UBC Dermatology
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BC Cancer Agency
CARE & RESEARCH

Auto-Inflammatory skin disease

What it is and why it matters

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Faculty Disclosure

- Faculty: Jan Peter Dutz
- Relationships with financial sponsors
  - » Clinical trials
    - Astra Zeneca, GSK
  - » Speaker's Bureau/Honoraria
    - Astra Zeneca, AbbVie, Amgen, Bausch, Bristol Myers Squibb, Celltrion, Galderma, Leo, Johnson & Johnson, Novartis, Pfizer, Sanofi

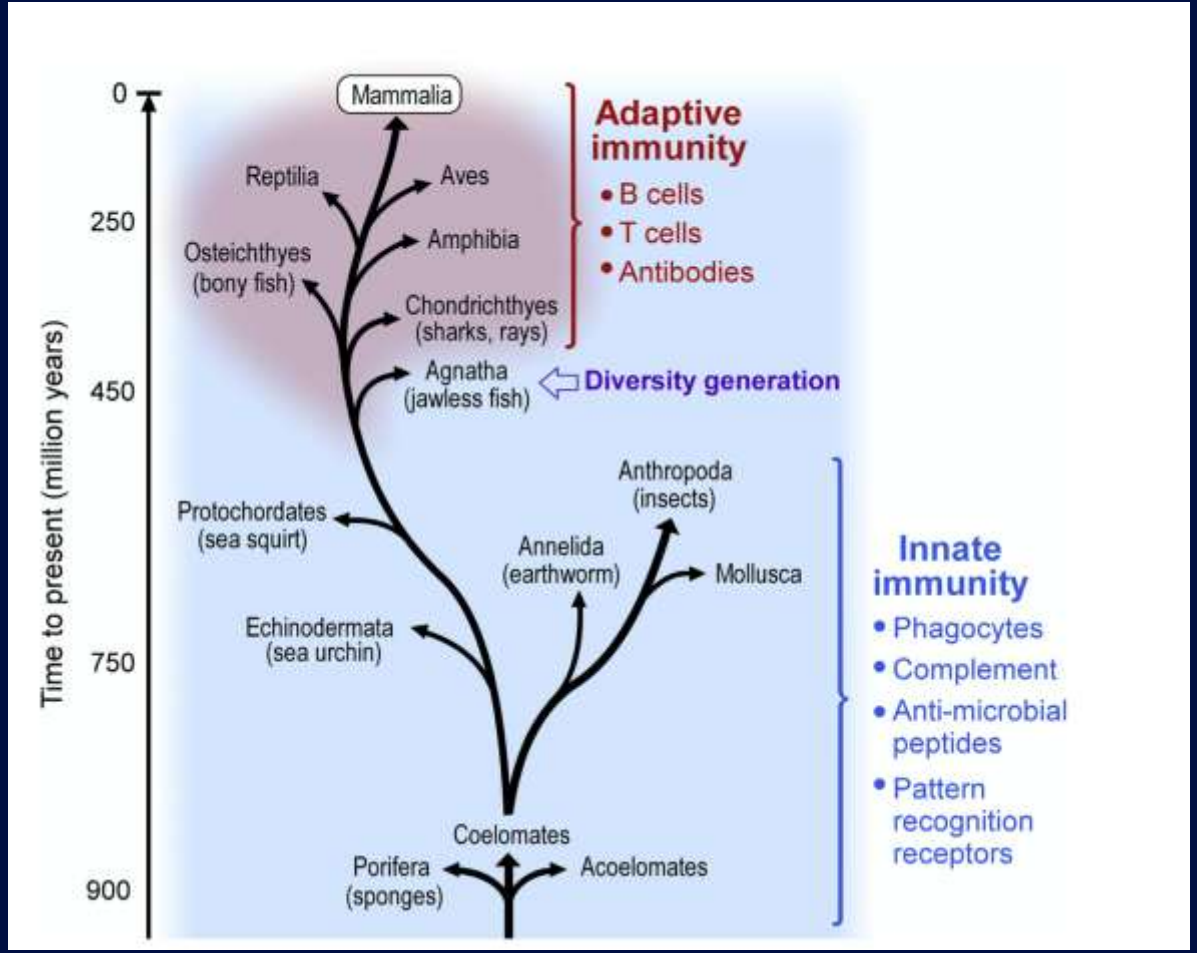
Learning Objectives

- **At the end of this session, attendees will:**
  - **Learn how to differentiate autoinflammatory skin disease from common skin diseases**
  - **Learn how to integrate cutaneous manifestations into the diagnosis of autoinflammatory syndromes**

Autoinflammatory syndromes

- Term coined in 1999 – Daniel Kastner
  - To separate inflammatory diseases from infectious, allergic and immunodeficiency
  - Inflammatory component with a genetic basis
    - » Dysregulation of innate immunity- neutrophils, monocytes, macrophages
  - No specific auto-antibodies or auto-reactive T lymphocytes
  - Familial Mediterranean Fever = most common

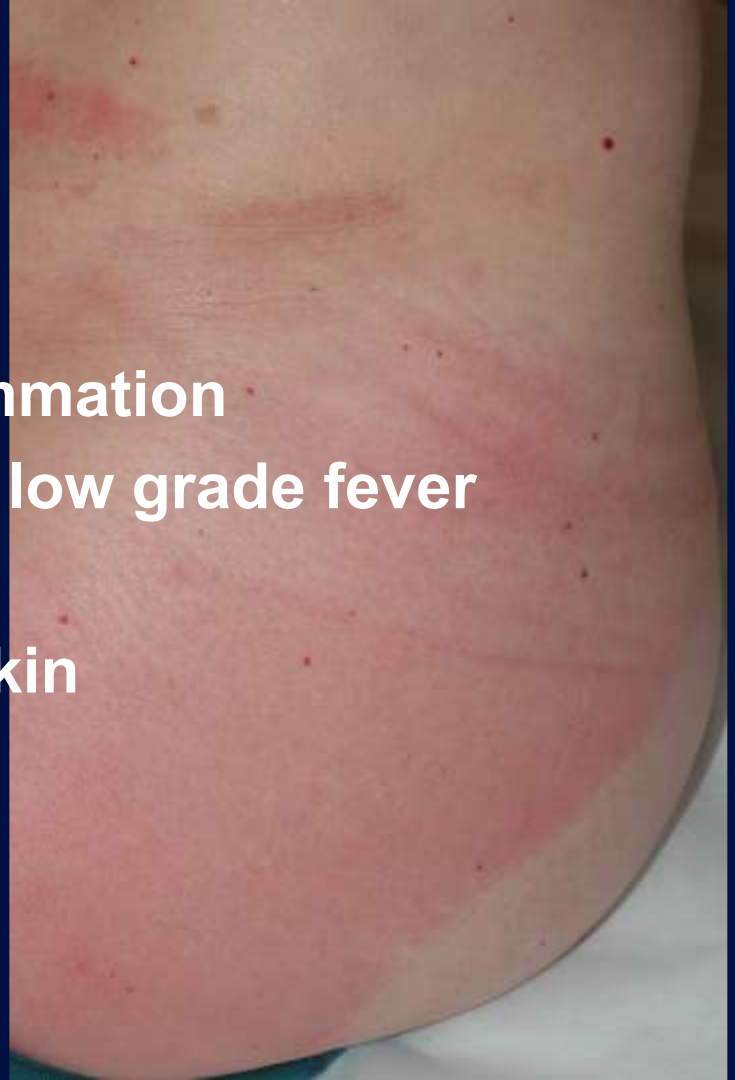
Autoinflammatory versus Autoimmune



Nigrovic J Allergy Clin Immunol 2020;146:925

Autoinflammation

- **65 YO F**
- **30+ year history of inflammation**
- **1-3 day long episodes of low grade fever**
- **Every 1-2 months**
- **Associated red, tender skin**



