Churg-Strauss Syndrome: Dispelling the Myths

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Facts or Fiction?
Controversies in Churg-Strauss Syndrome

1. Perinuclear (p) ANCA has limited utility in the diagnosis of CSS
2. pANCA levels do not correlate with disease activity
3. CSS carries a grave prognosis
4. Leukotriene receptor antagonists exacerbate CSS, playing a role in pathogenesis

Clinical Criteria for CSS

• Lanham’s criteria (all of the following)
  — Asthma
  — Peak eosinophilia >1.5 × 10^9 cells/L
  — Systemic vasculitis, two or >extrapulmonary sites
• American College of Rheumatology (4 of the following in the setting of vasculitis)
  — Asthma
  — Peak eosinophilia >10% total WBC
  — Peripheral neuropathy attributed to vasculitis
  — Transient pulmonary infiltrates
  — Paranasal sinus disease
  — Biopsy showing blood vessels with extravascular eosinophils

Clinical Criteria for CSS (continued)

• Chapel Hill Consensus Conference
  — Asthma
  — Peripheral Eosinophilia
  — Eosinophil-rich granulomatous inflammation involving the respiratory tract
  — Necrotizing vasculitis affecting small to medium vessels

These clinical criteria are consistent in the diagnosis of CSS. Mayo series shows 92% of subjects with CSS fulfill at least one of these classification schemes and 86% fulfill two or more (Keogh & Specks, American Journal of Medicine, 2003)

Utility of the pANCA in patients who fulfill clinical criteria for CSS

• Variable reported prevalence of positive pANCA in CSS
  — 38% Sinco, Arthritis & Rheum, 2005
  — 38% Sable-Fourtassou, Ann Intern Med, 2005
  • 73-75% diagnosis and during flare
  • 16-36% during remission or at Dx/after treatment
• Are the results of the ACNA be utilized correctly?

Utility of the pANCA in patients who fulfill clinical criteria for CSS

• CSS clinical entities based on MPO ANCA results.
  — MPO-ANCA positive subjects are more likely to display
  • Mononuclearis multiplex
  • Perpura
  • Renal vasculitis
  — ANCA negative patients
  • Tissue infiltrates with eosinophilia
  • More frequent cardiac and pulmonary disease
• CSS represents two distinct disease entities with distinct pathogenesis and genetics

Sinico, 2005, Sable-Fourtassou, 2005, Sinico 2005 (review)
ANCA recognition patterns
- Cyttoplasmic (c)ANCA
- Perinuclear (p)ANCA
- Recognition of Proteinase 3 (PR3)
- Recognition of Myeloperoxidase (MPO)
- Wegener's Granulomatosis
- Churg-Strauss Angitis

Factors associated with poor prognosis in CSS
- Factor 5 score- (French Vasculitis Study Group)
  - Elevated Serum Creatinine (> 1.58mg/dl)
  - Proteinuria
  - Severe GI tract involvement
  - Cardiomyopathy
  - Central Nervous System involvement

No factors present = five year mortality 12%
1 factor= five year mortality of 25%
> 2 factors= five year mortality of 46%

Can the ANCA's role in pathogenesis be used as a marker of disease activity?
  - 73% at diagnosis
  - 75% during flare
  - 16% during remission
  - 36% at diagnosis but after treatment
- ANCA positive more likely to have small vessel vasculitis
  - Renal disease, mononeuritis multiplex, alveolar hemorrhage, and purpura
  - Relapse more likely
  - Higher proportion treated with Cytoxan
  - HLA DRB4 association

ANCA Negative CSS
- Clinical patterns:
  - Pericarditis
  - Livedo
  - Symmetrical polyneuropathy
  - pleuritis
- Eosinophil rich tissue infiltrates
- IL-10 genetic polymorphisms

What criteria is needed for diagnosis of CSS? (Sinico 2009)
- Clinical criteria based on Lanham, ACR, or Chapel Hill
  - Asthma
  - Eosinophilia
  - Multi-system disease- renal, CNS, paranasal sinuses, pulmonary infiltrates
- At least one of the following:
  - Histologic proof of vasculitis
  - Positive ANCA
Surrogate markers of Vasculitis

Sinopulmonary Disease
- Lower Airways
  - Fixed infiltrates
  - Nodules
  - Cavitations
  - Stenosis
- Upper Airways
  - Chronic sinusitis
  - Sub-glottic stenosis
  - Saddle nose deformity

Key Considerations
- Histologic evidence is needed in the diagnosis and as prognostic guides for CSS
- Surrogate markers of vasculitis can be applied in the proper clinical setting
- While only positive in 40%, the ANCA has prognostic value in CSS
- Without poor prognosis factors, treatment need not be aggressive

Suggested treatment Algorithms
- Without Factor Five Score >90% successfully treated with corticosteroids alone
  - 35% relapse
  - Add azathioprine or cyclophosphamide pulse
- Factor Five Score >/= 1
  - Corticosteroids plus pulse cyclophosphamide
  - Treatment duration 6 to 12 months

What about Leukotriene Receptor Antagonists (LTRA)?
- Leukotriene receptors found in the endothelium and up-regulate p-selectin
- LTRA decrease leukotriene production and may increase receptor expression, promoting CSS
- Keogh/Specs-2005
  - 25% of subjects treated with LTRA
  - 80% treated prior to diagnosis
  - 30% relapse rate
  - No difference in relapse or vasculitis compared to subjects not treated with LTRA
  - LTRA unlikely to play a role in pathogenesis of CSS

Key Points
- MPO ANCA used valuable in the diagnosis and management of patients with CSS
- Clinical classification requires histologic assessment for vasculitis
- Use of evidenced-based prognostic criteria can be used prospectively to guide treatment and management
- Leukotriene Receptor Antagonists do not exacerbate the clinical course of CSS

References
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