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Aortitis, a Serious Diagnosis with Rare Etiologies

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Disclosures

- Speaking and consulting for Janssen, Novo Nordisk, and Lexicon (not relevant).
- No financial conflict related to this talk.
- Some of the cases were modified for teaching purposes.

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Objectives

- Discuss etiologies and differential diagnoses for aortitis.
- Share multiple cases with similar presentations but different etiologies.
- Review challenges making the right diagnosis.
- Discuss our published experience.
- Summary and recommendations.

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Aortitis

- **Rare disease with different underlying pathogenesis:**
 - Inflammatory
 - Infectious
 - Malignant and paraneoplastic
 - Idiopathic
- **Diagnosis and differential diagnoses:** very challenging!
 - Similar clinical presentations, imaging and lab findings
 - Different diseases or one disease with a wide spectrum!?
- **Management:**
 - Based on the underlying etiology
 - Expert multidisciplinary team including vascular medicine!

5 Skeik et al. Vasc Endovascular Surgery 20017 Oct;51(7):470-479

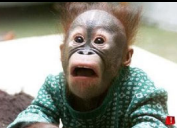


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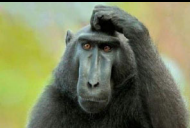


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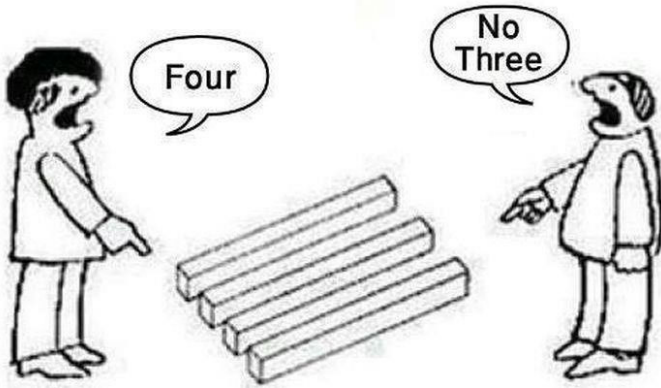
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Diagnosis and Management is Challenging



It is really confusing!!!





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Inflammatory Aortitis

- Giant cell arteritis (GCA)
- Takayasu arteritis (TA)
- Immunoglobulin G4-related disease (IgG4-RD)
- Periaortitis (previously known as retroperitoneal fibrosis)
- Secondary to other disorders:
 - *Other vasculitides* (Cogan disease, Behcet’s, Kawasaki, small vessel vasculitis “ANCA associated”)
 - *Connective tissue disorders*: RA, SLE, seronegative spondyloarthropathies
 - *Other autoimmune disorders*: Relapsing polychondritis, sarcoidosis
 - *Histocytosis*: Erdheim-Chester disease
 - *Radiation*
- Idiopathic inflammatory aortitis

Circulation 117, 3039–3051 (2008)

⁷ Ann. Vasc. Surg. 29, 839.e5–8 (2015)



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Infectious Aortitis

- **Bacterial**
 - Staphylococcus
 - Salmonella
 - Mycobacterium
 - Treponema
 - Neisseria
 - Rickettsia
- **Viral:**
 - Herpes
 - Varicella-zoster
 - Hepatitis B or C
- **Fungi**
 - Aspergillosis
 - Mucormycosis

⁸ Skeik et al. Vasc Endovascular Surgery 20017 Oct;51(7):470-479



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Malignancy and Paraneoplastic Aortitis

- **Primary:**
 - Malignant fibrous histiocytoma
 - Epithelioid angiosarcoma
 - Unclassified sarcoma

- **Paraneoplastic**
 - Leukemia
 - Lymphoma

JVS: Volume 38, Issue 6, Pages 1430–1433



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CASE: 1

- **History:** 52 y.o. F. with 5 years history of shoulders and hips pain

- **Presentation:** mid abdominal & lower back pain, fever, chills, and night sweats

- **VS:** normal

- **Exam:** Para-umbilical abdominal tenderness with tender shoulders and hips

- **Lab work:** WBC 11K, ESR: 48 and CRP: 22.7
 - Immunoglobulin G subclasses, C3 and 4, ANCA vasculitis panel, and ANA were unremarkable
 - Blood cultures, HIV antibodies, syphilis, and viral hepatitis were also negative



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CASE 1: CTA of Abdomen and Pelvis



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CASE 1: Diagnosis and Management

- **Diagnosis:** Giant cell arteritis
- **Management:** prednisone 40 mg po daily for 4 weeks and then slow taper
- Significant symptom improvement in first 3 weeks
- ESR/CRP normalized in 4 weeks
- Imaging improved significantly 1-3-6 months

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CASE 1: Follow-up Image After 6 Months



Giant Cell Arteritis (GCA)

- Granulomatous large vessel vasculitis mostly affecting females ≥ 50
- Large vessel or cranial GCA!
- **Diagnosis: consider if ≥ 3 of the followings**
 - Age ≥ 50 years
 - New headaches
 - Abrupt onset of visual disturbances (visual loss)
 - Jaw claudication
 - Unexplained fever, anemia, or other constitutional symptoms
 - High ESR and/or CRP
 - A current or prior diagnosis of PMR heightens the potential diagnosis
- **Now US is now proposed as the first and main imaging modality (OMERACT US {OGUS} score).**

Large Artery vs. Cranial GCA

- **Younger age:**
 - Mean age 66-68 vs 72-76 years
- **Delay in Diagnosis:**
 - Mean 3.5 to 8 months vs 2 months
- **Lower frequency:**
 - Cranial manifestations: <40% vs > 70%
 - Visual manifestations: 4% vs 11-19%
- **Positive temporal artery biopsy** in <50% !!
- **Less likely to meet ACR criteria**
 - 39% vs 95%

Brack A, et al. Arthritis Rheum 1999

Schmidt WA, et al. Rheumatology (Oxford) 2008

15 Muratore F, et al. Rheumatology (Oxford) 2015



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Disease Activity

- **Disease activity:** symptoms, inflammatory markers and imaging (US!, CTA, MRA, PET scan)
- **Elevated ESR or CRP:** not always indicate a flare (may also be normal in active disease)!!
- **PET scan can be positive in multiple conditions (sensitivity 85% and specificity 41%):**
 - Postop (open and endo)
 - Atherosclerosis
 - Inflammation
 - Infection (much higher SUV!)
 - New ligands !
 - *FDG-PET scan, increase recent interest (sensitivity 73% and specificity 97%)*

Arnaud L et al. Arthritis Rheum 2009 60 p1193

K-H Lee et al Arthritis Rheum 2012 64 p866

16 Alibaz-Oner et al. Mod Rheumatol 2015 25 p752



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GCA: Management

- Prednisone 1mg/kg daily (maximum 60 mg) for 2-4 weeks.
- Reduce by 5 mg every 2 weeks to 20 mg/day.
- Then by 2.5 mg every 2 weeks to 10 mg/day if there are no flares of disease activity.
- Then: prednisone taper should be slowed, over the ensuing 6-12 months.
 - Tapering by 1 mg decrements each month once the daily dose is less than 10 mg can be considered. *Recurrence!*

¹⁷ Skeik et al. Vasc Endovascular Surgery 20017 Oct;51(7):470-479



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Steroid Sparing Agents

- **Tocilizumab:** IL6 inhibitor, first FDA-approved drug for GCA!
 - Decreased rate of first relapse
 - Significant reduction in the cumulative dose of glucocorticoids
 - 162 mg SC qwk for a year
 - When to start and stop?! *New data: taper; weekly for 12 and then bi-weekly for another 12 months.*
 - How soon should prednisone be tapered? (3-4 months)!
- **Methotrexate:** at best, is only moderately effective!
- **Abatacept:** CD4+ inhibitor, borderline effective
- **Ustekinumab:** IL-12 (Th1) IL-23 (Th17) inhibitor, promising results
- **DMARDs:** Azathioprine, cyclophosphamide, leflunomide
- **TNF inhibitors:** not that effective!

