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Case Report

Acute rheumatic fever and multiple drug hypersensitivity: a case report

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ABSTRACT

Acute rheumatic fever (ARF) is an autoimmune-mediated inflammatory disorder precipitated by infection with group A *Streptococcus* (GAS) infection. The underlying pathogenesis is attributed to molecular mimicry, wherein antibodies directed against GAS antigens cross-react with host tissues. Diagnosis is established based on clinical evaluation using the revised Jones criteria in conjunction with laboratory evidence of recent GAS infection. Management involves antibiotic therapy, anti-inflammatory agents, and long-term prophylactic strategies to prevent recurrence. One of the potential adverse effects associated with these pharmacologic agents is drug hypersensitivity reactions (DHR). The recommended diagnostic approach to DHR is a graded challenge by introducing drugs safely and optimally under a threshold dose until the usual daily dose is reached. In the present case, due to the patient's documented history of multiple drug hypersensitivities, a graded drug challenge was performed to ensure medication tolerance and minimize the risk of hypersensitivity.

Keywords: Acute rheumatic fever, Drugs hypersensitivity, Graded challenges

INTRODUCTION

Acute rheumatic fever (ARF) is an abnormal immunologic response to GAS infection.[1,2] ARF usually occur two or three weeks following a throat infection, most commonly because of tonsillopharyngitis.[1,3] ARF effects multiple organs, including cardiac, neurologic, musculoskeletal or dermatological manifestations. While ARF most commonly occurs in children, it can affect people of any age.[1] The epidemiology of ARF shows a significant burden in low and middle-income countries, with an estimated 20 million people effected globally, and primarily affects children.[4,5]

The pathogenesis of ARF involves molecular mimicry, where antibodies generated against GAS antigens cross-react with host tissues, particularly in the heart, joints, skin, and central nervous system. The autoimmune response leads to inflammation and subsequent tissue damage and may manifest as carditis, valvulitis, arthritis, chorea, subcutaneous nodules, and erythema marginatum. Carditis and valvulitis resulting damage to the heart valves, that are the most severe acquired manifestation of ARF, which may progress to rheumatic heart disease (RHD).[6]

The diagnosis of ARF is clinical and requires evidence of preceding GAS infection and the presence of revised Jones criteria consisting of major (carditis, polyarthritis, chorea, erythema marginatum, and subcutaneous nodules) and minor (fever, arthralgia, elevated acute phase reactants, and prolonged PR interval) criteria.[7]

Management of ARF involves treating the acute infection, reducing inflammation, and preventing recurrence. The primary treatment for acute GAS infection consists of antibiotics, and penicillin is considered as the first line treatment in the absence of any known allergies. Anti-inflammatory drugs, typically aspirin or corticosteroids,

are used to manage arthritis and carditis.[8,9] Graded drug challenge involves the careful, incremental administration of a medication in gradually increasing doses, typically used when the likelihood of a true allergy is low. This approach is frequently employed to reintroduce antibiotics or other medications in patients with a reported history of adverse reactions, particularly when clinical assessment indicates a low probability of genuine drug allergy.[10]

In this case report, a 46-year-old male patient with ARF was presented. An unusual presentation of ARF in an adult who arrived at the emergency department (ED) with fever, polyarthralgia, sore throat, and a notable history of hypersensitivity reactions to multiple medications was discussed. Laboratory investigations revealed elevated Anti-Streptolysin O (ASO) titers and an increased erythrocyte sedimentation rate (ESR). Given the clinical suspicion of carditis and the potential risk for disease recurrence and progression to RHD, the patient was admitted for further evaluation and management.

