# Overlooking Recurrent Acute Rheumatic Fever in Adulthood

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## Abstract

*Acute rheumatic fever in an adult is a rare entity. We present a 29-year-old man of mixed ancestry, including Native Hawaiian and other Pacific Islander, who presented with a 6-week history of migratory polyarthralgia and fever with a recent history of purulent lower extremity wounds and a remote history of acute rheumatic fever in childhood. The diagnosis of recurrent acute rheumatic fever was confirmed by elevated Antistreptolysin-O titers and Anti-DNase B titers. This case presentation showcases a Native Hawaiian and other Pacific Islander with acute rheumatic fever in both childhood and adulthood following pyoderma infection, with a delay in diagnosis and management for both episodes. The patient had an excellent response to naproxen without developing complications and was restarted on secondary antibiotic prophylaxis. Health care providers in the Pacific region should understand the relationship between pyoderma and acute rheumatic fever in addition to including acute rheumatic fever in the differential diagnosis of polyarthralgia in an adult.*

## Keywords

*acute rheumatic fever, migratory polyarthritis, rheumatic heart disease, pyoderma, Pacific Islander*

## Abbreviations

*ARF = Acute Rheumatic Fever*
*ASOT = Antistreptolysin O Titer*
*CRP = C-Reactive Protein*
*ESR = Erythrocyte Sedimentation Rate*
*GAS = Group A Streptococcus*
*RHD = Rheumatic Heart Disease*

## Introduction

Acute rheumatic fever (ARF) is an autoimmune process secondary to cross-reactivity of antibodies against group A streptococcal (GAS) antigens with that of tissues throughout the body, including the heart, joints, nervous tissue, and subcutaneous tissue.[1-3] Untreated ARF is notorious for leading to the development of rheumatic heart disease (RHD), which is caused by autoimmune damage of cardiac tissue and can result in severe valvular damage and heart failure.[3] The involvement of joints in ARF includes a migratory polyarthralgia that can often be confused with other autoimmune systemic inflammatory conditions, such as rheumatoid arthritis or other collagen diseases. The recurrence of ARF is most commonly seen in children and adolescents given the increased risk of developing ARF secondary to untreated streptococcal pharyngitis.[1,4] However, recurrence of ARF is rarely encountered in adults in developed countries given the advent of antibiotics and secondary prophylaxis, which may lead to the condition going misdiagnosed or undiagnosed.[1] Treating ARF appropriately and in a timely manner is crucial for decreasing the risk of developing or worsening RHD.[2,5] Herein, we describe a patient with a delayed diagnosis of recurrent ARF complicated by crippling migratory polyarthralgia.

### Case Report

A 29-year-old Native Hawaiian and other Pacific Islander man presented to the emergency department with a 6-week history of migratory polyarthralgia and fever. He had a history of recently resolved non-healing wounds of 4-months duration of the right lower extremity, obesity, and acute rheumatic fever at the age of 5. He had taken penicillin V for secondary prophylaxis for rheumatic fever from the age of 5 until the age of 18, when he decided to self-discontinue the medication. He was in a motorcycle accident 6-months prior to admission and sustained multiple lacerations to his right lower leg and used hydrogen peroxide every other day to clean the wounds due to the presence of pus. The arthralgia first developed 6-weeks prior to admission when he first sought medical attention for his right lower leg non-healing wounds and was initially treated with clindamycin. The arthralgia first developed in the left knee and progressively spread to affect the right knee followed by the ankles, hips, shoulders, and multiple joints of the hands bilaterally. He additionally reported developing a fever, fatigue, a 40 lb. weight loss over this 6-week period, and diffuse muscle pain involving the lower back, upper back, neck, and both shoulders around the same time. After the development of arthralgia, he was switched to doxycycline, but the symptoms continued to worsen. Approximately 1-month prior to admission, he had an extensive rheumatologic workup at a community hospital that was unremarkable for autoimmune rheumatologic conditions and empirically given a 2-week course of prednisone 20 mg daily. Prednisone provided partial relief of his symptoms, but upon discontinuation without tapering, the arthralgia worsened eventually to the point of paralyzing the patient, which led his family to take him to the emergency department.

