



Educational Case

Educational Case: Rheumatic fever, acute and chronic manifestations

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see <https://www.journals.elsevier.com/academic-pathology/news/pathology-competencies-for-medical-education-pcme>.¹

Keywords: Pathology competencies, Organ system pathology, Cardiovascular-heart, Cardiac infection, Rheumatic fever, Carditis, Aschoff nodule

Primary objective

Objective CH4.1: Rheumatic fever: Describe the major manifestations of rheumatic fever and its effect on the endocardium, myocardium, and pericardium.

Competency 2: Organ system pathology, Topic: Cardiovascular-heart (CH); Learning goal 4: Cardiac infection

Patient presentation

A 12-year-old previously healthy girl is evaluated by her pediatrician because of dyspnea, chest pain, and fatigue. The patient and her father note that she had a sore throat approximately 2–3 weeks prior, but did not seek medical attention at the time. While her sore throat resolved on its own after several days, she recently developed the symptoms described above. She feels that she cannot take a deep breath, she describes her chest pain as sharp in nature and present at all times, and states that she feels tired when trying to do any physical activity, even walking. No one around her has similar symptoms and she has never had anything like this happen to her before.

Diagnostic findings, Part 1

On physical examination in the pediatrician's office, the girl appears to be in mild distress. She has the following vital signs: temperature of 38.7 °C, respiratory rate (RR) of 30 breaths per minute, and heart rate

(HR) of 160 beats per minute. Pulse is regular in rhythm. Her pharynx is non-erythematous in appearance. Auscultation of the chest reveals no murmur; however, a slight friction rub is identified. Breath sounds are shallow and clear to auscultation with no rhonchi, wheezes or rales. In addition, multiple subcutaneous, painless nodules 1–1.5 cm in size are present on the extensor surfaces of both arms. The rest of the physical examination is unremarkable.

Questions/discussion points, Part 1

What is the differential diagnosis for this patient given the history and physical examination findings?

With a child presenting with the symptoms and history as described above, the most likely differential diagnostic possibilities are acute rheumatic heart disease, viral myocarditis, infective endocarditis, autoimmune disease, pneumonia, and other pulmonary diseases.

What should be done to work up this patient?

In order to narrow the differential diagnosis, testing is necessary. Non-specific laboratory tests such as C-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR) can help identify underlying inflammation, which could be due to infection such as viral myocarditis or infective endocarditis. More specific laboratory testing, such as anti-streptolysin O and anti-DNAse B, must be done to aid in diagnosing

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Table 1
Summary of the 2015 modified Jones criteria^a.

Major criteria	Minor criteria	Supporting evidence of a preceding streptococcal infection
Carditis, clinical and/or subclinical ^b	Prolonged PR interval ^c	Elevated or rising anti-streptolysin O level
Polyarthritits	Arthralgia	or
Sydenham chorea	Fever $\geq 38^{\circ}\text{C}$	Positive throat culture for GABHS
Erythema marginatum	Markers of inflammation,	
Subcutaneous nodules	Peak ESR ≥ 60 mm in 1 h and/or CRP ≥ 3.0 mg/dL	

ARF: Acute rheumatic fever, CRP: C reactive protein, ESR: Erythrocyte sedimentation rate, GABHS: Group A beta-hemolytic Streptococcus, RHD: Rheumatic heart disease.

^a The criteria as listed are those for low-risk populations such as those in the United States and other developed countries. Moderate- and high-risk populations have slightly different criteria.

^b Subclinical carditis: seen only on echocardiography without auscultatory findings.

^c Accounting for age variability and only if carditis not counted as a major criteria.

past rheumatic fever. In addition to laboratory testing, an electrocardiogram (ECG) and echocardiogram would also be completed to examine the rhythm, structure, and function of the heart. A chest x-ray would also be performed to examine for lung disease.