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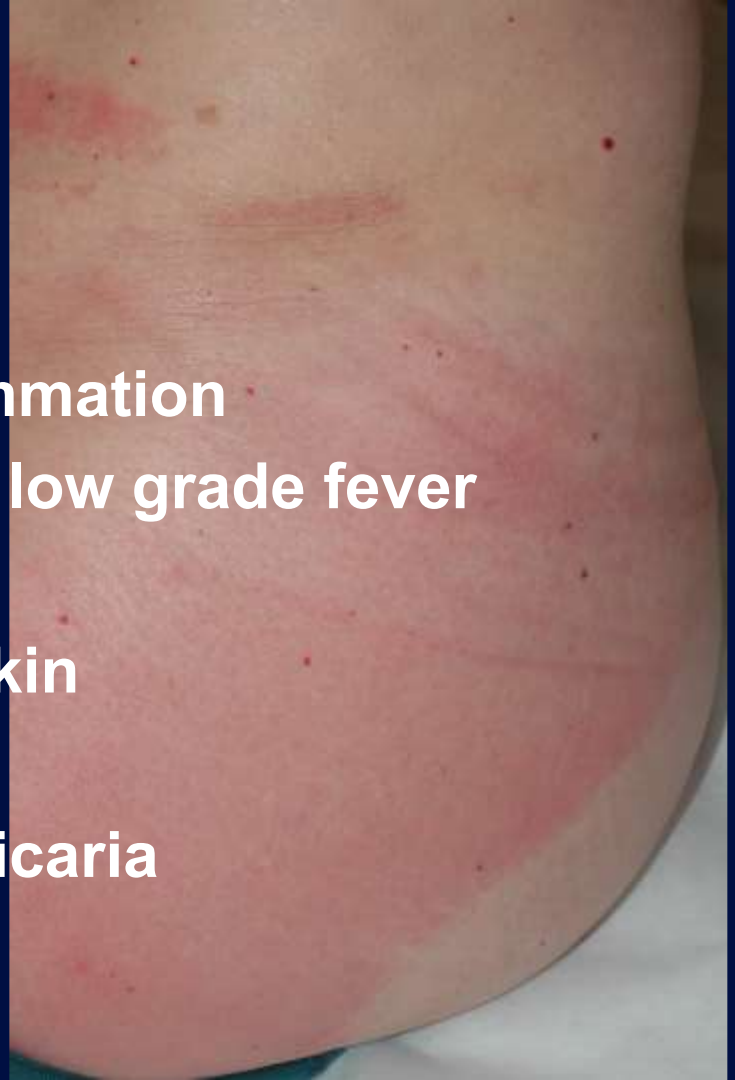
- Biopsy - Neutrophilic urticaria



Autoinflammation

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- 30+ year history of inflammation
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- Biopsy - Neutrophilic urticaria
- Treatment trial - Colchicine 0.6 mg BID = complete resolution

	Mechanism	Disease	Gene	Inheritance	Clinical presentation	Targeted therapy
Inflammasomopathies and other IL-1 family conditions	Pyrin activation	FMF	*MEFV*	AR or AD	fever, pain, (abdominal, chest, joint), rash	IL-1, colch.
		PAAND	*MEFV*	AD	fever, myalgia, myositis, rash, abscesses	IL-1, colch.
		MKD	*MVK*	AR	fever, pain (abdominal, extremity), vomiting, rash	IL-1
		PAPA	*PSTPIP1*	AD	pyoderma gangrenosum, arthritis	IL-1, TNF
		Hz/Hc[12]	*PSTPIP1*	AD	rash, FTT, hepatosplenomegaly, neutropenia	IL-1, TNF
		PFIT[13]	*WDR1*	AR	fever, infection, oral inflammation, perianal ulceration	IL-18
	Cryopyrin activation	FCAS	*NLRP3*	AD	cold urticaria, extremity pain, conjunctivitis, fever	IL-1
		MWS	*NLRP3*	AD	urticarial rash, extremity pain, hearing loss, conjunctivitis, fever	IL-1
		NOMID	*NLRP3*	AD	CNS inflammation, urticaria, knee arthropathy, fever	IL-1
		Majeed's[14]	*LPIN2*	AR	osteomyelitis, fevers, rash, dyserythropoietic anemia	IL-1
	NLRC4 activation	AIFEC	*NLRC4*	AD	enterocolitis, rash, arthritis, fever	IL-1, IL-18
		FCAS/ NOMID	*NLRC4*	AD	cold urticaria, extremity pain, fever, CNS disease	IL-1
	NLRP12 activation	FCAS	*NLRP12*	AD	cold urticaria, extremity pain, fever	TNF, IL-1
	NLRP1 activation	NAIAD[15]	*NLRP1*	AD	Ocular, laryngeal, skin dyskeratosis, fever, arthritis	IL-1, TNF
	Receptor antagonist deficiency	DIRA	*IL1RN*	AR	pustular rash, osteomyelitis, periostitis, fever,	IL-1
		DITRA	*IL36RN*	AR	pustular psoriasis, fever, malaise	TNF, IL-17/12/23?

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Familial Mediterranean Fever

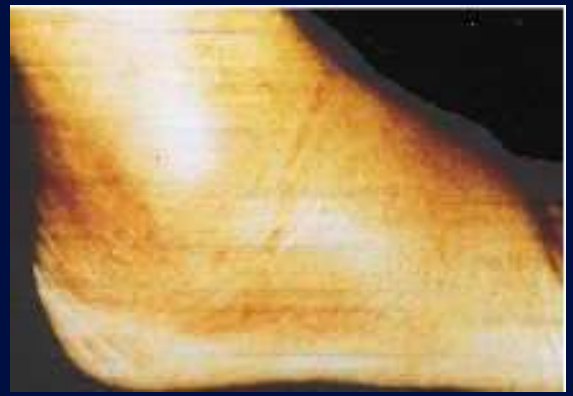
- **Siegal-Cattan-Mamou Syndrome, Maladie Arménienne, familial polyserositis**
- **Autosomal recessive mutations in *MEFV* (pyrin)**
- **Mutations in only 80%**
- **Decreased regulation of NLRP3 inflammasome = increased IL-1 release**

FMF - Classical features

- Onset prior to age 20
- 1-3 day long bouts of high fever
- Severe pain due to
  - Peritonitis
  - Pleuritis
  - Pericarditis
  - Joint pain

FMF - Cutaneous Features

- Purpura
- Erysipelas-like erythema - ankles
- Henoch-Schönlein purpura
- Angioedema
- Palmoplantar erythema
- Raynaud-like changes to hands



Barzilai A JAAD 42:791 (2000)

Colchicine

- Extracted from lily plant
- Adjust dose in hepatic or renal disease
- **Safe** in pregnant women
- Detected in lactating women's milk
- **Safe** in children

Colchicine

"Old" small molecule inhibitor

- Drug interactions
  - Hepatic deacetylation through CYP3A4
  - Can increase levels of HMG-CoA reductase inhibitors, cyclosporine
  - Levels increased by macrolides

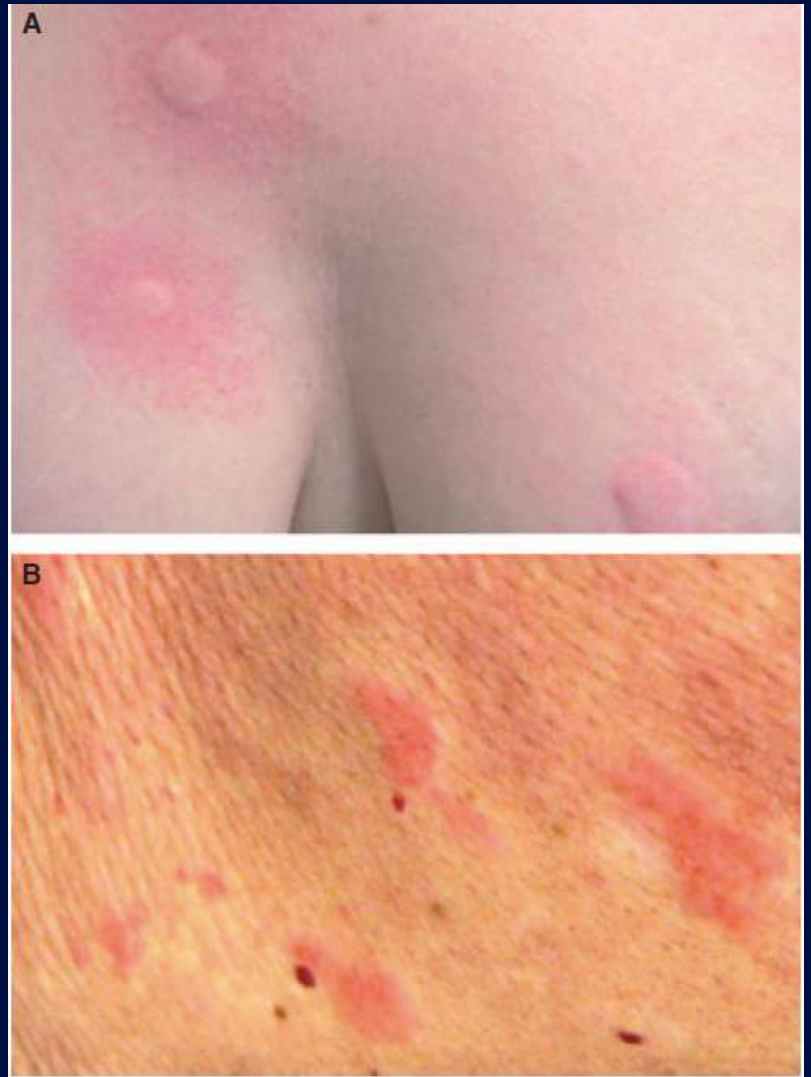
What if it's not urticaria?

- **Auto-inflammatory disorders**
  - **IL-1 driven diseases – innate immune response**
  - **Unexplained fever, pain in joints, pain in muscles, pain in bones**
  - **"feel ill"**

What if it's not urticaria?

