Fever of Unknown Origin (from the Rheumatology Perspective)

August 11, 2025

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Land Acknowledgement

I acknowledge that the land on which we gather is the traditional and unceded territory of the Coast Salish Peoples, including the Musqueam, Squamish, and Tsleil-Waututh Nations.

Objectives

1) Outline the (common) rheumatologic causes of fever of unknown origin.

2) Identify potential diagnostic clues through a thorough history & physical exam.

3) Choose clue-directed investigations to avoid excessive testing (when possible).

And eventually…

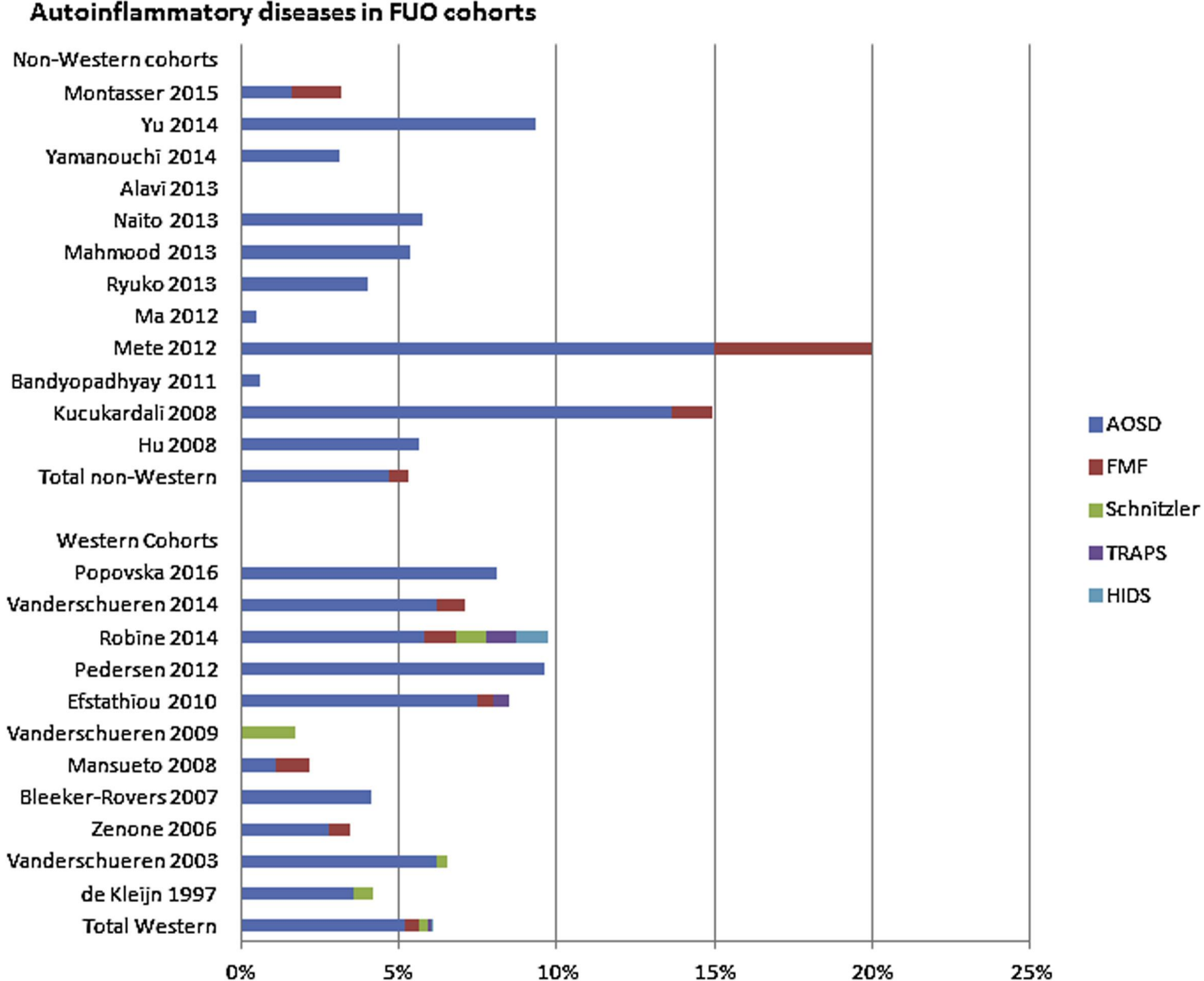
4) Evaluate a patient with fever of unknown origin for rheumatologic aetiologies.

Fever of Unknown Origin

- Definition:
  - Fever ≥38.3 °C (≥101 °F) on ≥3 occasions
  - Duration of illness ≥3 weeks
  - No diagnosis despite extensive evaluation
- Clinical Significance:
  - The search for a diagnosis is often resource intensive
  - Delayed diagnoses contribute to significant patient morbidity
- Role of Rheumatology:
  - Proportion of patients with FUO diagnosed with a rheumatic disorder:
  - Higher in high-income countries vs. lower-middle and upper-middle income countries (per one meta-analysis: 25.8% [95% CI 21.2 – 30.9%] versus 19.8% [95% CI 17.0 – 22.8%])

Overview of Rheumatologic Diseases

- Rheumatoid Arthritis
- Spondyloarthritis (PEAR)
  - Psoriatic arthritis
  - Enteropathic arthritis
  - Ankylosing spondylitis
  - Reactive arthritis
- Connective Tissue Disease
  - Systemic lupus erythematosus
  - Sjögren's syndrome
  - Scleroderma
  - Inflammatory myositis
  - Mixed connective tissue disease
- Vasculitis
  - Large: Giant cell arteritis (Polymyalgia rheumatica), Takayasu arteritis
  - Medium: Polyarteritis nodosa, Kawasaki disease
  - Small: ANCA-associated, Immune complex-mediated
- Crystal Arthropathy
  - Gout
  - Pseudogout
- Autoinflammatory Diseases: adult-onset Still's disease, other rare stuff
- Other: sarcoidosis, IgG4-related disease, etc.


