Temporal Artery Biopsy
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OUTLINE

TEMPORAL ARTERY BIOPSY: ACTIVE VERSUS HEALED, LENGTH, UNILATERAL VERSUS BILATERAL, AND MORE

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Introduction:

Temporal arteritis also known a giant cell arteritis (GCA) primarily affects medium and large-sized arteries such as superficial cranial arteries, especially temporal arteries, cervical and vertebral arteries, the aorta and its branches and coronary arteries and occasionally it can also involve small arterioles. The importance of this pathologic process is in the organs and systems that the arterial flow is diminished giving rise to blindness, jaw claudication, headaches and stroke, fever and weight loss, aortic aneurysm and myocardial infarction.

History:

The first to describe the clinicopathologic findings in temporal arteritis was Bayard Horton in 1932 in a report of two cases although the clinical presentation was first described in 1890. Horton in his chart entries of the first patient recommends a biopsy that is at least 2-3 cm long for histological examination (Boes DJ, 2007). The first to describe vision loss in association with temporal arteritis was Jennings in 1938. Horton and colleagues reported for the first time the successful treatment of these patients with cortisone and commented in that this may prevent blindness as well. Since then many reports have appear in the literature dealing with the importance of the adequacy of the temporal artery biopsy sample since as today this is the “gold standard” test for the diagnosis of giant cell arteritis.

Epidemiology:

Giant cell arteritis is the most frequent primary vasculitis. The incidence is of about 200/100 000 persons in the at risk population. The disease is most prevalent in the white population, especially those of Scandinavian descent, and is rare in Hispanic persons (Weyand et at. 2003; Liu et al. 2005). Women older than 50 years of age are more susceptible. The incidence increases with age. Of special importance is the prediction of the doubling of incidence of cases in the next 25 years given that the population in developed countries is increasingly getting older and surviving longer.

Pathogenesis:
The etiology of giant cell arteritis is currently unknown. Several reports have implicated viral or bacterial etiologic agents however; none had been reproducible (Mitchell et al. 2001; Helweg-Larsen, 2002; Alvarez-Lafuente et al. 2005).

Molecular and cellular pathogenesis of medium and large vessel vasculitis presents as a result of 2 different mechanisms: the localized vascular lesion (involves mainly CD4+ T-cells, macrophages, IL-6, PDGF, VGEF and IFN-gamma, TNF-alpha and MMPs) and the innate and adaptive systemic immune system (activated by production of cytokines (eg. IL-1, IL-6) with targeted organs and systems such as liver (acute phase response), CNS, vascular system, bone marrow and immune system). Based on these reports patients with recurrent or steroid-resistant giant cell arteritis are treated with immunosuppressant therapy and antitumor necrosis factor (TNF-alpha) therapies (Seko, 2007).

**Clinical presentation:**

The onset of the symptoms may be either abrupt or gradually progressive, depending on the artery (ies) involved. Systemic features include headache, scalp (temporal) tenderness, jaw claudication, malaise, anorexia, weight loss, fever, and arthralgia. Usually these symptoms precede ophthalmic manifestations. The incidence of ophthalmic involvement ranges from 15-70% with the majority of the series referring as 50% (Varma et al, 2004). Table 1 shows the ophthalmic manifestations in giant cell arteritis that may present in one or both eyes and may be single or combined symptoms (Paraskevas et al, 2006; Font et al, 1997).

**Table 1. Ophthalmic manifestations in Giant cell arteritis.**

| Blurry vision |
| Diplopia     |
| Amaurosis fugax |
| Field defects |
| Ophthalmoplegia |
| Ptosis       |
| Miosis       |
| Eye pain     |
| Horner’s syndrome |
| Blindness   |

These symptoms are usually secondary to ischemia of the optic nerve (anterior ischemic optic neuropathy), due to arteritis of the posterior ciliary, ophthalmic and superficial temporal arteries. Central retinal artery occlusion, cilioretinal artery occlusion and posterior ischemic optic neuropathy may also present.
The majority of the ophthalmic symptoms (~70) present early in the clinical presentation but are seldom recognized and may precede blindness. Ophthalmologist may be the first in seeing in consultation these patients in many cases and thus, obtaining temporal artery biopsies for confirmation of suspected giant cell arteritis. Failing to recognize the early symptoms may lead to blindness although a small percentage of patients that underwent vision loss (~20%) present with severe ocular symptoms as the earliest presentation sign of the disease. Furthermore, in a series 8% of the patients became blind during and despite steroid treatment (Font et al, 1997).