- **Key features of Auto-inflammatory disease**
  - **Recurrent, stereotyped episodes of recurrent fever unexplained by infection**
  - **Chronic inflammation = Unexplained acute phase reactant elevation even in absence of fever**
  - **Symptoms in multiple systems including skin, serositis, MSK, eyes, gastrointestinal and central nervous system**
  - **Early onset or familial**

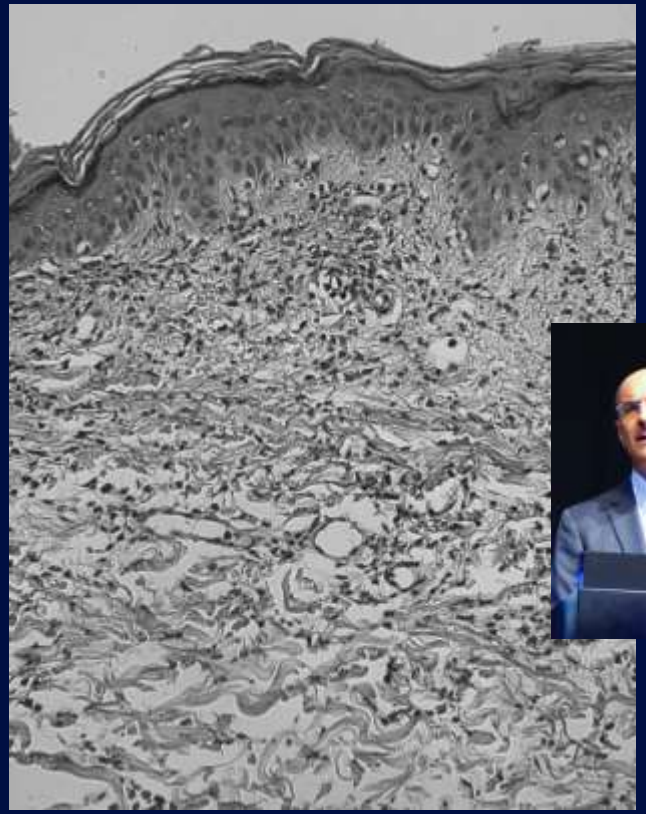
Chronic urticaria or Autoinflammation?



Neutrophilic Urticarial Histology

- 9 cases of non-edematous urticaria reviewed
  - Adult - onset Still's
  - SLE
  - Schnitzler
- All had neutrophilic urticaria

Kieffer Medicine 88:23 (2009)



Dan Lipsker
Strasbourg

Interferonopathies

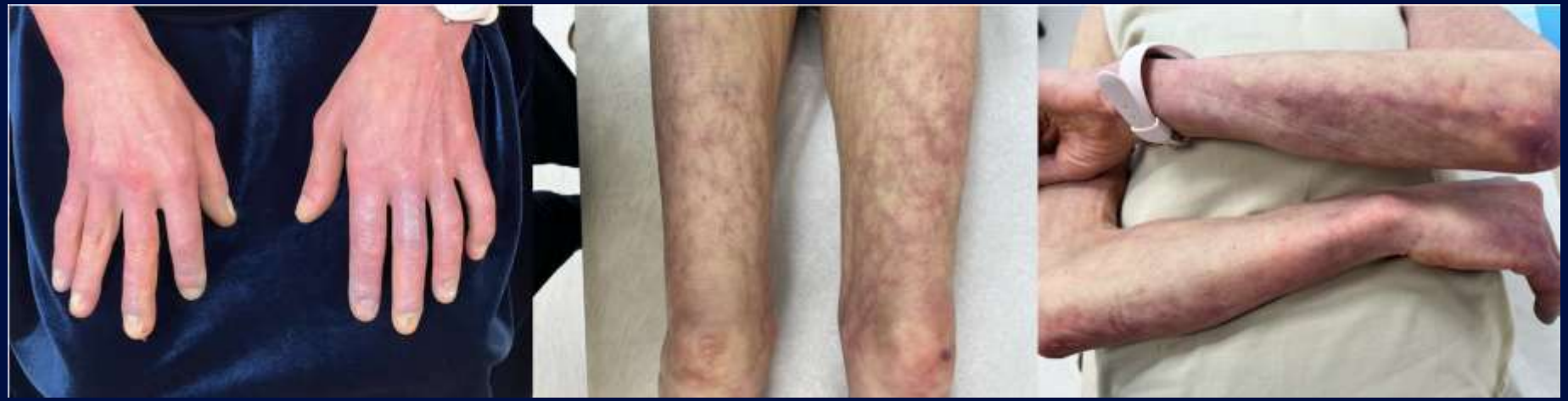
Type I Interferonopathies	Nucleic acid processing and degradation	Aicardi-Goutières syndrome	*TREX1, ADAR1, RNASEH2A/B/C, SAMHD1, IFIH1*	AR (AD: *IFIH1*)	fever, neurologic decline, encephalopathy, cerebral calcification, chilblains, autoantibodies	JAK, RTI?
		monogenic SLE	*DNASE1/2/1L3, complements*	AR (AD: *DNASE1*)	autoantibodies, cytopenias, glomerulonephritis, skin rash, oral ulcers, arthritis	JAK?
	Nucleic acid sensing	SMS	*IFIH1, DDX58a*	AD	calcification of aorta / cardiac valves, osteopenia, acro-osteolysis, dental anomalies	JAK?
		SAVI	*TMEM137*	AD	Chilblain's rash, small vessel vasculitis, arthritis, ILD	JAK
	Proteasome	CANDLE / PRAAS, PRAID[16]	*PSMB4, PSMA3, PSMB8, POMP, PSMG2,PSMB9, PSMB10*	Digenic, AR (AD: POMP)	fever, joint contractures, annular plaques, eyelid swelling, hepatosplenomegaly, lipodystrophy, FTT, developmental delay, anemia	JAK
	IFN signaling	AGS-like	*USP18, ISG15, STAT2*	AR	skin ulcerations, seizures, hydrocephalus, cerebral calcifications, respiratory failure	JAK
	other	SPENCD[17]	*ACP5*	AR	skeletal dysplasia, short stature, cerebral calcification, cytopenias, autoantibodies	?

Interferonopathy?

- 50 F Followed since 2016
- Weight loss, finger ulceration, osteoporosis, fatigue

- 20-year history of Raynaud
- Osteoporosis since age 20
- Ongoing pernio and vasculopathic skin changes
- Seen by multiple specialists
  - Vasculitis clinic, autoinflammatory disorders clinic, endocrinology clinic

Interferonopathy?



Interferonopathy?

2017 Gene DX – Genetic testing TREX1, RNASeH2A, RNASeH2B, RNASeH2C – negative

2019 MITOGEN - Cytokine testing

High levels of IL3, IL20, IL21, IL23, IL28A, IL33, TSLP, TARC

Interferonopathy?

Partial response to tofacitinib

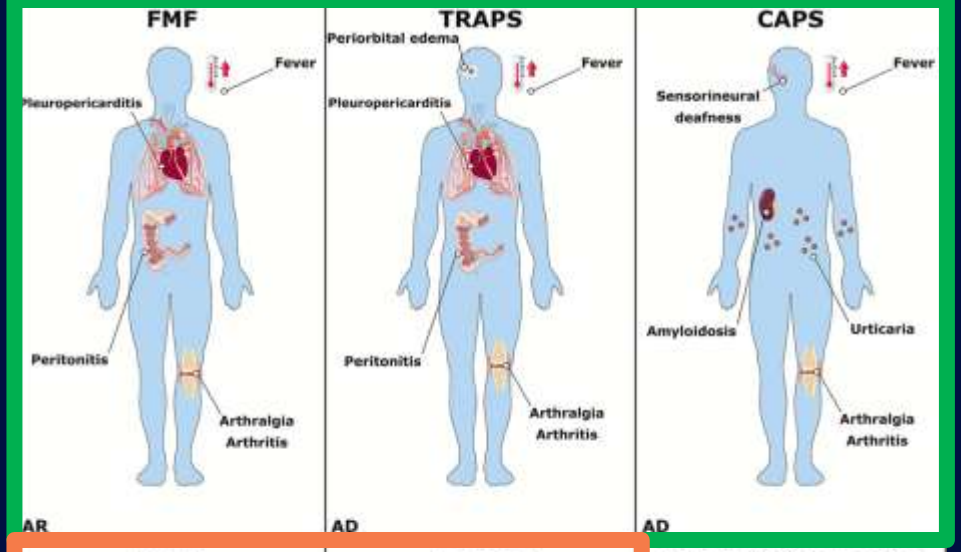
Partial response to baricitinib

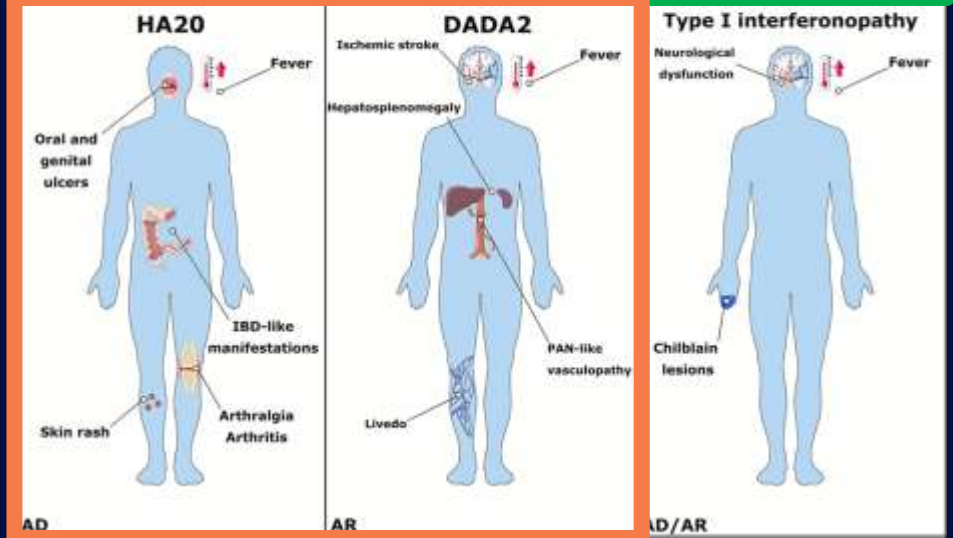
Potential candidate for anifrolumab – Need to show increased T1IFN

