

Identifying Atypical Familial SLE in the American Indian/Alaska Native Population

Caleb S. Alexander MPH¹ and Prashant Kaushik MD^{2*}

¹Osteopathic Medical Student IV, Oklahoma State University, Center for Health Sciences, College of Osteopathic Medicine, Cherokee Nation, Oklahoma, USA.

²Chief, Division of Rheumatology, Northeastern Health System (NHS), Tahlequah, OK; Clinical Professor of Medicine, Oklahoma State University Center for Health Sciences (OSU CHS) College of Osteopathic Medicine at the Cherokee Nation, Tahlequah, OK. Associate Program Director, Internal Medicine Residency Program, TMG/OMECO, 1373 East Boone St., Suite 2300, Tahlequah, Oklahoma.

*Correspondence:

Prashant Kaushik, Chief, Division of Rheumatology, Northeastern Health System (NHS), Clinical Professor of Medicine, Oklahoma State University Center for Health Sciences (OSU CHS) College of Osteopathic Medicine at the Cherokee Nation. Associate Program Director, Internal Medicine Residency Program, TMG/OMECO, 1373 East Boone St., Suite 2300, Tahlequah, Oklahoma..

Received: 25 Feb 2024; Accepted: 27 Mar 2024; Published: 02 Apr 2024

Citation: Caleb S. Alexander, Prashant Kaushik. Identifying Atypical Familial SLE in the American Indian/Alaska Native Population. J Med - Clin Res & Rev. 2024; 8(3): 1-3.

ABSTRACT

Systemic lupus erythematosus (SLE) is a major chronic systemic inflammatory autoimmune condition that affects all demographics of the population; however, it is typically thought to be a disease primarily of females since about 9 in 10 diagnosed cases are in female patients. While there are studies describing the prevalence of disease in the American Indian/Alaska Native (AI/AN) population, few individual cases are highlighted. We present a pair of cases among two AI/AN full-blood brothers, who are members of the Cherokee Nation (CN), Oklahoma.

Keywords

Systemic lupus erythematosus, Male, Siblings, American Indian/Alaska Native.

Introduction

Providing state-of-the-art healthcare to certain ethnic populations like the AI/AN communities has been at the very least “challenging.” Despite initiatives to improve the quality of care among the AI/AN population, these individuals are often grouped into the “Other” category in health reporting efforts leading to challenges in assessing health data [1]. It is more so a tall order when it comes to a subspecialty like Rheumatology with a worsening nationwide shortage of Rheumatologists especially in rural communities where most AI/AN live [2].

In January 2021, the first Division of Rheumatology was started at the Northeastern Health System, a health care facility in Tahlequah, Oklahoma, capital of the CN. It has been providing full-time Rheumatology services to a large population, including all of the Cherokee Natives, via a mixed-model offering both face-to-face and virtual Rheumatology visits [3]. This has been shown to be the

optimal combination, overcoming the barriers to accessing care posed by distantly living AI/AN patients, while also mitigating the limitations of virtual consultation [4]. One major chronic systemic inflammatory autoimmune rheumatologic condition that can cause severe and life threatening complications is SLE [5]. Due to the typical demographics of SLE, it can often be overlooked in the “atypical” patient especially with the atypical demographics. An international study of patients with SLE according to the Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) criteria found that of 823 patients across 8 countries, 93.2% of patients were female with a mean (SD) age of 45.3 (13.9) years and 11.1 (9.2) years since diagnosis [6]. Further, of the 779 patients reporting race, 9.1% were Asian, 16.4% Black, 69.5% White and 5.0% “Other”. Another study examining 5417 cases of SLE in the United States found that prevalence of disease was 9 times higher for females than males overall, with about 128.7 cases per 100,000 females and only 14.6 cases per 100,000 males [7]. This lower prevalence of SLE in males could lead to missed cases based on males not fitting the “typical” patient, especially in atypical demography.

As mentioned above, many studies lump the AI/AN population into the “Other” category when describing race/ethnicity [1]. However, studies that do include the AI/AN category often reveal health disparities among this population. For example, AI/AN people were found to have higher disease prevalence overall and for their respective sex in one study [7]. This study found that prevalence of SLE was 270.6 cases per 100,000 for females and 53.8 cases per 100,000 for males. Although data from the Indian Health Services registry that was used in this study revealed that the AI/AN population is at a greater likelihood to be diagnosed with SLE, there is paucity of literature on SLE in AI/AN males. Our intention is to add to the available literature and emphasize the importance of considering SLE diagnosis in appropriate AI/AN male patients.