Autoinflammatory diseases in FUO cohorts
Non-Western cohorts
Montasser 2015
Yu 2014
Yamanouchi 2014
Alavi 2013
Naito 2013
Mahmood 2013
Ryuko 2013
Ma 2012
Mete 2012
Bandyopadhyay 2011
Kucukardali 2008
Hu 2008
Total non-Western
Western Cohorts
Popovska 2016
Vanderschueren 2014
Robine 2014
Pedersen 2012
Efstathiou 2010
Vanderschueren 2009
Mansueto 2008
Bleeker-Rovers 2007
Zenone 2006
Vanderschueren 2003
de Kleijn 1997
Total Western
0%
5%
10%
15%
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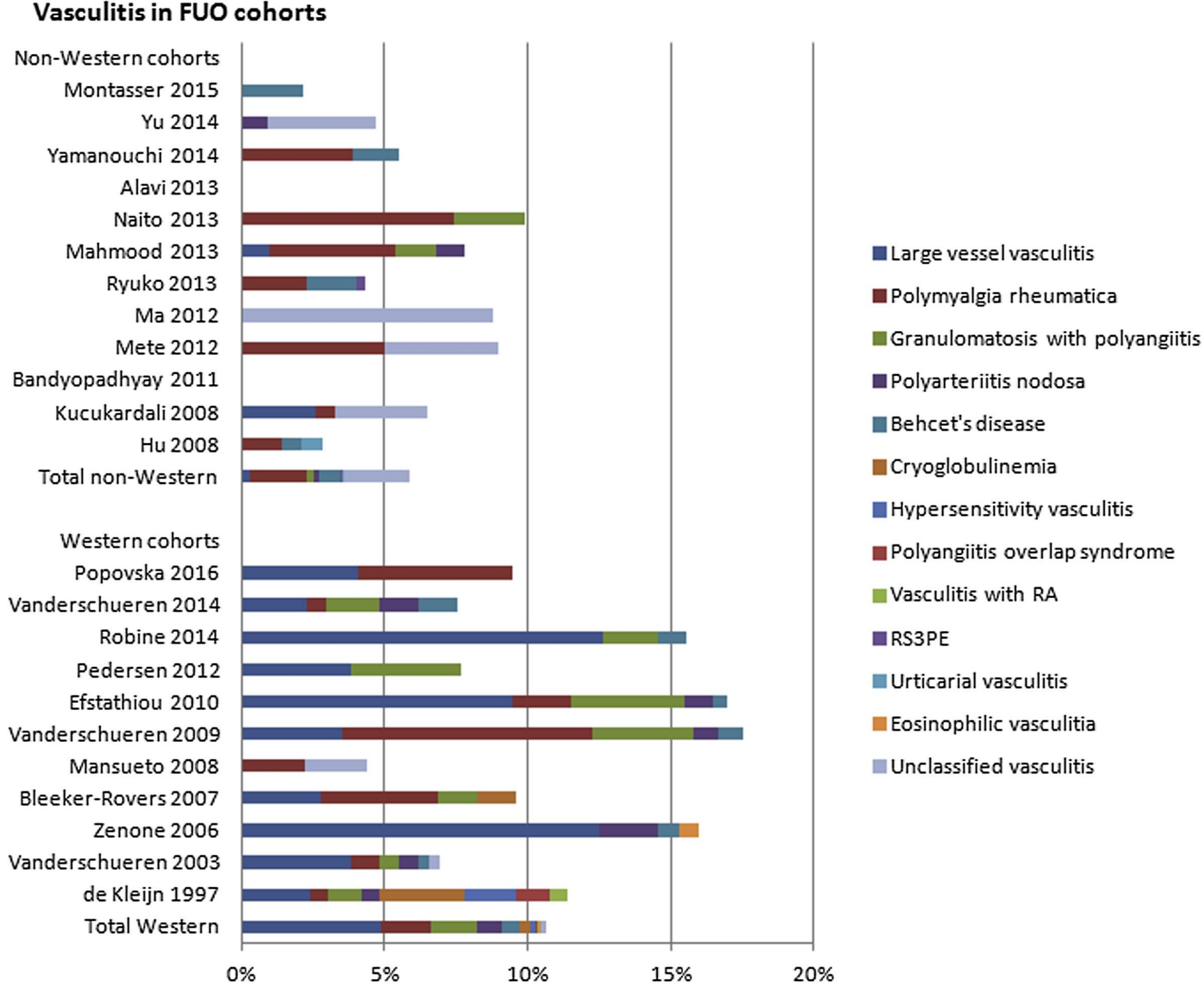
25%
AOSD
FMF
Schnitzler
TRAPS
HIDS


