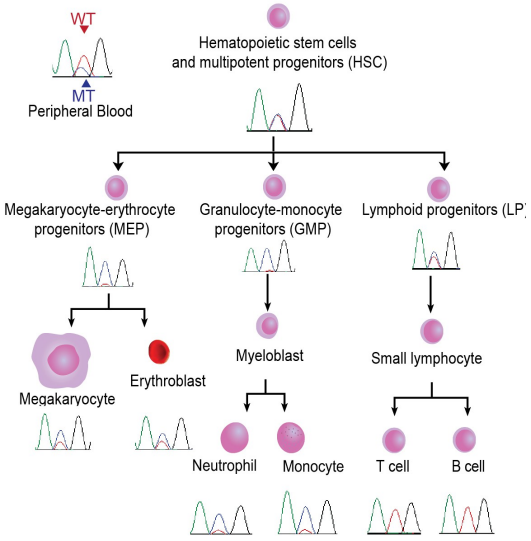


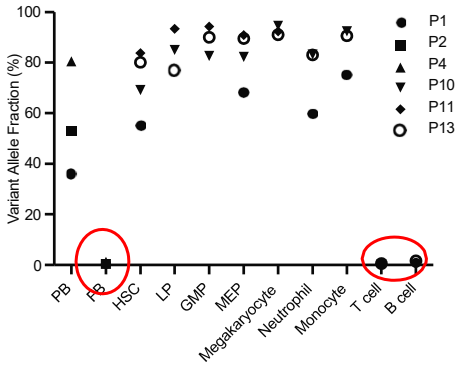


Beck et al NEJM 2020

6

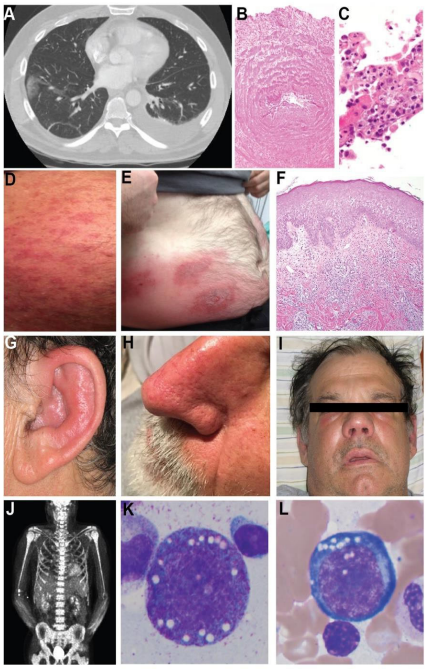
Somatic Mutations are Myeloid Restricted





Beck et al., *NEJM 2020*

7



V acuoles
E 1 enzyme
X - linked
A utoinflammatory
S omatic

Beck et al., *NEJM 2020*

8

Demographics of VEXAS

Age at Disease onset median (range)	64 (45-80)
Sex n(%)	
Male	25 (100)
Race n(%)	
White	25 (100)
Diagnosis n(%)	
Relapsing Polychondritis	15 (60)
Sweet Syndrome	8 (32)
Myelodysplastic Syndrome	6 (24)
Multiple Myeloma/MGUS	5 (20)
Polyarteritis Nodosa	3 (12)
Giant Cell Arteritis	1 (4)

n=25

Beck et al., *NEJM 2020*

9

VEXAS Syndrome

Prevalence Estimates

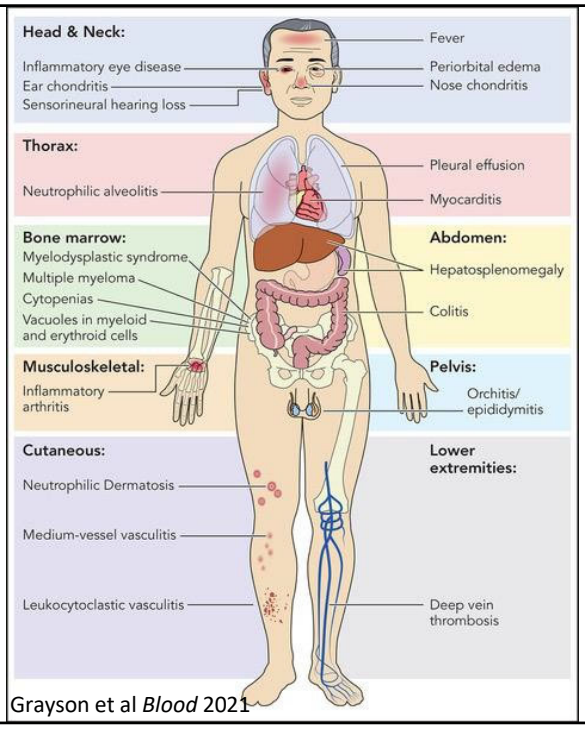
1 in 14,000

1 in 4000 men > 50 years

JAMA | Original Investigation

Estimated Prevalence and Clinical Manifestations of *UBA1* Variants Associated With VEXAS Syndrome in a Clinical Population

David B. Beck, MD, PhD; Dale L. Bodian, PhD; Vandan Shah, MD; Uyenlinh L. Mirshahi, PhD; Jung Kim, PhD; Yi Ding, MD, PhD; Samuel J. Magaziner, MPhil; Natasha T. Strande, PhD; Anna Cantor, MS; Jeremy S. Haley, MS; Adam Cook, MS; Wesley Hill; Alan L. Schwartz, MD, PhD; Peter C. Grayson, MD; Marcela A. Ferrada, MD; Daniel L. Kastner, MD, PhD; David J. Carey, PhD; Douglas R. Stewart, MD



Grayson et al *Blood* 2021

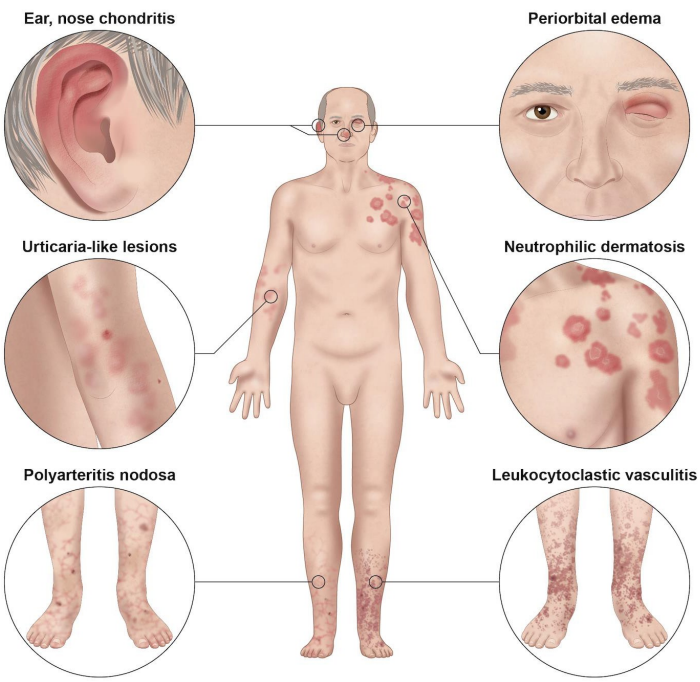
10

Typical Disease Features	
Inflammatory:	**Hematologic:**
• Fever of unknown origin • Auricular and/or nasal chondritis • Neutrophilic dermatosis or urticaria-like lesions(Bx) • Leukocytoclastic vasculitis (LCV) or leukocytoclasia (Bx) • Non-infectious periorbital swelling • Recurrent, non-infectious inflammatory eye disease • Non-infectious ground glass or nodular pulmonary infiltrate • Unprovoked or recurrent thromboembolic disease • Steroid dependency[4]	• Vacuoles in myeloid or erythroid precursor cells on marrow aspirate • Macrocytosis[1] or macrocytic anemia • MDS or myelodysplasia • Thrombocytopenia[2] • Monocytopenia[3] • Lymphopenia
Less Common Disease Features	
• Erythema nodosum (Bx) • Recurrent urticaria / urticarial plaque • Injection site reaction to anakinra • Inflammatory arthritis • Vasculitis (any size), relapsing / recurrent or with lack of response to SOC • Pericarditis / Myocarditis	• Exudative pleural or pericardial effusion • Testicular inflammation • Sensorineural hearing loss • Atypical or opportunistic infection including nontuberculous mycobacterial infection • Nephrotic syndrome with renal amyloidosis (Bx) • Interstitial nephritis (Bx)