¹⁸ Villiger PM et al. Lancet 2016; 387:1921

¹⁸ Skeik et al. Vasc Endovascular Surgery 20017 Oct;51(7):470-479



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Giant Cell Aortitis; Clinical Presentation and Outcomes in 40 Patients Consecutively Operated on

- 40 pts with postop F/U 4.2 ± 2.3 years, mean age 66.7 ± 9.1 years
- PMR or temporal arteritis in 22.5%
- All pts had ascending aortic involvement (aneurysm, dissection)
- 4 pts needed emergency repair for dissection
- 85% had an arch replacement; 79.4% a hemiarch and 20.6% a full arch
- 13 patients had elevated ESR and or CRP

- Postoperative Complications:
 - AF 40%, stroke 2.5%, SZ 10% and wound infection 2.5%

- Freedom from intervention 89.9% (4 cases had re-intervention)

- 7/13 pts with elevated and none with normal ESR+/-CRP had disease progression (increase aortic diameter)

- The 5-year overall survival rate was 91%

¹⁹ Gagne-Lorenger M, et al. Eur J Cardiothorac Surg 2016;50:555-9



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Prognosis and Relapse

- Relapse reported in 34-74% (more common in large vessel form).
- Late relapses of GCA have been described.
- 50% of patients were still on treatment after five years.
- 54%-75% off steroids after 5 years.
- Survivorship is similar to general population.
- Aneurysms are associated with higher mortality.
- Large vessel related complications may occur years after diagnosis.

²⁰ Hoffman GS. Ann Intern Med 2016; 165:ITC65.
Gagne-Lorenger M, et al. Eur J Cardiothorac Surg 2016;50:555-9



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CASE: 2

- **History:** 48-y.o. F. with tobacco abuse
- **Presentation:** One-month of malaise and progressive bilateral hip and buttock pain with walking, and acute painful and purple left foot
- **Vital signs:** unremarkable except P: 119/min
- **Exam:** left purple and cold foot
 - Non-palpable bilateral popliteal, DP and PT pulses

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CASE 2: Laboratory and Imaging Work Up

- CBC and CMP were normal
- ESR: 36 and CRP 2.76
- Lipid profile: Elevated TC, LDL and TG
- Bilateral ABI: 0.71 with diffuse monophasic waveform! Inflow disease!
- Immunoglobulin G subclasses, C3 and 4, ANCA vasculitis panel, and ANA were unremarkable
- Blood cultures, HIV antibodies, syphilis, and viral hepatitis were also negative

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CASE 2: CTA of Abdomen and Pelvis:



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CASE 2: CTA of Abdomen and Pelvis:



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CASE 2: CTA of Abdomen and Pelvis:



CASE 2: Diagnosis and Management

- Type IV Takayasu arteritis
 - Age, gender, severe stenoses and involvement
- Management:
 - Prednisone 60 mg daily
 - ASA and statins
 - Walking program

CASE 2: Complications

- **Presented 3 weeks later:** sudden onset of left leg pain
- **Exam:** cold left foot, non-palpable left DP and PT pulses, and livedo reticularis
- Acute CLI!? immediately started on IV UFH

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CASE 2: CTA of Abdomen



Improved Aortic Wall Thickness

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CASE 2: CTA of Abdomen

New Thrombosis of the Left CIA

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CASE 2: CTA of Abdomen

Improved Aortic Wall Thickness but New Thrombosis of the Left CIA

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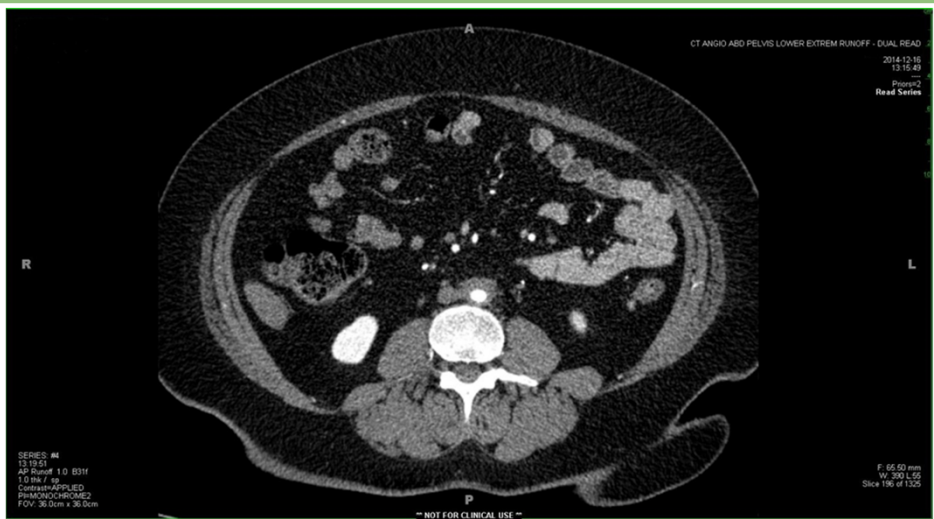
CASE 2: Management of Complications

- Catheter-directed lytic therapy with aspiration thrombectomy resulting in significant reduction of the clot burden
- Procedural complication: right iliac artery dissection managed by bare-metal stenting (*inflamed fragile vessel!!*)
- The patient continued to improve on prednisone taper, atorvastatin, aspirin and warfarin
- *2 Months:* Symptoms resolved, normalized ESR/CRP and ABIs

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CASE 2: CTA of Abdomen, 2 Months Later

