

## Case Report

### *Erythema Nodosum: A Possible Criterion for Diagnosing Acute Rheumatic Fever*

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#### ABSTRACT

The clinical features of acute rheumatic fever (ARF) are mainly the results of post-streptococcal mimicry. One of the major criteria to diagnose ARF is erythema marginatum. However, the involvement of erythema nodosum has not been reported yet. A middle-aged woman without comorbidities or addiction presented with breathlessness (NYHA-II) of 1 year's duration with acute exacerbation in the preceding 7 days with fever, dry coughs, bilateral chest pain, orthopnea, paroxysmal nocturnal dyspnea, palpitations, bilateral leg swellings, and multiple tender faint red maculopapular rashes over bilateral shins and posterior ankle regions. Two-dimensional echocardiography confirmed rheumatic heart disease (RHD) and showed mild mitral stenosis, mild-to-moderate mitral regurgitation, severe tricuspid regurgitation, moderate pulmonary arterial hypertension, and an approximate left ventricular ejection fraction of 60%. A skin lesion biopsy showed chronic inflammatory lesions, suggesting erythema nodosum. The patient's antistreptolysin O (ASO) titer was elevated, suggesting a prior streptococcal infection. Most of the major clinical criteria of ARF are the consequence of the molecular mimicry of Streptococci, especially such skin manifestations as erythema marginatum and subcutaneous nodules. Therefore, erythema nodosum, which also manifests itself as a delayed hypersensitivity reaction to Streptococci, can be considered a major criterion for diagnosing ARF/RHD. (*Iranian Heart Journal 2023; 24(1): 108-112*)

**KEYWORDS:** ASO titer, Erythema marginatum, Group A streptococcus, Rheumatic heart disease

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**A**cute rheumatic fever (ARF) and rheumatic heart disease (RHD) have a global burden. ARF is a nonsuppurative sequel occurring 2 to 4 weeks following Group A streptococcus (GAS) infection.<sup>1</sup> ARF is the body's autoimmune response to infection with GAS, while long-term cardiac insult is due to a single severe attack or recurrent episodes resulting in RHD. The pathological

mechanism is not clearly understood; nonetheless, most clinical features in ARF occur due to the body's cross-reactive immune responses to GAS.<sup>2</sup> Therefore, both cardiac and extracardiac manifestations of post-streptococcal mimicry decide the diagnosis of ARF with both major and minor criteria.

Erythema marginatum is an inflammatory evanescent, nonpruritic, faintly red or pink