Case 1

A 27-year-old CN male with a past medical history of SLE presented to the rheumatology clinic to establish care. He reported two hospitalizations for pericarditis over the past three years. His previous rheumatologist who diagnosed the patient with SLE had retired. His pericarditis was likely a complication of SLE, other causes having been eliminated carefully. He was being treated with hydroxychloroquine (HCQ) 200 mg orally twice a day, azathioprine 50 mg orally twice a day, and prednisone 10 mg orally daily. On this regimen, he endorsed extreme fatigue, significant inflammatory polyarticular joint pain (hands, wrist, elbows, shoulders, knees, ankles, and feet), xerostomia and xerophthalmia. His symptoms had worsened over the past 6 months to the point where he had to quit his employment completely. His joints took over an hour to limber up in the morning. He also endorsed swelling in elbows, hands, and feet (worse on right foot). He reported weakness and difficulty opening a jar. He had sensitivity to sunlight and a butterfly malar rash, worsening over the past few months. He stated that his fingers and toes turn white/blue with cold exposure. He did have a strong family history of autoimmune diathesis: Grave’s disease and rheumatoid arthritis in his maternal grandmother, SLE in his paternal aunt, and his full brother had a ‘hitherto’ unknown autoimmune disease.

Initial physical examination had shown a distinct erythematous malar rash classic of acute cutaneous lupus erythematosus, which was still present despite the maximal daily dose of HCQ and adjunct-prednisone. In addition, there was a discoid rash in his scalp. There was no pleural or pericardial rub on auscultation. Multiple peripheral small joints were clinically synovitic in a symmetrical fashion without any obvious deformities. Recent laboratory studies revealed a normal leukocyte count, hemoglobin and platelet count. Renal function was normal with an estimated glomerular filtration rate (GFR) for non-African Americans of >60 ml/min. Urinalysis was unremarkable. Liver chemistry tests were unremarkable. He did have 5 consecutive values of an elevated erythrocyte sedimentation rate (ESR) over the previous 12 months. Serum C-reactive protein (CRP) level was also elevated. Antinuclear antibodies (ANA) were strongly positive at 1:1280 titer, nuclear homogenous pattern. Anti-Smith antibodies, SS-A, chromatin, and ribonucleoprotein antibodies were positive.

Lupus anticoagulant was not detected. Double stranded (ds) DNA antibodies were normal at this time. Hepatitis B and C serology panel negative. Jo-1 antibodies were negative. C3 and C4 normal. QuantiFERON tuberculosis testing was negative. Cyclic citrullinated peptide (CCP), histone, centromere, Scl-70 and RNA polymerase III antibodies were negative. After extensive discussion with the patient, a shared informed decision was made to add belimumab once weekly injection to the existing HCQ 200 mg twice daily. A gentle corticosteroid tapering program was also initiated. He became virtually asymptomatic in 3 months and continues to do well clinically without any recurrence of pericarditis. His laboratory values especially the acute phase reactants ESR and CRP have normalized. He is back working again and remains gainfully employed.

Case 2

The above patient brought his full brother, 26 years of age, to be evaluated for the first time by a Rheumatologist to our clinic. Patient endorsed daily joint pain in his wrist, elbows, hips, knees, ankles, and feet going on for 2 years, achy in quality, 10/10 at worst, associated with occasional swelling, fatigue, morning stiffness lasting longer than 1 hour, dry mouth and eyes, a malar rash, Raynaud’s phenomenon to the fingers and toes, and recurrent sores in the mouth and nose. His primary care physician had started him on prednisone 15 mg daily and HCQ. There was no history suggestive of pleuritis, pericarditis, renal or neurological involvement.

The pertinent positive findings on physical examination revealed a distinct malar rash sparing the nasolabial folds, and clinical synovitis to several peripheral small joints of all four extremities. Initial laboratory evaluation showed leukocytosis and elevated ESR and CRP levels. On prednisone and low dose HCQ (200 mg daily) started by his primary care physician, that the patient was taking for the previous 3 months, the follow-up labs showed: Lymphopenia with a normal hemoglobin and platelet count. Estimated GFR was normal. In the liver chemistry panel, serum alanine aminotransferase (ALT) level was elevated at 50 (less than 3 times the upper limit of normal for the CN lab). Serum creatinine level was normal with an estimated GFR for non-African Americans of >60 ml/min. Urinalysis was unremarkable. ANA was positive 1:40 titer cytoplasmic pattern and 1:40 titer nuclear speckled pattern. Double-stranded DNA antibodies were negative. C3 and C4 levels were normal. CRP level was now normal. Hepatitis B core antibody was nonreactive. Hepatitis B surface antibody was reactive. Hepatitis B surface antigen was nonreactive. Hepatitis C antibody was nonreactive. Jo 1 antibodies were negative. Rheumatoid factor, RNP, Smith, centromere, CCP antibodies, RNA polymerase III, Scl 70, SSA and SSB antibodies were negative. QuantiFERON-TB testing was negative. Alpha gal IgE antibodies were elevated at 0.23. On deeper interrogation, he did mention having allergic reactions 3 to 6 hours after ingesting mammalian meat for 3 years now.