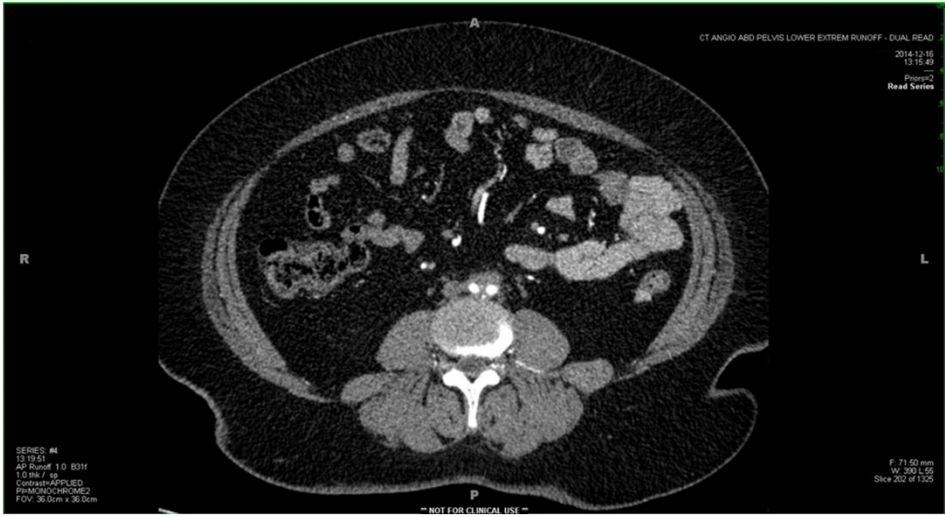


Further Improvement of Aortic Wall Thickening and Bilateral Iliac Artery Flow

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CASE 2: CTA of Abdomen, 2 Months Later



Further Improvement of Aortic Wall Thickening and Bilateral Iliac Artery Flow

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CASE 2: CTA of Abdomen, 2 Months Later



Further Improvement of Aortic Wall Thickening and Bilateral Iliac Artery Flow

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Takayasu Arteritis

- Rare, chronic large vessel granulomatous vasculitis
- Primarily affects the aorta and large vessels
- Manifestations usually start < age 40
- Females are 8.5 times more commonly affected
- **Prevalence:** highest in Japan (150 cases/yr), Southeast Asia, India, and Mexico
- **Incidence in U.S. and Europe:** 1-3 new cases per million persons per year

35 Skeik et al. Ann Vasc Surg. 2016 Apr;32:128.e7-128.e13



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Clinical Presentation

- **Early Symptoms:** fever, night sweats, malaise, weight loss, arthralgia, myalgia, and mild anemia.
- **Disease progression:** poor pulses, blood pressure discrepancies, vascular bruits, and hypertension due to renal artery stenosis.
- **Cardiovascular complications:** aneurysms, pulmonary hypertension, aortic rupture, and thrombosis.

36 Nat. Rev. Rheumatol. 6, 406–415 (2010).



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Takayasu: Age > 40 years

- **Late-onset TAK** (> 40 years) in 13-43% cases
- **Japanese registry of 1372 patients with TAK**
 - 594 patients (43%) >40 years
- **Differences > 40 years vs < 40 years:**
 - Delay in diagnosis: 45 vs 28 months
 - Dyslipidemia: 50% vs 21%
 - Hypertension: 49-61% vs 14-39%
 - Less carotid involvement: 60% vs 90%
 - More coronary involvement; female only: 11% vs 4%

Watanabe et al. Circulation 2015
Schmidt et al. Mayo Clinic Proc. 2013
37 Yoshida et al. Int J Rheum Dis 2016



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Diagnosis

- Clinical presentation, labs and imaging (US, CT, MR, or catheter-based angiography) showing stenoses of medium and large vessels
- Laboratory findings: Elevated ESR and CRP may reflect inflammation but can be unreliable in identifying disease activity!
- PET scan may also be helpful for initial diagnosis and monitoring of disease activity!

38 J. Nucl. Med. Off. Publ. Soc. Nucl. Med. 46, 917-922 (2005)



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Angiographic classification

(Based on the 1994 Tokyo International Conference on Takayasu Arteritis)

According to the vessels involved, the most recently proposed angiographic classification divides TA into six types :

- Type I involves only the branches of the aortic arch.
- Type IIa involves ascending aorta, aortic arch and its branches.
- Type IIb affects ascending aorta, aortic arch and its branches, and thoracic descending aorta.
- Type III involves the descending thoracic aorta, the abdominal aorta and/or the renal arteries. The ascending aorta, the aortic arch and its branches are not affected.
- Type IV involves only the abdominal aorta and/or renal arteries.
- Type V has combined features of Type IIb and IV.

Additionally, involvement of the coronary and pulmonary arteries should be indicated as C (+) or P (+), respectively. Type V has been documented as the most common type.

TAKAYASU ARTERITIS

39 Int. J. Cardiol. 54 Suppl, S155–163 (1996).

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Global Prevalence of Takayasu Arteritis by Type Based on Our Literature Review

Study	Location	Type I	Type IIa	Type IIb	Type III	Type IV	Type V
Singh et al. (2015) ¹⁶	India	32.2%	8.1%	1.6%	3.2%	17.7%	37.1%
Schmidt et al. (2013) ¹⁵	United States	20%	6%	7%	5%	5%	57%
Sahin et al. (2012) ¹⁷	Turkey	39.4%	6.4%	2.7%	3.9%	4.5%	43%
Cong et al. (2010) ¹⁸	China	40%	4.8%	1.6%	2.4%	20.8%	30.4%
Kechauo et al. (2009) ¹⁹	Tunisia	67.7%	0%	10.7%	0%	3.6%	25%
Petrovic-Rackov et al. (2009) ²⁰	Serbia	50%	19%	0%	0%	0%	31%
Park et al. (2005) ²¹	South Korea	36.1%	2.8%	4.6%	7.4%	15.8%	33.3%
Sato et al. (1998) ²²	Brazil	21%	4%	0%	4%	14%	57%
Suwanwela et al. (1996) ²³	Thailand	0%	0%	11.1%	3.2%	19%	66.7%

40 Skeik et al. Vasc Endovascular Surg. 2017 May;51(4):195-198

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Takayasu and Arterial Thrombosis

- **TA promotes a hypercoagulable state:** Significantly increase in PLT and coagulation activity
- Although TA-associated thrombosis has been reported in various inflamed vessels, we were unable to find any case of TA complicated by thrombosis of the iliac artery

41 Skeik et al. Ann Vasc Surg. 2016 Apr;32:128.e7-128.e13



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Takayasu Management

- **Prednisone:** initial dose 40-60 mg daily
- Slow taper: no faster than 10 mg a week when improve
- **Steroids sparing or resistant patients:**
 - **DMARDs** (Methotrexate, azathiopirine or leflunomide): effective
 - **Anti-TNF agents:** etanercept, adalimumab or infliximab are effective
 - **IL-6 inhibitor:** Tocilizumab, based on study cohorts (CRT: low number!)
- **Revascularization:** when disease is inactive!
- *Patency in 9.4 years:*
 - Open: 79%
 - Endo 52%
 - Failure can be reduced by medical therapy