- **Gene signature**
- **Flow cytometry for CD169**
- **Repeat cytokine analysis**

Relopathies – NFKB (RelA-RelB)

NF-κB and/or aberrant TNF activity	dysregulation of NFκB signaling	HA20	*TNFAIP3*	AD	oral, gastrointestinal and genital ulcerations, fever, arthritis, recurrent infection	TNF, IL-1, JAK?
		RELA haploinsuf.[18]	*RELA*	AD	oral and gastrointestinal ulcerations, cytopenias, lymphoproliferative disease	TNF
		ORAS	*OTULIN*	AR	fever, panniculitis, diarrhea, arthritis, FTT	TNF
		LUBAC deficiency[19,20]	*HOIL1, HOIP*	AR	fever, recurrent infection, FTT, hepatosplenomegaly, amylopectin-like deposits in muscles	TNF?
	Dysregulation of TNF	Blau	*NOD2*	AD	granulomatous dermatitis, uveitis, polyarticular arthritis	TNF
		TRAPS	*TNFRSF1A*	AD	episodic fever, abdominal pain, headache, conjunctivitis, painful centrifugal rash	IL-1, TNF
		DADA2	*ADA2*	AR	systemic vasculitis, fever, rash, stroke, cytopenias, hypogammaglobulinemia	TNF, HSCT
		CRIA[21,22]	*RIPK1*	AD	fever, lymphadenopathy, hepatosplenomegaly	IL-6?





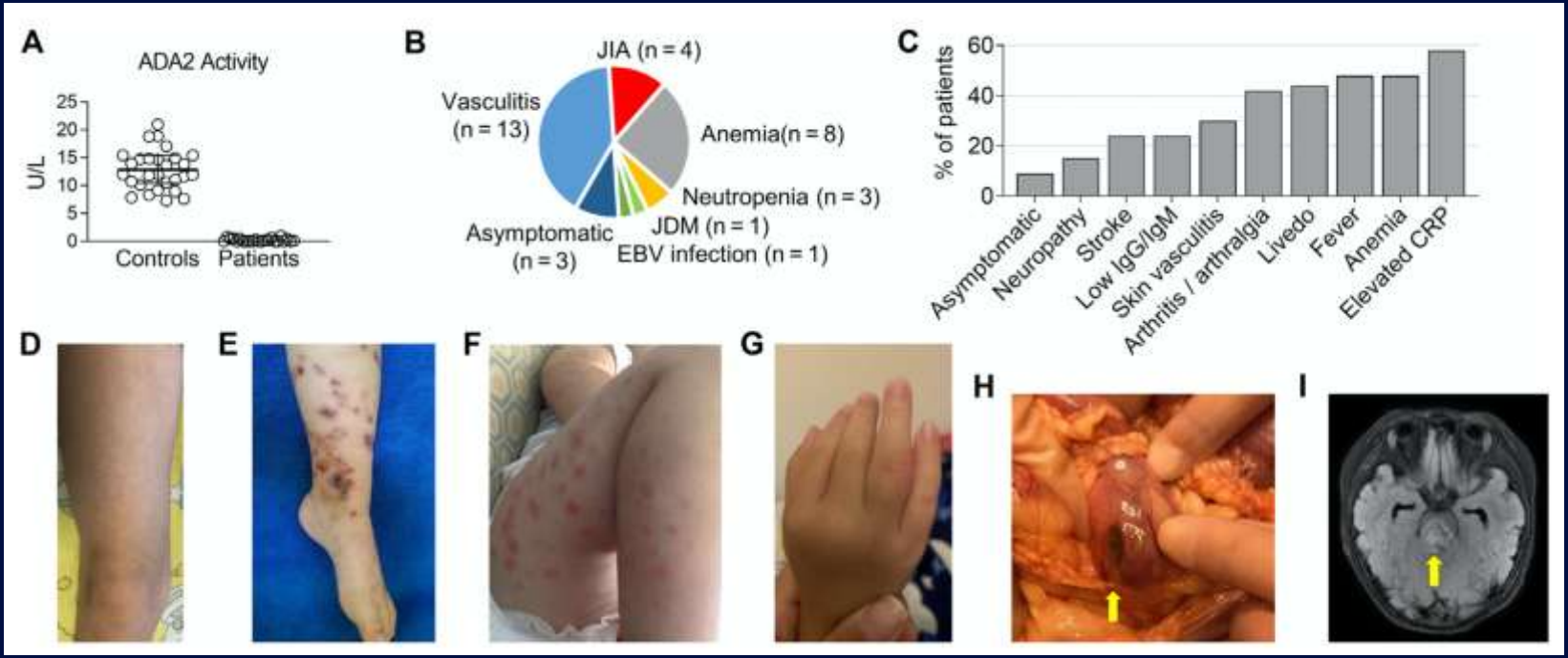
- **Cutaneous features are common**
  - **Evanescent MPs**
  - **Urticaria**
  - **Livedo**
  - **Oral ulcers**
  - **Chilblains**

Betrains Autoimmunity Rev 2021

Deficiency of Adenosine Deaminase 2 (DADA2) – When livedo is complicated….

- **Described in 2014 – Autosomal recessive**
- **PAN like disease – Livedo reticularis**
- **Risk of strokes reduced by TNFi**
- **Expected prevalence 1 per 222,000 based on carrier frequency = sequence patients with unexplained livedo**
- **ADA2 testing in patients with HBV negative PAN or cPAN**

Deficiency of Adenosine Deaminase 2 (DADA2)



Chen L J Allergy Clin Immunol 2023;152:771

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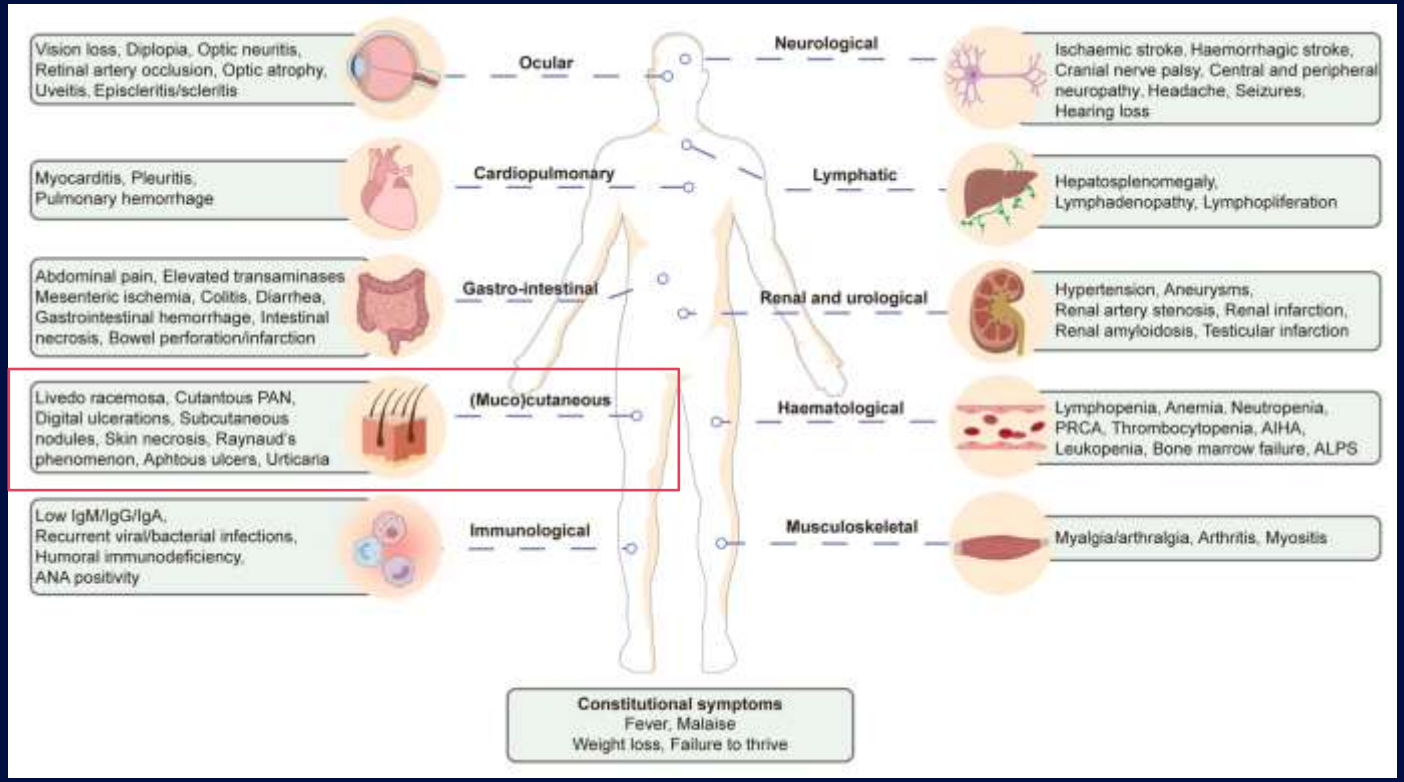