Diagnostic findings, Part 2

Laboratory findings are significant for anti-streptolysin O level 287 (reference range: ≤ 200 Todd units), CRP 4.6 mg/L (reference range: ≤ 3.0 mg/L) and ESR 65 mm/h (reference range: 0–29 mm/h). Anti-DNAse B is not elevated. ECG shows sinus tachycardia and echocardiogram shows normal ejection fraction and no evidence of valve disease with the absence of vegetations. Chest x-ray shows no evidence of consolidation of the lungs with normal heart and lung size and structure.

Questions/discussion points, Part 2

What is this patient's most likely diagnosis?

The most likely diagnosis is acute rheumatic heart disease due to rheumatic fever caused by a previously untreated streptococcal pharyngitis.

What are the revised Jones criteria for diagnosing rheumatic fever?

The revised Jones criteria are guidelines set forth by the American Heart Association to aid in the initial diagnosis of rheumatic fever.² Laboratory evidence of a preceding group A streptococcal (GAS) infection plus two major criteria or one major and two minor criteria are required to make the diagnosis of acute rheumatic fever (ARF).² Laboratory evidence of a preceding GAS infection can be obtained through a throat culture growing GAS or elevated anti-streptolysin O titers. Major criteria are as follows: carditis, polyarthritits, Sydenham chorea, erythema marginatum, and subcutaneous nodules. Sydenham chorea is rapid and irregular jerking movements, which usually begin in the hands, but can involve the face and the feet. Erythema marginatum is an annular erythematous rash. Minor criteria are as follows: prolonged PR interval, arthralgia, fever, ESR ≥ 60 mm in 1 h or CRP ≥ 3.0 mg/dL. ESR and CRP are markers of inflammation. Major and minor criteria are outlined in Table 1. The criteria as listed are those for low-risk populations such as those in the United States and other developed countries. Moderate- and high-risk populations have slightly different criteria. Also, the criteria in Table 1 are not used for diagnosis of subsequent episodes of rheumatic fever.² This patient presented with two major criteria: carditis and subcutaneous nodules, three minor criteria: fever to 38.7°C , ESR 65, CRP 4.6, and evidence of a previous GAS infection with an elevated anti-streptolysin O titer, and, thus clearly met the criteria for ARF.

What populations are at greatest risk for rheumatic fever?

ARF is most common in developing countries due to decreased prevention and treatment of GAS infections. It carries a significant burden worldwide and is responsible for 250,000 deaths in young people each year. Additionally, over 15 million people have evidence of rheumatic heart disease (RHD) worldwide.³ ARF largely affects children between the ages of five and 14 years.⁴ Approximately 35–72% of patients who experience ARF will develop clinical carditis.⁴ Previous attacks of rheumatic fever place an individual at increased risk of recurrent rheumatic fever, and thus at increased risk of RHD.^{4,5}

What is the pathogenesis of rheumatic heart disease?

The pathogenesis of RHD is not entirely known, thus the subsequent explanations are postulated. ARF results from an autoimmune response to infection of the pharynx caused by *Streptococcus pyogenes*, a group A beta-hemolytic streptococcus. RHD is the long-term cardiac damage caused by either a single severe episode or multiple recurrent episodes of ARF.⁴ Acute RHD typically develops two to three weeks following an episode of ARF and is thought to be caused by tissue injury through an immune-mediated mechanism initiated via molecular mimicry, however, the full pathogenesis is unknown. It develops weeks after an episode due to the time it takes for an adaptive immune response to develop, much like post-infectious glomerulonephritis. The structural similarity between the infectious agent and human proteins, such as M protein, myosin, and human valvular endothelium, leads to the cross-activation of antibodies and/or T cells directed against these proteins, causing tissue injury, specifically carditis.⁴ This cross-reactive immune response leads to the clinical features of rheumatic fever. This includes carditis, due to antibody binding and infiltration of T cells; transient arthritis, due to the formation of immune complexes and their deposition causing damage and scarring of the joint space; Sydenham chorea, due to the binding of antibodies to basal ganglia; and skin manifestations, due to a delayed hypersensitivity reaction.⁴ Widely disseminated, focal inflammatory lesions are found in various sites throughout the body, including the heart. Owing to involvement of the immune system, the most common presenting features of ARF are fever and arthritis, and the most serious manifestation is carditis because it can lead to acute or chronic RHD, while all other clinical features fully resolve, often within weeks.⁴

What are the cardiac effects of acute rheumatic fever?