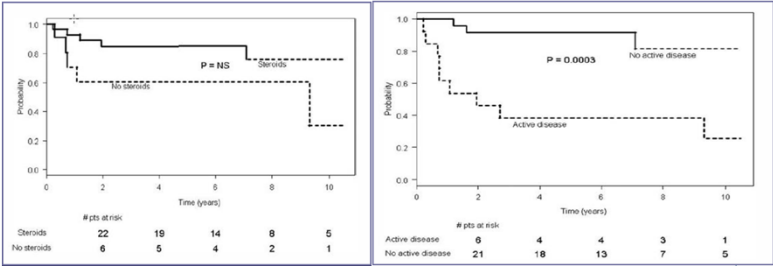
42 Bredemeier M, et al. Clin Exp Rheumatol 2012; 30:S98
Hoffman GS et al Arthritis Rheum 2004; 50:2296.
BJS 2014;101:43-50



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Takayasu's Arteritis; Operative Results and Influence of Disease Activity (J Vasc Surg, Jan 2006)

- Minority of patients require operation (42/251, 17%)
- Operation was safe, no significant increased mortality, MI, major stroke or renal failure (3 early graft thrombosis, 2 minor stroke)
- Patients with active disease (31%) are more likely to require revision or develop disease in another site



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Freedom of revision based on steroid use Freedom of revision based on disease activity



Prognosis

- **5 years survival:** 80 to 90 %
- **15-year survival:** 66 and 96 % for patients with and without a major complication
- **The long-term prognosis among patients who required surgical revascularization (106 Japanese patients followed for a mean of 19.8 years):**
 - Survival to hospital discharge was 89%
 - Overall survival at 20 years was 73.5%.
 - Anastomotic aneurysms developed in 13.8 % at various times following surgery.

⁴⁴ Ishikawa K, et al. Circulation 1994; 90:1855.
Miyata T, et al. Circulation 2003; 108:1474.



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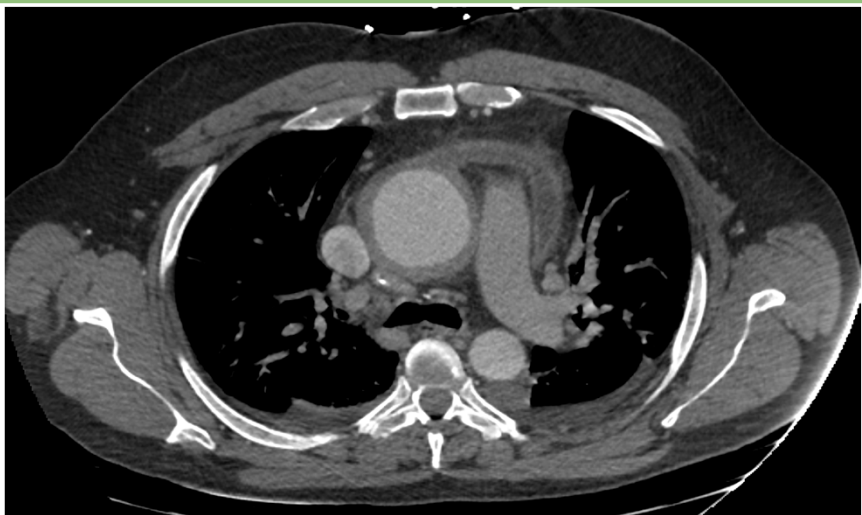
CASE: 3

- **Presentation:** 51 y.o. M. presented with 2 wks of fever, night sweats and chest pain.
- **Exam:** friction rub, erythematous rash all four extremities
- **Labs:** WBC: 17.1, Hgb: 10.4, ESR: 96, CRP 24.28, and normal troponin
- **CXR:** cardiomegaly
- **EKG:** AV flutter
- **TTE:** LV EF 30%, moderate pericardial effusion, thickened enlarged ascending aorta 6.5 cm

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CASE 3: CTA of Chest



Ascending Aortic Wall Thickening with Aneurysm: 6.5 cm

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CASE 3: CTA of Chest



Ascending Aortic Wall Thickening with Aneurysm: 6.5 cm

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CASE 3: CTA of Abdomen



Significant wall thickening of The Abdominal Aorta

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CASE 3: Further Work-up

- ANA positive
- C-ANCA (PR3-ANCA) strongly positive: > 1:160
- RF positive: 33.3 (Normal < 15.9)
- Rest of rheumatology work up was negative including IgG4 level

- **Chest CT:** diffuse mediastinal lymph node prominence
- **PET scan:** increased uptake around the ascending and abdominal aorta

- **Multiple sets of blood cultures:** negative

- **Skin biopsy:** perivascular neutrophilic infiltrate (nonspecific!)

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CASE 3: Differential Diagnoses and Treatment

- **Differential Diagnoses:**
 - Inflammatory Aortitis!
 - GCA?
 - ANCA associated vasculitis?
 - Rheumatoid arthritis related aortitis?

- **Management:**
 - Failed high dose steroids plus methotrexate and tocilizumab
 - Finally significant symptom, lab and imaging improvement on rituximab!
 - Prednisone dose is down to 20 mg and then had open repair

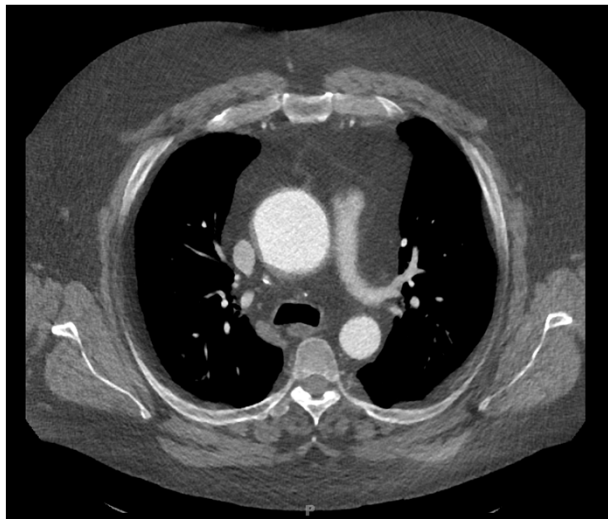
- **Final diagnosis:** C-ANCA related vasculitis

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CASE 3: CTA after Treatment



51 Improved Abdominal Aorta Wall Thickening

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CASE 3: Final Diagnosis: C-ANCA (PR3-ANCA) Vasculitis

- **ANCA associated vasculitis (AAV): necrotizing small vessel vasculitis**
 - C-ANCA (PR3- ANCA) : Granulomatosis with polyangiitis
 - P-ANCA (MPO-ANCA): Microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis, or renal-limited vasculitis
- **ACR Criteria for diagnosis of GPA:**
 - Nasal or oral inflammation
 - Abnormal chest radiograph showing nodules, fixed infiltrates, or cavities
 - Abnormal urinary sediment (microscopic hematuria)
 - Granulomatous inflammation on biopsy of an artery or perivascular area
- **Management:** Glucocorticoids combined with rituximab, or less favorably with cyclophosphamide.