A shared informed decision made towards going up on the dose of HCQ to 200 mg orally twice a day on Mondays, Wednesdays

and Fridays and 200 mg orally once a day on the other 4 days of the week based on the maximal daily dose of 5 mg/kg actual body weight, not to exceed 400 mg per day. A whole-food plant-based nutrition, carrying an epinephrine pen for any incidental exposure to animal (especially non-primate mammalian) products and a regular follow up with Rheumatology with pertinent laboratory evaluation was agreed upon.

Discussion

There are several strengths to reporting these cases of SLE among two full CN brothers. First, discussing these cases increases the literature available and awareness of SLE in young, AI/AN males. Since SLE is much more prevalent in women, and most studies do not include AI/AN as a distinct race/ethnicity variable, the health disparities in this population are often understated. A few studies that have looked at SLE among AI/AN males report that the age-adjusted prevalence (95% CI) of disease is about 54 (36-77) per 100,000 population - more than three times the prevalence among all males [7,8]. Although the overall number of AI/AN males is a small proportion of all SLE cases, it is important for healthcare providers to recognize that their AI/AN male patients are more likely to have SLE than their other male patients. Further, this report adds to the awareness of genetic components to SLE. Although the presentation and cause of SLE are both multifactorial, studies have shown that siblings of SLE cases are at an 8-20 times increased relative risk of disease over the general population [9]. In our submission, two full-blood brothers are both diagnosed with SLE within a short period of time. While one brother (Case 1) had a more significant symptomatology including recurrent pericarditis prior to diagnosis, it is unknown how significant the disease complications would have been in the younger brother if the diagnosis and treatment had been delayed furthermore.

In addition to the increasing awareness of SLE among AI/AN males, and the AI/AN population at large, this submission raises some questions for future study. While there are studies that look at the prevalence of SLE in the AI/AN population, it is unknown if there are variations among the different tribes - such as the Cherokee population of which these brothers belong. Further, the possibility of differences in disease burden among the AI/AN population, such as age of development, disease severity and organ system involvement could be better described in future studies. Overall, reporting the AI/AN population in study demographics would help increase awareness of health disparities and disease burden in this population.

Another important observation in Case 2 was the Alpha-gal syndrome (AGS), a novel IgE mediated condition recognized by us more and more in the AI/AN population of the CN [10]. It can be a potentially lethal condition with severe delayed allergic reaction typically to non-primate mammalian meat consumption and

products derived thereof. It has a therapeutic implication as well. All medications, including HCQ, have to be free of mammalian products in AGS patients. This is particularly challenging despite our continuing efforts because even most compounding pharmacies in the country have not been able to provide a continuous supply of the medication.

Conclusion

SLE remains a challenging systemic inflammatory autoimmune rheumatologic disease. We hereby submit a situation of two full AI/AN brothers with SLE, with the younger one also having AGS. To the best of our knowledge this is the first such observation from the AI/AN population. Our intention is to add to the available 'sparse' literature on some unique features of systemic rheumatic diseases like SLE in the AI/AN population. This will increase the awareness about SLE in the "atypical" patient, especially from the deserving yet underserved AI/AN population.

References

1. Sequist TD. Improving the Health of the American Indian and Alaska Native Population. *JAMA*. 2021; 325: 1035-1036.
2. Lennep DS, Crout T, Majithia V. Rural health issues in rheumatology: a review. *Curr Opin Rheumatol*. 2020; 32: 119-125.
3. Kaushik P, Ashraf A, Marak CP, et al. Virtual Rheumatology during COVID-19 A gift in a seemingly ugly package. *Oklahoma State Medical Proceedings*. 2021; 5: 2.
4. Kaushik P, Bastible S, Marak C. On telemedicine in rheumatology. *Arthritis Care Res*. Hoboken. 2022; 22.
5. Bernatsky S, Boivin JF, Joseph L, et al. Mortality in systemic lupus erythematosus. *Arthritis Rheum*. 2006; 54: 2550-2557.
6. Arnaud L, Furie R, Morand EF, et al. Burden of systemic lupus erythematosus in clinical practice baseline data from the SLE Prospective Observational Cohort Study SPOCS by interferon gene signature. *Lupus Sci Med*. 2023; 10: e001032.
7. Izmirly PM, Parton H, Wang L, et al. Prevalence of Systemic Lupus Erythematosus in the United States Estimates From a Meta-Analysis of the Centers for Disease Control and Prevention National Lupus Registries. *Arthritis Rheumatol*. 2021; 73: 991-996.
8. Ferucci ED, Johnston JM, Gaddy JR, et al. Prevalence and incidence of systemic lupus erythematosus in a population-based registry of American Indian and Alaska Native people 2007-2009. *Arthritis Rheumatol*. 2014; 66: 2494-2502.
9. Harley IT, Sawalha AH. Systemic lupus erythematosus as a genetic disease review. *Clin Immunol*. 2022; 236: 108953.
10. Kaushik P, Kaushik AA. Palindromic rheumatism as a feature of alpha-gal syndrome Initial observation on 18 patients from the capital of the Cherokee Nation. *Int J Rheum Dis*. 2023; 2.