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Granulomatosis with Polyangiitis at Age 13 in an American Indian/Native American Patient

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ABSTRACT

Granulomatosis with polyangiitis (GPA), previously known as Wegener's granulomatosis, is a rare small vessel vasculitis that is a part of the ANCA-associated family. First distinctly identified by Fredrick Wegener in 1936, GPA has had little light shed on the direct pathophysiology for the development of the disease. Classically the disease presents in Caucasian males during the fifth to seventh decades of life [1]. GPA can present with a wide array of symptoms and therefore the diagnosis can be easily missed. Unfortunately, without proper prompt treatment the disease can progress causing irreversible organ damage leading to chronic, relapsing dysfunction and possible death. Given this, early recognition and treatment of the disease is essential. This becomes difficult when given an atypical patient presentation compounded with nondescript symptoms. In this case-presentation, we review an atypical presentation of GPA from a rural rheumatology clinic in the United States with the intention of expanding the current limited literature. Through thorough literature-search we were able to find reports of a 12 year old female that was diagnosed with GPA, and a young 8 -year old American Indian/Native American (AI/NA) female diagnosed with microscopic polyangiitis, however, to our knowledge this is the youngest known AI/NA patient to be diagnosed with GPA at 13 years of age [2,3].

Abbreviations and Keywords

GPA: Granulomatosis with polyangiitis, ANCA: Antineutrophil Cytoplasmic Antibody, PR3-ANCA: Serum anti-proteinase 3 antineutrophil cytoplasmic antibody, AI/NA: American Indian/Native American.

Background

Granulomatosis with polyangiitis (GPA), previously known as Wegener's granulomatosis is a type of necrotizing vasculitis that typically affects small sized vessels, a classic antineutrophil cytoplasmic autoantibody (ANCA) associated vasculitis with ANCA being detected in approximately 40 – 60% of affected patients [4]. Of those with ANCA associated disease, 90% have been found to be associated with PR3-ANCA [4]. ANCA is believed to play a key role in the pathogenesis of GPA by forming heterogeneous antibodies that attack antigens on polymorphonuclear leukocytes [5]. Although the most common ANCA-related disease, GPA is still a rare disease with an incidence of only 3 per 1 million in the

United States [5]. Of the individuals that are found to have GPA, the majority are adults aged 50 to 70 years of age, making the onset of GPA in pediatrics incredibly rare with an incidence rate of 1.8 per million in the pediatric population age 0-18 years [1,5,6]. The majority of juvenile patients diagnosed with GPA are Caucasian females [7]. With this being said, it has been shown that the prevalence of rheumatologic disease is high in American Indian/ Native American (AI/NA) populations, as much as 2-4 times as great as non-native populations [8,9]. A previous population-based study found the prevalence for vasculitis in the AI/NA population as high as 7.9% and that ANCA-associated vasculitis caused more deaths in AI/NA populations than any other race [10]. In addition, comparative to all other vasculitis, GPA was most likely to cause death [10].

The most commonly affected organ system in patients with GPA is the respiratory system regardless of age [11]. In juvenile GPA, respiratory involvement is seen in up to 82% of cases followed by nephropathy at 65% and musculoskeletal at 55% [3]. Other symptoms that are less specific such as fever and fatigue are also frequently seen in up to 73% of patients [3,8]. Considered fairly uncommon, subglottic stenosis affects only 10% of adults diagnosed with GPA, however has been shown to be 5 times more common among patients diagnosed at a pediatric age [12,13]. EULAR/PRINTO/PRES criteria for diagnosis of childhood GPA require three of six of the following: (1) evidence of granulomatous inflammation via histology; (2) upper respiratory involvement; (3) laryngo-tracheo-bronchial involvement; (4) pulmonary involvement seen on imaging via radiography or CT; (5) antineutrophil cytoplasmic antibody positivity; (6) renal involvement [14]. Laryngo-tracheo-bronchial involvement with subglottic, tracheal or bronchial stenosis has a 99.8% specificity. The recommended treatment for severe active disease is combination therapy of cyclophosphamide/rituximab and glucocorticoids. Following induction of remission, continuation of rituximab has shown decreased incidence of relapse, however based on the patient's clinical presentation, methotrexate may be used as an alternative [15-17]. Unfortunately, even with strict adherence to the aforementioned therapy, there continues to be significant amounts of relapse in the pediatric population [3,15].