Bx, biopsy confirmation required; MDS, Myelodysplastic syndrome; SOC, standard-of-care. (1) MCV ≥ 98 femtoliter on one or more occasions without associated folate or vitamin B12 deficiency (2) platelet count ≤ 100 x 10^9/L (3) monocyte count < 0.5 x 10^9/L (4) Requirement of ≥ 10 mg/day oral prednisone (or equivalent) for inflammatory syndrome symptomatic control; acute phase reactants-ESR and CRP increase in the absence of infectious origin

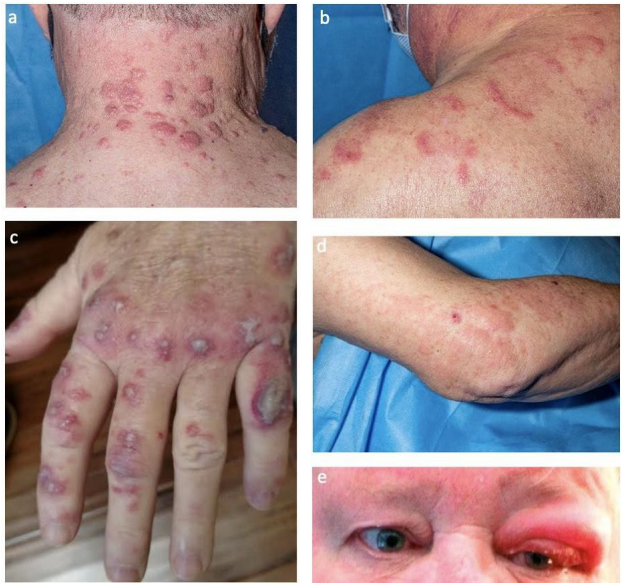
ACR VEXAS Guidance Paper, *A&R* 2025

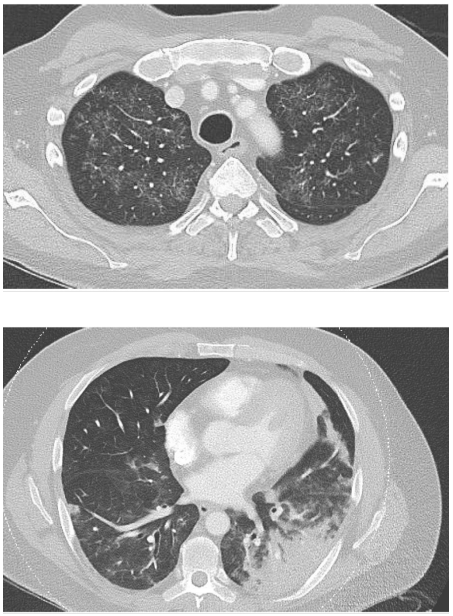
11



Jama Derm 2024

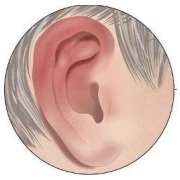
12



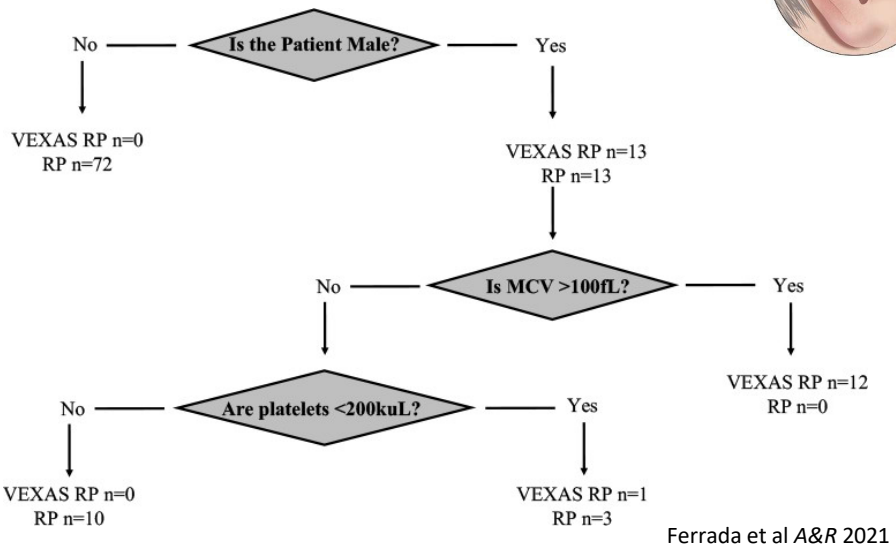


13

Clinical Algorithm to Recognize VEXAS



In a patient with ear or nose chondritis…



Ferrada et al *A&R* 2021

14

Typical Laboratory Abnormalities in VEXAS

Laboratory Test	Relative to Reference Value
Complete Blood Count	
White Blood Cell count	↓
Neutrophil count	—
Lymphocyte count	↓↓
Monocyte count	↓↓
Hemoglobin	↓↓
Mean Corpuscular Volume	↑↑↑
Platelets	↓
Peripheral Flow Cytometry	
CD3	↓
CD4/CD3	↓
CD8/CD3	↓
CD19	↓↓
NK Cells	↓↓

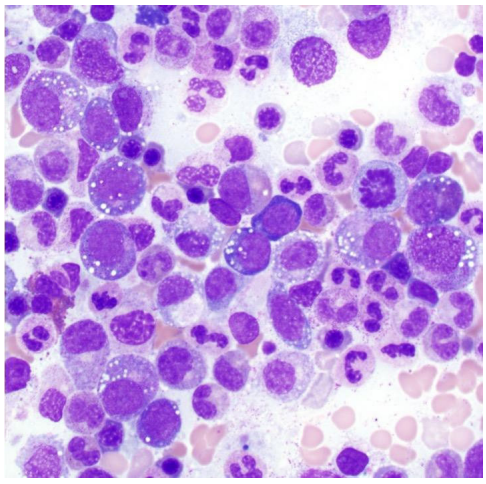
— No change relative to reference value

↓ Decreased relative to reference value

↑ Increased relative to reference value

15

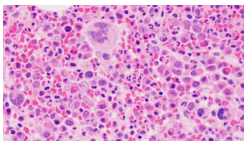
Typical Marrow Findings in VEXAS



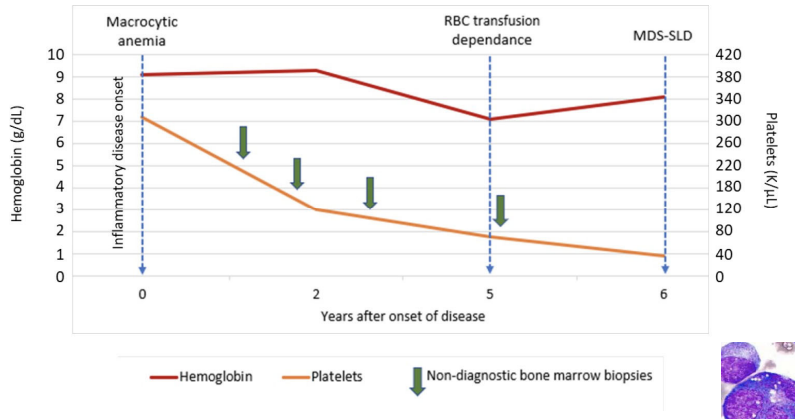
- Hypercellular marrow
- Myeloid predominance
- Vacuolated erythroid/myeloid precursor cells