Other symptoms, signs and laboratory findings of the disease include: polymyalgia rheumatica, facial ischemic manifestations other than jaw claudication, transient or permanent ischemic cerebral damage, aortic aneurysm, myocardial infarction, renal insufficiency, elevated sedimentation rate (>50mm/h) by the Westergren method, elevated C-reactive protein, anemia, thrombocytosis, and abnormal liver function test.

**Diagnosis:**

In 1990 the American College of Rheumatology published the criteria for the diagnosis of GCA. Accordingly at least 3 of the following five criteria need to be met:

1. Age at onset of 50 years or older
2. New onset of localized headache
3. Temporal artery tenderness or decreased pulse
4. Elevated erythrocyte sedimentation rate
5. Positive histologic findings in the temporal artery biopsy

However, the temporal artery biopsy finally establishes the diagnosis. The importance of a positive temporal artery biopsy is even greater when there is atypical or vague clinical presentation.

**Temporal Artery Biopsy:**

Temporal artery biopsy thus has been accepted as the gold standard for the diagnosis of giant cell arteritis even though it is of low sensitivity and specificity. Reports show that patients with GCA may have 15-40% negative temporal artery biopsies. The number of biopsies performed (unilateral versus bilateral, synchronous versus sequential), specimen length, the presence of skip lesions (in up to 8% of cases), the pathological sectioning techniques, adequate interpretation of atypical histopathologic presentations and the duration of treatment before biopsy all are contributing factors to the false negative rate (Chong et al, 2005). Current medical practice recommends initiation of high dose steroids before performing a biopsy, to avoid serious complications such as blindness, and the continued use of long-term steroids (during 2-3 years) even if biopsy is negative but clinical suspicion of diagnosis is high. Reports (Chong et al, 2005) have demonstrated that management of 76% of patients remains unchanged after biopsy. This may be an argument to avoid all together temporal biopsies. However, temporal artery biopsy is a minor procedure with acceptable rate of complications that can yield important results for
management of the disease, which if untreated, can lead to serious complications, and there is also the possibility of litigation in the event of a corticosteroid-induced complication in a patient treated for presumed GCA without a tissue diagnosis, thus, most clinicians perform temporal artery biopsy even in the most “classic” clinical cases of giant cell arteritis.

Since many of the symptoms are ophthalmologic, ophthalmic pathologists are faced frequently with the challenges of temporal artery biopsies. The following points address the main controversial and important issues in obtaining a positive diagnostic temporal artery biopsy.

**Histopathologic Findings:**

Recognition of the histopathologic presentations in temporal arteritis is essential, especially in atypical presentations (Boyev et al, 1999; . These findings are described in Table 2.

**Table 2. Histopathologic diagnosis in temporal arteritis.**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Histopathologic criteria</th>
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<tbody>
<tr>
<td>Active giant cell arteritis</td>
<td><em>Lumen:</em> Thrombosed, occasional recanalization</td>
</tr>
<tr>
<td></td>
<td><em>Intima:</em> Irregularly thickened with myxoid edema</td>
</tr>
<tr>
<td></td>
<td><em>Elastic lamina:</em> Disrupted/lost or phagocytosed by giant cells</td>
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<tr>
<td></td>
<td><em>Media:</em> Dense chronic inflammatory infiltrate with occasional giant cells, macrophages, eosinophils and foci of necrosis, fibrosis and thickened.</td>
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<td><em>Adventitia:</em> Thickened with lymphocytic infiltrate and may show fibrosis</td>
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<tr>
<td>Steroid-treated temporal arteritis</td>
<td><em>Lumen:</em> Frequently narrowed or open</td>
</tr>
<tr>
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<td><em>Intima:</em> Irregularly thickened with or without edema</td>
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<td><em>Media:</em> Mild chronic inflammatory infiltrate with occasional macrophages, foci of irregular fibrosis and thickened.</td>
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</tbody>
</table>
Healed giant cell arteritis

| Lumen: Frequently narrowed or open |
| Intima: Marked diffusely or irregularly thickened |
| Elastic lamina: Segmental fragmentation or loss of lamina |
| Media: Localized full-thickness loss or fibrous replacement. |
| Adventitia: Rare lymphocytic infiltrate and may show fibrosis |