RHD is composed of two phases: acute and chronic. Acute RHD is associated with pancarditis involving active inflammation of endocardium, myocardium, and pericardium. Microscopically, the pericardium is affected in almost all patients with active rheumatic fever, and a pericardial rub may be heard when there is extensive involvement of the pericardium.^{4,6} Pericarditis in ARF is an acute fibrinous pericarditis.

Grossly, the pericarditis has a “bread-and-butter” appearance, which is best appreciated to the naked eye when the visceral and parietal layers of the pericardium are peeled away from one another.^{6,7} Inflammation of the myocardium leads to chest pain, shortness of breath, and commonly arrhythmias. In general, endocardial involvement in ARF presents as an acute inflammatory process involving valve leaflets. These small, friable inflammatory lesions of the valve, known as vegetations, are sterile, since the pathogenetic process involves a post-infectious immunologic cross-reaction to the tissue. The acute valvulitis can result in valve dysfunction (e.g. regurgitation). Recurrent episodes of ARF or persistent inflammation of the affected valve(s) following ARF, can lead to long-term valve damage resulting in functional stenosis or regurgitation of the affected valve(s).⁴ Unlike the myocardium and pericardium, the endocardial valvular damage does not resolve with time. Patients with suspected ARF should have an echocardiogram to confirm clinical findings and to grade severity of valvular regurgitation, to evaluate cardiac function, and to diagnose any subclinical involvement.⁴

What are the characteristic histologic features of acute rheumatic heart disease?

The characteristic disseminated, focal inflammatory lesion of ARF is known as the Aschoff body. Such lesions are especially distinctive in the hearts of patients with ARF. These granuloma-like lesions are classically composed of plump, activated histiocytes (the characteristic Anitschkow cell) and lymphocytes that surround a central region of fibrinoid necrosis. Chromatin of the Anitschkow cell can be seen as a central, slender ribbon, which may appear to resemble a caterpillar when seen on longitudinal section in H&E stained sections of affected cardiac tissue (hence the name “caterpillar cell” that is sometimes used to describe such cells).^{6,7} (Fig. 1). With valvular pathogenesis, most commonly mitral regurgitation, the lungs may be involved and become firm and heavy with chronic passive congestion or pulmonary hypertension. This may progress to heart failure. Acute valvular disease with heart failure or chronic valvular disease account for most of the morbidity and mortality associated with rheumatic fever.⁸

Diagnostic findings, Part 3

At age 37-years-old, 25 years following her initial presentation with ARF, the patient presents with dyspnea on exertion, fatigue, and heart

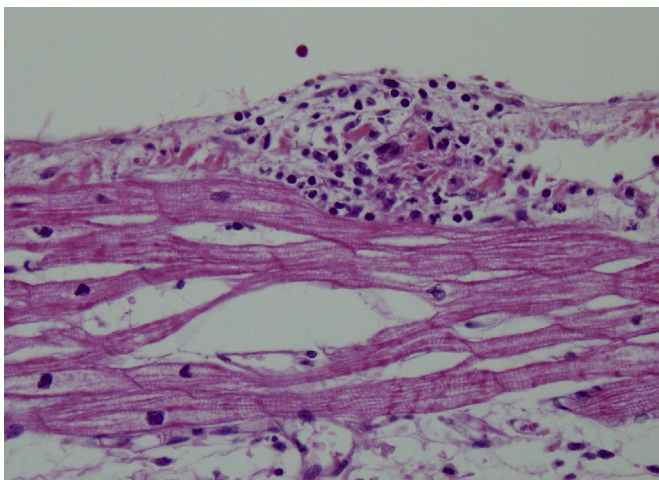


Fig. 1. Aschoff nodule. An Aschoff nodule is present in the endocardium. It is a collection of mononuclear cells that is characteristic of acute rheumatic fever. No central fibrinoid necrosis or Anitschkow cells, which are enlarged macrophages within an Aschoff nodule, are easily identifiable (Hematoxylin and eosin, 200x).