16

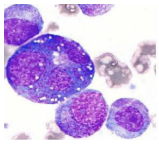
Natural History of VEXAS Syndrome



Hypercellular marrow



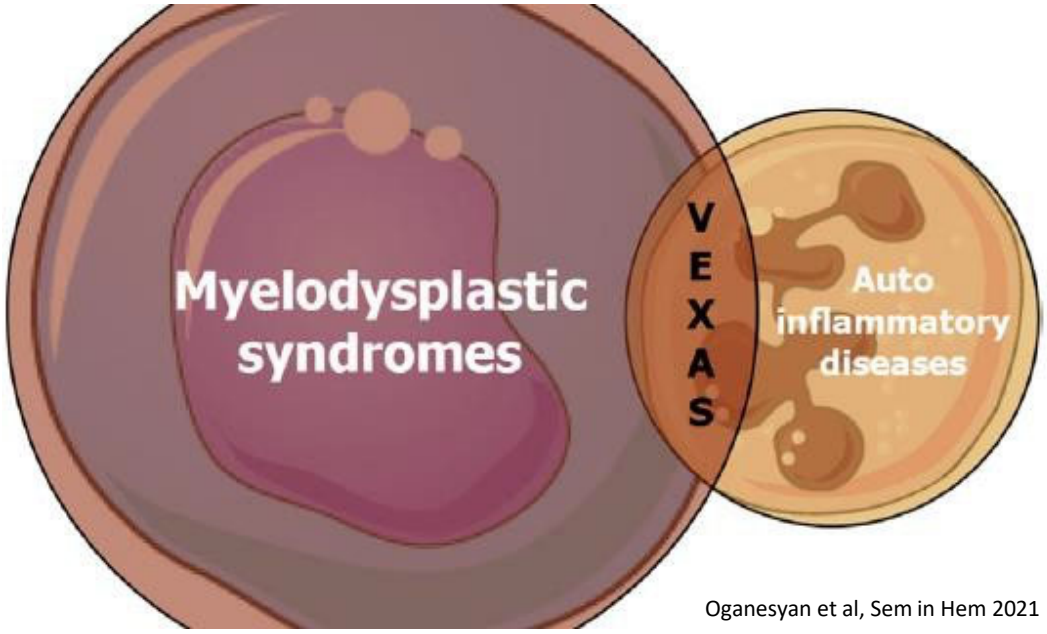
Disease progression to MDS



Abnormal myeloid cells

Oblorah et al., *Blood Adv, 2021*

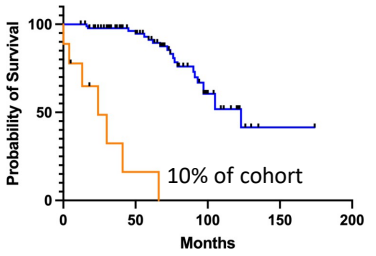
17

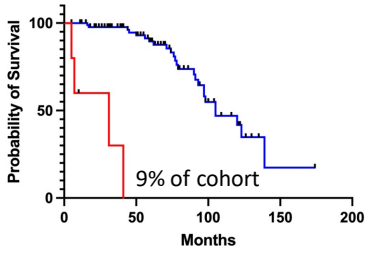


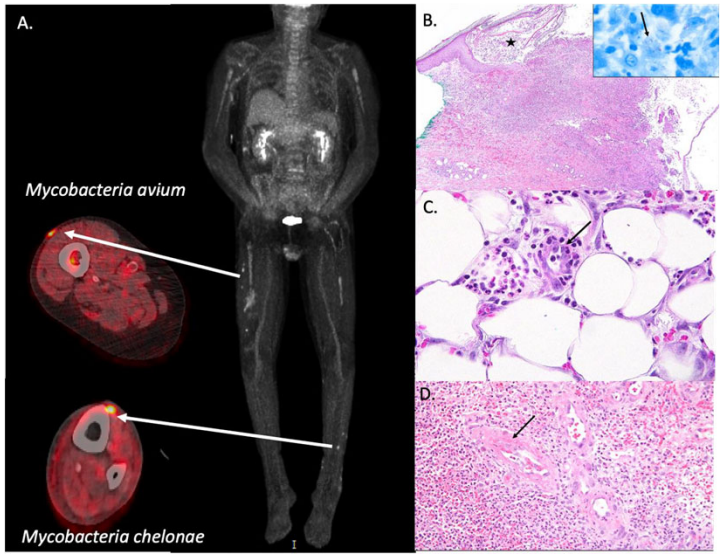
Oganesyan et al, Sem in Hem 2021

18

Atypical Infections are Common







Czech et al *Open Forum ID* 2024, de Valence et al *ARD* 2024

19

How to test for VEXAS?

- Commercially available testing: blood or bone marrow sample
- Single gene testing of UBA1
  - Sanger sequencing: not sensitive VAF<20%
  - ddPCR: sensitive and provides quantifiable VAF
- Next Generation Sequencing Panels
  - Includes genes related to myeloid neoplasms/MDS (additional prognostic value)

20

VEXAS IS THE NEW GREAT MIMIC IN MEDICINE

Expanding the spectrum of **VEXAS syndrome**: association with acute-onset CIDP.
Bert-Marcaz C, Briantais A, Faucher B, Corazza G, Ebbo M, Attarian S, Delmont E, Fortanier E.
J Neurol Neurosurg Psychiatry. 2022 Jul;93(7):797-798. doi: 10.1136/jnnp-2021-327949. Epub 2021 Dec 6.

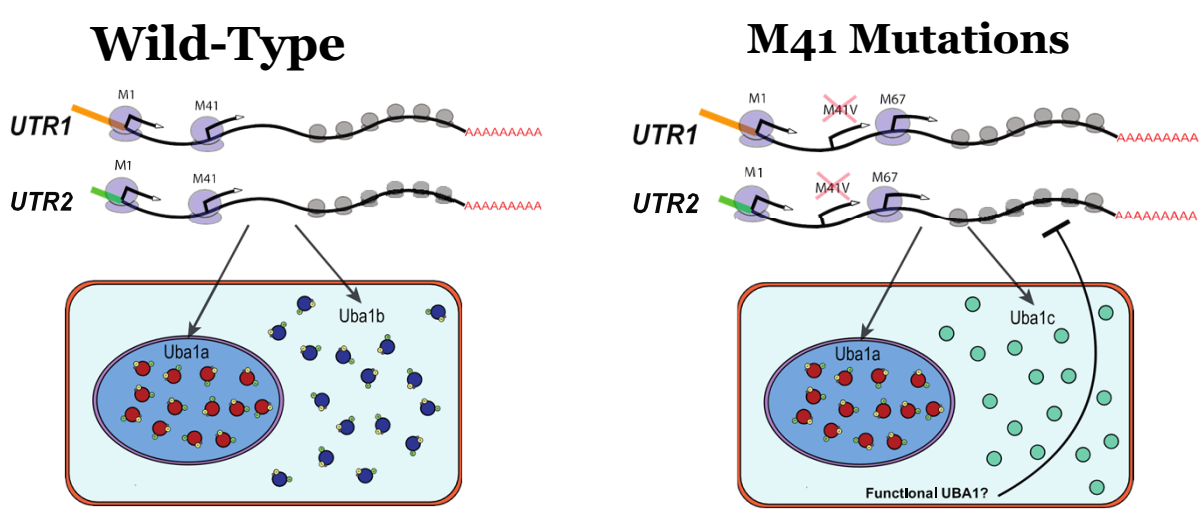
Lee SMS, Fan BE, Lim JH, Goh LL, Lee JSS, Koh LW.
Rheumatology (Oxford). 2021 Sep 1;60(9):e304-e306. doi: 10.1093/rheumatology/keab200.