On physical examination, he was in no acute distress at rest with a temperature of 37.2 C, a heart rate of 88 beats/min, a blood pressure of 124/68 mmHg, a respiratory rate of 20/min, an oxygen saturation of 97% on room air, and a body mass index (BMI) of 40.69. No pharyngeal erythema, tonsillar exudate, or cervical lymphadenopathy were found on the physical exam. A 3/6 holosystolic murmur was heard loudest at the left midclavicular line between the 5$^{th}$ and 6$^{th}$ ribs with radiation

to the axilla. There were no extra heart sounds, opening snaps, rubs, or diastolic murmurs heard on the physical exam. There were no physical exam findings suggestive of heart failure such as crackles upon auscultation of the lungs, lower leg pitting edema or elevated jugular venous pressure. Swelling, warmth, and tenderness to palpation over the right temporomandibular joint, shoulders, wrists, metacarpophalangeal joints, proximal interphalangeal joints, hips, knees, and ankles bilaterally were found on the physical exam, and these were worse in the right hand that elicited tearing upon manipulation (Figure 1). There were no apparent joint effusions in both hands. Range of motion in affected joints was limited by pain with passive motion. Multiple healing ulcerated lesions of the anterolateral surface of the right lower extremity with no exudate or surrounding erythema were noted.

Laboratory studies revealed an elevated white blood cell count of 14,800/µl with 73.4% neutrophils, hemoglobin of 12.3 g/dL, and platelet count of 391,000/µl. Additional significant laboratory values include C-reactive protein (CRP) of 146.0 mg/L, erythrocyte sedimentation rate (ESR) of >130 mm/hr, Antistreptolysin O Titer (ASOT) of 525 IU, Anti-DNase B of 1240 units/mL, and ferritin of 992 ng/mL. Extensive autoimmune workup including Human Immunodeficiency Virus, Epstein-Barr Virus, Hepatitis B, Hepatitis C, and Lyme disease were negative. Thyroid stimulating hormone, aldolase, creatinine kinase, lactic acid, lactate dehydrogenase, C3, and C4 were all within normal limits. Blood cultures on admission were negative. Synovial fluid analysis and culture showed many leukocytes but no bacteria. Electrocardiogram revealed sinus tachycardia with no PR interval prolongation. Echocardiogram revealed an ejection fraction of 55%-60%, no valvular vegetations, mild mitral regurgitation, mild mitral stenosis with mitral valve leaflets appearing rheumatic, mild aortic regurgitation, and a mean transmitral gradient of 4 mmHg.

The patient was diagnosed with a recurrent bout of rheumatic fever using the World Health Organization (WHO) criteria for the diagnosis of rheumatic fever and rheumatic heart disease.[6] On the day of admission, the patient was empirically treated with one dose of 20 mg of prednisone due to his previous improvement of his arthralgias on this regimen when treated at the community hospital a few weeks prior. He was then switched to 500 mg of naproxen twice a day, given his history of developing severe epistaxis with aspirin and naproxen being an acceptable alternative with outcomes comparable to aspirin.[7] On the second day of admission, the patient's symptoms dramatically improved, with a decrease in pain with passive movement and full range of motion in all affected extremities. Prophylactic penicillin V with instructions was initiated and prescribed to be continued until the age of 40. Upon discharge on the 4th day of admission, the patient's polyarthralgia was completely resolved and CRP returned to within normal limits.