Vasculitis in FUO cohorts
Non-Western cohorts
Montasser 2015
Yu 2014
Yamanouchi 2014
Alavi 2013
Naito 2013
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Ryuko 2013
Ma 2012
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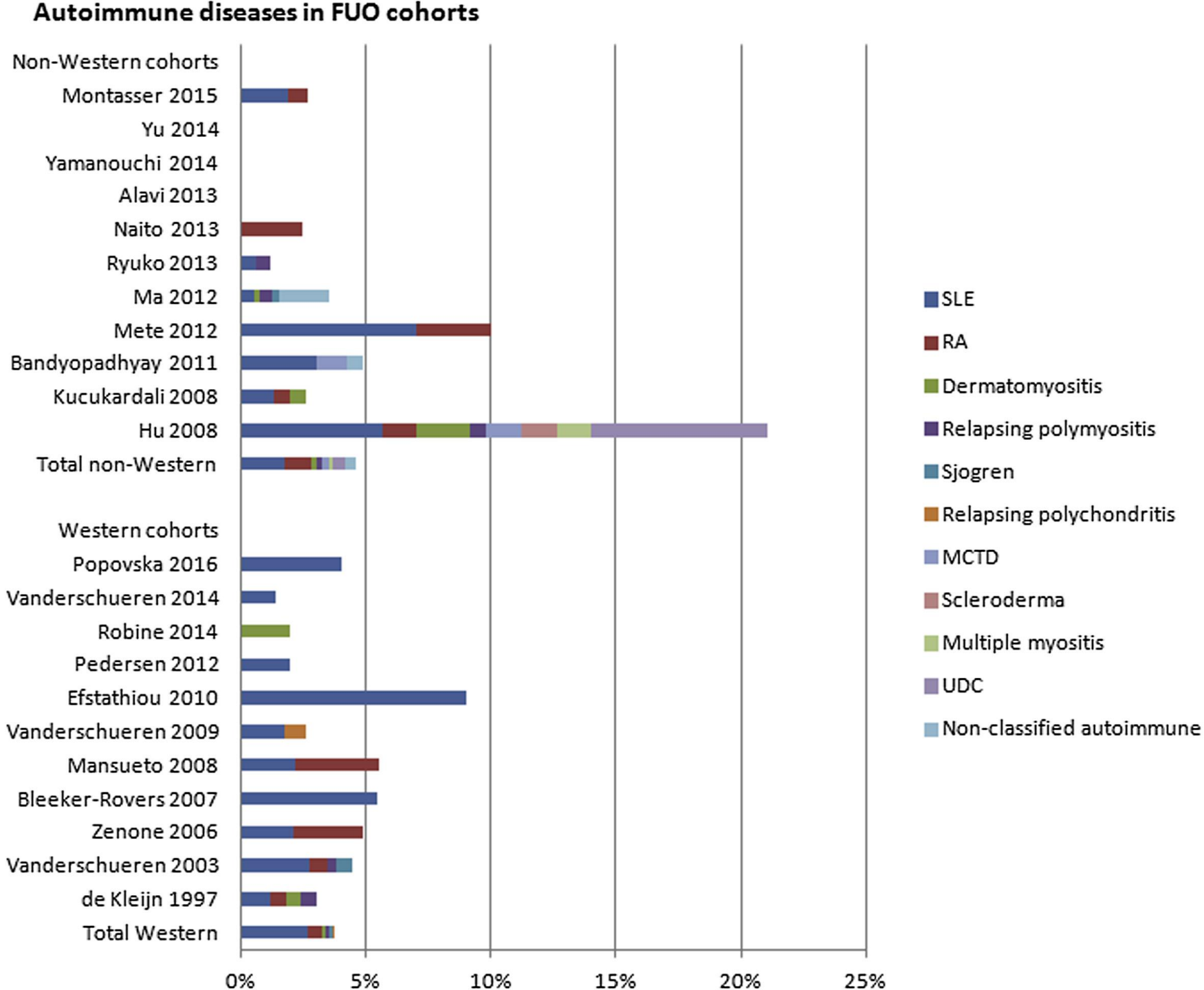
Mansueto 2008
Bleeker-Rovers 2007
Zenone 2006
Vanderschueren 2003
de Kleijn 1997
Total Western
0%
5%
10%
15%
20%
Large vessel vasculitis
Polymyalgia rheumatica
Granulomatosis with polyangiitis
Polyarteriitis nodosa
Behcet's disease
Cryoglobulinemia
Hypersensitivity vasculitis
Polyangiitis overlap syndrome
Vasculitis with RA
RS3PE
Urticarial vasculitis
Eosinophilic vasculitia
Unclassified vasculitis


