St. Joseph's Healthcare Hamilton

McMaster University

Large Vessel Vasculitis Clinical Update

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The Arthritis Society

CANVASC

Disclosures

Abbott
Wyeth Amgen
BMS
Schering Plough
Roche Pharmaceuticals

Objectives

1. Review signs, symptoms and lab findings in GCA
2. Review role of TA biopsy in GCA
3. Review clinical features of Takayasu's arteritis

Case Presentation

- 80 yo woman referred to hematologist for anemia with Hgb 95
- Her examination was essentially negative except for mildly tender R Temporal region with a thickened cord
- No headaches, jaw claudication, or diplopia
- Past medical history negative

Case Presentation

- Not on any medications
- ESR 10
- Should a TA biopsy be carried out?

Giant Cell Arteritis

•Giant cell arteritis (GCA) is a systemic vasculitis that affects the aorta and its major branches.

•Involvement of the ciliary artery can result in ischemic optic neuropathy and subsequent blindness, which is typically irreversible.

•If GCA is suspected, treatment with glucocorticoids should be initiated promptly to prevent further vision loss.

•Clinical features and laboratory findings are neither sensitive nor specific for GCA.

•The mainstay of diagnosis remains histopathologic examination of a section of the superficial temporal artery.

Kermani, Warrington. Curr Neurol Neurosci Rep (2012) 12:138–144

ACR 1990 criteria for the classification of giant cell (temporal) arteritis

- Must have at least 3 of the 5 criteria present.
  - Age > 50 years at disease onset
  - New headache
  - Temporal artery abnormality (tender or decreased pulse)
  - Elevated Westergren ESR > 50 mm/hr
  - Abnormal artery biopsy: mononuclear cell infiltrate, granulomatous inflammation, usually multinucleated giant cells

- Sensitivity 93.5% and specificity 91.2%
- A Meta analysis revealed only 2 patients of 1435 patients with biopsy proven GCA were under 50

Table 2. Specificity and Sensitivity of Signs and Symptoms in Patients with Suspected Giant-Cell Arteritis*

Sign or Symptom	Sensitivity (95% CI)†	Positive Likelihood Ratio (95% CI)‡
Jaw claudication	0.34 (0.29–0.41)	4.2 (2.8–6.2)
Diplopia	0.09 (0.07–0.13)	3.4 (1.3–8.6)
Prominent or enlarged temporal artery	0.47 (0.40–0.54)	4.3 (2.1–8.9)
Synovitis		0.4 (0.2–0.7)
Headaches	0.76 (0.72–0.79)	1.2 (1.1–1.4)
Erythrocyte sedimentation rate	0.96 (0.93–0.97)	1.1 (1.0–1.2)

* Modified with permission from Smetana and Shmerling (52).
† Defined as the frequency in patients with biopsy-proven giant-cell arteritis.
‡ Defined as the frequency of the sign or symptom in patients with giant-cell arteritis compared with the frequency in patients who had a negative result on temporal artery biopsy.

Please note that synovitis is associated with a reduced likelihood of a positive TA Biopsy indicating that joint inflammation and vasculitis may be inversely related

Weyand, Gorozny. GCA &PMR. Ann Intern Med, 2003;139: 505-515

Symptoms

- Jaw claudication and diplopia are not sensitive features despite their high LR's
- Jaw claudication appears to be present in only 34% of patients
- Diplopia is present in about 9% of patients
- Therefore their absence does not exclude GCA

Lab Features

- Erythrocyte sedimentation rates are not elevated in all patients
- Elevated ESR has been considered a hallmark of this disease and is one of the ACR classification criteria for GCA
- The sensitivity of elevated ESR was estimated at 96%(95% CI, 93–97).
- Only 4% patients with GCA had normal ESR at diagnosis
- Therefore, although the presence of a normal ESR renders the diagnosis of GCA unlikely, a normal ESR does not preclude the diagnosis.

Smetana GW, Shmerling RH JAMA. 2002;287:92–101.

Lab Features

•CRP is often considered a more sensitive marker of inflammation than the ESR.

•Although CRP is increasingly being used in the evaluation of patients with suspected GCA, its utility in these patients has not been well studied.

•In a recent study of 3001 subjects who underwent TAB, CRP was available in 591 patients (20%)

•Elevated CRP (defined as a value of >24.5 mg/L) was associated with significantly increased odds of a positive biopsy result (OR 5.3; 95% CI, 3.1–8.9)

Walvick MD, Walvick MP. Ophthalmology.2011;118:1201–4..