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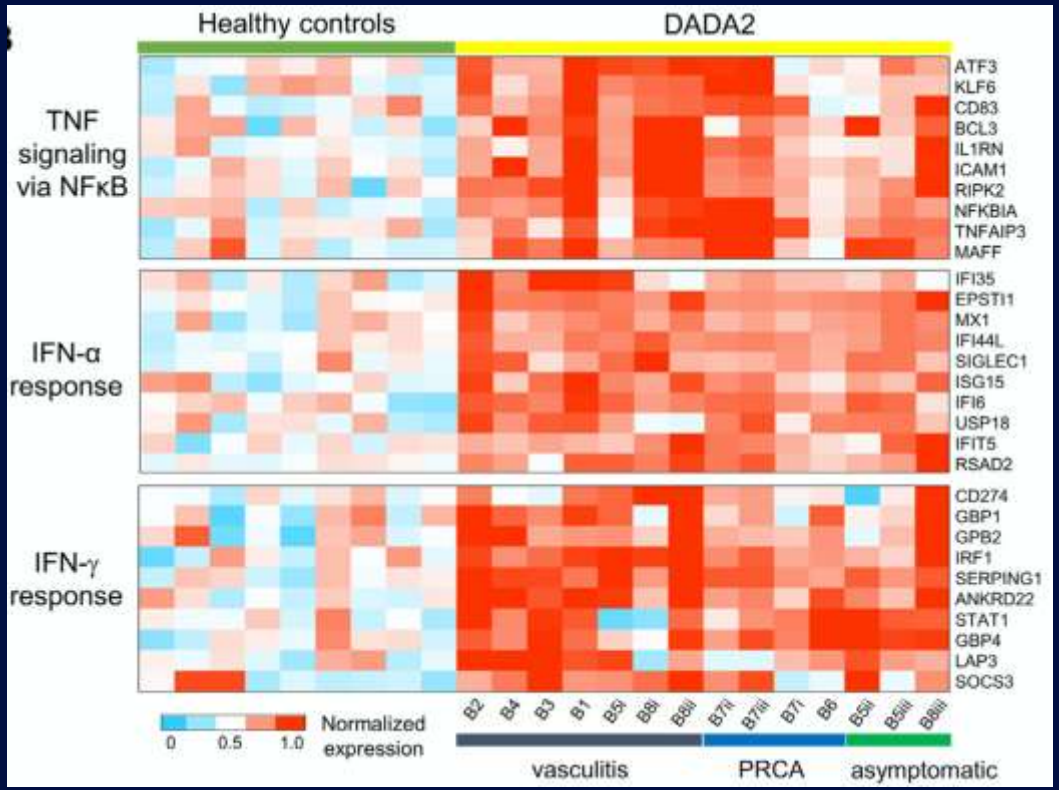

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When Behçet's Disease is not

- **Monogenic mimics of Behçet**
  - **UK study n=31 with suspected Behçet**
  - **Median onset age 5**
  - **29% had monogenic disease – Early onset, FHx, atypical presentation**
  - **HA20 – haploinsufficiency of TNFAIP3 is a common cause**

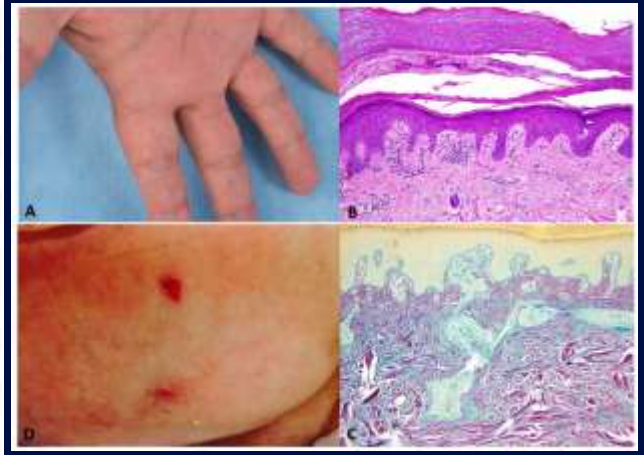
Burleigh A Rheumatology 2023

When Behçet's Disease is not

Table 1 Characteristics of patients with A20 haploinsufficiency

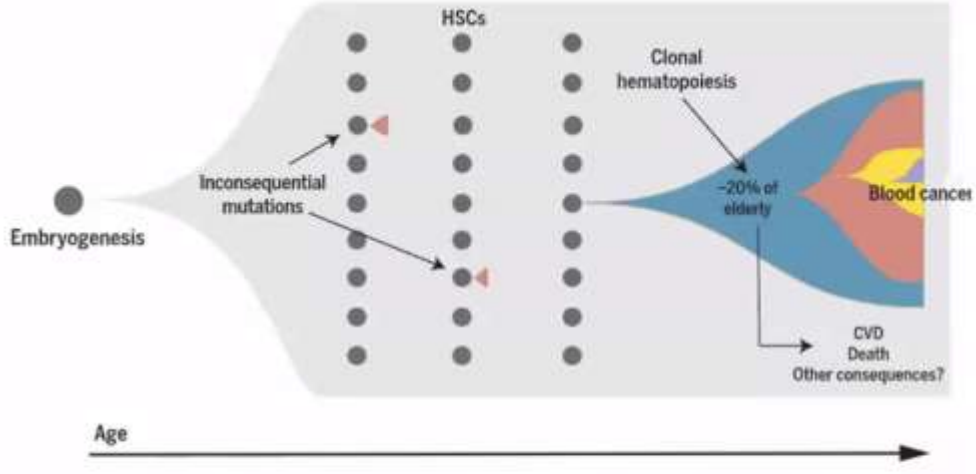
Patient no	Family	Sex	Current age	Age at onset	Previous diagnosis	Previous treatment	Current treatment
1	Family 1	F	25 years	10 months	JIA, Behçet disease	CS, MTX, CYS	MTX, thalidomide
2	Family 1	F	23 years	15 months	JIA, Behçet disease	CS, MTX, CYS, AZA, thalidomide, IVIG, ETN	IFX
3	Family 1	F	51 years	Early 20s	Rheumatoid arthritis (RF−), Behçet disease	None	Colchicine
4	Family 2	F	25 years	10 years	JIA, undifferentiated connective tissue disease/cutaneous vasculitis, SLE with CNS vasculitis	CS, MMF, ETN, thalidomide, RTX, IFX, MTX, ADA, cyclo, IVIG, autologous haematopoietic stem cell transplant	Anakinra, AZA, CS
5	Family 2	F	29 years	Around 8 years	Behçet disease, lupus nephritis	CS, colchicine, ETN, hydroxychloroquine	Anakinra
6	Family 2	F	51 years	Around 6 years	Rheumatic fever, arthritis	None	Anakinra
7	Family 2	F	56 years	Around 6 years		None	Anakinra
8	Family 3	M	9 years	9 months	Behçet disease	CS, colchicine, AZA	Colchicine
9	Family 3	M	46 years	?	Behçet disease		On treatment (not specified)
10	Family 4	F	15 years	8 weeks	Suspicion of PFAPA	CS, colchicine, ETN, anakinra, ADA, MTX	Tofacitinib
11	Family 5	F	17 years	Around 4 years	Suspicion of Behçet disease	CYS, dapsone, CS, AZA, IVIG for Ig deficiency	IFX
12	Family 5	F	47 years	Infancy	Suspicion of Behçet disease	CS, colchicine, AZA, IFX, IVIG for Ig deficiency	None
13	Family 6	F	38 years	29 years	Behçet disease	None	Colchicine
14	Family 6	F	19 years	15 years	Suspicion of Behçet disease	None	Colchicine
15	Family 6	F	15 years	13 years	Suspicion of Behçet disease	None	Colchicine
16	Family 7	M	(8 years)†	1 week	Crohn's disease, Behçet disease	CS, mesalamine, dapsone, MTX, AZA, colchicine, IFX, ADA, certolizumab, anakinra, canakinumab, tacrolimus, IVIG, tocilizumab	NA

ADA, adalimumab; AZA, azathioprine; CNS, central nervous system; CS, systemic corticosteroids; cyclo, cyclophosphamide; CYS, ciclosporin; ETN, etanercept; F, female; IFX, infliximab; IVIG, intravenous immunoglobulin; JIA, juvenile idiopathic arthritis; M, male; MTX, methotrexate; NA, not applicable; PFAPA, periodic fever, aphthous stomatitis, pharyngitis, adenitis; RF, rheumatoid factor; SLE, systemic lupus erythematosus.