Skip lesions and length of specimen:

One of the factors that has made responsible for the false negative biopsy results is the “skipping” nature of the inflammatory involvement in GCA, thus, histopathologic findings may be missed in an arteritis-free segment. This belief has caused the assumption that the longer the biopsy the better the chances of a positive diagnosis. Conflicting data have been published (Mahr et al, 2006) as for the optimal length of the specimen although it has always been recommended that 2-3 cm or even 3-5 cm would be ideal. Original studies about the nature of skip lesion showed that the areas were around 1 mm long (Klein et al, 1976). Most studies do not find differences in false-negative rate and size of biopsy. A recent study (Mahr et al, 2006), shows that the necessary size of the biopsy to show diagnostic yield is 0.5cm (or more) of fixed artery. The mean (SD) length of artery biopsies in this study was 1.33 cm. Furthermore, it has been demonstrated that temporal arteries can contract substantially after excision and before tissue fixation in formalin. The same study showed that GCA positive biopsies contracted less (12%) than negative biopsies (22%) (Su et al, 2006). Other studies have shown also contraction of the sample post-fixation. The majority of the studies, including Mahr’s, take in account the size of the artery after fixation. Thus, the biopsy obtained by the surgeon may indeed be larger in situ than the biopsy received in the pathology laboratory after fixation. Given the conflicting data formal recommendation of the ideal length of the biopsy is not possible although one may assume that biopsies larger than 0.5cm (fixed tissue) may be sufficient for diagnosis and that the larger the biopsy the better the chances of getting diagnostic tissue.

Unilateral versus bilateral (synchronous versus sequential) temporal artery biopsy:

Reports in the 1970-80s show that patients with initially diagnosed false-negative arteries, subsequently showed giant cell arteritis by a biopsy of the contralateral artery suggesting that performing bilateral temporal artery biopsies could increased the sensitivity of the diagnosis. However, a large prospective study showed that subsequent contralateral biopsies in only atypical cases increased the diagnostic yield in 7% of cases.
Other data supported this study and confirmed that the utility was in cases of atypical or unclear histopathologic findings in the first biopsy, thus, only in these cases a subsequent contralateral biopsy increased to 2.7% the diagnostic yield. The conclusion then is that in the majority of the cases unilateral biopsies are sufficient for the diagnosis and only in cases that show atypical or unclear histologic findings and that have high clinical suspicion for GCA a bilateral subsequent biopsy may be useful (Boyev et al, 1999).

Handling of the temporal biopsy specimen:

To increase the yield of a positive diagnosis appropriate handling and sectioning of the temporal artery biopsy is essential. To interpret the findings in the artery the best orientation is obtained by cross sections of the artery rather than longitudinal sections. As mentioned before the nature of the skip lesions in giant cell arteritis also requires examination of at least every 1mm and ideally every 0.5mm of the artery. There are different techniques published and employed by pathologist that deal with relative large numbers of temporal artery biopsies. Here we will describe the two that seem to give the best histologic sections for interpretation.

1. After adequate fixation and measuring of the length and diameter, the artery is submitted intact in a cassette for processing (a). Before embedding the artery is cross sectioned at 1 to 2 mm segments and embedded (b). The sectioned pieces of artery should be embedded sequentially as to have the cut surface down to be sectioned (c).
2. Histogel or Agar embedded tissue. With this technique the artery is measured after adequate fixation and cross sectioned at the same 1-2mm segments. Then the tissue is embedded in melted agar or histogel (using microwave or hot plate) that is poured into a regular metal mold. Then the segments are embedded in the gel similarly to technique number 1. Then the gel is let to cool down until solid (refrigerated for about 5 mins). The solid square of gel with the well oriented pieces is then wrapped in lens tissue and submitted in a cassette for processing (long program). After processing the gel is embedded in paraffin flat and then sectioned (LoRusso, 1999; Chévez-Barrios, 2005).