Lab Features

Based on the data provided, the sensitivity of CRP in this study can be calculated at 79%.

The prevalence of normal CRP at diagnosis in GCA has only been evaluated in small studies, some of which also included subjects with polymyalgia rheumatica

In a study of 119 patients with GCA, only 3 subjects (1.7%) had a normal CRP at the time of GCA diagnosis

Therefore, a normal CRP also has an excellent negative predictive value for GCA.

Kyle V, Cawston TE, Hazleman BL. Ann Rheum Dis. 1989;48:667–71.
Pountain GD, Calvin J, Hazleman BL. Br J Rheumatol. 1994;33:550–4.
Myklebust G, Gran JTBr J Rheumatol. 1996;35:1161–8.
Parikh M, Miller NR, Lee AG, et al. Ophthalmology. 2006;113:1842–5.

Lab Features

Although acute-phase reactants are often elevated at diagnosis, they are nonspecific.

Conversely, the presence of normal inflammatory markers has a high negative predictive value for GCA.

However, a small proportion of patients with GCA can present with normal markers of inflammation.

Therefore, in cases where clinical suspicion is high, a TAB and/or imaging studies should be pursued even in the absence of a systemic inflammatory response.

Kyle V, Cawston TE, Hazleman BL. Ann Rheum Dis. 1989;48:667–71.
Pountain GD, Calvin J, Hazleman BL. Br J Rheumatol. 1994;33:550–4.
Myklebust G, Gran JTBr J Rheumatol. 1996;35:1161–8.
Parikh M, Miller NR, Lee AG, et al. Ophthalmology. 2006;113:1842–5.

Back to Case

- CRP available 7 days later at level of 105
- TA biopsy available 7 days later revealed florid granulomatous vasculitis with near total luminal occlusion

Temporal Artery Biopsy

- The diagnosis of giant cell arteritis is felt to be most solidly established by the demonstration of granulomatous inflammation in a temporal artery biopsy (TAB)

- However, is this really the Gold Standard?

Temporal Artery Length

•1821 TAB reports reviewed, 287 (15.8%) were excluded because of missing data, sampling errors, or age < 50 years.

•Mean TAB length of the 1520 datasets finally analysed (67.2% women; mean (SD) age, 73.1 (10.0) years) was 1.33 (0.73) cm

Mahr et al Ann Rheum Dis 2006;65:826–828

Temporal Artery Length

•Histological evidence of giant cell arteritis was found in 223 specimens (14.7%), among which 64 (73.5%) contained giant cells

Mahr et al Ann Rheum Dis 2006;65:826–828

Giant Cell Arteritis: Biopsy

Retrospective review of patients who underwent temporal artery biopsy (TAB) during a 6 year period at St. Joseph's Healthcare, Hamilton, McMaster Hospital, Henderson Hospital, and Hamilton General Hospital (2002-2008)

- Among 261 charts reviewed, 3 were excluded due to an age less than 50 years old.
- Mean age was 72.8 years with a standard deviation of 9.6.
- There were 203 females (78%) .
- Mean arterial temporal artery length was 1.9 cm with a standard deviation of 1.8 .
- Biopsy proven for temporal arteritis was 34 (13%)

Famorca L, Khalidi N, Temporal Artery Biopsy, Does Length Really Matter? 2010 CRA Meeting, Quebec

Reasons for Negative Biopsies

Cranial Arteries Other than Frontal Temporal Artery

•Evidence of parietal temporal and occipital arteries involved in the absence of frontal temporal arteries on MRI

Bley et al ARTHRITIS & RHEUMATISM Vol. 52, No. 8, August 2005, pp 2470–2477

Reasons for Negative Biopsies

Large Vessel Vasculitis

•Inflammation of the aorta and its upper extremity branches can occur, but is only found in a subset of patients (15%) but, because of clinical silence, this involvement may be more frequent

•Patients with LV-GCA had a lower rate of vision loss, had a higher relapse rate, greater CS requirements and an increased incidence of aortic aneurysm compared with C-GCA.

1. ***Evans JM, Bowles CA, Bjornsson J, Mullany CJ, Hunder GG.****.Arthritis Rheum. 1994;37:1539-47*
2. ***Mohan N, Kerr G. Aortitis. Curr Treat Options Cardiovasc Med. 2002;4:247-254***
3. **Kermani et al Abstract 2358 ACR November 2012 S994 Abstract Supplement**

Identification of a *Burkholderia -Like Strain From Temporal Arteries of* Subjects with Giant Cell Arteritis.