Aeschlimann FA Ann Rheum Dis 2018

Acquired autoinflammatory disease



Somatic mutations, clonal hematopoiesis, and aging. Somatic mutations are acquired by all cells throughout life. Most are inconsequential, but rare mutations will lead to clonal expansion of hematopoieti stem cells (HSCs). If additional mutations are acquired, blood cancers may result. Emerging data also associate the presence of such clones with increased risk of cardiovascular disease (CVD) and death. Clonal hematopoiesis provides a glimpse into the process of mutation and selection that likely occurs in all somatic tissues.

S Jaiswal *Science* 2019

ORIGINAL ARTICLE

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

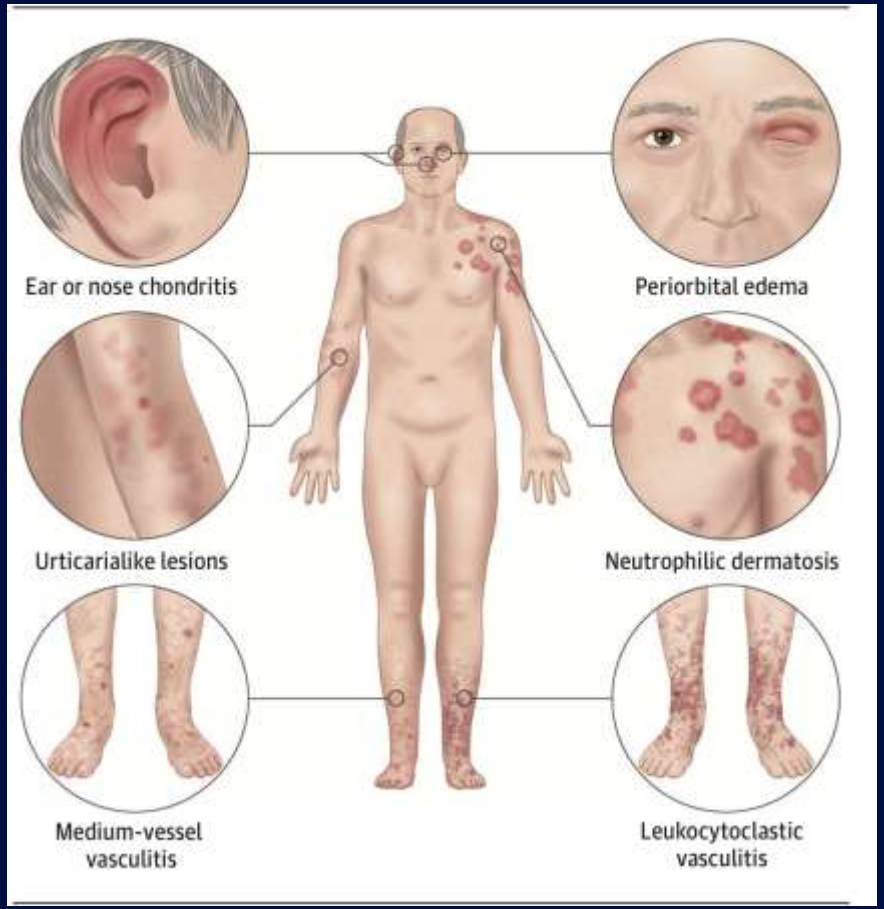
Beck D **N Engl J Med 2020;383:2628**

VEXAS – Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic

- **Skin involvement in common – 83% in 112 patients**
- **Skin is the most frequent presenting feature**
- **Histopathology**
  - **Leukocytoclastic vasculitis 36%**
  - **Neutrophilic dermatosis 34%**
  - **Perivascular dermatitis 30%**

Tan IJ, JAMA Dermatology 2024 160:822

VEXAS



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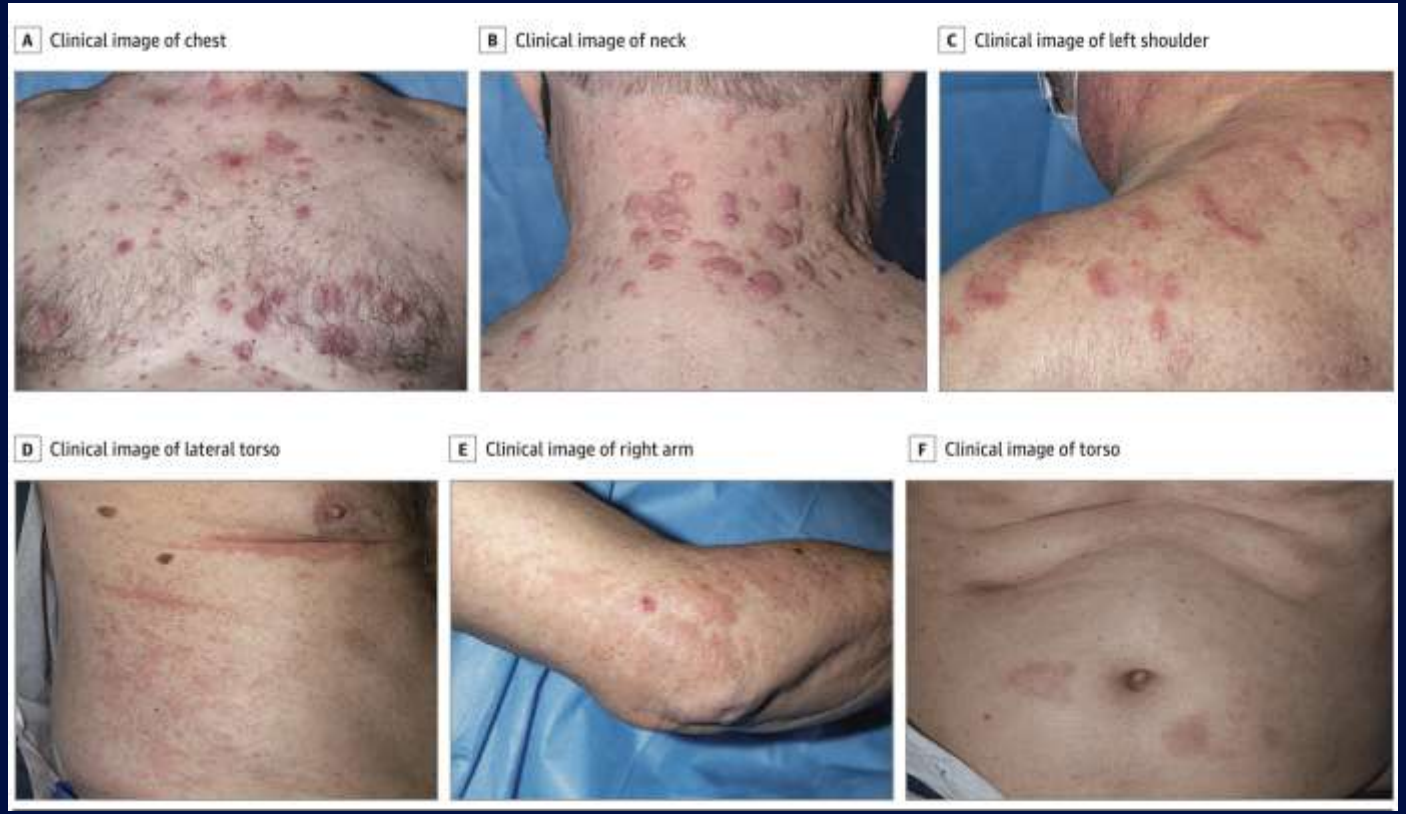