52 Skeik N et al. *Rheumatol Int.* 2019 Nov;39(11):1983-1988.

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CASE: 4

- **Presentation:** 70 y.o. with hx of HTN and DM presents with left side neck mass, right eye lid swelling, night sweat, significant weight loss, and abdominal pain
- **Physical Exam:** left submandibular tender mass, and periumbilical abdominal tenderness
- **Labs:** WBC: 12000, Hgb 11, ALT 350, AST 250, ALP: 300, Lipase 870, ESR: 70, CRP 1.5
- **CXR:** mediastinal lymphadenopathy
- **Abdominal CT:** pancreatitis with sausage-shaped pancreas!
- **Rest of autoimmune w/u and cultures:** unremarkable

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Courtesy to Dr. John Stone, Harvard Medical School, Rheumatology



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CASE 4: Abdominal CT with Contrast



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Courtesy to Dr. John Stone, Harvard Medical School, Rheumatology

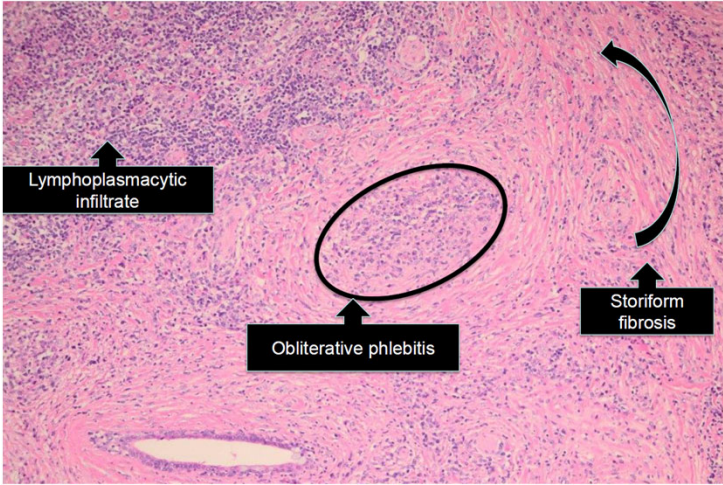


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CASE 4: Submandibular Gland Biopsy



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Courtesy to Dr. John Stone, Harvard Medical School, Rheumatology



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IgG4 Related Disease

- Immune-mediated condition with multiple disorders sharing particular pathologic, serologic, and clinical features
- **Shared features:**
 - Tumor-like swelling of involved organs
 - Lymphoplasmacytic infiltrate with IgG4-positive plasma cells
 - Variable degree of fibrosis “storiform” pattern
 - Elevated serum IgG4 in 60 to 70 % of patients
- **Major Presentations:**
 - *Salivary gland disease*
 - *Orbital disease:* lacrimal gland inflammation, proptosis
 - *Retroperitoneal disease:* periaortitis, pancreatitis, cholangitis, hydronephrosis
 - *Others:* thyroid (Riedel’s thyroiditis), renal (nephritis), lungs and CNS

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Wallace et al. Rheumatology 2016



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IgG4 Related Disease Diagnosis and Treatment

Diagnosis

- *Clinical*: classic organ involvement
- *Serology*: elevated serum IgG4, depressed C3/C4
- *Radiology*: periaortitis, sausage-shaped pancreas
- *Pathology*: classic pathology and positive stain for IgG4

Treatment

- Prednisone: initial dose 40 mg po daily
- Rituximab: as a sparing agent or in resistant cases

57 Wallace et al. Rheumatology 2016



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CASE: 5

- **Presentation**: 55 y.o. M. with hx of HTN presents with abdominal and left flank pain that radiates to the groin area
- **Physical exam**:
 - Periumbilical and left flank moderate tenderness
- **Labs and Images**:
 - WBC 11.6, Hgb: 10.5
 - Creatinine 3.2
 - ESR: 80, CRP 4.6
- **Abdominal ultrasound**: left side hydronephrosis
- Rest of autoimmune work up as well as blood cultures are negative

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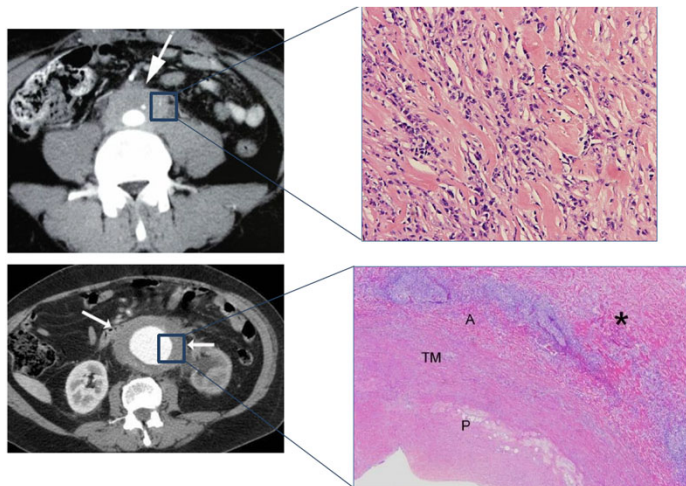


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CASE 5: Imaging and Pathology



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Courtesy of Augusto Vaglio, MD PhD, Parma University Hospital



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Periaortitis (Retroperitoneal Fibrosis)

- Rare condition with presence of inflammatory and fibrous retroperitoneal tissue that often encases the ureters or abdominal organs (hydronephrosis!)
- Idiopathic or secondary to other causes (IgG4 disease, autoimmune disorders, lymphoma, infection, radiation, meds <Ergots>, surgeries ..)
- **Diagnosis:** clinical, labs, biopsy (fibrous tissue with inflammation)
- **Treatment:** Prednisone, methotrexate, tocilizumab, rituximab

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Vaglio A et al. Lancet 2006; 367:241
Cronin CG, et al. AJR Am J Roentgenol 2008; 191:423



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CASE: 6

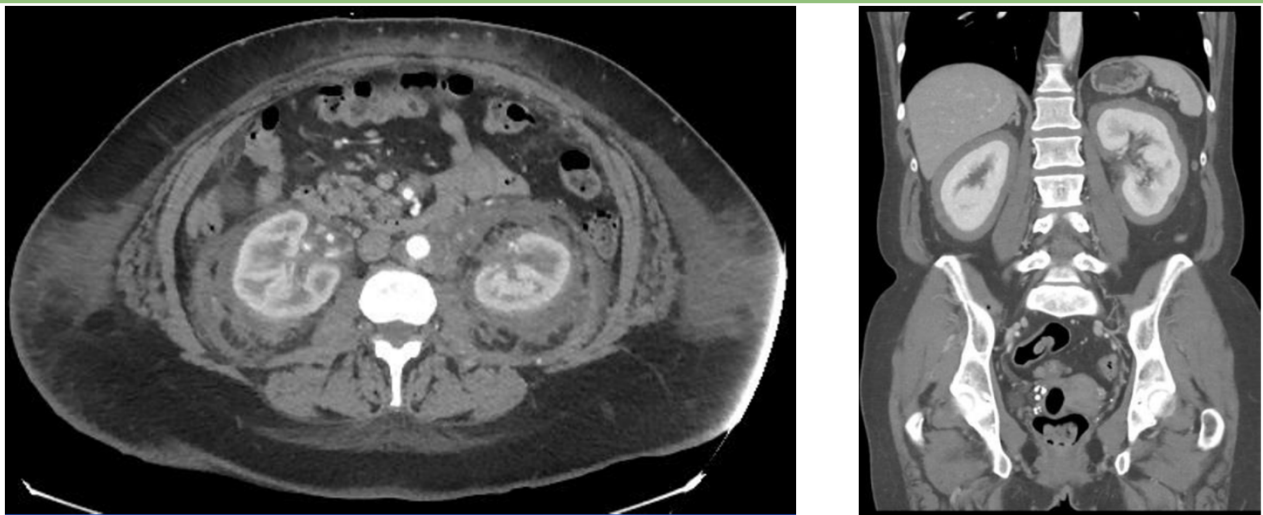
- **Presentation:** 51 y.o F. presents with chronic legs and periumbilical abdominal pain
- **Labs:**
 - Normal CBC
 - ESR 32, CRP 1.5
- **Leg X ray:**
 - Bilateral and symmetric osteosclerosis of the diaphysis of the long bones



