ANCA VASCULITIS

Developed by Adesewa Adeleye and Dr. Daniah Basodan for PedsCases.com.
November 2023

Introduction
Hi everyone, welcome to PedsCases podcast. My name is Adesewa Adeleye and I'm a first-year pediatrics resident at the University of Alberta. This podcast was developed in collaboration with Dr. Daniah Basodan, a pediatric rheumatologist at the Stollery Children's Hospital in Edmonton, Alberta. In this podcast, I will be discussing ANCA-associated vasculitis.

Learning Objectives
By the end of this podcast, listeners will be able to:

1. Provide an overview of the classification of vasculitis
2. Discuss the clinical presentation of ANCA-associated vasculitis in pediatrics
3. Identify the differential diagnosis of ANCA-associated vasculitis
4. Understand the treatment principles and prognosis of ANCA-associated vasculitis

What is vasculitis?
Primary vasculitis can be classified into small, medium, and large vessel disease.[1] Patients can develop vasculitis secondary to an infection, malignancy, drug exposure, systemic lupus erythematosus, and other rheumatological conditions.[2] The most common childhood vasculitis syndromes, HSP and Kawasaki disease are covered in other podcasts and infographics.[2]

This podcast will focus on ANCA-associated vasculitis, or AAV, a group of chronic small vessel vasculitis characterized by positive anti-neutrophil cytoplasmic antibodies (ANCAs). There are three types of AAV: granulomatous polyangiitis (GPA), the most common in children, microscopic polyangiitis (MPA), and eosinophilic granulomatous polyangiitis (eGPA).[3]

Let us begin with into our clinical case.

Clinical Case (pt. 1)
Amber is a 15-year-old female who presents with a four-week history of progressive weakness, joint pain and feeling "stiff as a board in the morning". She also complains of a few weeks of fatigue, fever, a rash on her legs, and a 20lb weight loss.

What are the key features on history and examination?
On history you should find out if weakness is more proximal versus distal, impact on daily function, and progression of the weakness. Symptoms of dysphagia, dyspnea, dysarthria, and dysphonia must be specifically elicited on history. You will also want to identify what joints are affected and how long the morning stiffness lasts. Remember to ask about systemic symptoms such as fatigue, fever, night sweats, swollen lymph nodes, rashes and weight loss. There is a

significant overlap in the clinical presentation of AAV and other rheumatologic disorders such as SLE and JDM; thus, it's important to complete a thorough history. This includes a review of systems to assess the extent of organ involvement. Finally, evaluating the acuity and severity of the patient's clinical presentation is important. Please refer to the "Physical Examination in a Patient with a Suspected Systemic Rheumatic Disease" for further guidance on physical examination.[4]

We'll return to the case for a history and physical examination.

Clinical Case (pt. 2)
Amber tells you that she has been tired over the past four weeks. She has low-grade fevers at night which are associated with night sweats. Her appetite has decreased significantly. She's had nasal congestion and a dry cough for the past month. The congestion has been getting worse and she now has trouble hearing. In the last week, her voice has become quite hoarse, and her throat makes a weird sound when she takes deep breaths.

She also describes daily joint pain and morning stiffness in her knees, ankles, and wrists, which lasts 1-2 hours. She finds it challenging to climb stairs at her home throughout the day because her legs feel weak. Lastly, she reports that her urine is frothy and pink in color. The review of systems was otherwise negative. There is no family history of SLE, JDM, RA, JIA, or vasculitides.

You examine her and notice that she is stridorous. She requires help to reposition during your examination but is appropriate and alert. Her vitals show an elevated heart rate of 110, a normal blood pressure and respiratory rate and no fever.

Additionally, you note a petechial rash on her shins bilaterally, gums, hard palate, and buccal surfaces, but she does not have a malar rash. She has numerous small, tender, and mobile cervical lymph nodes. She has notable inspiratory and expiratory stridor. She has good air entry bilaterally and is not in respiratory distress. 3/4 PIPs and 3/5 MCPs are swollen and tender bilaterally, her knees and ankles are also swollen bilaterally, but she has full range of motion. Her neurological, gastrointestinal, and cardiovascular exams are normal.

In summary, she has systemic features of fatigue, weight loss, petechial rash, lymphadenopathy, polyarthritis, myalgia, fevers, and night sweats. She has upper airway symptoms of nasal congestion, and stridor. She has a cough which is a pulmonary symptom.

Now we have gotten a thorough history and physical we can consider how Amber's features compare to a classic presentation of AAV.