VEXAS syndrome with **systemic lupus erythematosus**: expanding the spectrum of associated conditions.

Behçet's disease with a somatic UBA1 variant:Expanding spectrum of autoinflammatory phenotypes of **VEXAS syndrome**.
Matsumoto H, Asano T, Tsuchida N, Maeda A, Yoshida S, Yokose K, Fujita Y, Temmoku J, Matsuoka N, Yashiro-Furuya M, Sato S, Irie K, Norikawa N, Yamamoto T, Endo M, Fukuchi K, Ohkawara H, Ikezoe T, Uchiyama Y, Kirino Y, Matsumoto N, Watanabe H, Migita K.
Clin Immunol. 2022 May;238:108996. doi: 10.1016/j.clim.2022.108996. Epub 2022 Apr 7.
PMID: 35398520 No abstract available.

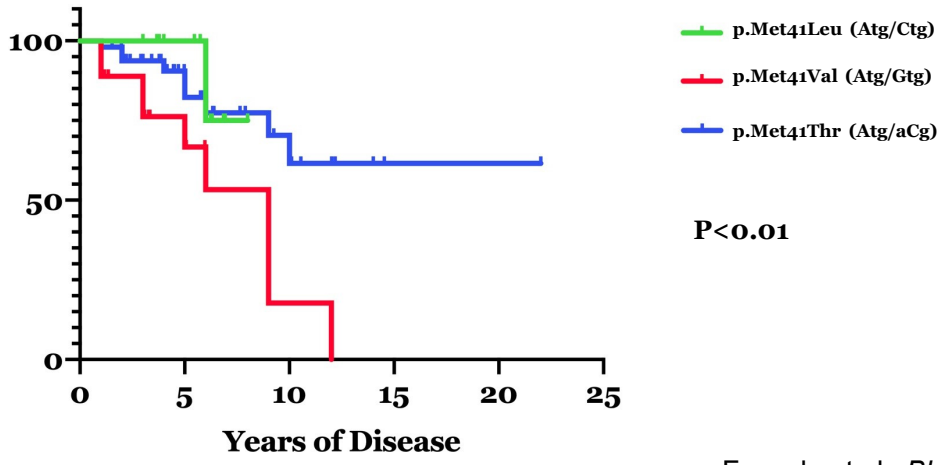
21

Mutational Hotspot at Codon 41



22

Genotype associated Mortality



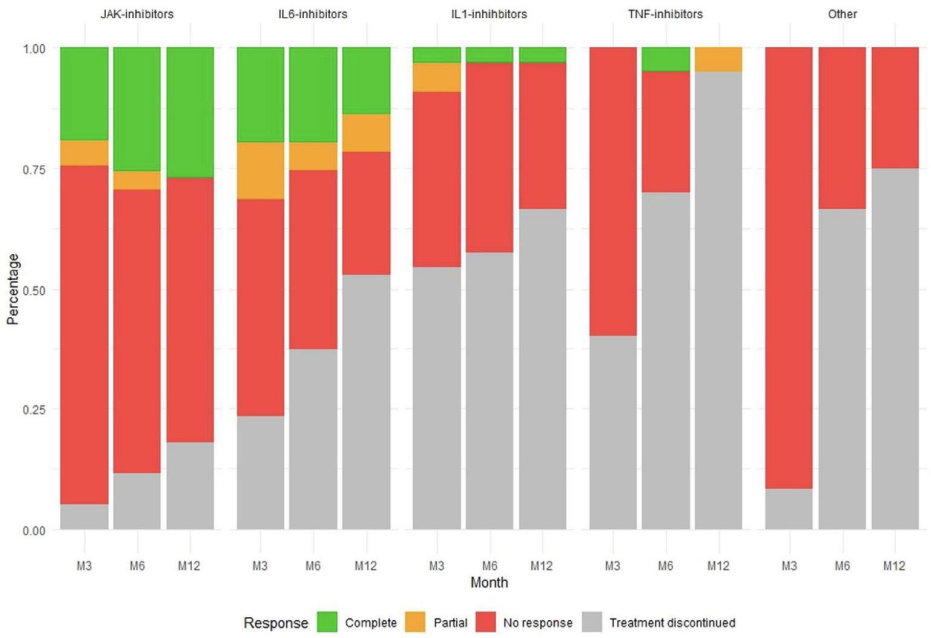
Ferrada et al., *Blood* 2022

23

Goals of Medical Therapy

- **Control inflammation**
- **Eradicate the clone**
- **Prevent complications**
  - Infectious Prophylaxis
  - Anticoagulation

24



Complete response:
Clinical remission
CRP <10mg/L
Pred ≤ 10mg / day

Hadjad et al *ARD* 2025

25

Biggest Mistakes in VEXAS Management

- Expect to taper completely off glucocorticoids
  - On average 15 – 30 mg prednisone / day to control inflammation
- Taper glucocorticoids too quickly
- Taper below glucocorticoid threshold dose
- No prophylaxis for PJP and Herpes

26

Hypomethylating Agents

- Hematologic response
- Molecular remission
- Clinical improvement
- Steroid sparing effects
- Lots of complications

	Overall
Overall hematological response	51 / 74 (69%)
Erythroïd response	
HI-E achieved	49 / 71 (69%)
among NTD patients at AZA onset	18 / 25 (72%)
among LTB patients at AZA onset	4 / 10 (40%)
among HTB patients at AZA onset [1]	27 / 36 (75%)
RBC transfusion independence achieved [2]	30 / 46 (65%)
Platelet response	
HI-P achieved	36 / 47 (77%)
Neutrophil response	
HI-N achieved	7 / 9 (78%)

Jachiet et al, *Blood* 2025

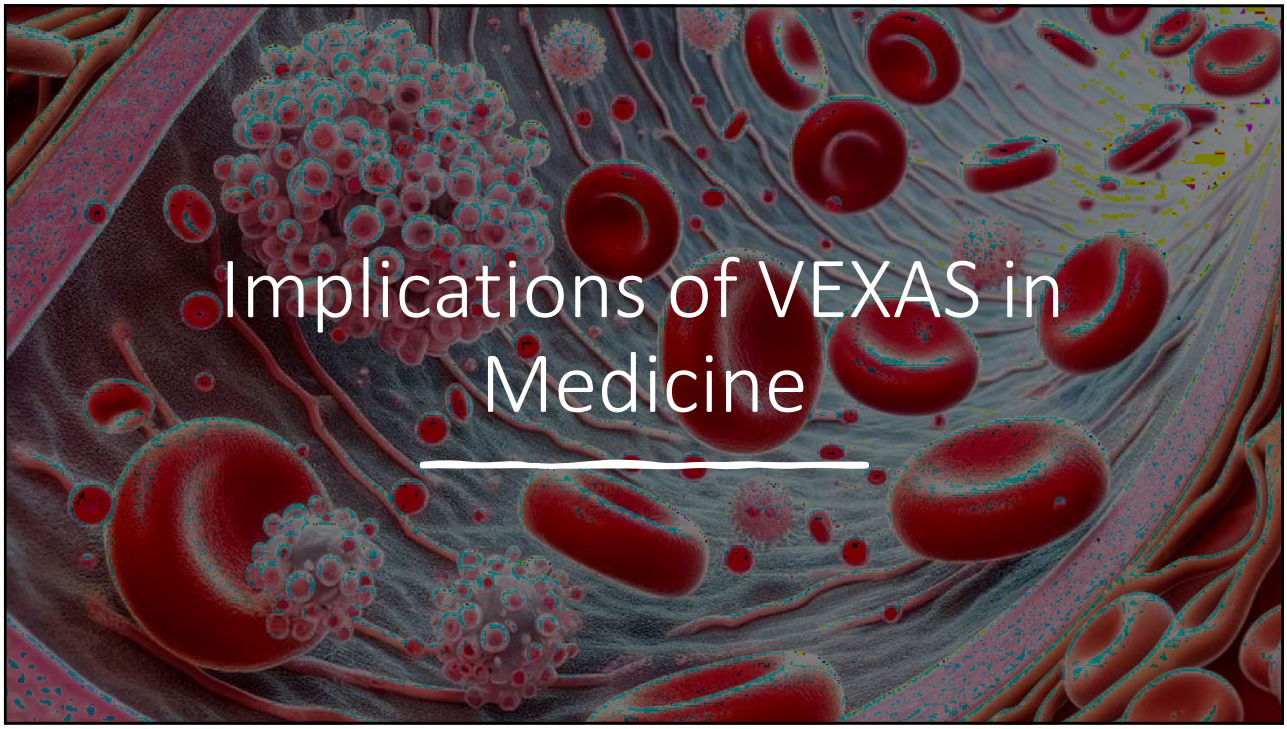
27

Bone Marrow Transplant

Curative but Complicated

- Case report and case series level data
  - Ongoing trial at NIH
- Morbidity
  - Infections
  - Graft versus host disease
- Mortality
- Selection of appropriate candidates is key