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CASE 6: CTA of Abdomen



62 Courtesy to Matthew Koster, M.D., Mayo Clinic Rheumatology

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Erdheim-Chester Disease

- Multisystem non-Langerhans cell histiocytosis
- Periadventitial infiltrate can mimic: IgG4-RD, TAK, GCA
- BRAF V600E in approximately half of cases
- Work Up:**
 - Biopsy: non-Langerhans histiocytosis
 - BRAF V600E
 - Some cases with elevated ESR and CRP
 - Imaging: Hairy kidney/Coated aorta
- Management:**
 - BRAF V600E (+): Vemurafenib, Dabrafenib
 - BRAF V600E (-): Steroids, IFN- α , anakinra
tocilizumab, infliximab

Frequency of clinical or radiologic characteristics in Erdheim - Chester	
Osteosclerosis *	96%
Bone Pain *^	40-50%
CNS Involvement *#	15-51%
Diabetes Insipidus *^#	25-27%
Exophthalmos *^	24-32%
Xanthelasmas *^	19-28%
Cardiac Involvement *^	42-52%
Pulmonary Involvement *^	22-43%
Periaortic Infiltration *^#	60-66%
"Coated Aorta" *#	23-30%
"Hairy Kidney" *	68%

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Haroché et al Curr Opin Rheumatol 2012

Cavalli G, et al. Ann Rheum Dis 2013; 72:1691.

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CASE: 7

- Presentation:** 59 y.o man with hx of obesity and HTN, presented with abdominal pain
- Exam:**
 - Periumbilical moderate tenderness
- Labs:**
 - ESR 34 and CRP 2.72
 - CBC and CMP are unremarkable
- Extensive unremarkable rheumatological work up
- Negative multiple blood cultures

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CASE 7: CTA of Abdomen and Pelvis



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Idiopathic Inflammatory Aortitis

- Treated successfully with taper down steroids and methotrexate
- **Diagnosis:** clinical presentation, labs (ESR and CRP elevation), and imaging findings when all other etiologies are ruled out
- **Management:** steroids, methotrexate, tocilizumab!

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66 Skeik et al Vasc Endovascular Surg. 2017 Oct;51(7):470-479

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CASE 7: CTA of Abdomen 3 Months after Initial Treatment



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CASE: 8

- **Presentation:** 79 y.o. M with RA, DM, HTN, HL presented with chronic abdominal and lower back pain
- **Medications:** infliximab and methotrexate
- **Exam:** periumbilical abdominal and lower back tenderness
- CBC: WBC: 13.1, ESR 64, CRP 3.85
- Blood cultures and lumbar MRI negative for infection
- Urine culture was positive for MSSA
- **I.D. Recommendation:** ceftriaxone then cefalexin.
- **Management:** prednisone taper and continue on other immunosuppressive meds



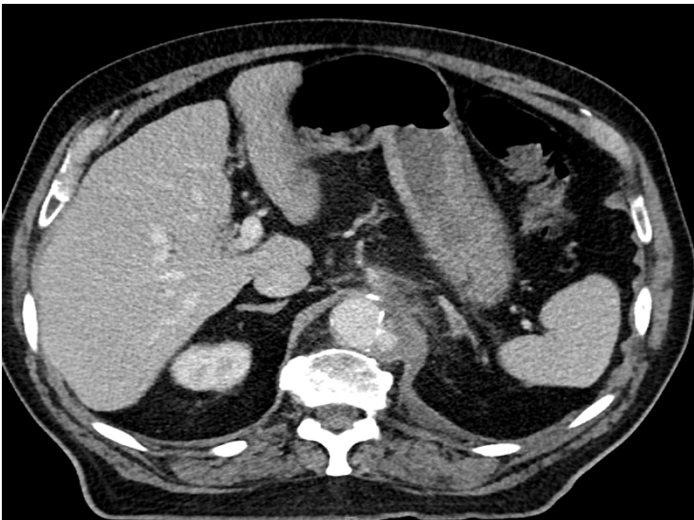
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CASE 8: Management and Follow up

- **1 month clinic F/U:** improved symptoms but ESR and CRP were still elevated
- **Blood cultures** were still negative!
- **CTA:** ulcerated ASO plaque!?
- **Plan:** add statins, risk factor reduction, and bring back in 2-4 weeks for follow up



CASE 8: CTA 4 Days Later



Blood cultures came back positive for MSSA

Infectious Aortitis

- Rare and very hard to differentiate from inflammatory:
- Leukocytosis (left shift)
- Procalcitonin elevation
- Hx of recent infection
- Positive blood or tissue culture (50-75%)
- Worsening symptoms on immunosuppression
- Asymmetric aortic wall thickening or periaortic soft tissue
- Very high SUV uptake with PET scan



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Topel et al, Gefasschirurgie. 2016; 21(Suppl 2): 87–93.



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Diagnosis, Management, and Outcome of Aortitis at A Single Center

Nedaa Skeik, Claire A. Ostertag-Hill, Ross F. Garberich, Peter B. Alden, Jason Q. Alexander, Andrew H. Cragg, Jesse M. Manunga, Elliot J. Stephenson, Jessica M. Titus, Timothy M. Sullivan

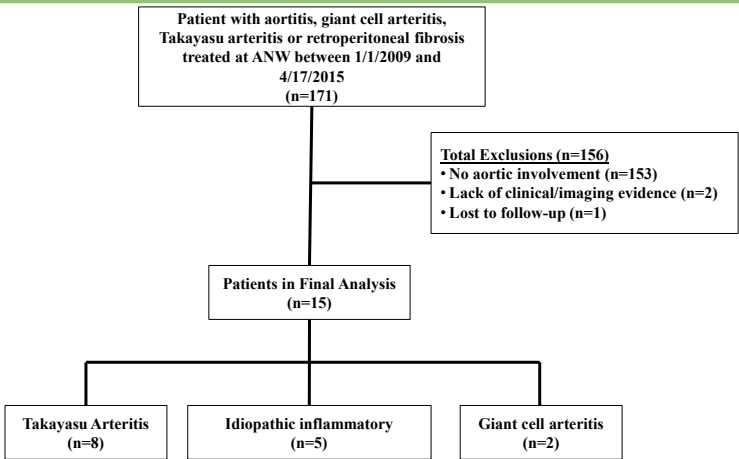


Figure: Flow chart of the selection of aortitis study population with exclusion criteria