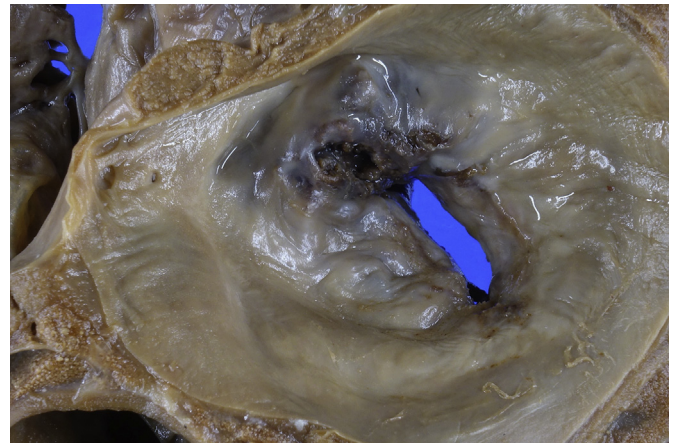


Fig. 2. Mitral stenosis. A view of the mitral valve from the atrial surface. The leaflets are fused and fibrotic, imparting the characteristic fish-mouth appearance. The left atrium is dilated.

palpitations for the past few months. She is afebrile, tachypneic (RR 24), tachycardic (HR 120), and normotensive. On physical exam, she appears in mild distress, using accessory muscles to breathe. Breath sounds are remarkable for bilateral rales. Auscultation of the chest reveals an opening snap, followed by a low-pitched decrescendo-crescendo rumbling diastolic murmur, consistent with a murmur of mitral stenosis. ECG shows sinus tachycardia and echocardiogram is remarkable for ejection fraction of 40% and commissural fusion and thickening of the mitral valve leaflets with restricted movement of the leaflets.

Questions/discussion points, Part 3

What are the cardiac effects of chronic rheumatic heart disease?

The effects of ARF may resolve completely or, in some cases, progress to scarring and development of chronic valvular deformities many years after the acute disease. The incidence and prevalence of chronic RHD are variable amongst different countries. Recurrent episodes generally affect older children and can occur into young adulthood. Because chronic RHD results from cumulative damage, chronic RHD has a latency averaging 20–25 years or longer.⁴ If the manifestations of ARF are not present or addressed, RHD can remain asymptomatic for a long period of time. It is possible that RHD is not noticed until heart failure develops.⁹ The main



Fig. 3. Chordae tendinae of mitral valve. The chordae tendinae and their attachment to the leaflets and papillary muscles have been excised. The chordae tendinae are fused together, shortened, and fibrotic, which is characteristic of chronic rheumatic mitral valvulitis.

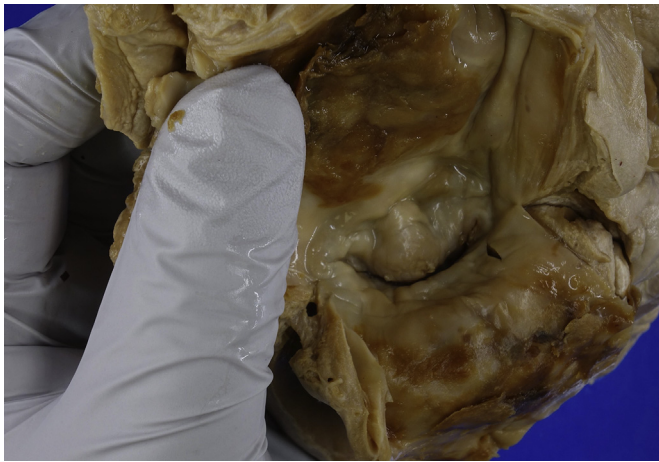


Fig. 4. Mitral stenosis with dilated left atrium. The mitral valve is stenotic and the left atrium is dilated. The endocardial surface of the dilated left atrium has adherent mural thrombus caused by a jet lesion due to regurgitation with endothelial damage.