•An infectious organism has been hypothesized to cause GCA

•Used a 16S rRNA analysis to amplify a bacterial genomic sequence unique to the temporal arteries of GCA subjects

•Frozen and paraffin-embedded temporal arteries from biopsy proven GCA subjects and controls were used for analysis

•A *Burkholderia* anti-LPS monoclonal antibody was used to perform immunofluorescence (IF) and ELISA

•*Burkholderia was cultured* from a temporal artery and the isolate was injected into C3H/HeSnJ mice

ACR Concurrent Abstract Session Vasculitis: Pathogenes Sunday, November 11, 2012, 4:30 PM–6:00 PM Curry L. Koening et al

Identification of a *Burkholderia -Like Strain From Temporal Arteries of* Subjects with Giant Cell Arteritis.

•16S rRNA analysis identified a genomic sequence within an affected artery that was 100% homologous to the genus *Burkholderia*

•Primers specific for the bacteria identified the organism in 9/10 GCA arteries but in none of the controls

•*B. pseudomallei-like (*BpGCA) may appear to be a critical factor in the pathogenesis
of GCA

ACR Concurrent Abstract Session Vasculitis: Pathogenes Sunday, November 11, 2012, 4:30 PM–6:00 PM Curry L. Koening et al

Case Presentation

26 year old woman presents in May 2010 with a chronic dry cough and associated dyspnea while going up stairs.

September 2010 -She saw her family doctor and referred her to respirologist who noted her to have HTN and was prescribed Advair and referred to an Internist. She was started on Cozaar.

Anemic with Hgb 102. An endoscopy was done to r/o celiac findings were normal.

February 2011 - She had a coughing spell and noted some blood in her sputum. She sought at the ER (Welland hospital) and ESR was elevated to 37 and CRP 29. CXR normal.

Case Presentation

Antihypertensive pill was changed to Avapro "medication induced cough". She was referred back to her internist and noted in her urinalysis having both hematuria and proteinuria .

April - May 2011 She was then referred to Nephrologist who ordered the following tests and results;

Ultrasound - renal asymmetry (?) renal artery stenosis , abdominal aortic wall thickening

CT chest - soft tissue around abdominal aorta (?) retroperitoneal fibrosis

What diagnostic test should be ordered now?

Case Presentation

MRI of the abdomen -Diffuse abdominal aorta wall thickening extending into proximal common iliac arteries, proximal arteries, superior mesenteric artery, and possibly the proximal celiac artery.

The right renal artery severely narrowed with secondary right renal atrophy

Subsequent MRI of subclavians revealed complete obliteration of the truncus anterior and severe stenosis in the interlobar artery of the right pulmonary artery.

Takayasu Arteritis

Takayasu's disease is relatively uncommon in Europe and North America.

In 1990, the Japanese government added Takayasu's disease to the list of intractable diseases, with 5000 cases added to the list
over the subsequent decade.

A North American study of patients in Minnesota found the incidence to be 2.6 cases per million population in each year

Numano F, Okawara M, Inomata H, Kobayashi Y. The Lancet 2000; 356: 1023–1025.
Hall S, Barr W, Lie JT, Stanson AW, Kazmier FJ, Hunder GG. Takayasu arteritis. A study of 32 North American patients. Medicine (Baltimore) 1985; 64: 89–99.

Takayasu Arteritis – Comprehensive Analysis of Recent 120 Patients in Japan

Objectives:

•Clarify the clinical characteristics of TA in a Japanese population, and to investigate changes in TA patient characteristics over the past decade (2000–2010) in a single center (Department of Cardiovascular Medicine at Tokyo Medical and Dental University Hospital (Tokyo, Japan))

•Disease activity was determined according to National Institutes of Health criteria, which define the clinical status on the basis of 4 elements: systemic features, elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) level, features of vascular ischemia or inflammation, and angiographic changes.

Ohigashi et al Circ J 2012; 76: 1004 – 1011

Takayasu Arteritis – Comprehensive Analysis of Recent 120 Patients in Japan Patient Characteristics

•7% of the patients developed TA after the age of 50.

•The most common signs and symptoms of TA before diagnosis were systemic:
-Fever- temperature >37.0°C; (53%)
-Easy fatigability (39%),
-Decrease/lack of pulse in the radial artery (38%), d
-Difference in blood pressures of left and right arms (37%),
-Neck bruit (30%).

•More than 90% of the patients had some lesions in the branches of the aortic arch.