Case

A young AI/NA female presented for an evaluation in our Rheumatology Clinic at the age of 32 years. She was accompanied by her mother who was her acting power of attorney and her 'voice'. She acted as the primary historian as the patient could not speak clearly due to dysphonia. A detailed history revealed that at the age of 11 years the patient started experiencing multiple episodes of frequent upper respiratory tract symptoms, stridor, and multiple hospitalizations for pneumonitis. For a significant period, the patient was given the diagnosis of a recurrent infectious pharyngitis, sinusitis and pneumonia. However, with conventional treatment including antibiotics prescribed for the above diagnoses the patient's respiratory symptoms continued to progress. It took an advancement of her condition leading to hemoptysis and a horrifying incident of cardiac arrest to further investigate other causes of her ongoing problems. Now, quite emotional, the patient's mother recalled that her primary care provider seemed to begin to dismiss the patient's concerns and symptoms, even after being seen in the emergency department multiple times for the same ongoing symptoms. After the patient's cardiac arrest episode, finally there began an exhaustive workup, which consisted of numerous bronchoscopies, a total of 14 as the mother recalled. Subsequently, she developed dysphonia and signs of renal involvement including decreased renal function and proteinuria.

A multidisciplinary approach at a leading academic Children's Hospital led to extensive investigation, which included bronchoscopy and lung biopsy. Tracheal stenosis with granulation tissue within the proximal trachea leading to partial obstruction of the airway was found along with multiple nodules. Immunology work-up revealed a significantly positive proteinase-3 ANCA. In view of the patient's declining renal function, a renal biopsy was performed. It showed classic pauci-immune crescentic glomerulonephritis. A diagnosis of juvenile GPA with respiratory involvement and rapidly progressive renal dysfunction was established. Initially, plasmapheresis was started for the bronchoalveolar hemorrhage that developed synchronously, along with induction therapy with rituximab infusions in conjunction with corticosteroids, followed by maintenance with six-monthly rituximab infusions for 3 years.

As an adult now, at her initial rheumatology visit in the clinic with us, she was further evaluated with detailed laboratory studies. Results showed high proteinase 3 antibodies however, c-ANCA, p-ANCA, and anti-MPO antibodies were negative. Quantitative immunoglobulins revealed hypogammaglobulinemia consisting of decreased levels of IgA and IgG most likely due to B-cell depletion related to the use of rituximab leading to a decrease in plasma cells. At this time, a shared informed decision was made to replace rituximab with methotrexate, which is also recommended for maintenance treatment of GPA [4]. She has remained free of any further respiratory, renal or other vital organ involvement by GPA so much so that she has agreed to taper her methotrexate dose while staying off prednisone. Unfortunately, the patient's trachea and larynx sustained permanent damage and thus she is unable to articulate well. Although her speech is limited, her smile and stoic perseverance fills up the clinic with hope and admiration.

Discussion

Diagnosis of juvenile GPA can be difficult due to the varying symptomologies as well as the rarity of early onset of this disease, however, due to the significant burden of disease-related morbidity and mortality, it should be thoughtfully considered. The disease is rapidly progressive and thus if misdiagnosed and left untreated, the mean life expectancy of a patient with GPA is 5 months [4]. It is imperative that when a diagnosis of GPA is made, prompt treatment be initiated. Current revelations in initiation as well as maintenance treatment have shown that rituximab prevails as a reasonable choice for both initiation as well as maintenance compared to cyclophosphamide and methotrexate especially when considering their risk profiles [18,19]. Officially, however, the CanVasc as

well as EULAR/ERA-EDTA recommends remission maintenance treatment with a combination of low-dose glucocorticoids and either azathioprine (AZA), rituximab, methotrexate or mycophenolate mofetil. Methotrexate is recommended in combination with glucocorticoids in those with limited or non-organ threatening AAV. Methotrexate and azathioprine have comparable efficacy rates for remission maintenance [16]. As stated before, rituximab is favored, however due to factors such as cost and limited long term safety data its use may be limited [16,20]. 2021 American College of Rheumatology/Vasculitis Foundation Guidelines for Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis, Recommendation: for patients with severe GPA/MPA whose disease has entered remission after treatment with cyclophosphamide or rituximab, we conditionally recommend treatment with methotrexate or azathioprine over leflunomide for remission maintenance [21]. There has been much debate as of late on appropriate duration of treatment with some advocating for a tailored approach. The most recent recommendation from MAINRITSAN calls for rituximab twice yearly for 18 months [19]. Further, even with adequate treatment, children who were diagnosed with GPA went on to develop chronic conditions such as chronic kidney disease, hearing loss, subglottic stenosis, and avascular necrosis [5].

Conclusion

After thorough literature research, this is the youngest onset of juvenile GPA in an AI/NA patient. Due to the substantial morbidity and mortality risk of GPA, especially seen in the AI/NA population, it is critically important to recognize juvenile GPA early and offer swift attention and aggressive treatment in order to improve patient outcomes.

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