Skeik et al Vasc Endovascular Surg. 2017 Oct;51(7):470-479



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METHODS			
Takayasu Arteritis	Giant Cell Arteritis	IgG4-related systemic disease	Inflammatory Idiopathic Aortitis
Criteria (3 or more): ²³	Criteria (3 or more): ²⁹	Criteria (all) ^{6,7}	Based on exclusion (criteria for other diagnoses are not met)
Age at onset: <40 years	Age at onset: ≥ 50 years	Diffuse or local swelling, masses, or thickness in single or multiple organs	
Claudication of extremities	New headache	Characteristic histopathological appearance (dense lymphoplasmacytic infiltrate, fibrosis, obliterative phlebitis)	
Decreased brachial artery pulse	Temporal artery abnormality	Increased numbers of IgG4 ⁺ plasma cells or IgG4 ⁺ /IgG ⁺ plasma cell ratio of >40%	
Blood pressure difference >10 mm Hg	Elevated erythrocyte sedimentation rate		
Bruit over subclavian arteries or aorta	Abnormal artery biopsy		
Arteriogram abnormality			

Table 1: Clinical criteria used to categorize patients with aortitis

⁷³ Skeik et al Vasc Endovascular Surg. 2017 Oct;51(7):470-479

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METHODS: Study Definitions
• An ESR >21 mm/hr, a CRP > 0.50mg/dL, and an IgG4 > 135 mg/dL were considered abnormal • Normal aortic thickness was considered to be <4 mm • Follow-up was defined individually as the most recent hospital encounter or clinic visit during which imaging was performed • Combined outcome was assessed using clinical presentation, laboratory data, and imaging findings. In cases of discordance between these three variables, imaging findings were considered to be the most accurate

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RESULTS: Study Population

	All aortitis (n=15)	Takayasu arteritis (n=8)	Inflammatory idiopathic aortitis (n=5)	Giant cell arteritis (n=2)
Age (years), mean (SD)	51 (17)	41 (17)	57 (4)	75 (8)
Race				
Caucasian, (%)	8 (53)	5 (63)	1 (20)	2 (100)
Hispanic, (%)	1 (7)	1 (13)	0 (0)	0 (0)
Asian, (%)	3 (13)	1 (13)	2 (40)	0 (0)
African American, (%)	3 (13)	1 (13)	2 (40)	0 (0)
Male, (%)	4 (27)	1 (13)	3 (60)	0 (0)
BMI, mean (SD)	25 (5)	23 (5)	28 (3)	24 (8)
History of Tobacco Use, (%)	6 (40)	1 (13)	4 (80)	1 (50)
Current Tobacco Use, (%)	2 (13)	0 (0)	2 (40)	0 (0)
Diabetes Mellitus, (%)	2 (13)	1 (13)	1 (20)	0 (0)
Hypertension, (%)	6 (40)	3 (38)	1 (20)	2 (100)
Hyperlipidemia, (%)	5 (33)	3 (38)	2 (40)	0 (0)
Peripheral arterial disease, (%)	1 (7)	1 (13)	0 (0)	0 (0)
Autoimmune disease				
Rheumatoid Arthritis, (%)	1 (7)	0 (0)	0 (0)	1 (50)

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⁷⁵ Skeik et al Vasc Endovascular Surg. 2017 Oct;51(7):470-479

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⁷⁶ Skeik et al Vasc Endovascular Surg. 2017 Oct;51(7):470-479

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Patient baseline clinical and laboratory characteristics	All aortitis (n=15)	Takayasu arteritis (n=8)	Idiopathic inflammatory aortitis (n=5)	Giant cell arteritis (n=2)
Length of hospital stay (days), median (25 th , 75 th percentile)	2 (0, 4.5)	0 (0, 0.5)	3 (2, 5)	7.5 (5.8, 9.3)
Systemic Complaints (%)	7 (47)	5 (63)	2 (40)	0 (0)
Type of imaging				
MRA, (%)	8 (53)	5 (63)	2 (40)	1 (50)
CTA, (%)	6 (40)	3 (38)	2 (40)	1 (50)
PET, (%)	1 (7)	0 (0)	1 (20)	0 (0)
Location of inflammation				
Thoracic, (%)	6 (40)	4 (50)	0 (0)	2 (100)
Abdominal, (%)	6 (40)	2 (25)	4 (80)	0 (0)
Thoracoabdominal, (%)	3 (20)	2 (25)	1 (20)	0 (0)
Stenosis	9 (60)	6 (75)	2 (40)	1 (50)
Thoracic, (%)	5 (33)	4 (50)	0 (0)	1 (50)
Abdominal, (%)	2 (13)	2 (25)	0 (0)	0 (0)
Cerebrovascular, (%)	2 (13)	2 (25)	0 (0)	0 (0)
Upper extremity, (%)	6 (40)	5 (62)	0 (0)	1 (50)
Lower extremity, (%)	2 (13)	1 (13)	2 (40)	
Occlusion	5 (33)	4 (50)	0 (0)	1 (50)
Thoracic, (%)	1 (7)	0 (0)	0 (0)	1 (50)
Upper extremity, (%)	3 (20)	3 (38)	0 (0)	0 (0)
Aneurysm	6 (40)	3 (38)	2 (40)	1 (50)
Thoracic, (%)	3 (20)	2 (25)	0 (0)	1 (50)
Abdominal, (%)	2 (13)	0 (0)	2 (40)	0 (0)
ESR				
Normal, (%)	4 (29)	2 (25)	2 (40)	0 (0)
High, (%)	10 (71)	6 (75)	3 (60)	1 (100)
CRP				
Normal, (%)	2 (15)	1 (14)	1 (20)	0 (0)
High, (%)	11 (85)	6 (86)	4 (80)	1 (100)
C-ANCA				
Positive, (%)	1 (14)	0 (0)	1 (25)	-----
Negative, (%)	6 (86)	3 (100)	3 (75)	
P-ANCA				
Positive, (%)	1 (14)	1 (33)	0 (0)	-----
Negative, (%)	6 (86)	2 (67)	4 (100)	
IgG4				
Normal, (%)	5 (100)	2 (100)	3 (100)	
Microscopic Tissue Exam	7 (47)	4 (50)	1 (20)	2 (100)



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⁷⁸ Skeik et al Vasc Endovascular Surg. 2017 Oct;51(7):470-479

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Aortitis Management Regimen				
	All aortitis (n=15)	Takayasu arteritis (n=8)	Inflammatory idiopathic aortitis (n=5)	Giant cell arteritis (n=2)
Steroids, (%)	15 (100)	8 (100)	5 (100)	2 (100)
Other immunosuppressants/ modulators, (%)	10 (67)	6 (75)	4 (80)	0 (0)
Surgical Intervention,(%)	5 (33)	4 (50)	0 (0)	1 (50)