28



29

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early-Onset Stroke and Vasculopathy Associated with Mutations in ADA2

Q. Zhou, D. Yang, A.K. Ombrello, Andrey V. Zavialov, C. Toro, Anton V. Zavialov, D.L. Stone, J.J. Chae, S.D. Rosenzweig, K. Bishop, K.S. Barron, H.S. Kuehn, P. Hoffma
T. Heller, D
S.J. Kelly,
F. Canc
J.F. Meschia
E. Chalon
N.G. Singe
S.M. Bui

The NEW ENGLAND JOURNAL of MEDICINE

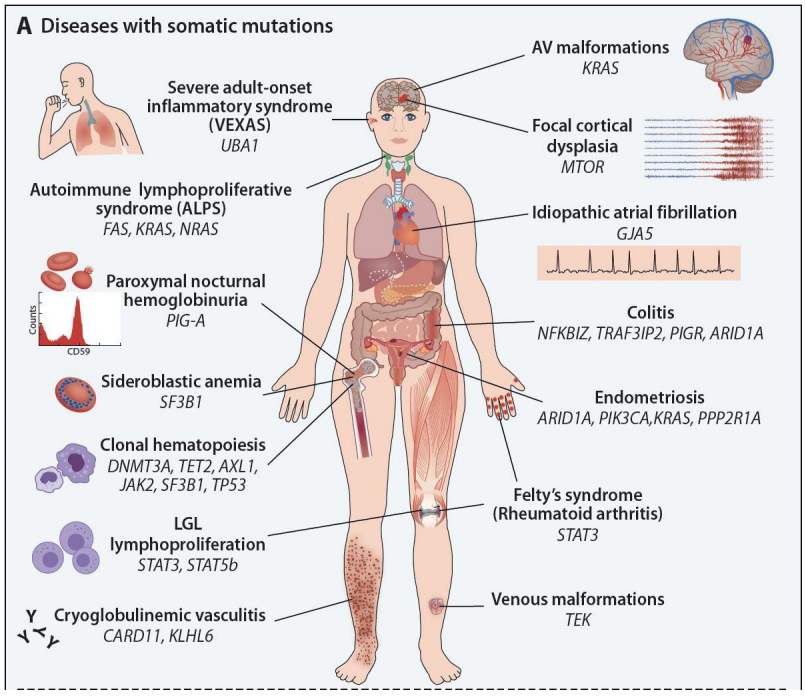
ORIGINAL ARTICLE

Mutant Adenosine Deaminase 2 in a Polyarteritis Nodosa Vasculopathy

Paulina Navon Elkan, M.D., Sarah B. Pierce, Ph.D., Reeval Segel, M.D., Tom Walsh, Ph.D., Judith Barash, M.D., Shai Padeh, M.D., Abraham Zlotogorski, M.D., Yackov Berkun, M.D., Joseph J. Press, M.D., Masha Mukamel, M.D., Isabel Voth, M.D., Philip J. Hashkes, M.D., Liora Harel, M.D., Vered Hoffer, M.D., Eduard Ling, M.D., Ph.D., Fatos Yalcinkaya, M.D., Ozgur Kasapcopur, M.D., Ming K. Lee, Ph.D., Rachel E. Klevit, D.Phil., Paul Renbaum, Ph.D., Ariella Weinberg-Shukron, B.Sc.Med., Elif F. Sener, Ph.D., Barbara Schormair, Ph.D., Sharon Zeligson, M.Sc., Dina Marek-Yagel, Ph.D., Tim M. Strom, M.D., Mordechai Shohat, M.D., Amihood Singer, M.D., Alan Rubinow, M.D., Elon Pras, M.D., Juliane Winkelmann, M.D., Mustafa Tekin, M.D., Yair Anikster, M.D., Ph.D., Mary-Claire King, Ph.D., and Ephrat Levy-Lahad, M.D.

- Most forms of vasculitis start late in life
- Most forms of vasculitis are not heritable

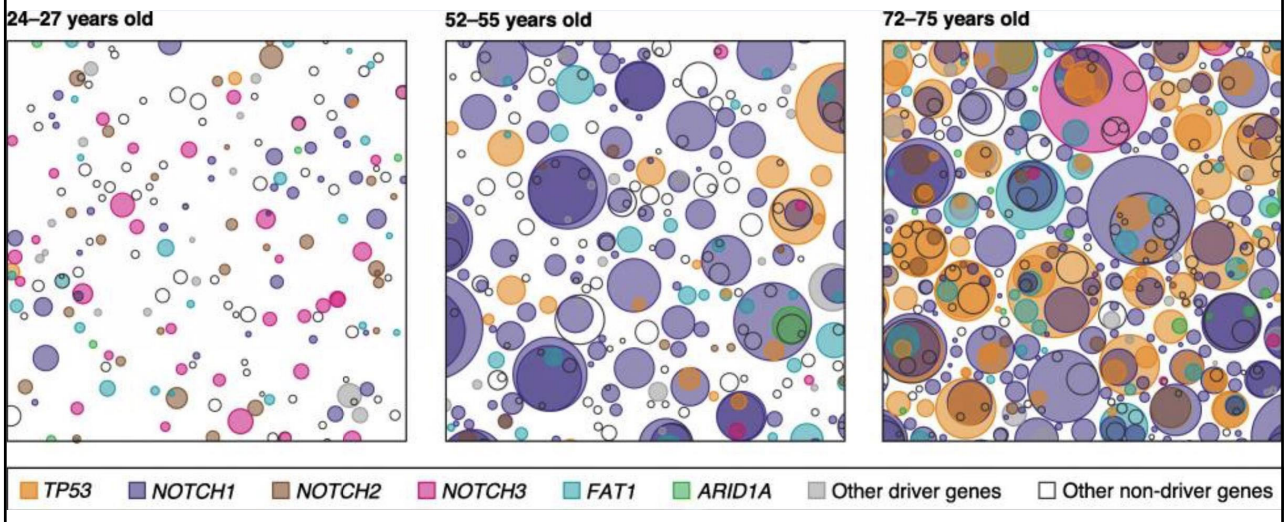
30



Young & Mustjoki NEJM 2021

31

Healthy esophageal epithelium with age

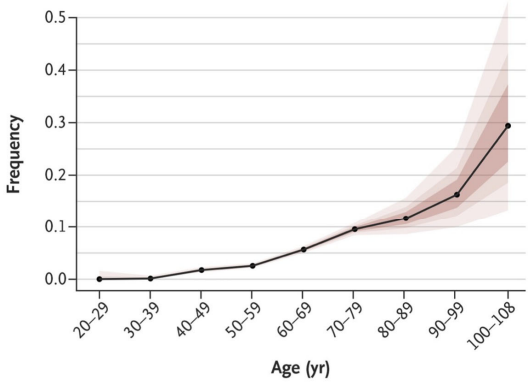


Martincorena Genome Med 2019

32

Clonal Hematopoiesis of Indeterminate Potential (CHIP)

