Rituximab for the management of severe recurrent granulomatosis with polyangiitis

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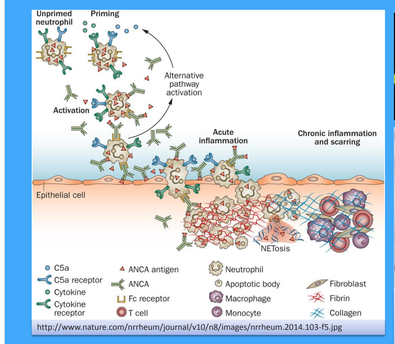
Introduction:

Granulomatosis with polyangiitis (GPA) is a small-vessel, immune-mediated vasculitis associated with increased production of autoantibodies known as anti-neutrophil cytoplasmic antibodies (ANCA).
Prior to the availability of immunosuppressive therapy, the mortality rate of ANCA-associated vasculitis (AAV) was nearly 100%.



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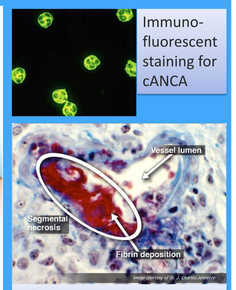


Inflammation of blood vessel walls causing vessel occlusion, ischemia, and necrosis
From http://www.ancasssociatedvasculitis.com/overview/what-is-vasculitis

Traditionally, the gold standard for induction and maintenance was cyclophosphamide in combination with high-dose corticosteroids. However, relapse rates on this regimen can be as high as 50% and chronic cyclophosphamide is associated with a significant risk of toxicity. This case describes the use of rituximab for induction and maintenance in a patient with severe, recurrent GPA.

Case:

24 yo male with history of GPA presenting with

2 weeks of:
- Hemoptysis
- Sore throat
- Mouth sores
- Fever

2 days of:
- Dyspnea
- Pleuritic chest pain

PMH:

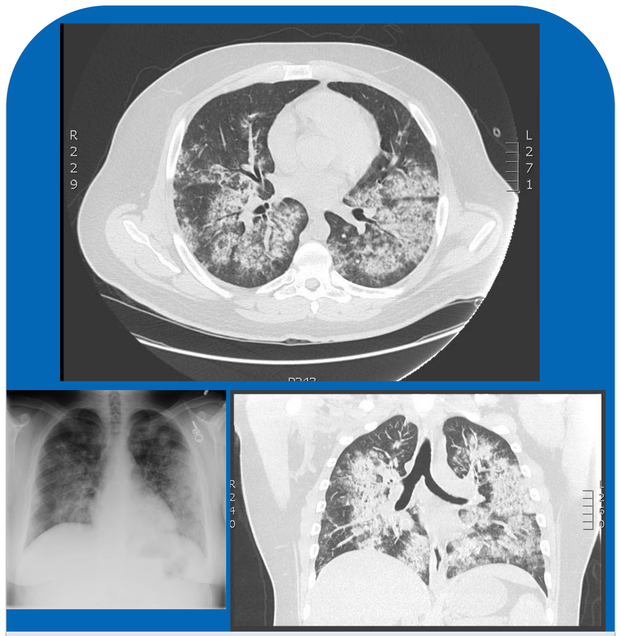
- 2009 (age 18): P/w epistaxis, hemoptysis, pleuritic chest pain, and a 100-lb weight loss.
  - Dx with GPA by lung biopsy.
  - Tx with cyclophosphamide/prednisone induction therapy and maintained on MTX.
- 2013: Recurrence with renal involvement.
  - Induction with rituximab followed by azathioprine/prednisone for maintenance.
- 2014-2015: Noncompliance with maintenance therapy

Hospital course:

VS: AF, 110, 125/76, RR 40, SpO2 95% on BiPAP
CXR and CT chest are shown.
Labs: WBC 17, Hgb 9, Cr 1.8 (baseline)
Bronchoscopy: Diffuse alveolar hemorrhage
- Supported with BiPAP and HFNC
- Continued high dose steroids.
- Plasmapharesis initiated - 4 times over 6 days
- Rituximab started

Outpatient course:

- 4-6 weeks of high-dose prednisone
- Rituximab once a week for four doses then once every 6 months for maintenance



Admission CXR and CT chest showing diffuse ground glass opacities

Discussion:

- **RAVE trial**: cyclophosphamide vs. rituximab for induction in severe AAV → rituximab non-inferior
  - Relapsing disease: rituximab superior to cyclophosphamide for induction
- **RITUXVAS trial**: rituximab vs. cyclophosphamide as induction in newly dx AAV with renal involvement → equivalent rates of relapse and adverse events
- Rituximab has been shown to be effective as maintenance therapy as well
- Our patient had relapsed despite treatment with cyclophosphamide in the past.
- Infrequent dosing of rituximab is appealing in the setting of historical non-compliance.

Discussion (cont.):

This patient also received plasmapharesis to temporarily reduce the burden of circulating autoantibodies until rituximab could take effect.
- Retrospective cohort studies of patients with diffuse alveolar hemorrhage 2/2 AAV who received plasmapharesis in addition to some kind of immunosuppressive therapy had excellent results – close to 100% resolution of alveolar hemorrhage.
- The upcoming PEXIVAS trial is an RCT investigating the role of plasmapharesis in AAV patients with DAH and glomerulonephritis.

Learning objectives:

1) Rituximab is an effective therapy for induction and maintenance for patients presenting with AAV, especially in those who have relapsed after treatment with cyclophosphamide.
2) Patients presenting with pulmonary hemorrhage due to AAV should be treated with plasmapharesis and high-dose steroids initially.

Citations:
- Hoffman GS, et al. "Wegener granulomatosis: An analysis of 158 patients." Annals of Internal Medicine. 1992 March; 116(6): 488-498.
- Stone JH, et al. "Rituximab versus cyclophosphamide for ANCA-associated vasculitis." *New England Journal of Medicine*. 2010 July; 363(3): 221-32.
- Jones RB, et al. "Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis." *New England Journal of Medicine*. 2010 July; 363(3): 211-20.
- Calich AL, et al. "Rituximab for induction and maintenance therapy in granulomatosis with polyangiitis (Wegener's). Results of a single-center cohort study on 66 patients." *Journal of Autoimmunity.* 2014 May; 50: 134-41.
- Guillevin L, et al. "Rituximab versus Azathioprine for Maintenance in ANCA-associated vasculitis." *New England Journal of Medicine*. 2014 November; 371(19): 1771-80.
- Klemmer PJ, et al. "Plasmapharesis Therapy for Diffuse Alveolar Hemorrhage in Patients With Small-Vessel Vasculitis." *American Journal of Kidney Diseases*. 2003 December; 42(6): 1149-53.
- de Luna G, et al. "Plasma exchanges for the treatment of severe systemic necrotizing vasculitides in clinical daily practice: Data from the French Vasculitis Study Group." *Journal of Autoimmunity*. 2015 August; 1-7.
- Krause M, et al. "Update on Diffuse Alveolar Hemorrhage and Pulmonary Vasculitis." *Immunology And*
- *Allergy Clinics of North America.* 2012 November; 32(4): 587-600.