What are the key features of the clinical presentation of AAV?
GPA is characterized by necrotizing granulomatous vasculitis of the upper and lower airways and kidneys. [2,5] Along with the vasculitic rash, most children present with constitutional symptoms such as fever, fatigue, weight loss, lymphadenopathy, myalgias, arthralgias, and arthritis.[2] Pulmonary manifestations can include cough, SOB, hemoptysis, and respiratory failure while renal manifestations include elevated serum creatinine, hematuria, proteinuria, and glomerulonephritis.[2] In children, upper airway involvement such as recurrent epistaxis, sinusitis, nasal septum perforation leading to saddle nose deformities, erosive sinusitis, and subglottic stenosis occurs more commonly than in adults.[1, 2] Potentially life-threatening presentations not to be missed include pulmonary hemorrhage, stridor and airway obstruction. [5]

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A pediatric-specific classification criteria for GPA, known as the EULAR/PReS/PRINTO criteria was adapted from the adult criteria. Children need to meet 3 of the following 6 criteria: upper airway involvement, pulmonary involvement, renal involvement, granulomatous inflammation, laryngotracheal stenosis, and ANCA positivity.[1, 5] Amber so far meets two criteria with upper airway involvement and pulmonary involvement, she likely has renal involvement but will need further investigations to confirm that.

MPA similarly presents as a necrotizing vasculitis with predominant renal involvement. [3] Additionally, patients may rarely present with pulmonary involvement, and more rarely necrotizing skin lesions and ischemic brain lesions.[2] eGPA is exceedingly rare in the pediatric population. eGPA patients often have long standing refractory asthma and recurrent allergic sinusitis.[3] Renal manifestations are uncommon with eGPA in children. However skin, peripheral nerve, cardiac, and gastrointestinal involvement can occur.

Now, let us review Amber's initial investigations.

Clinical Case (pt. 3.)

Her CBCd showed hemoglobin of 65 and a WBC count of 5.5. with elevated neutrophils. Her inflammatory markers were elevated with a CRP of 40 and an ESR of 50. Her electrolytes and creatinine were normal, however, her urinalysis showed 1+ protein and 1+ hemoglobin. Her liver enzymes, INR, and albumin were normal. She had a chest x-ray which showed nodules in her right and left upper lobes.

In summary, her initial labs are notable for anemia, neutrophilia, elevated CRP and ESR, proteinuria, hemoglobinuria, and nodules on the chest x-ray.

Next, we need to develop a differential diagnosis based on the clinical information and results we have so far.

What is the differential for AAV?

Considering the wide range of symptoms patients with AAV can present with, it is helpful to break down the differential by clinical presentation. The differential for systemic symptoms includes malignancies, SLE, JDM, systemic JIA, and other rheumatologic conditions. The differential for pulmonary-renal syndromes (cough, shortness of breath, hemoptysis, elevated serum creatinine, hematuria, proteinuria) includes Goodpasture's (Anti-GBM) disease, SLE, mixed connective tissue disease, other vasculitic diseases such as HSP and malignancies.[5]
Presentation with a petechial or purpuric rash and normal liver function and coagulation profile should prompt consideration of other vasculitic conditions, particularly polyarteritis nodosa. HSP, cryoglobulinemic vasculitis, and other small vessel vasculitis. [3,5, 5]
Imaging findings of pulmonary nodules can be due to sarcoidosis, tuberculosis, and fungal infections; therefore, these are also on the differential.[3] In a patient with weakness and myositis, consider JDM and other rheumatologic disorders, which is why it is important to assess findings of dysphonia, dysphagia, dysarthria and examine for skin findings of these disorders.[5]
Lastly, drug-induced AAV, caused by drugs such as propylthiouracil, hydralazine, and minocycline, can mimic the presentation of AAV.[3]

What are the key investigations for the diagnosis of AAV?

Nonspecific measures of inflammation can be seen in general lab investigations such as increased ESR, CRP anemia, neutrophilia, thrombocytosis, and hypoalbuminemia. Significant eosinophilia and elevation of serum levels of IgE are typical in eGPA. Urinalysis may show proteinuria and microscopic hematuria. Patients may develop elevated serum creatinine and decreased renal function.[5]

ANCA testing

Anti-neutrophil cytoplasmic antibody testing is a cornerstone of the diagnosis of AAV. It is important to note is that a negative ANCA screen does not rule out the presence of the condition. ANCA testing screens for antibodies that bind to certain antigens in a specified pattern (for example, c-ANCA for central, p-ANCA for peri-nuclear). If the screen is positive, specific autoantibodies- anti-MPO and anti-PR3- can be tested.[5] ANCAs can be positive in other conditions, for example in anti-GBM disease and IBD.[5]

In GPA, approximately 90% of ANCA testing is positive with c-ANCA, or anti-PR3 positive.[2,3] In MPA, the yield of ANCA screening tends to be lower (approximately 70%) are ANCA screen positive. They are more likely to be p-ANCA positive and have anti-MPO positivity.[2,3] ANCA testing for eGPA has the lowest yield of all three.