- 40-50 genes associated with myeloid malignancy and MDS
- Prevalence of somatic mutations in hematologic precursor cells in these genes increases with age
  - DNMT3A and TET2

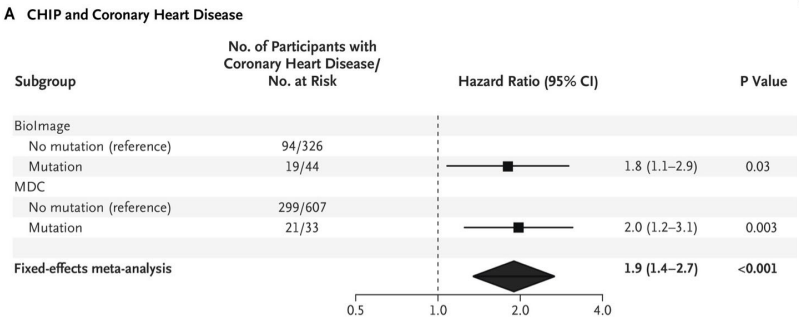


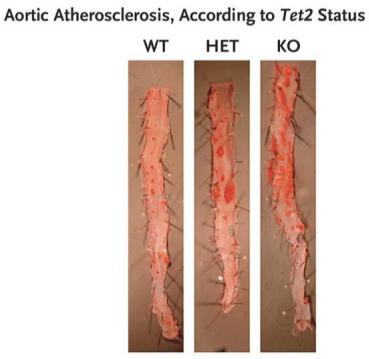
No. with Mutation	0	1	50	138	282	219	37	14	5
Total	240	855	2894	5441	5002	2300	317	86	17

Jaiswal et al NEJM 2014

33

Clonal Hematopoiesis and Cardiovascular Disease



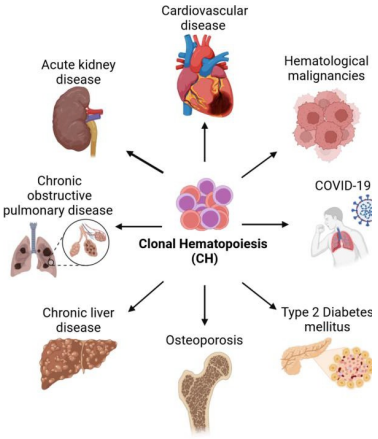


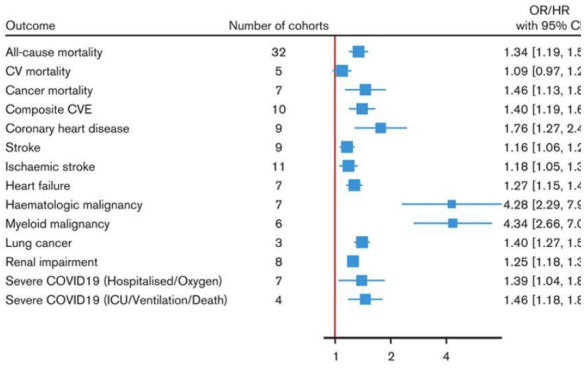
↑ IL-6, IL-1

Jaiswal et al NEJM 2017

34

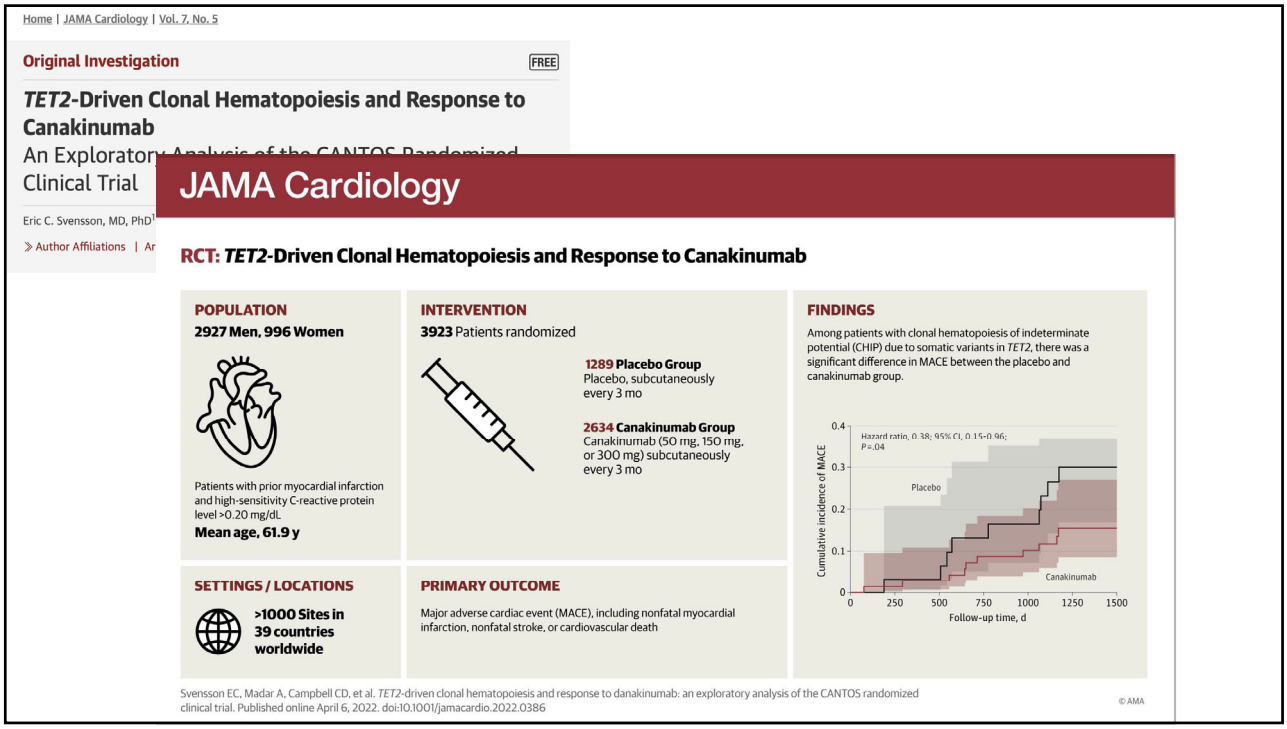
CH Associated with many diseases





Singh *Blood Advances* 2024

35



36

Clonal Hematopoiesis in Internal Medicine

- Independent risk factor for cardiovascular disease
- Associated with a number of diseases
- May modify diseases by contributed to myeloid-driven inflammation

37

Multiple Clones in a VEXAS Patient

						VAF		
UBA1	NP_695012.1:p.Met41Thr	NM_153280.2:c.122T>C	M/T	aTg/aCg	missense_variant	71.08	80	tolerated (0.1)
DNMT3A	NP_783328.1:p.Arg882Cys	NM_175629.2:c.2644C>T	R/C	Cgc/Tgc	missense_variant	34.27	283	deleterious (0.02)
TET2	NP_001120680.1:p.Val1371HisfsTer29	NM_001127208.2:c.4107_4108delAG	SG/SX	tcAGgg/tcgg	frameshift_variant	32.63	236	0