clinical manifestation of chronic RHD reflects involvement of the endocardium, which presents as valvulitis of the mitral valve and, less frequently, of the aortic valve, and even less commonly, the tricuspid valve.⁴ Mitral regurgitation due to chronic scarring is the most common valvular pathology in chronic RHD.⁷ Endocarditis heals by progressive fibrosis, thus chronic scarring of the valves may become clinically evident decade(s) after the acute phase. In mitral valve stenosis, components of the valve apparatus, including the leaflets and chordae tendineae, are thickened, fibrotic, and shrunken with eventual fusion of the valve commissures and secondary deposition of calcium, which results in the creation of the classic “fish-mouth” appearance of the valve (Figs. 2 and 3).⁹ Stenosis of the mitral valve can lead to pressure overload on the left atrium, causing dilation and hypertrophy of the atrial chamber (Fig. 4). With a functionally regurgitant mitral valve, significant volume overload of the left ventricle usually leads to ventricular dilation over time. Residual damage of the myocardium and pericardium are not typically observed after the acute episode of rheumatic fever has resolved.⁹ The second most common valvular pathology is aortic regurgitation. Chronic scarring of the aortic valve leaflets impairs the ability of the valve to close properly, leading to the leakage of blood back into the left ventricle. The chronic volume load on the left ventricle that occurs from the regurgitation results in dilation and eccentric hypertrophy of the ventricle over time.⁷ Stenosis of the aortic valve can also potentially occur in RHD due to leaflet thickening and fusion of the commissures in a manner similar to that seen in chronic rheumatic mitral valve stenosis.⁷

What is the treatment recommendation for RHD?

Primary prevention of RHD is key to the management of this condition. Appropriate antibiotic treatment of GAS infections with penicillin prevents acute rheumatic fever in most cases, and thus prevents RHD.⁵ It is crucial that streptococcal pharyngitis is treated before it progresses to ARF and potentially RHD. Additionally, individuals who have developed ARF are at risk for additional attacks of ARF following GAS infections, thus secondary antibiotic prophylaxis is essential following the initial ARF episode. To treat ARF, some recommend corticosteroid treatment in patients with severe carditis, however, there is no evidence that anti-inflammatory therapy alters the long-term outcome of patients with ARF.⁵ Further management of severe carditis consists of standard heart failure treatment. Valve surgery is rarely necessary in patients with acute rheumatic carditis, but can be life-saving in situations where acute rupture of a valve leaflet or chordae tendineae has occurred. Surgical management for chronic RHD include valve repair, open valvuloplasty, or replacement.⁴ Recurrent

attacks can be associated with worsening of the severity of RHD that developed after a first attack, or less frequently with the new onset of RHD in individuals who did not develop cardiac manifestations during the first attack.

Teaching points

- ARF results from an autoimmune response to infection of the pharynx caused by *Streptococcus pyogenes*, a group A beta-hemolytic streptococcus. Rheumatic heart disease (RHD) is the long-term cardiac damage caused by either a single severe episode or multiple recurrent episodes of ARF.
- RHD is composed of two phases: acute and chronic. Acute RHD is associated with pancarditis involving active inflammation of endocardium, myocardium, and pericardium. The acute changes may resolve completely, or, in some cases, may progress to scarring and development of chronic valvular deformities many years after the acute disease.
- The revised Jones criteria are guidelines set forth by the American Heart Association to aid in the initial diagnosis of rheumatic fever. Laboratory evidence of a preceding group A streptococcal (GAS) infection plus two major criteria or one major and two minor criteria are required to make the diagnosis of acute rheumatic fever (ARF).
- Mitral regurgitation due to chronic scarring of the mitral valve is the most common valvular pathology seen in chronic RHD.
- Acute valvular disease with heart failure or chronic valvular disease account for most of the morbidity and mortality associated with rheumatic fever.
- Appropriate antibiotic treatment of streptococcal pharyngitis with penicillin prevents acute rheumatic fever in most cases, and thus prevents RHD.

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