Ohigashi et al Circ J 2012; 76: 1004 – 1011

Takayasu Arteritis – Comprehensive Analysis of Recent 120 Patients in Japan Mortality

•Three patients died during the observation period: 1 died of pulmonary hypertension (age 68), 1 was sudden cardiac death (age 40), and 1 died of cancer (age 58).

Ohigashi et al Circ J 2012; 76: 1004 – 1011

Takayasu Arteritis – Comprehensive Analysis of Recent 120 Patients in Japan
Medical Treatments

•79% of the patients were treated with glucocorticoids.

•Immunosuppressive agents were prescribed to patients who were resistant to glucocorticoids and to patients in whom glucocorticoid withdrawal was difficult (19%).

•Methotrexate was the most commonly used first-line immunosuppressive agent (50%), followed by cyclosporine A (35%); the immunosuppressive agent was changed in 12 patients (60%) because of resistance to the agent or adverse effects.

An antitumor necrosis factor (TNF)-α agent was administered to 4 patients after failure of treatment with 3 or more immunosuppressive agents, and all of them showed remission without significant adverse effects, except for 1 patient who developed tuberculosis.

Ohigashi et al Circ J 2012; 76: 1004 – 1011

Takayasu Arteritis – Comprehensive Analysis of Recent 120 Patients in Japan Surgical Treatments

•Surgical treatment was indicated for patients with hemodynamically significant lesions:

-clinical features of cerebral ischemia
-ischemia of extremities
-coronary artery disease,
-renovascular hypertension with resistance to hypertensive drugs
-progressive enlargement of an aortic aneurysm
-severe aortic regurgitation (AR).

Ohigashi et al Circ J 2012; 76: 1004 – 1011

Takayasu Arteritis – Comprehensive Analysis of Recent 120 Patients in Japan Changes in the past decade - Diagnosis

- Time from onset to diagnosis was significantly shortened

- Combined use of imaging tools (CTA/MRA/PET-CT) to improve the diagnosis of TA had also increased

- The frequency of occlusion in branches of the aortic arch and the incidence of moderate or severe AR had significantly decreased.

- In TA patients with onset after 2000, there were no cases of loss of vision, dialysis for chronic renal failure, or deaths.

Ohigashi et al Circ J 2012; 76: 1004 – 1011

Takayasu Arteritis – Comprehensive Analysis of Recent 120 Patients in Japan Changes in the past decade - Medical

•The number of patients treated with glucocorticoids and immunosuppressive agents had significantly increased, and the maximum dose of prednisolone had increased.

•Even if corticosteroid therapy is effective, 72% of cases experience multiple recurrences within 6 months after the dose of prednisolone was tapered to <10 mg daily.

•The mean prednisolone dose at relapse was 13.3±7.5 mg, and the mean duration until relapse was 15.4±17.3 months.

•The overall use of immunosuppressive agents (18.9%) was relatively low compared with other cohort studies reported from other countries such as Italy (54%), US (73%), and Turkey (84%).

Ohigashi et al Circ J 2012; 76: 1004 – 1011

Takayasu Arteritis – Comprehensive Analysis of Recent 120 Patients in Japan Changes in the past decade - Surgical

•The number of patients who require surgical treatment has not changed, which may be related to recent technical advances in vascular surgery

•However, the treatment approach has tended to shift slightly toward less invasive endovascular treatment with percutaneous transluminal angioplasty/stenting having a much higher restenosis rate (12–71.4% with a follow-up period of 0.5–5 years)

Ohigashi et al Circ J 2012; 76: 1004 – 1011

Takayasu Arteritis – Comprehensive Analysis of Recent 120 Patients in Japan Changes in the past decade - Surgical

•The restenosis rate was reduced when surgical treatment was performed during the inactive stage of the disease,
and when the patient was treated with both glucocorticoids and immunosuppressive agents

Ohigashi et al Circ J 2012; 76: 1004 – 1011

Conclusions

1. Etiology/trigger is still unknown for the Large Vessel Vasculitides
2. A negative biopsy can occur for a variety of reasons in cranial GCA
3. ESR and CRP are important components of lab collection and both a a normal ESR AND CRP likely rule out GCA but if clinical suspicion remains high, a TA biopsy should be carried out
4. Treatment with steroids should NOT preclude TAB in GCA even after treatment for 2 weeks or perhaps longer
5. The initial symptoms and signs of Takayasu's are non-specific, and a high index of suspicion is needed if the diagnosis is to be made.