Imaging

Often plain chest radiographs are the first line of imaging ordered, particularly in patients with vague pulmonary symptoms. However, high-resolution computed tomography (HRCT) is the modality of choice for patients with suspected pulmonary hemorrhage. Chest imaging in GPA and eGPA may show nodules, fixed infiltrates, cavitations, pleural effusions, and pneumothoraxes. MPA doesn't have the same pulmonary findings on imaging due to a different pathologic process that does not involve granuloma formation.[5]

Biopsy

If a patient's presentation includes renal involvement, a renal biopsy is the tissue specimen of choice due to being a relatively safe procedure and a high-yield test.[5] While a tissue diagnosis is not required for the diagnosis of AAV, it is included in diagnostic criteria. Pauci-immune glomerulonephritis with granuloma is diagnostic for GPA, and similar findings can be seen in MPA without granuloma formation. Lung biopsies have variable yield, as disease tends to be patchy, and the risks may outweigh the benefits. A bronchoscopy is useful diagnostically for patients with upper airway involvement and allows bronchoalveolar lavages and biopsies to be done, although these may also be low yield. Other less common sites may be biopsied in eGPA, such as muscle.[5]

Clinical Case (pt. 4)

Amber was admitted for further workup and management of her symptoms. She required a large multidisciplinary team, including general pediatrics, rheumatology, pulmonology, nephrology, and ENT specialists. Her ANCA screen came back positive for cANCA and was anti-PR3 positive. She was ANA, anti-dsDNA, and anti-GBM negative.

She had a bronchoscopy which identified blood in the trachea and bronchi and firm subglottic narrowing. She had an audiology assessment which showed a conductive hearing loss. She underwent a renal biopsy which shows pauci-immune crescentic glomerulonephritis.

Given her additional investigations and clinical presentation Amber is diagnosed with GPA. The next question is how to treat her.

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Nov 2023.

What are the treatment principles and prognosis in ANCA-associated vasculitis?
The mainstay of treatment in AAV is immunosuppression. Treatment has two phases, induction therapy which usually involves high dose steroids, and rituximab or cyclophosphamide and maintenance therapy. Induction therapy is maintained until remission is achieved in about 3-6 months, and then patients are transitioned to maintenance therapy.[3] Maintenance therapy should continue for at least 18- 24 months.[5] Choice of induction agent varies based on the predominant organ involved, the severity of the disease, and initial response to therapy. Therefore, treatment is often co-managed between rheumatologists and other specialists. In patients with eGPA, Mepolizumab, an anti–IL-5 monoclonal antibody, may have a role in treatment.[3]

Lastly, in patients who are significantly immunosuppressed from cyclophosphamide or rituximab, infectious prophylaxis with Trimethoprim-sulfamethoxazole should be considered. [5] Once patients improve clinically, they may require further management from other healthcare professionals, including rehabilitation specialists.

Clinical Case (pt. 5)
Given her extensive organ involvement with renal, upper airway, and pulmonary symptoms, Amber had an induction with high dose steroid therapy and rituximab. She went into remission after two months and continues to do well on standard maintenance therapy. Her stridor improved after an intralesional steroid injection on bronchoscopy.

Prognosis
ANCA associated vasculitis was previously associated with significant mortality and remains so if untreated. The mortality has been reduced with cyclophosphamide and rituximab as treatment options.[3] There is a wide range of reported remission rates in children with GPA ranging from 40% to 90%.[5] Disease relapse can occur in up to 60% of patients with AAV.[3]

Conclusion
Let us review the key learning points of this podcast:

- Vasculitis is a broad term referring to multiple diseases often classified by size of vessels predominantly affected.
- GPA presents with sinus, pulmonary and renal manifestations of necrotizing granulomatous inflammation.
- MPA has predominantly renal involvement with rare pulmonary involvement organs.
- Patients with eGPA almost always have a history of asthma and can have skin and cardiac manifestations
- Given the broad range of symptoms and differential for AAV, investigations should include general markers of inflammation, a peripheral blood smear, urinalysis, serum creatinine, and ANCA testing.
- Tissue diagnosis can help separate AAV from other rheumatologic conditions, but it is not mandatory for diagnosis.
- Treatment should focus on induction, followed by maintenance therapy, and is managed longitudinally by a multidisciplinary team
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