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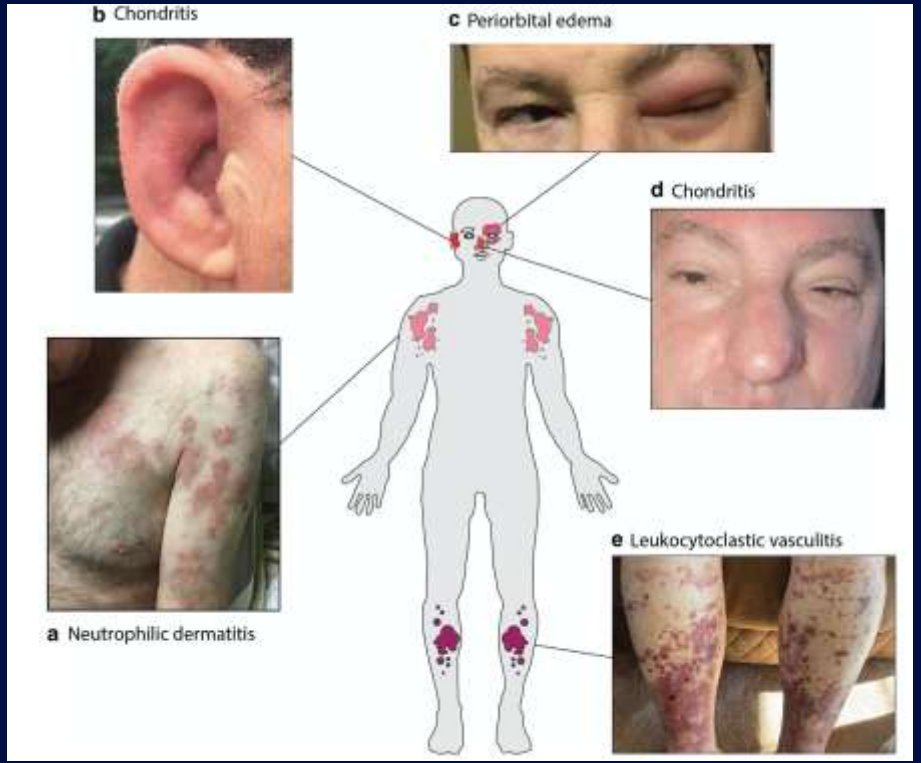
VEXAS – Clues to diagnosis

- **Morphology: Chondritis, Sweet's like, vasculitis in combination**
- **Demography: Elderly males**
- **Systemic disease: Association with cytopenias**
- **Injection site reactions**

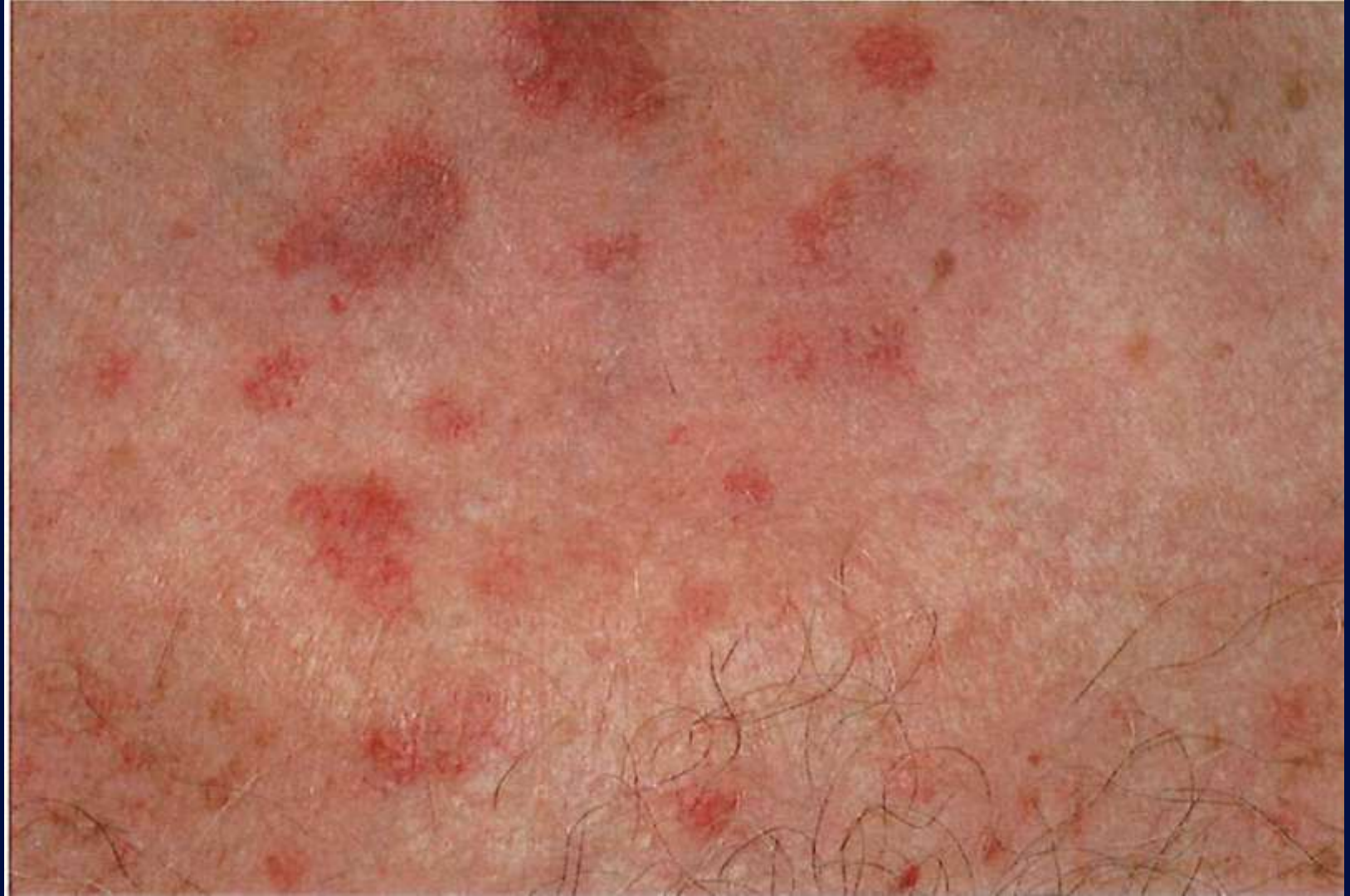


Nicholson LT JID Innovations 2024 4:100242

Case – Presented at RDS 2019

- **July 2011 72M**

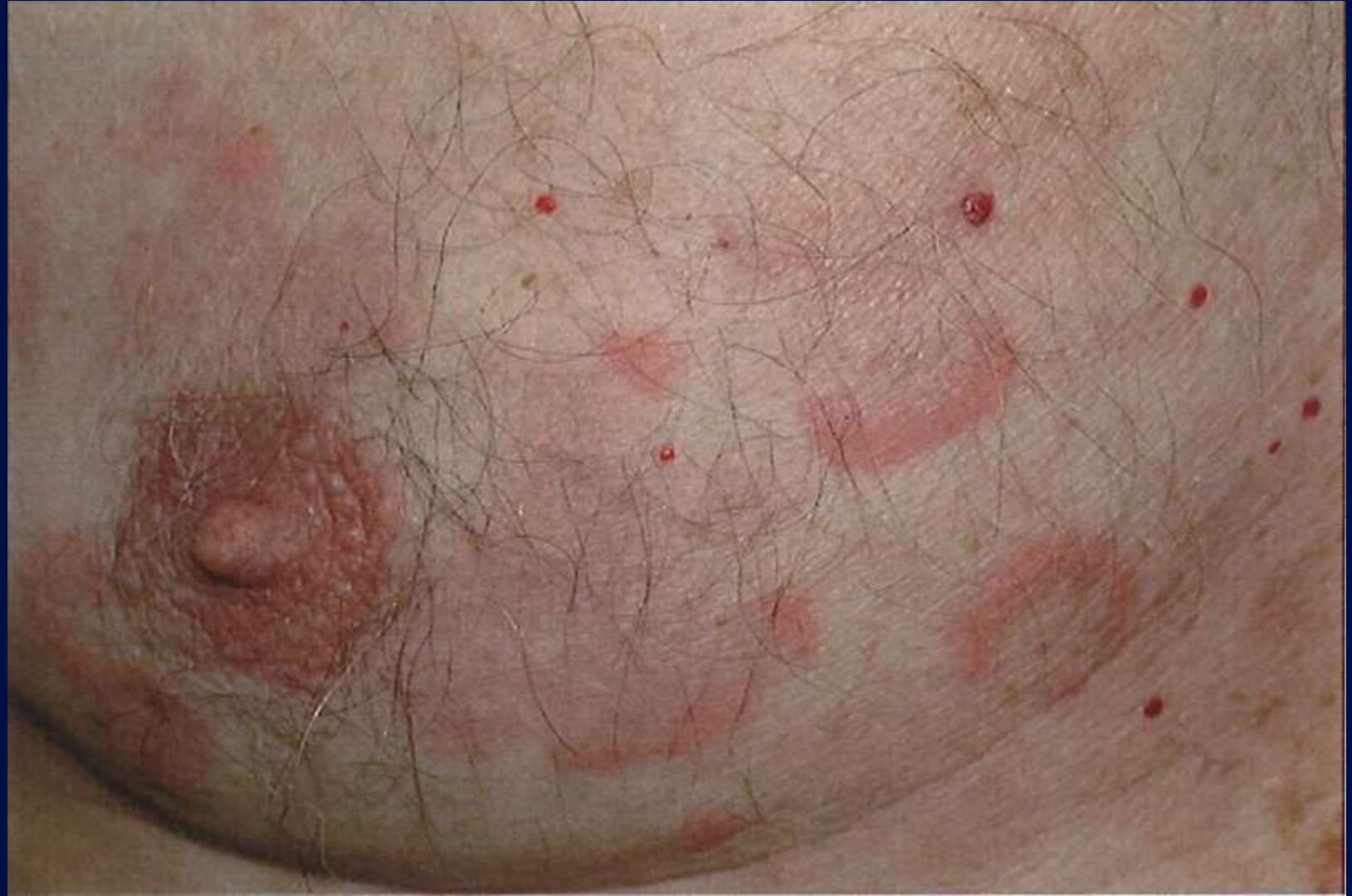
- **1 year history of polycyclic eruption to face chest back and arms**
- **Worsened by sun exposure**
- **Lab ESR 82mm Ferritin 560 p-ANCA mild + CRP 51**
- **Skin Bx – Sup + deep perivasc ly infiltrate + atypia**
- **RX - Predn 15 – 7.5, HQ 400**