The two techniques should yield adequate cross sections of the artery and allow for 4 levels at 500 micra apart of the specimen that should sample adequately the entire biopsy. Hematoxylin and eosin stained sections are then obtained of these levels. A Movat pentachrome (combined special stain for elastic lamina-black, fibrous tissue – blue, cells -red) should be ordered when suspicious lesions are found to confirm steroid-treated or healed-temporal arteritis. These techniques avoid extensive sectioning and many sections to evaluate.

Frozen sections of the artery should be avoided as skip lesions may be missed during sectioning. If frozen sections are necessary to confirm presence of vessel, it is recommended to obtain a central cross section of the specimen and only submit this for frozen sectioning and save the remainder for adequate formalin fixation and sectioning (Chevez-Barrios P, 2005).

References:


Temporal Artery Biopsy: Active versus healed, length, unilateral versus bilateral, and more

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Background

• Giant cell arteritis (GCA)
  – Most frequent primary vasculitis.
  – Incidence ~200/100 000 persons in the at risk population
• Medium and large-sized arteries
  – superficial cranial arteries (temporal arteries, cervical and vertebral arteries)
  – aorta and its branches and coronary arteries
• Ischemic events
  – blindness, jaw claudication, headaches and stroke, fever and weight loss, aortic aneurysm and myocardial infarction.
Temporal artery

Internal carotid artery

Patrick Lynch medical illustrator (web)
Optic Nerve Vasculature

- Internal carotid artery
- Ophthalmic artery
- Central retinal artery
- Posterior ciliary arteries
Symptoms, signs and laboratory findings

- Polymyalgia rheumatica, facial ischemic manifestations, ophthalmic symptoms and jaw claudication, transient or permanent ischemic cerebral damage, aortic aneurysm, myocardial infarction, renal insufficiency
- Elevated sedimentation rate (>50mm/h) by the Westergren method
- Abnormal C-reactive protein
- Anemia, thrombocytosis, and abnormal liver function test
Ophthalmic manifestations in Giant cell arteritis

- Blurry vision
- Amaurosis fugax
- Blindness
Optic Nerve – Ischemic Changes

Normal

Atrophy

Acute Ischemic
Ophthalmic Manifestations

Diplopia
Ophthalmoplegia
Miosis
Horner’s syndrome

Field defects
Ptosis
Eye pain
Clinical presentation

• Usually systemic symptoms precede ophthalmic manifestations.
• Incidence of ophthalmic involvement 15-70% (mean 50%)
Why Ophthalmologist Perform Most of TABs?

• Ophthalmologist may be the first to suspect diagnosis and obtain temporal artery biopsies
• Failing to recognize the early symptoms may lead to blindness
• ~20% present with severe ocular symptoms at onset (blindness)
• 8% of patients may become blind during and in spite of steroid treatment
Challenges for the Surgical Pathologist and Treating Physician

- Low sensitivity and specificity temporal artery biopsy (TAB).

- Patients with GCA may have 15-40% negative temporal artery biopsies.
Diagnosis

American College of Rheumatology criteria for the diagnosis of GCA. (at least 3 should be met)

• Age at onset of 50 years or older
• New onset of localized headache
• Temporal artery tenderness or decreased pulse
• Elevated erythrocyte sedimentation rate
• Positive histologic findings in the temporal artery biopsy
Giant Cell Arteritis

• Current medical practice recommends:
  – initiation of high dose steroids before performing a biopsy, to avoid complications (blindness)
  – continued use of long-term steroids (2-3 years) even if biopsy is negative

• Then: Why to perform temporal artery biopsy?
  – TAB is gold standard for the diagnosis
  – minor procedure
  – acceptable rate of complications
  – if positive it yields results for management, which if untreated, can lead to serious complications
  – avoids possibility of litigation (corticosteroid-induced complication in treatment of presumed GCA without a tissue diagnosis)
The Challenges for the Surgical Pathologist