CASE REPORT

A 46-year-old male patient with a past medical history of recurrent *Streptococcal* pharyngitis infections presented to the ED with two days of fever, sore throat, and polyarthritis. Moderate pain in bilateral knee joint was reported, which was associated with mild swelling, localized erythema, and warmth on palpation. The pain significantly impaired ambulation, and range of motion was limited due to discomfort. Polyarthralgia that affecting multiple large joints was reported. He also reported a rash on his trunk which prompted he to seek medical attention as he thought it may be secondary to an allergic reaction. The patient often experiences a sore throat but does not seek treatment immediately. The patient denied visual changes, headache, cough, and shortness of breath. The patient reported a fever of 39.0 degrees Celsius, one hour prior to arrival. The patient has documented hypersensitivity reaction to following medications: Paracetamol, ibuprofen, gentamycin eye ointment, ceftriaxone, antibiotic from "-lin" class (e.g., Penicillin and ampicillin), Neuralgyn, sulfonamide-containing drugs (sulfa drugs) and ambroxol. Importantly patient has a history of Steven-Johnson syndrome (SJS), which occurred in 2006 and was induced by a hypersensitivity reaction to ceftriaxone. Since then, the patient has avoided all suspected triggers. No other severe cutaneous adverse reactions (SCARs) have been reported since that episode.

On examination, he was alert (GCS E4V5M6), blood pressure was 110/70 mmHg, pulse 104 bpm, respiratory rate 20 breaths/min, temperature 38.9°C, and oxygen saturation 99% on room air. On general examination; head, eyes, nose and ears are normal. No enlargement of lymph node was palpable on the neck, tonsil was T1/T1 and mild erythema. Thorax and cardiovascular examination were within normal limit. There was no murmur or gallop. On extremities, patient felt pain in knee and elbow join on palpation. Both knee joint showed mild swelling, localized erythema and warmth on palpation. There was a limited range of motion due to pain. The patient also reported pain in the fingers (bilateral digital pain), without visible swelling or deformity. Erythema was observed on the neck and chest (trunk region), with no signs of blistering or mucosal involvement at the time of examination.

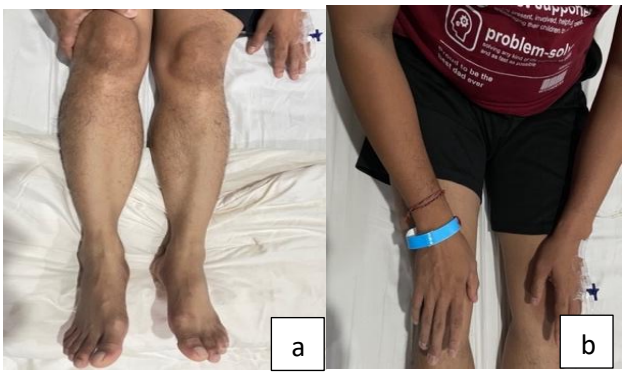

Figure 1 (a and b): ECG clinical appearance of upper and lower extremity.

Additional examination was performed on the patient, including laboratory test, electrocardiography (ECG), thorax X-ray, and echocardiography. From the complete blood count test, the result obtained are: leucocytes are 6.52/µl, Hb 15.4 g/dL, hematocrit 47.2%, and thrombocyte 247,000/µl. Electrolyte examination found sodium 131 mmol/L, potassium 3.3 mmol/L, chloride 94 mmol/L. these laboratory test revealed low potassium levels. The ESR and c-reactive protein (CRP) level were elevated (34 mm/hour) (0-20 mm) and 19 mg/dL (<1.00 mg/dL) troponin level XX (ng/mL) (0.000-0.034 ng/mL). Basic metabolic panel blood glucose exam 252 mg/dL, triglycerides 103 mg/dL, total cholesterol 170 mg/dL, HDL direct 50 mg/dL, and LDL 127 mg/dL. From ECG examination, it was found a normal sinus rhythm, with no prolong PR interval. Thorax x-ray found lung and heart within normal limit, with normal cardio thoracic ratio.

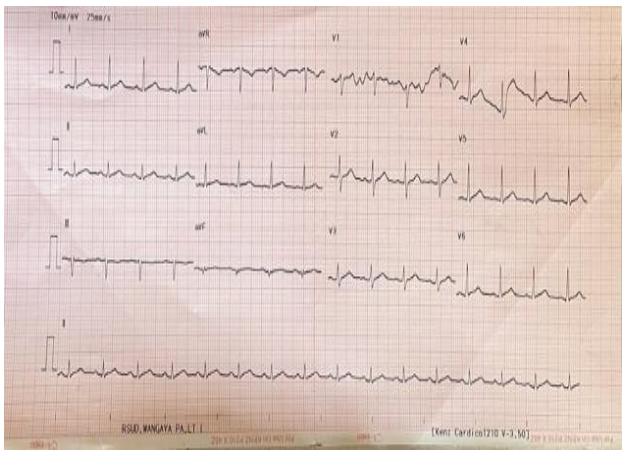

Figure 2: ECG examination.