Autoimmune diseases in FUO cohorts
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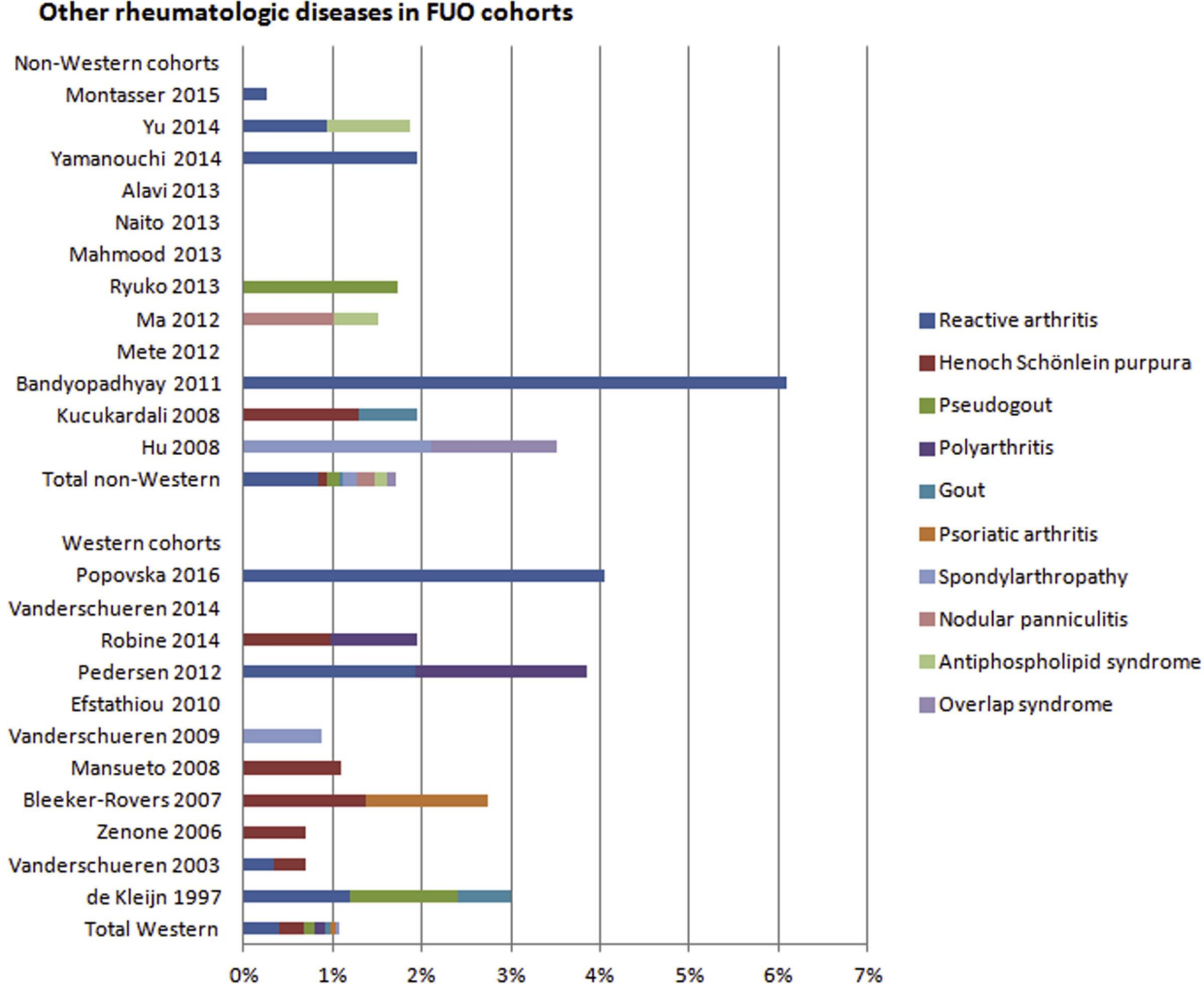
Kucukardali 2008
Hu 2008
Total non-Western
Western cohorts
Popovska 2016
Vanderschueren 2014
Robine 2014
Pedersen 2012
Efstathiou 2010
Vanderschueren 2009
Mansueto 2008
Bleeker-Rovers 2007
Zenone 2006
Vanderschueren 2003
de Kleijn 1997
Total Western
0%
5%
10%
15%
20%
25%
SLE
RA
Dermatomyositis
Relapsing polymyositis
Sjogren
Relapsing polychondritis
MCTD
Scleroderma
Multiple myositis
UDC
Non-classified autoimmune


Other rheumatologic diseases in FUO cohorts
Non-Western cohorts
Montasser 2015
Yu 2014
Yamanouchi 2014
Alavi 2013
Naito 2013
Mahmood 2013
Ryuko 2013
Ma 2012
Mete 2012
Bandyopadhyay 2011
Kucukardali 2008
Hu 2008
Total non-Western
Western cohorts
Popovska 2016
Vanderschueren 2014
Robine 2014
Pedersen 2012
Efstathiou 2010
Vanderschueren 2009
Mansueto 2008
Bleeker-Rovers 2007
Zenone 2006
Vanderschueren 2003
de Kleijn 1997
Total Western
0%
1%
2%
3%
4%
5%
6%
7%
Reactive arthritis
Henoch Schönlein purpura
Pseudogout
Polyarthritis
Gout
Psoriatic arthritis
Spondylarthropathy
Nodular panniculitis
Antiphospholipid syndrome
Overlap syndrome

When to Suspect a Rheumatic Disease

- Joint pain, especially if there is synovitis on physical exam
- Skin rash (esp. urticaria)
- Longer symptom duration
- Family history of rheumatic disorders
- Persistently elevated inflammatory markers
- Clinical syndrome c/w a rheumatologic disease
- Chills and rigors point more towards an infectious cause
- Early anorexia and significant weight loss raise suspicion for malignancy