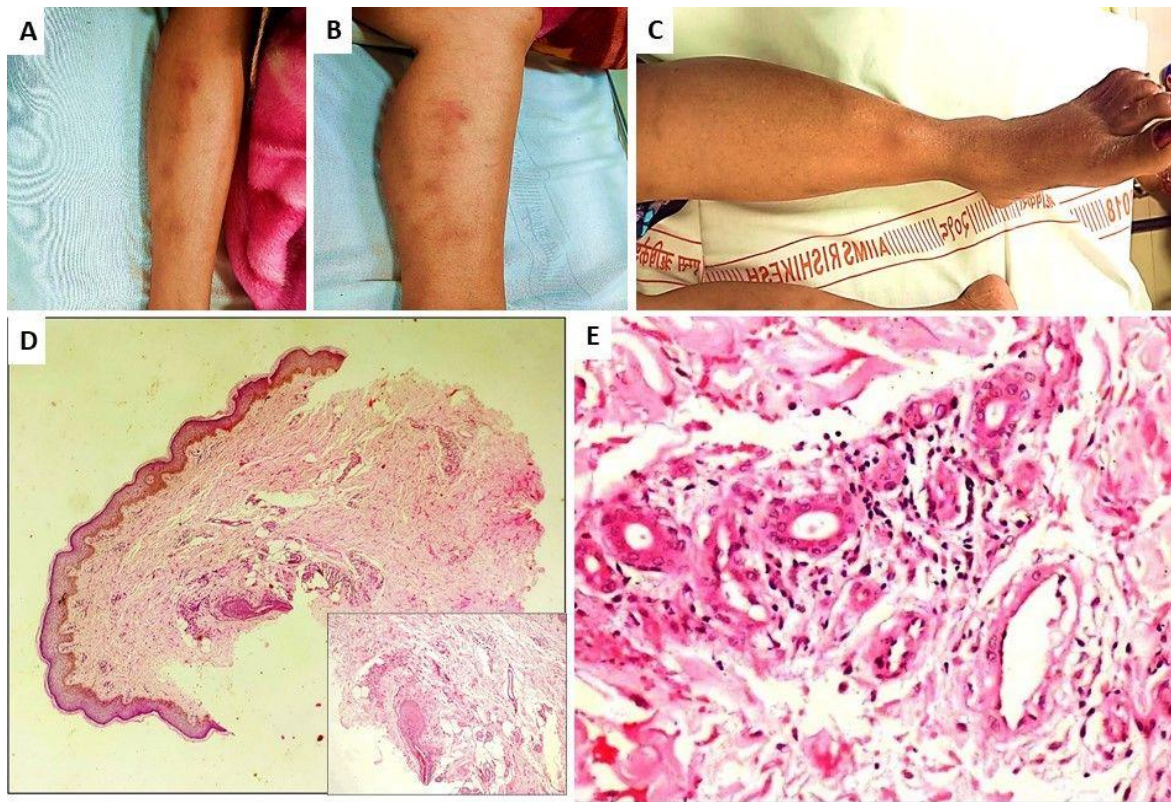
rash involving the trunk and occasionally the limbs but not the face. However, it rarely occurs as a sole manifestation of ARF.<sup>4</sup> In contrast, erythema nodosum is a common form of acute nodular hypodermis characterized by a delayed hypersensitivity reaction that presents as the sudden onset of erythematous, solid, firm nodules that are painful on palpation and usually localized on leg extensors.<sup>5</sup> The pathogenesis of erythema nodosum is not well understood, but it is the result of nonspecific cutaneous reactions resulting from the exposure to various antigens. Most cases are seen after streptococcal infections.<sup>6</sup> Furthermore, erythema nodosum is not known to be associated with post-streptococcal ARF. We herein describe a middle-aged woman diagnosed with erythema nodosum and RHD.

### Case Report

A 51-year-old woman without known comorbidities or any addiction history presented with baseline shortness of breath (NYHA-II) of 1 year's duration. Her condition had exacerbated in the preceding 7 days, and she had acute-onset undocumented intermittent fevers with chills and dry coughs. Additionally, she complained of bilateral chest pain with increased bouts in the evening without diurnal and positional variations. Her shortness of breath and coughs were also associated with orthopnea, paroxysmal nocturnal dyspnea, intermittent palpitations, and bilateral limb swelling. She had also developed multiple tender faint red maculopapular rashes over bilateral shins and posterior ankle regions (Fig. 1A & B).

On presentation, the patient was tachycardic and tachypneic and showed bilateral pitting edema, bilateral inspiratory crepitation, and wheezing. Local examination revealed multiple irregular lesions on bilateral shins. The largest lesion was approximately 11×14×1 mm<sup>3</sup> and was tender and non-blanching.

Two-dimensional echocardiography confirmed RHD and showed mild mitral stenosis, mild-to-moderate mitral regurgitation, severe tricuspid regurgitation, moderate pulmonary arterial hypertension, and an approximate left ventricular ejection fraction of 60%. Skin lesion biopsy demonstrated chronic inflammatory lesions (Fig. 1D & E). The patient's antistreptolysin O (ASO) titer was positive (400 IU/mL). Electrocardiography was suggestive of a fast ventricular rate with irregularly irregular rhythms and no signs of heart block or prolonged PR intervals. The erythrocyte sedimentation rate was elevated. The patient had no complaint of joint pain, chest pain, skin nodules, and abnormal jerky and purposeless limb movements. She was then acutely managed with diltiazem and Acitrom for atrial fibrillation with a fast ventricular rate and other supportive management. After stabilization, she was treated for RHD with the injection of benzathine penicillin G (1.2 million units) and was advised to continue the injection every 28 days for 10 years. She was subsequently discharged from the hospital. On follow-up, the patient was symptomatically better, and her skin lesions had also healed (Fig. 1C). Accordingly, in this context, erythema nodosum was seen as one of the clinical manifestations of ARF.