The patient was assessed for the ASO, which returns a result of 200 IU/ml. Echocardiography found a result of

ejection fraction of 76%, no regional wall motion abnormalities, and valve appear within normal. According to all the accumulated data, the patient was diagnosed with ARF. The patient was then given of infusion 0.9% NaCl 20 drops per minutes, azithromycin 500 mg PO every 24 hr, omeprazole 2×20 mg PO, and methylprednisolone 2×8 mg PO. The patient was then undergone daily follow up, and after 3 days of hospitalization, patient feels better and has no more complaints or symptoms, and considers healthy enough to send home.

DISCUSSION

ARF is an autoimmune reactive disease caused by untreated *Streptococcus pyogenes* or GAS, infection in genetically susceptible hosts; it often occurs 2-3 weeks after GAS infection.[1,11] There are 3 stages in the development of ARF: bacterial sore throat, ARF and RHD.[12] Their incidence is influenced by various factors such as geographic location, climate, season, economic status, nutritional status, housing and sanitation, gender, age, GAS infection rate, ethnicity, and family susceptibility.[11,13] Interms of age, ARF mostly affects children aged 5-14 years. While ARF most commonly occurs in children, it can affect people of any age.[1] Factors such as cold weather, humidity; autumn, winter, and spring (especially spring) seasons; poverty; overcrowded households; and prevalence of GAS infection are associated with increased prevalence of ARF and RHD.[11,13] Recurrent episodes generally affect older children and can occur in young adults.[13] In these patients, prevalence of GAS infection were risk factors for being affected ARF.

The autoimmune response leads to inflammation and subsequent tissue damage and may manifest as carditis, valvulitis, arthritis, chorea, subcutaneous nodules, and erythema marginatum.[6] Persistent damage to the heart valves and active inflammation of the heart tissue caused by ARF may cause chronic damage known as RHD. ARF and RHD occur worldwide.[11,13] The exact pathogenic mechanisms of ARF remain unclear. However, the development of ARF seems to require a pharyngeal infection by *Streptococcus pyogenes* in individuals who are genetically predisposed to the condition.[15]

ARF is diagnosed based on clinical guidelines known as the Jones criteria. The criteria are categorized into major and minor manifestations, and further differentiated based on whether the patient belongs to a low-risk or moderate-to high-risk population. A definitive diagnosis of ARF requires the presence of either two major criteria or one major criterion in conjunction with at least two minor criteria.[1,7] For patients with evidence of a previous group A *Streptococcal* infection: (1) diagnosis of first ARF can be made when there are two major manifestations, or one major plus two minor manifestations, (2) diagnosis of recurrent ARF can be made when there are two major manifestations, or one major plus two minor manifestations, or three minor manifestations.[7]

ARF can present with several different clinical manifestations such as arthritis, carditis, chorea, skin findings.[15]

Table 1: Revision of Jones criteria.[7]

Jones Criteria	Low-risk population	High-risk population
Major criteria		
Carditis	Clinical and/or subclinical	Clinical and/or subclinical
Arthritis	Only polyarthritis	Monoarthritis or polyarthritis poliarthralgia
Sydenham chorea	Sydenham chorea	Sydenham chorea
Erythema marginatum	Erythema marginatum	Erythema marginatum
Subcutaneous nodules	Subcutaneous nodules	Subcutaneous nodules
Major criteria		
Arthralgia	Polyarthralgia	Monoarthralgia
Fever	≥38.5°C	≥38.0°C
ESR/CRP	ESR ≥60 mm in the first hour and/or CRP ≥3.0 mg/dL	ESR ≥60 mm in the first hour and/or CRP ≥3.0 mg/dL
PR interval	Prolongation after age adjustment (except if carditis is a major criterion)	Prolongation after age adjustment (except if carditis is a major criterion)