Workup for Rheumatic Diseases

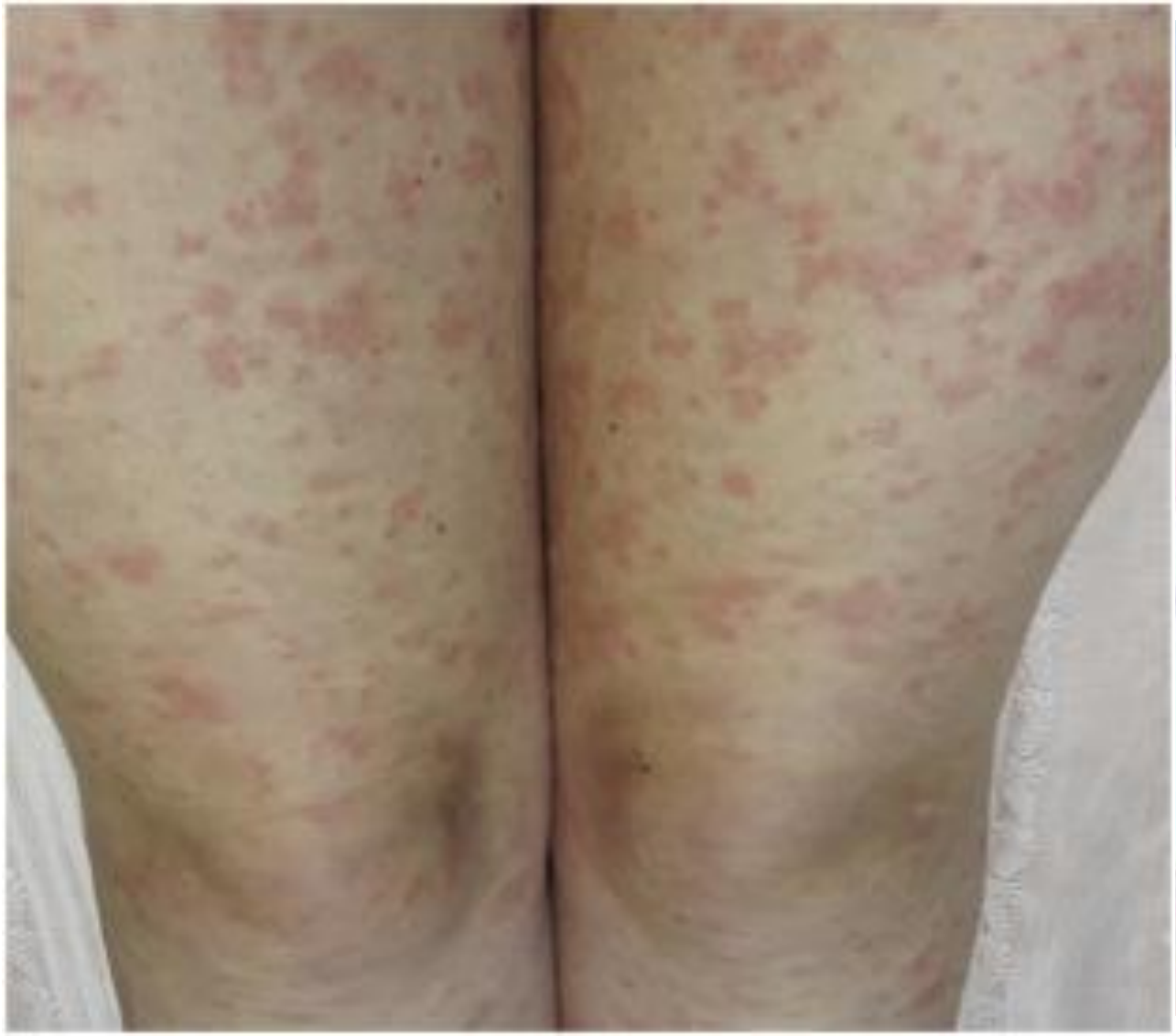
- Blood work: ANA +/- ENA, dsDNA, RF, CCP, ANCA, C3/C4, SPEP, SFLC, IgA/IgG/IgM, cryoglobulins, CRP, ferritin, sIL2R
- Urine studies: Urinalysis, uACR/uPCR
- Imaging: US abdomen, CT chest/abdomen/pelvis, CTA head/chest/abdomen/pelvis, US temporal artery, echocardiogram, PET scan
- BIOPSY: Skin, kidney, liver, lungs, etc. guided by history and physical exam*
- *In elderly patients, random temporal artery biopsy can be considered