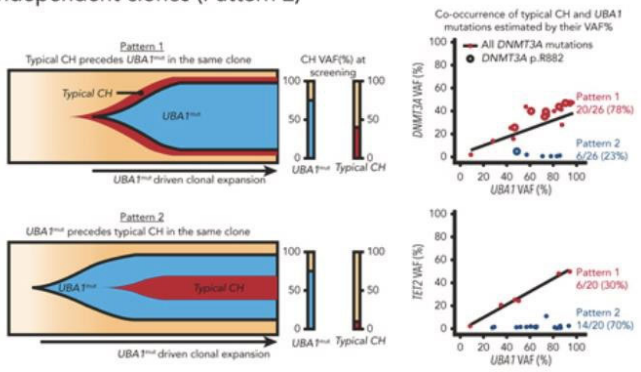
38

RESEARCH ARTICLE | APRIL 21, 2023

Spectrum of clonal hematopoiesis in VEXAS syndrome

Fernanda Gutierrez-Rodrigues, Yael Kusne, Jenna Fernandez, Terra L Lasho, Ruba N Shalhoub, Xiaoyang Ma, Hugh Alessi, Christy M. Finke, Matthew J. Koster, Abhishek A. Mangaonkar, Kenneth J Warrington, Kebede Begna, Zhuoer Xie, Amanda K Ombrello, David S Viswanatha, Marcela A. Ferrada, Lorena Wilson, Ronald S. Go, Taxiarchis V. Kourelis, Kaaren K Reichard, Horatiu Olteanu, Ivana Darden, Dalton Hironaka, Lemlem Alemu, Sachiko Kajigaya, Rodrigo T. Calado, Emma M. Groarke, Sofia Rosenzweig, Daniel L Kastner, Katherine R Calvo, Colin O. Wu, Peter C. Grayson, Neal S Young, David B. Beck, Bhavisha A. Patel ✉, Mrinal M. Patnaik

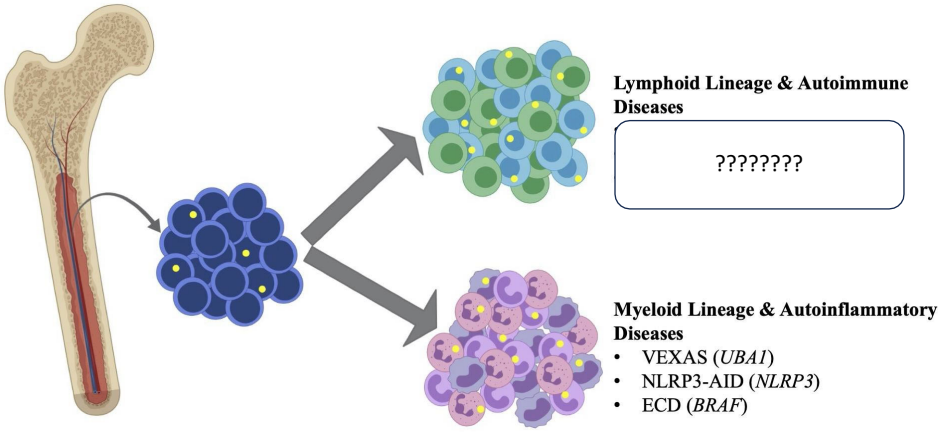
Clonal patterns: Based on integrated bulk and scDNA analyses, clonality in VEXAS followed two major patterns: with either typical CH preceding *UBA1*^{mut} selection in a clone (Pattern 1), or occurring as an *UBA1*^{mut} subclone or in independent clones (Pattern 2)



Typical CH mutations associated with increased mortality risk

39

Myeloid and Lymphoid Mutations



Lymphoid Lineage & Autoimmune Diseases

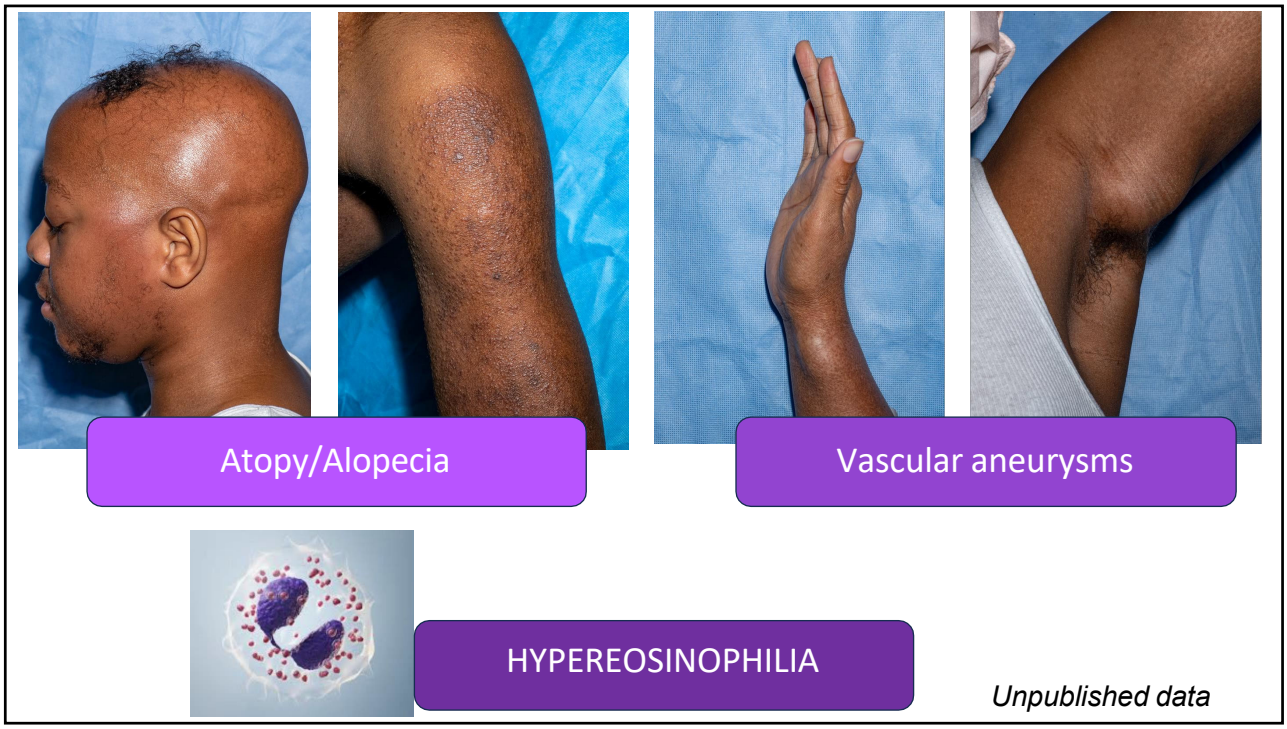
????????

Myeloid Lineage & Autoinflammatory Diseases

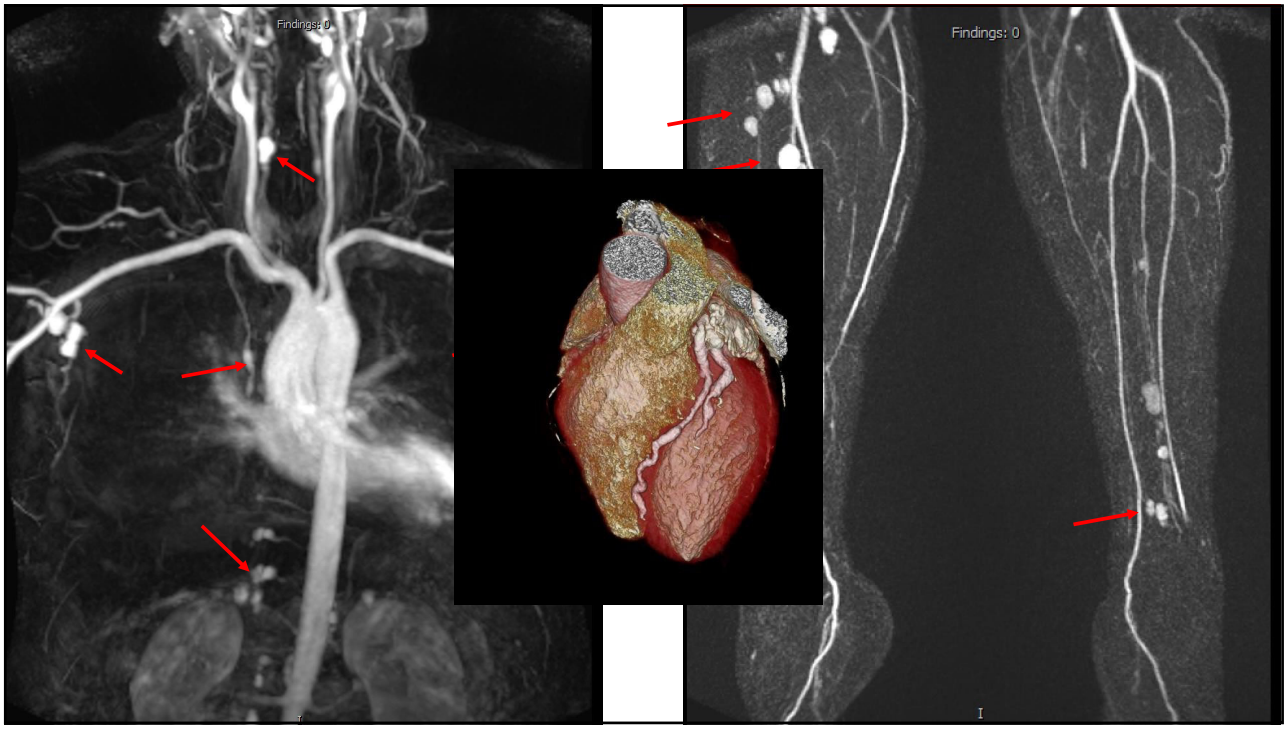
- VEXAS (*UBA1*)
- NLRP3-AID (*NLRP3*)
- ECD (*BRAF*)