Skin finding in ARF is erythema marginatum and subcutaneous nodules.[15] Arthritis in ARF typically involves large joints, particularly the knees, ankles, elbows, and wrists. It often affects several joints simultaneously or sequentially. The pattern of joint involvement, which can shift from one joint to another or accumulate over time, is commonly referred to as "migratory" or "additive" polyarthritis.[15] ARF may lead to pancarditis, affecting all layers of the heart, the pericardium, epicardium, myocardium, and endocardium. Despite this, the predominant clinical sign of carditis in ARF is due to endocardial involvement, typically presenting as valvulitis of the mitral valve, resulting in mitral regurgitation, and less commonly affecting the aortic valve, leading to aortic regurgitation.[7] The chorea associated with ARF, known as Sydenham's chorea, is marked by involuntary, irregular, and aimless movements

affecting the trunk and extremities. These movements are frequently asymmetrical, with one side of the body being more prominently affected.[15] Erythema marginatum, also referred to as "erythema annulare," is characterized by bright pink, blanching, non-pruritic macules or papules that spread outwards in a serpiginous pattern, usually on the trunk and proximal limbs.[7]

In this patient, two major and two minor criteria was found. The symptoms are fever, redness on the trunk and polyarthritis. Moderate pain in bilateral knee joint was reported, which was associated with mild swelling, localized erythema, and warmth on palpation. The pain significantly impaired ambulation, and range of motion was limited due to discomfort. Polyarthralgia that affecting multiple large joints was reported. He also reported a rash on his trunk. On physical examination, the patient body temperature was found to be 38.9°C. On extremities, patient felt pain in knee and elbow join on palpation. Both knee joint showed mild swelling, localized erythema and warmth on palpation. There was a limited range of motion due to pain. The patient also reported pain in the fingers (bilateral digital pain), without visible swelling or deformity. Erythema was observed on the neck and chest (trunk region). Further laboratory test revealed increased CRP and ESR. The ESR and CRP level were elevated (34 mm/hour) (0-20 mm) and 19 mg/dL (<1.00 mg/dL).

Therapeutic management of ARF involves addressing the initial infection, initiating long-term prophylaxis to prevent recurrence, and managing any arising complications.[1] The primary aim is to eliminate GAS infections and penicillin is considered the first line. For patients allergic to penicillin, alternatives such as azithromycin or erythromycin can be used. To control inflammation and ease symptoms, non-steroidal anti-inflammatory drugs (NSAIDs) like aspirin or naproxen are commonly used, with corticosteroids reserved for more severe cases.[16] A graded drug challenge is a controlled approach involving the gradual administration of increasing doses of a medication in patients who are unlikely to have a true allergy. It is commonly utilized to reintroduce antibiotics and other drugs in individuals with a history of suspected adverse reactions, provided clinical evaluation indicates low risk of hypersensitivity. Successful completion of a graded challenge confirms the absence of a drug allergy. Typically, the procedure consists of 2 to 3 dosing steps, beginning with approximately $1/10^{th}$ to $1/100^{th}$ of the full therapeutic dose. Although initiating the challenge with a lower dose and incorporating additional steps is possible, doing so increases the risk of inadvertently performing rapid desensitization-an unintended induction of temporary drug tolerance. This poses a potential danger, as a truly allergic patient who has been unknowingly desensitized may experience an allergic reaction upon subsequent exposure to the same or a related drug.[10] In this patient, due to a drug allergy to the penicillin class, a macrolide antibiotic, azithromycin, was administered instead. To control inflammation, the patient was given a corticosteroid, methylprednisolone 2×8 mg twice daily. NSAIDs were not administered due to the patient's allergy to this drug class.

CONCLUSION

ARF in a patient with multiple drug hypersensitivity was discussed. In managing ARF in patients with multiple drug hypersensitivity, careful medication selection is essential to prevent allergic reactions. When standard treatments such as penicillin and NSAIDs are contraindicated, alternative options like macrolide antibiotics and corticosteroids may be considered. A comprehensive drug allergy history and close monitoring are crucial to ensure safe and effective therapy. Additionally, a graded challenge with antibiotics can be performed when appropriate.

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