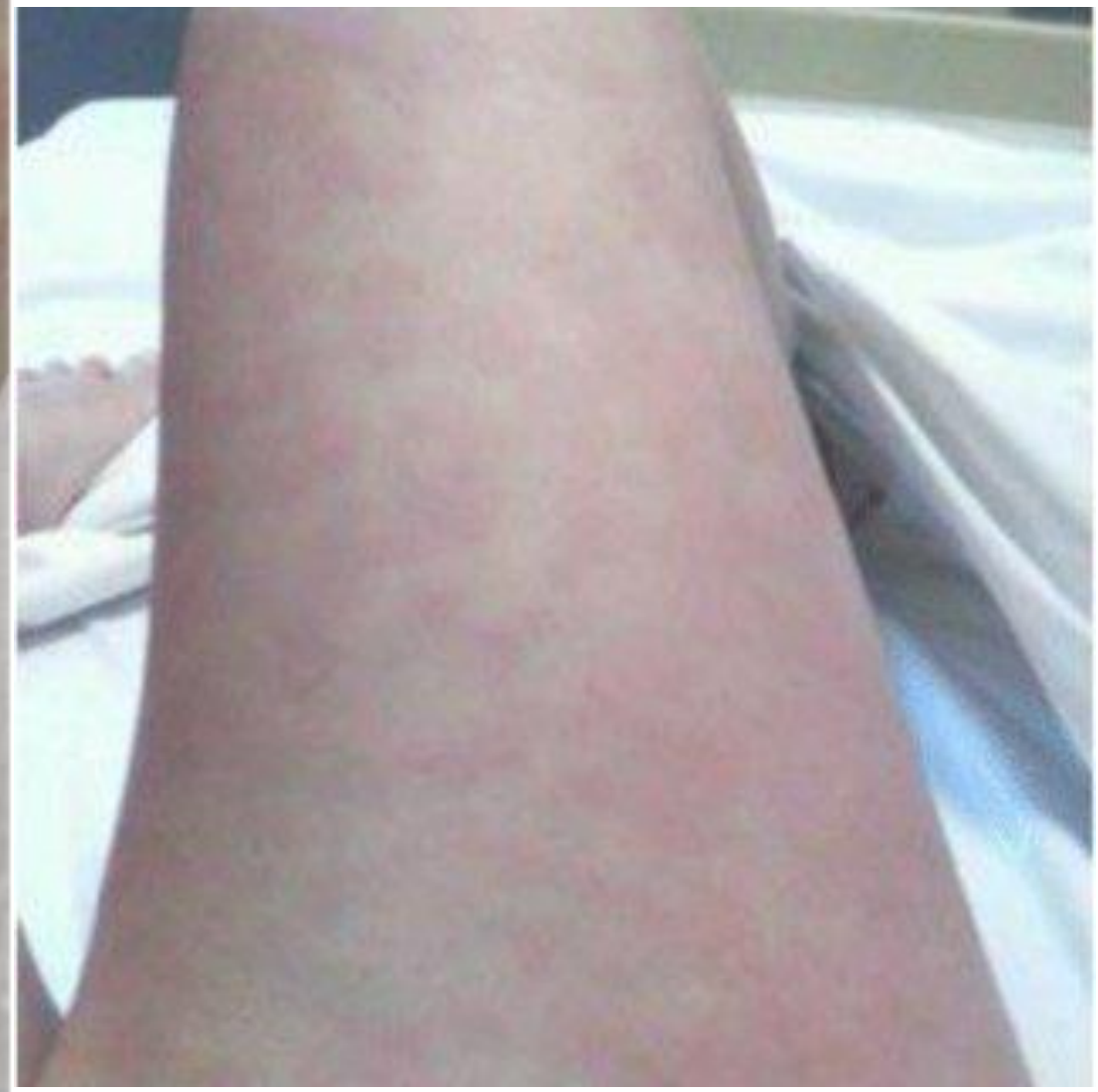
Case #1

41F G2A1 with BMI 42.6 s/p gastric sleeve surgery 2021, type 2 diabetes, polycystic ovarian syndrome, and hypertension. Developed progressive myalgias, arthralgias, and rash within 5-6 hours of receiving the COVID and Influenza vaccines at 24 wks gestation. Presented to hospital 1 wk later due to concerns about reduced fetal movement. Febrile at 38.4 *C on presentation with sore throat.

Preliminary investigations notable for neutrophilic leukocytosis, microcytic anemia, mixed liver enzyme elevation, CRP >200, and ferritin >5000s. Normal renal function. Negative infectious workup and CTPA.

While in hospital, she had no further fevers on acetaminophen 4 g/day, and her rash improved. However, she then developed pericarditis (classic chest pain, diffuse STE, elevated troponin), and her myalgias and arthralgias progressed, with synovitis on physical exam.





Case #1

Further investigations notable for negative ANA, CCP, ANCA, HLA-B27; RF 21 (borderline positive). Upper airway endoscopy showed generalized inflammation from her nasal cavities to her vocal cords. SIL2R later returned elevated at 1000.

Her chest pain resolved with colchicine. She was started empirically on prednisone with modest improvement in her arthralgias, myalgias, and sore throat, but still required regular acetaminophen and opioids for symptom management. Her rash mostly resolved, with a transient patch here and there.

What do you think is going on? Are there any additional investigations you would like?

Skin biopsy showed scattered dyskeratotic keratinocytes involving the upper layer of the epidermis.

What is the diagnosis?

Adult-Onset Still's Disease

- Systemic inflammatory disorder characterized by inflammatory polyarthritis, daily fever, and a transient salmon-pink maculopapular rash.
- Often associated with ferritin >1000 ug/L, CRP >100 mg/L, and elevated sIL2R
- Clinical course can be monophasic, intermittent, or chronic
- May be triggered by infection and vaccines
- Treatment involves NSAIDs, steroids, and anakinra

Major criteria	Minor criteria
Temperature of > 39°C for > 1 wk	Sore throat
Leukocytosis > 10 000/mm^3	Lymph node enlargement
Typical rash	Splenomegaly
Arthralgias > 2 wk	High transaminases
	Negative ANA, RF

Case #2

70F with history of bronchitis and osteoarthritis admitted with 1 month of fever of unknown origin, not responsive to multiple courses of antibiotics. Rheumatology consulted 2 weeks into admission as workup negative for infection and malignancy.

Review of systems was notable for double quotidian fever >39 *C, general malaise, drenching night sweats, intermittent nausea, and arthralgias in knees. FamHx of sarcoidosis in sister and nephew.

Workup to date was notable for negative ANA, normal ACE, neutrophilic leukocytosis, microcytic anemia, reactive thrombocytosis, and cholestatic liver enzyme elevation. CRP >200, ferritin ~500. Pan-CT scan showed centrilobular and tree-in-bud nodules within right middle lobe and lingula; no intra-abdominal abnormality. Bone marrow biopsy, bronchoscopy, lumbar puncture, and echocardiogram all unremarkable.

What investigations would you recommend next?

Case #2

CTA Head/Chest/Abdomen/Pelvis showed no evidence of vasculitis.

PET scan showed low-grade inflammatory changes in RML and lingula along with low-to-moderate grade inflammatory/reactive lymphadenopathy within bilateral axilla, bilateral hila and mediastinum.

Additional autoimmune workup showed strongly positive RF and MPO with negative PR3, CCP, GBM.

While awaiting the results of the above investigations, patient develops new thigh pain, worsening liver enzyme elevation, and new acute kidney injury. She continues to have daily fevers and elevated inflammatory markers.

What would you do now?

Case #2

Liver biopsy showed fibrinoid/necrotizing granulomatous vasculitis involving portal tract arteries. Background liver showing portal fibrosis (stage 1/4).