Sikora et al., *Rheumatology, 2022*

40

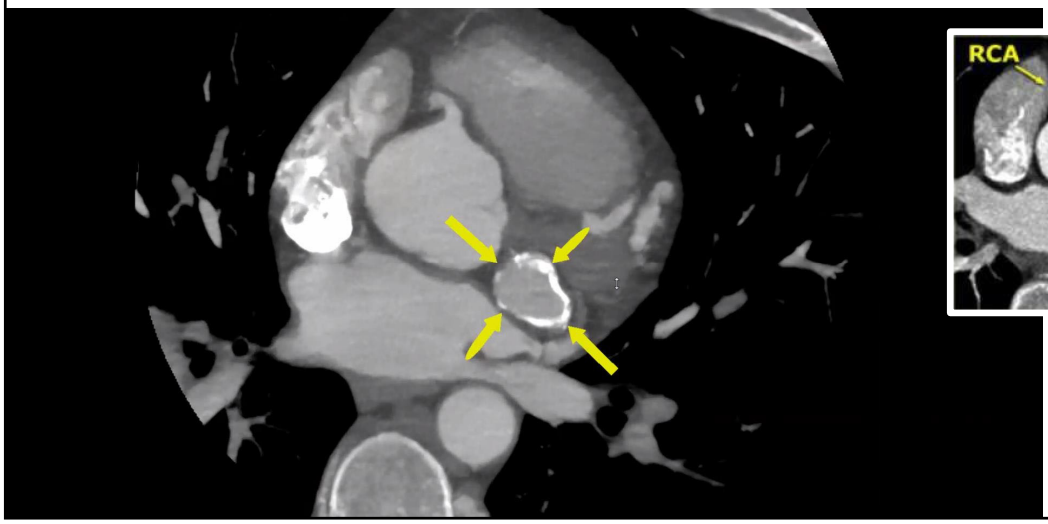

Atopy/Alopecia
Vascular aneurysms
HYPEREOSINOPHILIA
Unpublished data

41

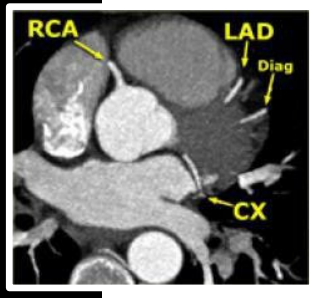

Findings: 0
Findings: 0

42

Left Circumflex Artery Aneurysm

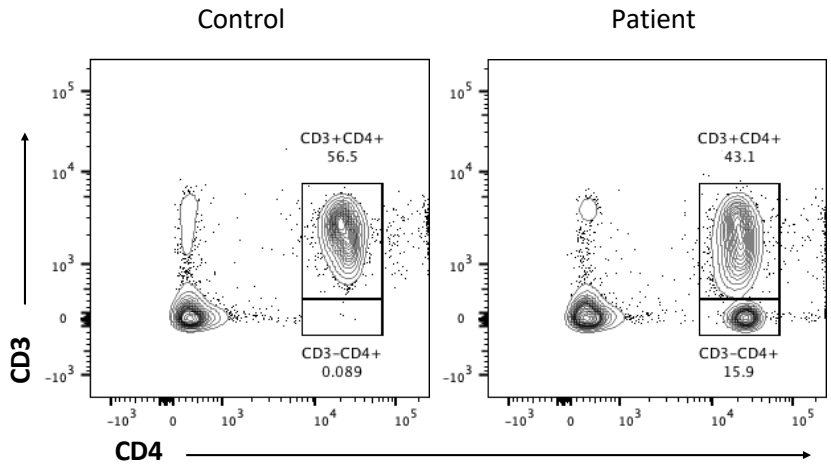


Normal:



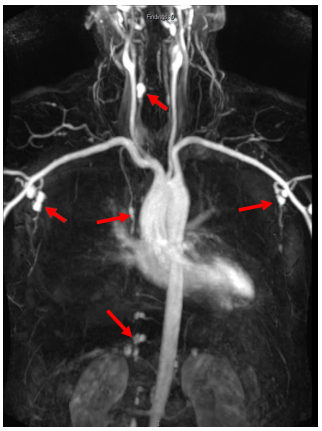
43

Patient T-cell clone



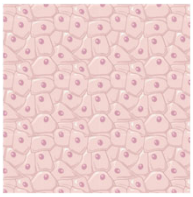
44

Hunting for clonal forms of vasculitis

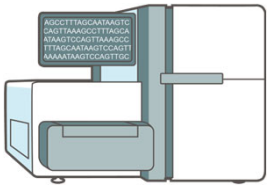


DNA/RNA Source

Blood



Skin

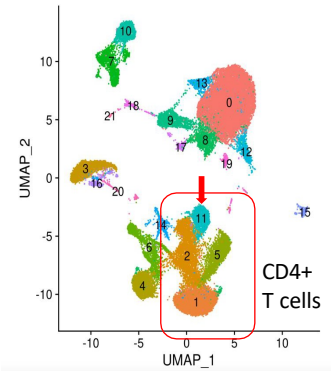


Next Gen Sequencing

45

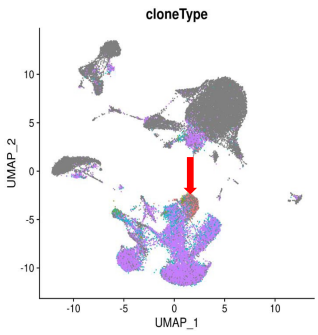
Discovery of a Th2 Cell Clone

A.



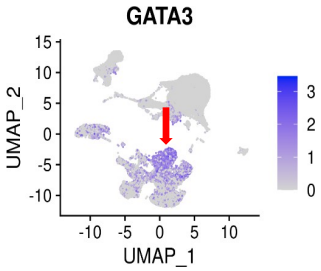
Single Cell RNA SEQ

B.



Integrated TCR Seq

C.



Marker Genes

46

Conclusions

- Somatic mutations play a causal role in some forms of adult-onset systemic inflammatory diseases
  - Monogenic drivers of disease
  - Modifiers of immune response
- Classification of vasculitis by molecular mechanisms is within reach
  - Complement the small / medium /large distinction with biologic classification schemes!
- **Molecular diagnostics is coming to internal medicine**
  - **Need to develop research and clinical pipelines to discover and screen**

47

National Institute of Arthritis and Musculoskeletal and Skin Diseases

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48