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Research Article

14.3.3 ETA positivity in GPA in an American Indian/Native American male

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Abstract

As of 2024, the Oklahoma population consists of about 535,675 American Indians, which makes up about 13.1% of the state's total population. We present a case of a 46-year-old American Indian/Native American (AI/NA) male in Tahlequah, the capital of Cherokee Nation, Oklahoma who presented with symptoms and laboratory markers consistent with c-ANCA (antineutrophil cytoplasmic antibody) granulomatosis with polyangiitis (GPA), which is a small-medium vessel vasculitis. The annual worldwide incidence of GPA is about 10-20 cases per one million and the incidence in the United States is 3 per one million population. In a previous study, the incidence of GPA was reported in the predominantly Inuit population of Greenland and the Caucasian population of the Faroe Islands. To our knowledge, this is the first case report in the medical literature about an AI/NA with c-ANCA positive vasculitis who was also strongly positive for 14.3.3 ETA, but without classical features of rheumatoid arthritis (RA) for which 14.3.3 ETA is considered a novel specific dynamic biomarker.

Keywords: 14.3.3 ETA positivity

Introduction

Vasculitis refers to a group of diseases which involve inflammation of the blood vessels. This includes small, medium and large blood vessels. Vasculitis may be autoimmune in etiology, but can also be due to medications, malignancy or viral infections such as hepatitis B or C.[1] One form of vasculitis is known as GPA, previously known as Wegener's granulomatosis, which is a small-medium vessel vasculitis. GPA can be further sub-classified as one of the ANCA associated vasculitides (AAV), with others being microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA or Churg Strauss syndrome).[2] GPA is typically associated with cytoplasmic/c-ANCA. In GPA, antibodies typically react with proteinase 3 (PR3), an enzyme present in neutrophil granulocytes. This activates the neutrophils and induces de-granulation which damages the vascular endothelium.

GPA classically presents with a triad of upper respiratory, lower respiratory, and kidney involvement. Upper respiratory tract symptoms may include sinusitis, rhinitis, mastoiditis, and hearing loss. Lower respiratory tract symptoms are characterized by lung nodules which can

cavitate and serious alveolar hemorrhage. Pauci-immune glomerulonephritis with or without crescents is the hallmark of renal involvement in GPA. It is the most common of the three AAV's. The annual worldwide incidence is about 10-20 cases per one million, with a higher incidence found in colder regions.[2] The incidence in the United States is 3 per one million population, and found to be more common in adults with a peak incidence of 64 to 75 years of age.[2] More cases have been reported in the Caucasian population, but it has been seen in all racial and ethnic cohorts.

RA is a systemic inflammatory autoimmune disease which presents with symmetrical joint pain, stiffness, and swelling, most commonly in the small joints of the hands and feet but can involve the larger joints.[3] In general, RA is more prevalent in women compared to men, with women having a lifetime risk of 3.6% compared to 1.7% in men.[3] RA also increases with age, with a peak incidence between 65-80 years old. Notably, Native Americans have a higher rate of RA, due in part to a combination of genetics, environmental factors, and immune dysregulation.[3]
Rheumatoid factor (RF), a widely used marker for RA, is not very sensitive especially in the early stages of RA, and not very specific either. Anti-cyclic citrullinated peptide (CCP) antibodies are more specific (98%) and can be a prognostic marker for aggressive erosive disease with a higher propensity for extra-articular manifestations.[4]

14.3.3 ETA protein is a relatively novel dynamic inflammatory marker for rheumatoid arthritis which is released into synovial fluid and peripheral blood in RA.[5] This marker has an 88% specificity in patients with RA.[5] Unlike RF and CCP, 14.3.3 ETA protein is a dynamic biomarker that can be monitored to gauge response to therapy.[5] A decrease in 14.3.3 ETA protein can be seen in response to disease modifying anti-rheumatic drugs (DMARDs) and an increase in its level has been associated with worse outcomes even during stages of clinical remission.[5]

Methods

We followed the course of a 46-year-old AI/NA male who started experiencing abrupt pain and stiffness to the joints of his bilateral lower extremities in February 2023. At the time, he was only taking ibuprofen with minimal relief in pain. Later in April, he developed redness to the left eye, which was suspected to be episcleritis. Around May 16, his right middle finger started becoming necrotic, and a week later he went to the emergency room (ER) for further evaluation. During his stay he was discovered to have Raynaud's disease. By the end of May, the pain in the right third digit had escalated to 6/10 and was worse with lying supine.

In early June, the patient developed another black spot on the radial aspect of the right third fingertip which had become scabbed. He went to the ER yet another time with pain and new onset numbness in the right third digit, as well as swelling to the left ankle. The patient was then seen by Vascular Medicine/Surgery. Ultrasonography of the fingertips and toes did not demonstrate medium to large arterial insufficiency. The patient was subsequently referred to rheumatology for further evaluation for concerns of an autoimmune etiology. The patient was started on clopidogrel 75 mg/day and hydroxychloroquine 200 mg/day orally. However, the patient started noticing similar black lesions to the left second and third toes. In conjunction with black lesions to his digits, the patient had developed redness to his right eye with significant photophobia and the ocular findings were suggestive of acute anterior uveitis. While this was all going on, the patient also developed concomitant inflammatory pain to his bilateral shoulders and knees, and the right ankle which he rated as a 6-7/10. It was difficult for the patient to even raise his arms above his head to perform activities such as brushing his hair.