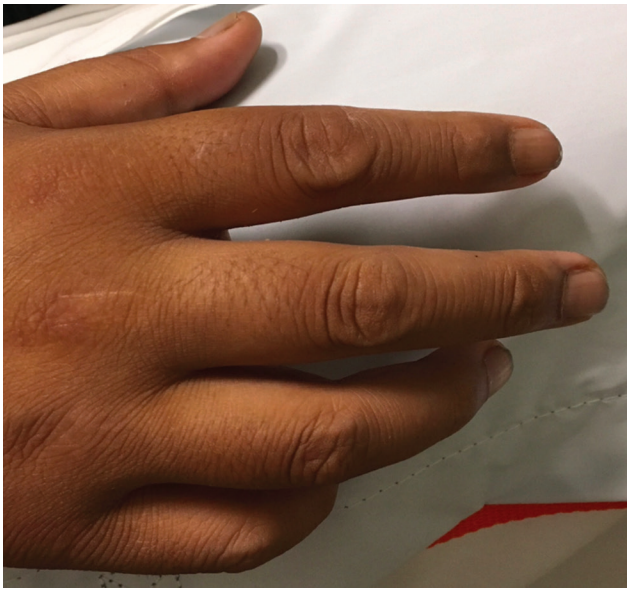

Figure 1. Picture Depicting Patient Attempting to Fully Extend Fingers of Right Hand, which were Limited by Pain.

## Discussion

ARF is an autoimmune process by which antibodies against GAS antigens cross-react with and damage native tissues throughout the body.[2] Autoimmune damage of the heart is the most notorious of the complications associated with ARF given the association of developing RHD in untreated patients, which may consist of irreversible valvular damage and heart failure. Since the advent of antibiotics, the incidence of RHD is low in developed countries.[8,9] However, clinically inapparent streptococcal infections or symptomatic patients not seeking care are common reasons for a delay in diagnosis and management of ARF in developed countries.[9] The patient in our report had a delayed diagnosis of recurrent ARF presumed to be secondary to lower extremity cellulitis. Because early management of ARF can decrease the risk of developing valvular damage, the early diagnosis and management of ARF is crucial.[9] Recurrence of ARF can result from subsequent GAS infections, in which each recurrence can cause further valvular damage and thus worsen RHD. Additionally, in one study, recurrent episodes of ARF were associated with higher mortality compared to the first episode of ARF.[4,10] Thus secondary prophylaxis with long term antibiotics, prompt diagnosis, and antibiotic management of underlying GAS infections is of utmost importance to prevent worsening of RHD and decrease mortality in patients with a history of ARF.[4,9] Although we were able to appropriately manage our patient's condition and provide almost instantaneous relief of his symptoms, this delay in diagnosis and proper management may have contributed to further irreversible valvular damage that could potentially increase his risk for developing complications in the future and require valvular surgery.[11]

Our patient met the WHO criteria for a recurrent episode of rheumatic fever due to his history of rheumatic fever as a child, evidence of polyarthritis (one major manifestation), fever and elevated acute phase reactants (two minor manifestations) with supporting evidence of elevated ASOT and pyoderma as a source of infection.[6] Unlike the Jones criteria that was previously used to diagnose rheumatic fever, the WHO criteria is a revision that further categorizes patients based on the presence or absence of RHD. The WHO criteria still holds onto the major and minor manifestations used in the Jones criteria that are key for recognizing and diagnosing ARF. Major manifestations consist of polyarthritis, carditis, subcutaneous nodules, erythema marginatum and chorea. Minor manifestations consist of fever, polyarthralgia, elevated acute phase reactants.[1] The WHO criteria additionally takes into account supporting evidence of a streptococcal infection in the last 45 days such as a PR prolongation on echocardiogram, elevated or rising ASOT or anti-DNase B titers, a positive throat culture or rapid antigen test for group A streptococci, or recent scarlet fever.[6] For the appropriate diagnosis of a recurrent episode of rheumatic fever without heart disease, either 2 major criteria or 1 major criteria and 2 minor criteria plus evidence of a preceding GAS infection is required, which is the same for diagnosing an initial bout of ARF. However, if the patient has established RHD, then less is needed for the diagnosis, as only 2 minor criteria plus a preceding GAS infection is required for diagnosis.[6] Although echocardiogram is not necessary for diagnosis and is viewed as a supportive test, it can be an important tool for further determining the extent and severity of RHD.[1,6] Thus, ARF should be in the differential diagnosis for patients who present with combinations of these clinical exam findings to allow for an appropriate and timely work-up.