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Indications, Outcomes, and Complications of Interventional Procedures				
Patient	Indication for Procedure	Type of Procedure	Procedure Outcome	Complication
2	Severe stenosis of left main coronary artery	Coronary artery bypass grafting	Successful	N/A
4	Severe stenosis and thrombosis of bilateral common iliac artery	Aspiration thrombectomy, bilateral drug-eluting balloon angioplasty, left stenting	Successful	Right iliac artery dissection
9	Severe stenosis of right renal artery, induced hypertension	Angioplasty and stenting of the right renal artery	Successful	N/A
	Symptomatic severe stenosis of bilateral subclavian artery	Balloon angioplasty and stenting of bilateral subclavian artery	Successful	Right subclavian artery re-stenosis
11	Aortic valve insufficiency	Ascending aortic aneurysm repair with Hemashield Dacron Graft	Successful	Ischemic brain lesion
12	Occlusion of right carotid artery	Left-to-right carotid-carotid bypass	Successful	Seizure



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⁸⁰ Skeik et al Vasc Endovascular Surg. 2017 Oct;51(7):470-479

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Case Study Conclusion

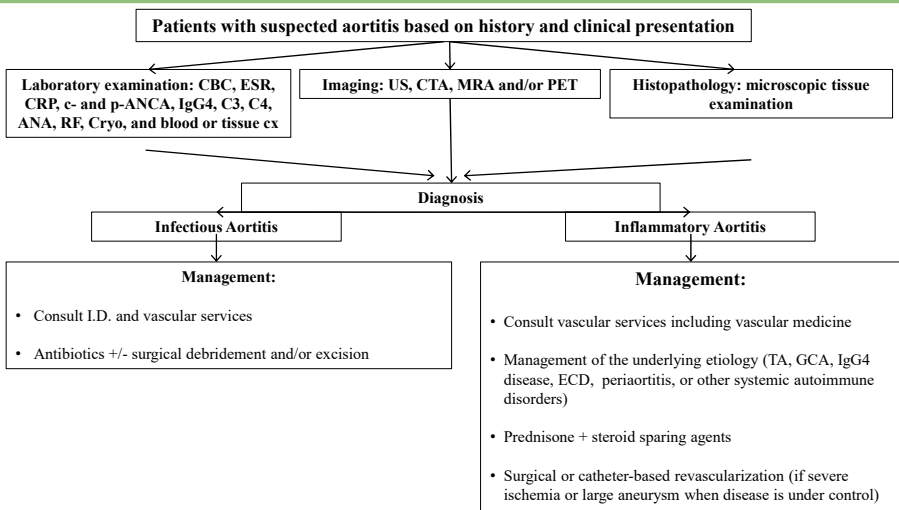
- More prevalent in females except in idiopathic inflammatory aortitis.
- 4/5 of pts with idiopathic type had hx of smoking.
- All idiopathic cases involved the abdominal aorta.
- Most patients with TA presented with arterial stenoses and/or occlusion.
- All patients received medical therapy and 33% underwent interventional procedures leading to 67% improvement of disease activity or related complications.

⁸¹ Skeik et al Vasc Endovascular Surg. 2017 Oct;51(7):470-479



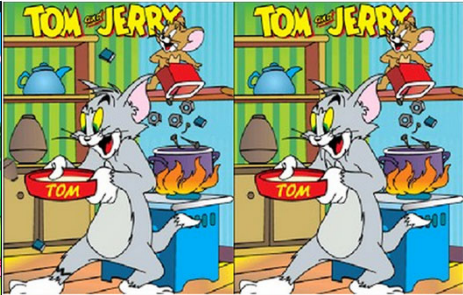
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Vascular Medicine Work-up Algorithm for Patients with Aortitis



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Noticing the Difference ..





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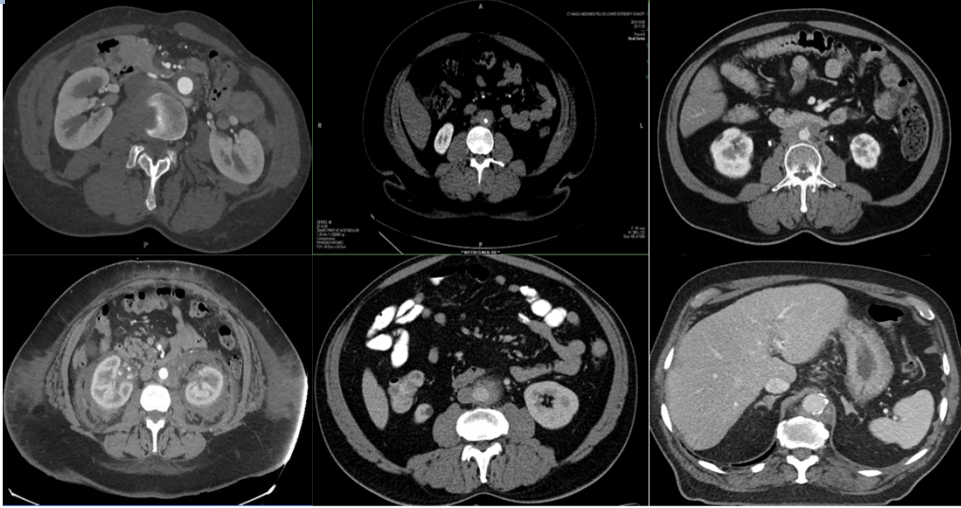


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Which is Which?!?





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Differential Diagnoses: Very Challenging !



- **GCA:** F, ≥50 age, headache, elevated markers, PMR, temporal artery biopsy
- **TA:** F, < 40, BP difference, poor pulses, imaging findings
- **IgG4-RD:** classic organ involvement, elevated serum IgG4, imaging (periaortitis, sausage-shaped pancreas), pathology (storiform fibrosis, lymphoplasmacytic infiltrates with positive stain for IgG4)
- **Periaortitis:** ureter and periaortic involvement with fibrosis and inflammation
- **ECD:** multisystem non-Langerhans cell histiocytosis, periadventitial infiltrate, BRAF V600E, imaging (hairy kidney/coated aorta)
- **Idiopathic inflammatory aortitis:** exclusion of others

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Life is Full of Mysteries and Unknowns



- There are known knowns
- These are things we know that we know
- There are known unknowns
- That is to say, there are things that we know we don't know, but there are also unknown unknowns
- There are things we don't know we don't know

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Conclusion

- Aortitis (inflammatory, infectious, neoplastic, idiopathic) are very rare disorders.
- More research is needed to characterize and classify these disorders.
- Differential diagnoses can be very difficult.
- Requires extensive work up involving multidisciplinary approach including vascular medicine.
- Determining disease activity needs to be standardized.
- Management includes steroids and steroid sparing agents (new agents!).
- Revascularization when disease is inactive. Increasing interest in endovascular approach.

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Thank you! Questions?



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