The patient was seen in the rheumatology clinic with the following laboratory results. The patient's urinalysis was significant for 3+ blood and 1+ protein, and his urine microscopy was significant for 6-10 WBCs and >20 RBCs. His hemoglobin was low at 12.3 g/dL and serum creatinine was elevated at 1.3 mg/dL. WBC, platelet count, absolute lymphocyte count, AST/ ALT, alkaline phosphatase, total bilirubin and serum albumin were within normal limits. He had a c-ANCA positive titer of 1:160, which was where the initial concern for GPA came about. The ESR was significantly elevated at 86 mm/hour and his CRP was elevated at 85.4 mg/L. Rheumatoid factor was positive at 51 Units but then became negative. The 14.3.3 ETA marker was significantly elevated at 14.2 (normal <0.2) and the anti-histone antibody level was elevated at 1.4 on 7/31/23. He had not taken any known pharmaceuticals that can induce lupus. Antinuclear antibodies, anticardiolipin IgG and IgM antibodies, dsDNA antibodies, hepatitis B surface antigen and surface antibody, hepatitis B total core antibody, complement C3, C4 levels, RNP, Smith, Jo-1, CCP, anti-centromere, anti Scl-70, SS-A, SS-B, and RNA polymerase III antibodies were all negative. The serum angiotensin converting enzyme level was within normal limits. Hepatitis C antibody and TB QuantiFERON Gold were negative as well. With a significantly positive c-ANCA, and an active urinary sediment, a kidney biopsy was performed, which demonstrated pauci-immune crescentic glomerulonephritis with active and chronic components. This confirmed the diagnosis of GPA, in conjunction with the patient's clinical and laboratory picture.

Given the severity of this patient's disease with the renal and cutaneous vasculitic involvement and a history of uveitis, the decision was made to initiate intravenous rituximab infusions 1000 mg at week 0 and 2 weeks in conjunction with prednisone 40 mg orally daily which was tapered off over 6 weeks. The patient improved symptomatically within 6 weeks with this treatment. His uveitis, arthralgia and cutaneous ischemic vasculitic symptoms quickly resolved. The hydroxychloroquine was subsequently discontinued, and the patient is on maintenance 1000 mg rituximab infusion every six months from the previous set. He has not had not relapse at the 18-month follow up.

Discussion

The patient's 14.3.3 ETA marker was significantly elevated, and as

mentioned earlier, this marker is specific for RA. Two studies in particular have demonstrated the correlation between 14.3.3 ETA and rheumatoid arthritis. In a study by Kilani et. al, the purpose was to investigate whether 14.3.3 ETA proteins were detectable in synovial fluid of patients with inflamed joints. This study found that of the seven 14.3.3 isoforms, 2 isoforms in particular, ETA and gamma, were detectable in synovial fluid samples from patients with inflammatory joints, and the level of the proteins were significantly elevated in inflammatory and synovial fluid samples compared to controls.[6] Another study highlighting the significance of 14.3.3 ETA was completed by van Beers-Tas et. al. This was a prospective cohort study in which 144 subjects with arthralgia and positivity for rheumatoid factor (RF) and/or anti-citrullinated protein antibody were followed to investigate the relationship between the presence/levels of 14.3.3 ETA and the development of arthritis. The results of this study demonstrated arthritis occurred in 43 of 144 subjects after 15 months, and 14.3.3 ETA was detectable up to 5 years before onset of clinical arthritis and was present significantly more often (36 % versus 14 %; relative risk 2.5, 95 % confidence interval 1.2-5.6; p = 0.02) and at significantly higher levels (median 0.95 versus 0.28 ng/ml; p = 0.02) in subjects developing arthritis compared with those who did not.[7] The only study in the literature to our knowledge which has been completed assessing the incidence of GPA in a Native American population was completed by Faurschou et. al. In this study, they assessed the incidence of GPA in the predominantly Inuit population of Greenland and the Caucasian population of the Faroe Islands from 1992-2011.[8] People from Greenland and the Faroe Islands were referred to the National University in Copenhagen if symptoms suggestive of a severe rheumatic disorder develop. However, no formal diagnoses of rheumatoid arthritis based on lab markers were made in this study to our knowledge. The study used one GPA patient from Greenland and 6 from the Faroe Islands. The Greenlandic-born patient was of Inuit ethnicity. The incidence of GPA in Greenland was 1.0/million/year (95% CI 0.02-5.6) over the 19-year period, with an incidence of 4.1/million/year calculated for those aged greater than or equal to 45 years of age. During the period of the study, no cases of GPA were found among Greenlanders aged 0-44 years.[8]

Conclusion

To our knowledge, this is the first observation of an unusual situation in which 14.3.3 ETA was strongly positive without fulfilling the criteria for full RA. Instead, the patient presented with c-ANCA positive organ-threatening GPA with cutaneous ischemic, inflammatory articular, ocular and renal components. The patient responded well to rituximab induction therapy, and his GPA has been in remission for 18 months now, on maintenance rituximab infusions 1000 mg every 6 months. Of course, this is just one case of such a presentation, and more research will need to be done to add to this observation especially in the AI/NA population in the future.

Conflict of interest: None

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