- Skip involvement of the arteries
- Processing of the artery
- Interpretation histopathologic changes in previously treated GCA
The Challenges for the Surgical Pathologist

• Skip involvement of the arteries
  – Diagnostic findings may be missed in an arteritis-free segment
  – Conflicting data = formal recommendation of the ideal length of the biopsy is not possible

CONCLUSION
  – At least 0.5 - 1.0 cm (fixed tissue) but the larger the biopsy the better the chances of getting diagnostic tissue (~2.0 cm)

Then, bilateral temporal artery biopsies will increase sensitivity?
  – Large prospective studies only atypical cases increased the diagnostic yield (2.7 - 7%)
  – Unilateral biopsies are sufficient for the diagnosis in most cases

CONCLUSION
  – Only atypical or unclear histologic findings in initial TAB with high clinical suspicion for GCA should undergo bilateral subsequent biopsy
The Challenges for the Surgical Pathologist

• Processing of the artery
  – Cross sections of the artery rather than longitudinal sections
  – Adequately fixed tissue
  – Embedding to preserve orientation
    • Pre-processing (gel/agar)
    • Post-processing (sectioning before embedding)
  – Histologic examination of at least every 1mm and ideally every 0.5mm of the artery to avoid missing skip lesions (~ 3-4 levels)
Sectioning after processing

1. After adequate fixation
2. Artery is submitted intact in cassette for processing
3. Artery is cross sectioned at 1 to 2 mm segments
4. Embedded in paraffin
5. Embed sequentially to sample all artery (surface down to be sectioned)
Embedding before Processing
Agar/gel technique

Measure

Cross section every 2 mm
Embedding before Processing
Agar/gel technique

Hot Plate

Cold Plate
Embedding before Processing
Agar/gel technique

Into cassette for long processing

Well oriented cross sections

3 H&E levels
The Challenges for the Surgical Pathologist

• Skip involvement of the arteries

• Processing of the artery

• Interpretation histopathologic changes in previously treated GCA
  – Active giant cell arteritis
  – Steroid-treated temporal arteritis
  – Healed giant cell arteritis
Histopathologic Findings

Active giant cell arteritis

- **Lumen**: Thrombosed, occasional recanalization
- **Intima**: Irregularly thickened with myxoid edema
- **Elastic lamina**: Disrupted/lost or engulfed by giant cells
- **Media**: Dense chronic inflammatory
  - occasional giant cells, macrophages, eosinophils and foci of necrosis, fibrosis and thickened.
- **Adventitia**: Thickened with lymphocytic infiltrate and may show fibrosis
Active Giant Cell Arteritis
Histopathologic Findings

Steroid-treated temporal arteritis

_Lumen:_ Frequently narrowed or open

_Intima:_ Irregularly thickened with or without edema

_Elastic lamina:_ Disrupted/lost (segmental) (_Elastic fiber stain_ (VVG or Movat))

_Media:_ Mild chronic inflammatory infiltrate with occasional macrophages, foci of irregular fibrosis and thickened

_Adventitia:_ Thickened with absent or rare lymphocytic infiltrate and may show fibrosis
Histopathologic Findings

Healed giant cell arteritis

- **Lumen**: Frequently narrowed or open
- **Intima**: Marked diffusely or irregularly thickened
- **Elastic lamina**: Segmental fragmentation or loss of lamina (Movat pentachrome)
- **Media**: Localized full-thickness loss or fibrous replacement
- **Adventitia**: Rare lymphocytic infiltrate and may show fibrosis
Arteriosclerosis

- Irregular intimal hyperplasia
- Small breaks in elastic lamina
Conclusions

- Giant cell arteritis is the most frequent arteritis
- TAB is gold standard for diagnosis
- TAB has a low sensitivity and specificity (skip lesions, length of biopsy, steroid treatment, atypical presentation)
- Definite diagnosis is necessary to avoid
  - unnecessary lengthy steroid treatment
  - devastating complications (blindness, stroke) of undiagnosed GCA
- Adequate handling of the specimen and awareness of the atypical histopathologic presentations should increased the diagnostic yield