**Figure 1:** The images show the patient's skin lesions on presentation. (A & B) The images depict multiple erythematous, painful, nonpruritic, and firm nodules localized on the shin (bilateral leg extensors and laterals) in various stages of development, suggestive of erythema nodosum. The lesions can be seen on follow-up after 2 weeks of penicillin therapy. (C) The image shows the absence of erythematous lesions on bilateral shins, except for faintly darkened skin somewhere (not visualized). Histology of the biopsied skin lesions on the shin: The hematoxylin and eosin (H&E) stained section shows unremarkable epidermis with the upper and mid dermis, suggestive of mild-to-moderate perivascular and periadnexal inflammatory cell infiltrates (Dx40, Inlet Dx100). Higher magnification shows lymphocytic and sparse neutrophilic perivascular and periadnexal inflammatory cell infiltrates (Inlet Dx100, Ex400).

## DISCUSSION

Although ARF and RHD are showing a declining incidence trend worldwide, they remain 2 of the major causes of cardiovascular morbidity and mortality in populations who are socially and economically backward, especially in developing and underdeveloped countries.<sup>7</sup> The criteria for ARF, known as the Jones criteria, were first developed in 1944 and further modified by the American Heart Association in 1992 based on echocardiographic findings. The criteria were further revised in 2015 by offering 2 separate diagnostic pathways in 2 groups among those with low risks and moderate-

to-high risks.<sup>8</sup> The Jones criteria consist of major criteria (migratory polyarthritides, carditis, erythema marginatum, subcutaneous nodules, and Sydenham chorea) and minor criteria (a history of a previous rheumatic fever, arthralgia, fever, increased inflammatory markers [eg, the erythrocyte sedimentation rate and C-reactive protein], and electrocardiographic findings [eg, PR prolongation and heart blocks]).

The pathogenesis of the clinical features of ARF is mostly related to antigenic mimicry, resulting in an abnormal immune response, along with manifestations caused by direct pathogens, usually Streptococci, and the

effects of streptococcal toxins.<sup>9</sup> The formation and deposition of immune complexes in the joints manifest arthritis. Cardiac myosin shares epitopes with M protein and N-acetyl-beta-D-glucosamine of GAS, resulting in cross-reactivity and causing inflammation in cardiac muscles (ie, carditis). Antibodies react with the brain gangliosides in the basal ganglia and manifest as chorea. In addition, the delayed hypersensitivity reaction of the body to Streptococcus antigens manifests as erythema marginatum and subcutaneous nodules.<sup>3</sup> Therefore, all symptoms are related to the body's immune response to Streptococci or their toxins.

Erythema nodosum is a common form of acute nodular hypodermal lesion characterized by a delayed hypersensitivity reaction that presents as the sudden onset of erythematous, solid, firm nodules that are painful on palpation and are usually localized on the leg extensors. It can be caused by vast number of causes. Most causes are idiopathic; however, the known causes include infectious causes (bacterial, viral, and fungal) and noninfectious causes (drugs [eg, penicillin and sulfonamides], malignancies, and inflammatory conditions [eg, IBD]). Most cases are seen in the wake of streptococcal infections. The most common pathogenesis is the deposition of immune complexes in the septal venules of subcutaneous fat, neutrophil recruitment with the production of oxygen-free radicals, tumor necrosis factor- $\alpha$  production, and the formation of granulation.<sup>10</sup> Like the other major criteria of Jones that are the result of the body's immune response to Streptococci, erythema nodosum has the same pathophysiology. Therefore, this skin manifestation can also be considered a major criterion for ARF.

In summary, most of the major clinical criteria of ARF are the consequence of the molecular mimicry of Streptococci,

especially skin manifestations like erythema marginatum and subcutaneous nodules. Thus, erythema nodosum, which also manifests as a delayed hypersensitivity reaction to Streptococci, can be regarded as a major criterion for diagnosing ARF/RHD.

**Conflicts of Interest:** None

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