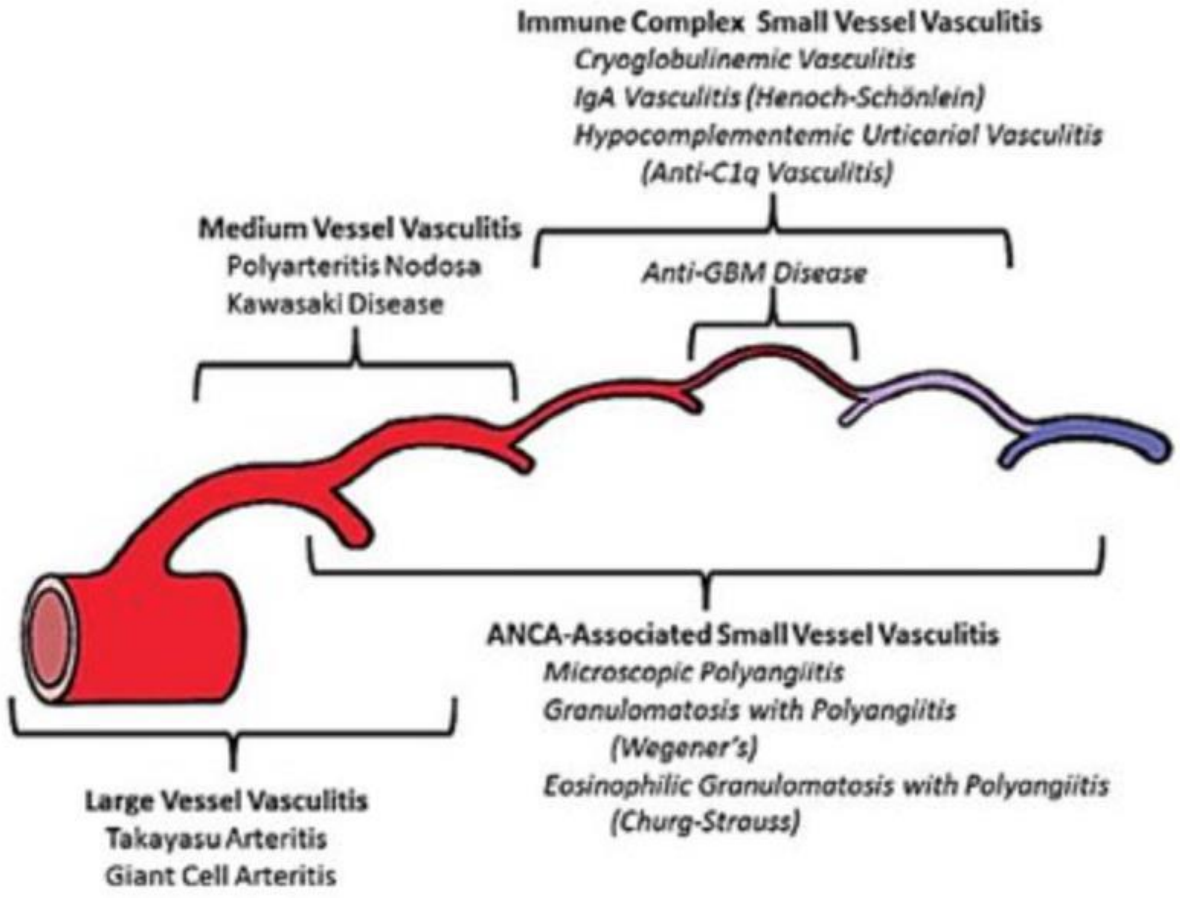
MRI thighs showed widespread symmetrical muscle and fascial edema/thickening suggestive of inflammatory myositis/fasciitis. Left vastus lateralis biopsy showed fulminant vasculitis.

Renal biopsy showed pauci-immune glomerulonephritis with focal crescent/necrosis and fibrinoid/necrotizing vasculitis of the extraglomerular arteries.

Vasculitis

- **Vasculitis** = **inflammation of blood vessel(s)** – consider consequences of LOCAL and SYSTEMIC inflammation
- Consequences of LOCAL inflammation include…
  1. **Lumen narrowing/stenosis** = ISCHEMIA/CLAUDICATION
  2. **Vessel wall damage** = ANEURYSMS, DISSECTIONS
- Consequences of SYSTEMIC inflammation include…
  1. **Constitutional symptoms** (fevers, weight loss, night sweats)
  2. **Arthralgias** or arthritis, **myalgias**
  3. **Clots** (i.e. venous thromboembolism)

Vasculitis Classification



Vasculitis Classification Continued

Cutaneous SOV (not included in CHCC2012)
- IgM/IgG vasculitis
- Nodular vasculitis (erythema induratum of Bazin)
- Erythema elevatum et diutinum
- Hypergammaglobulinemic macular vasculitis
- Normocomplementemic urticarial vasculitis

Variable vessel vasculitis (VVV)
- Behçet's disease (BD)
- Cogan's syndrome (CS)

Single-organ vasculitis (SOV)
- Cutaneous leukocytoclastic angiitis
- Cutaneous arteritis
- Primary central nervous system vasculitis
- Isolated aortitis
- Others

Vasculitis associated with systemic disease
- Lupus vasculitis
- Rheumatoid vasculitis
- Sarcoid vasculitis
- Others

Vasculitis associated with probable etiology
- Hepatitis C virus–associated cryoglobulinemic vasculitis
- Hepatitis B virus–associated vasculitis
- Syphilis-associated aortitis
- Drug-associated immune complex vasculitis
- Drug-associated ANCA-associated vasculitis
- Cancer-associated vasculitis
- Others

Bonus Case:

19M, Indian, previously healthy, referred to hospital by outpatient Internist for several months of constitutional symptoms, including 1 month of daily fevers (≥39 *C), small joint arthralgias, oral ulcers, and non-resolving cough. There was no improvement with multiple courses of antibiotics and antivirals. Infectious workup was negative.

Physical exam showed synovitis at the bilateral elbows, wrists, finger PIPs, and ankles (L > R). He also had a 2-cm right anterior cervical chain lymph node.

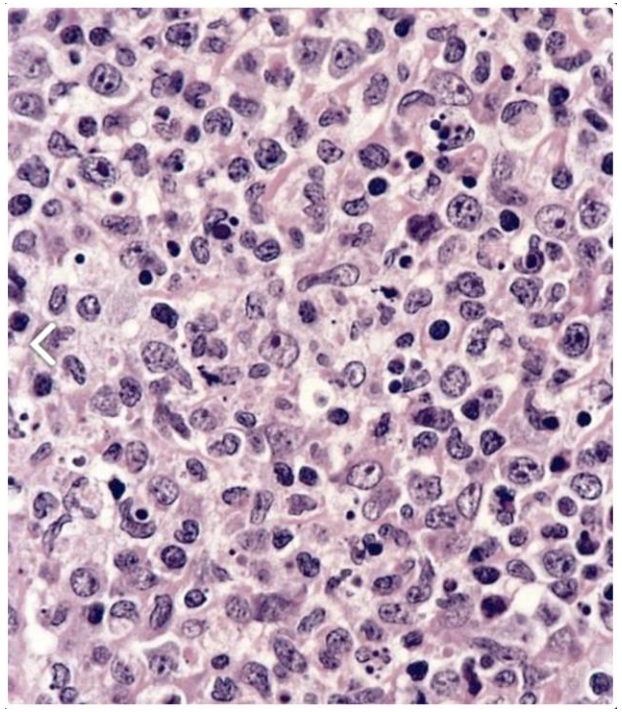
Autoimmune workup showed ANA 1.0 (N <0.7), dsDNA 10.0 (N <10.0), normal C3/C4, and negative ANCA, RF, and CCP.