Case

- Jan 2012 (6 month after presentation)
- Ongoing arthralgias to wrists and elbows

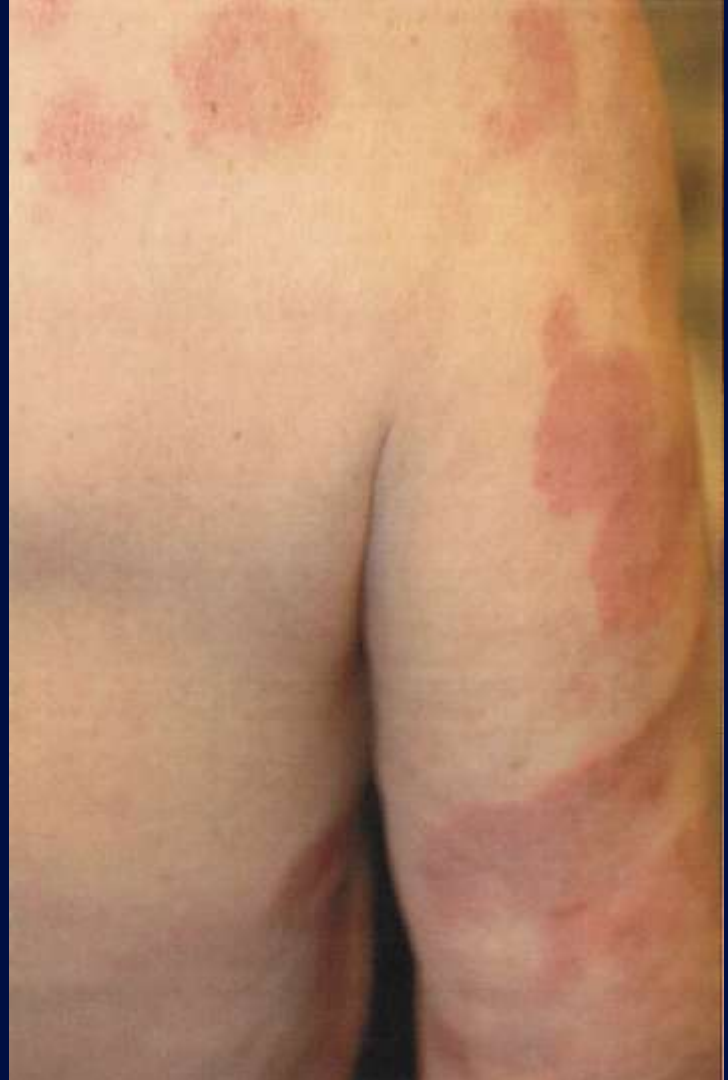
- Bx – sup + deep perivasc infiltrate DDX Tumid LE, Jessner, Viral
- Impr – Tumid LE with failure of HQ
- RX - MTX



Case

- Oct 2013 (12 month after presentation)
- Ongoing low grade fevers (39 C)

- BX – Neutrophilic dermal infiltrate c/w Sweet S
- Lab – CRP 139 Ferritin elevated
- IMPR – Atypical SS or AOSD
- RX – Pred 40 mg + MMF



Case

- **Mar 2014 (18 month after presentation)**
- **Recurrent fevers – failure of anakinra**

- **Lab – Pancytopenia (transfusion, BM normal)**
  Increased IL-6 Ferritin 1596
- **IMPR – Atypical AOSD**
- **RX – Tocilizumab 8 mg/kg q 4 weeks**

= excellent control x 4 yrs, recurrence upon taper

Sweet Syndrome – AOSD or other?

- **Sweet Syndrome – hyperferritinemia *not* described**
- **AOSD – Persistent skin lesions uncommon – arcuate plaques *not* described**
- **Auto inflammatory disease – TRAPS MWS – do not usually present in 70s**

Sweet Syndrome – AOSD or other?

- **Sweet Syndrome – hyperferritinemia *not* described**
- **AOSD – Persistent skin lesions uncommon – arcuate plaques *not* described**
- **Auto inflammatory disease – TRAPS MWS – do not usually present in 70s**

VEXAS

Sweet Syndrome – AOSD or other?

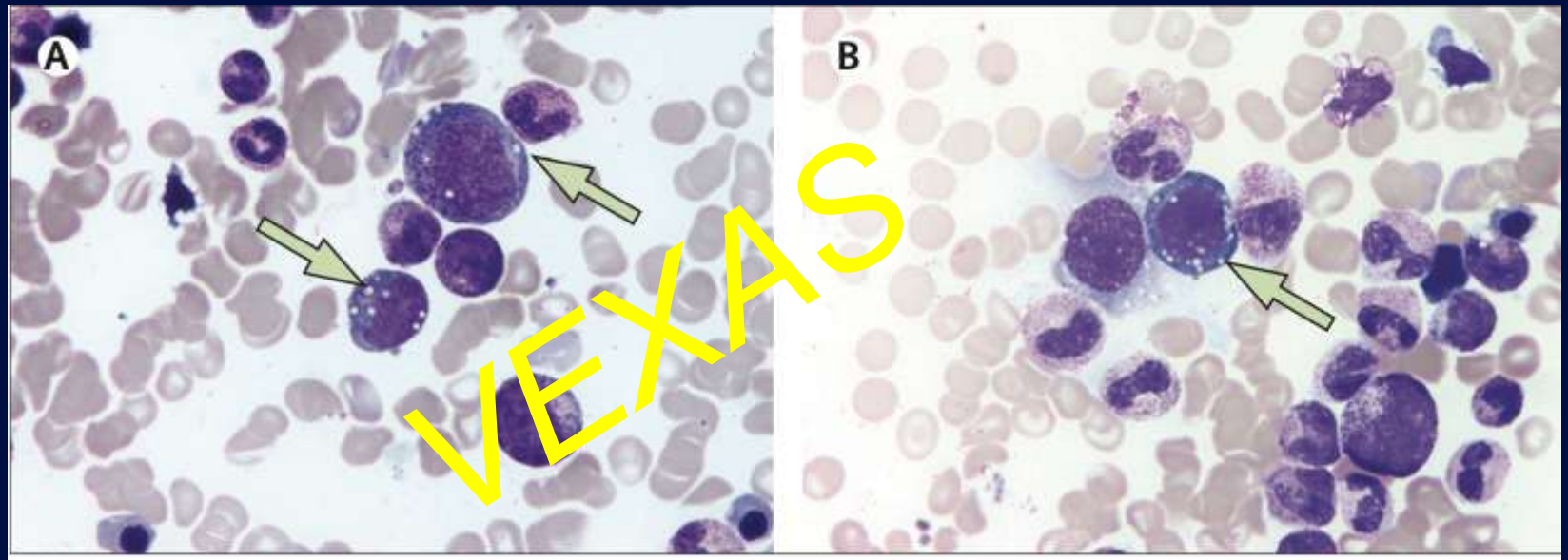


Figure: **Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome**
Bone marrow aspirate shows vacuolation in granulocyte precursors (A) and a proerythroblast cell (B; arrows; Wright-Giemsa stain). Original magnification ×100.

Dehghan N Lancet 2021; 398:261

Auto-inflammation – Take home

- Autoinflammatory diseases are rare – but not so rare

- Maintain a high index of suspicion if
  - Fevers or high CRP
  - Multi generational immunologic disease

Auto-inflammation – Take home

- Cellphone camera to document inflammatory episodes
- Test repeatedly: CBC, CRP, ferritin, D-dimer
- Ask about family history
- Consider if interstitial neutrophils on biopsy
- Consider if unusual vasculitis/vasculopathy
- Proceed with genetic testing

1	Suspect autoinflammation	• Fever, rash, or unexplained multisystem inflammation • Early age of onset • Consanguinity or family history
2	Pattern recognition	• Pattern/duration of fever • Ethnicity • Inheritance pattern • Suggestive features: rash, vasculitis, conjunctivitis, CNS calcifications, stroke, lung disease, colitis • Expert consultation
3	Testing	• Directed gene sequencing • NGS panels for AID/PID • Cytokines, other (CXCL9, ADA2) • Whole-exome/genome sequencing • Interferon signature genes • Functional studies
4	Treatment (Targeted/Empiric)	• NSAIDs (low diagnostic value) • Corticosteroids (limited diagnostic value) • Colchicine • IL-1 blockade • TNF inhibition • IFN inhibition (JAKinibs)

Nigrovic J Allergy Clin Immunol 2020;146:925

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