Although ARF predominantly affects the pediatric population, young to middle-aged adults are also affected by ARF, however, at a much lower frequency.[12] It is rare for adults older than age 35 to have their first episode of ARF and most adults with ARF have had their first episode as a child.[10,12,13] However, having no history of ARF as a child does not rule out the diagnosis of ARF in an adult, as multiple cases have been reported with the first-episode of ARF occurring in adulthood.[14,15] One of the most recent studies conducted in 2000 that observed ARF cases in adults reported that the clinical manifestations of ARF in adults were similar to that seen with ARF in children, with migratory polyarthritis being the most common complaint.[15] Our patient fit this classic picture of having a migratory polyarthritis, a history of ARF in childhood and the additional history of discontinuing his antibiotic prophylaxis regimen prematurely. Therefore, despite the lower incidence of ARF in adults, ARF should still be included in the differential diagnosis, especially when accompanied by suggestive history and physical exam findings.

ARF is most commonly secondary to pharyngitis from a pathogenic strain of GAS in genetically predisposed individuals, in which Pacific Islanders, Australian aborigines, and New Zealand Māori experience the highest incidence of ARF globally.[5,16,17] However, ARF secondary to pyoderma or cellulitis is an additional, less common and less known condition. In multiple studies observing ARF in aboriginal communities in the northern territories of Australia, Fiji, and New Zealand, there is a high prevalence of cases of ARF in the absence of GAS pharyngitis, but in the presence of GAS pyoderma.[18-22] Given that our patient was from the Pacific region and had a recent history of purulent right lower extremity lesions, his recurrent ARF was likely secondary to GAS pyoderma. Wound cultures approximately 6-weeks prior to his admission grew GAS, but wound cultures were not repeated during his hospitalization under our care due to the lack of exudate or surrounding erythema in addition to the ASOT and Anti-DNase B titers. Our patient had two separate occasions of a delay in the diagnosis and management of ARF, which were both suspected to be secondary to GAS skin infections. This may be due to the lack of understanding and the importance of recognizing the association of GAS skin infections and the development of ARF, especially in Pacific Islanders. Thus, understanding this association is of importance for health care providers practicing in Hawaii and the Pacific region. Further research is needed to elucidate this relationship, as these implications are based off of small studies and case reports given the small subject population and the relative rarity of GAS pyoderma causing ARF.[18-22]

Migratory polyarthritis is another component of ARF associated with autoimmune damage of the joints.[1,4] Particularly, febrile polyarthritis is the most common presentation of ARF in adults.[4,15,16,23] Although the polyarthritis that ensues with ARF is most commonly non-degenerative in nature, the symptoms can be severe to the point of immobilization.[4] This was seen in our patient, who presented with no spontaneous movement and unbearable pain with mild manipulation of his joints. Because ARF is an inflammatory condition, the lab values and clinical picture of polyarthritis secondary to ARF can mimic that of systemic inflammatory arthritides. Elevated ESR, CRP, and warm, erythematous, tender joints can occur with rheumatoid arthritis, psoriatic arthritis, reactive arthritis, systemic lupus erythematosus, and other systemic inflammatory conditions.[4,16,24-26] Important lab and clinical findings that can help differentiate ARF from other systemic inflammatory arthritides include ASOT, Anti- DNase-B antibody and most importantly the history and physical exam. In our patient, a history of rheumatic fever in childhood with discontinuation of secondary prophylaxis increased our clinical suspicion, despite the patient's clouded clinical presentation with worsening after initial attempt to treat lower leg non-healing wounds with antibiotics and only partial response to glucocorticoids. This led us to ordering ASOT and Anti-DNase B to further solidify our diagnosis and rule out other potential systemic inflammatory conditions with other laboratory testing.

In conclusion, we report a case of recurrent ARF following GAS pyoderma in a Native Hawaiian and other Pacific Islander who

presented with migratory polyarthralgias. This was his second diagnosed bout of ARF, both bouts occurring secondary to skin infections and having a delay in diagnosis with potential worsening of cardiac valvular damage. It is important to understand the association of pyoderma and ARF in Native Hawaiian and other Pacific Islanders in addition to including ARF in the differential diagnosis of polyarthralgias in adults. The appropriate and timely diagnosis and management of ARF is of significance for lowering the risk of developing RHD and its complications.

## Conflict of Interest

None of the authors identify any conflict of interest.

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