If you had to choose one additional investigation, what would you do?

Bonus Case:

Lymph node biopsy showed florid follicular hyperplasia with **scattered foci of apoptosis and necrosis** admixed with histiocytes and lymphocytes, but no neutrophils.

What is the diagnosis?



Kikuchi-Fujimoto Disease

- AKA histiocytic necrotizing lymphadenitis
- Rare, self-limiting inflammatory condition primarily affecting young or pediatric patients of Asian descent
- Acute to subacute presentation characterized by painful, tender, mobile cervical lymphadenopathy associated with systemic symptoms, including fevers, malaise, weight loss, arthralgias, and various skin manifestations
- Treatment is primarily supportive, with corticosteroids and immunosuppression reserved for cases of severe or recurrent disease

Clinical Pearls

1) Patients are more likely to have an uncommon presentation of a common disease than a rare disease.

2) Allow diagnostic clues to guide your investigation; sometimes, time can also be a useful diagnostic tool.

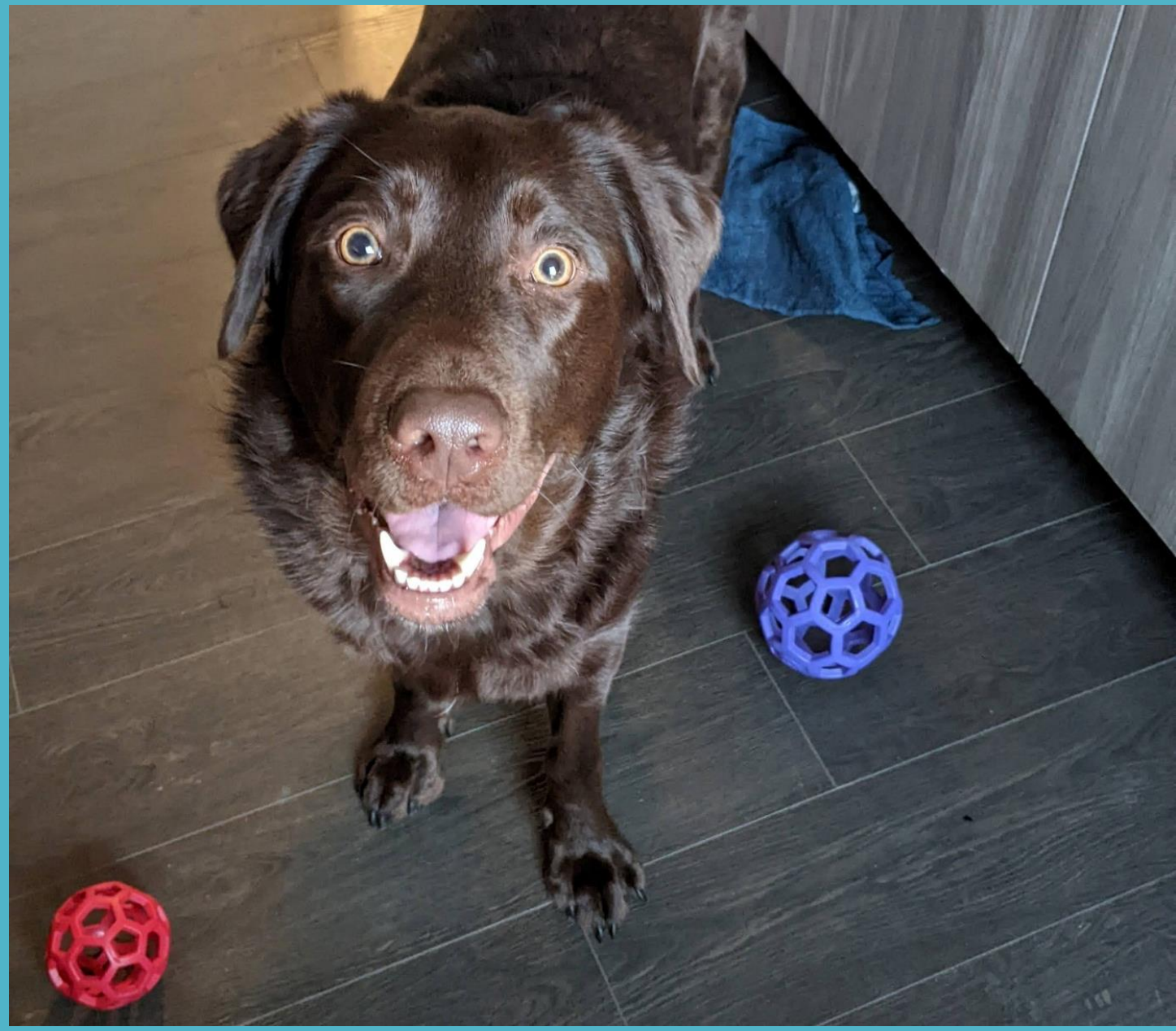
3) Treatment with anti-inflammatory drugs should be postponed as much as possible in patients in whom no diagnosis has been made yet, as it may mask important clinical features.

- Exception: If there is concern for cranial GCA (especially vision changes), start empiric steroids right away and arrange for temporal artery biopsy as soon as possible

4) When in doubt, consult your friendly neighbourhood rheumatologist!

Thank you for your attention!

Please feel free to ask questions ☺



References

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