

Acute and Chronic Complications of Rheumatic Heart Disease



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INTRODUCTION

Acute rheumatic heart disease (RHD) can be a devastating illness. It has a disproportionate prevalence in young, indigenous and lower socioeconomic status populations. This leads to difficulty not just with initial identification and management, including delayed presentation and poor adherence to therapy, but also with long-term follow-up and management of these patients with a higher risk for complications.

CASE PRESENTATIONS

We present two cases demonstrating some of the acute and long-term consequences of RHD.

The first patient was a 15-year-old Samoan boy who presented in late April 2019 with acute rheumatic fever (ARF). The diagnosis was based on a history of a recent sore throat 2 weeks prior, pain and swelling of his hands and feet (particularly wrist arthralgia), and a nonspecific rash that was not characteristic of erythema marginatum. The first echocardiogram showed trace aortic regurgitation (Video 1) and mitral regurgitation (Videos 2 and 3). The patient was discharged home on appropriate antibiotic therapy with a diagnosis of probable ARF and evidence of only mild valvulitis.

Over the next 2 weeks he became more unwell, with vomiting and shortness of breath on exertion, and was readmitted. His family thought this might have been a reaction to the antibiotics and therefore had stopped them without consulting a medical professional. Repeat echocardiography demonstrated moderate aortic and mitral regurgitation. Again he was treated symptomatically, with alleviation of symptoms, and was discharged home. Over the following 3 to 4 weeks the carditis progressed, with severe valvulitis of both the aortic (Video 4, Figures 1 and 2) and mitral (Videos 5 and 6) valves and myocarditis with severe biventricular dysfunction and pulmonary hypertension (Figure 3). Over this period of time, antistreptolysin O titers also climbed markedly, confirming this to be a case of ARF. The patient proceeded to urgent inpatient aortic valve replacement with a 23-mm prosthetic valve (St. Jude Medical, Minneapolis, MN) and mitral valve replacement with a 33-mm prosthetic valve (St. Jude Medical) in mid-June 2019.

Several risk factors for developing ARF were identified. The patient lives with seven siblings and his parents in a small house. He has an older brother who had a confirmed episode of ARF 12 years prior. He had also presented to the hospital 1 year prior with a sore throat, arthralgia, and abdominal pain that, in retrospect, may have represented a previous episode of ARF. Episodes of sore throat over several years had been noted, but most of these had been mild without any associated sequelae.

The second patient was a 24-year-old Tongan woman with severe RHD who underwent triple valve replacement in 2014 with a 23-mm aortic valve prosthesis, a 29-mm mitral valve prosthesis, and a 31-mm tricuspid valve prosthesis (all from St. Jude Medical). After surgery, she has had a history of poor attendance and compliance with medical therapy, attending fewer than a quarter of offered outpatient appointments.

The patient presented in 2015 with an episode of presumed endocarditis with high fever, increased levels of inflammatory markers, and transesophageal echocardiography that demonstrated an echo-dense mobile mass on the prosthetic aortic valve. She was treated with 6 weeks of intravenous (IV) antibiotics, with good systemic, biochemical, and echocardiographic response. She also had two presentations to the hospital with right lower limb cellulitis in October and December 2017. Apart from regular international normalized ratio (INR) checks around these episodes of illness, the patient had only managed three INR checks in the 12 months before her current presentation, with most of these revealing subtherapeutic values (target INR, 3–3.5). Her weight had also increased from 108 kg in 2014 to >160 kg. At that time she was living in a rural town and receiving sick-ness benefits.

The patient presented in December 2018 with a high fever and progressive dyspnea. She had positive blood cultures, and methicillin-susceptible *Staphylococcus aureus* was isolated. She was transferred to our institution for further investigation and management. There was evidence of multiple-organ dysfunction, with rapid atrial fibrillation, symptoms and signs of severe biventricular failure, acute renal failure, and deranged liver function with an elevated INR (in the setting of an unchanged warfarin dose); a brain magnetic resonance imaging study showed small acute cerebrovascular infarctions (left parieto-occipital, right parietal, and left cerebellar). Transthoracic echocardiography and transesophageal echocardiography were performed. The transthoracic images showed very poor biventricular function and raised the suspicion of abnormal prosthetic tricuspid valve function (Video 7, Figure 4). Transesophageal echocardiography showed that the mitral valve prosthesis was functioning normally but with obvious mobile echo-dense masses attached, consistent with infective endocarditis (Video 8). The tricuspid valve prosthesis was thrombosed in the open position with elevated forward velocities and no obvious tricuspid regurgitation because of very poor right ventricular function (Video 9). It also demonstrated significant spontaneous echocardiographic contrast and an echo-dense mass in the right atrium, consistent with right atrial thrombus (Video 10). The prosthetic aortic valve was not well visualized, because of acoustic shadowing.

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VIDEO HIGHLIGHTS

Video 1: Case 1: transthoracic echocardiography, apical three-chamber view. Color Doppler demonstrating trace aortic regurgitation.

Video 2: Case 1: transthoracic echocardiography, apical two-chamber view. Color Doppler demonstrating trivial mitral regurgitation.

Video 3: Case 1: transthoracic echocardiography, apical four-chamber view. Color Doppler demonstrating trivial mitral regurgitation.

Video 4: Case 1: transthoracic echocardiography, apical five-chamber view. Color Doppler demonstrating severe aortic regurgitation.

Video 5: Case 1: transthoracic echocardiography, apical four-chamber view. Color Doppler demonstrating severe mitral regurgitation.

Video 6: Case 1: transthoracic echocardiography, apical two-chamber view. Color Doppler demonstrating severe MR.

Video 7: Case 2: transthoracic echocardiography, parasternal long-axis view, tricuspid valve. Color Doppler demonstrating almost continuous forward flow.

Video 8: Case 2: transesophageal echocardiography of the mitral valve prosthesis demonstrating one of the mobile echodense masses consistent with endocarditis.

Video 9: Case 2: transesophageal echocardiography. Tricuspid valve prosthesis. Three-dimensional image of thrombosed tricuspid valve prosthesis in open position.

Video 10: Case 2: transesophageal echocardiography. Tricuspid valve prosthesis thrombosed in open position. Right atrial thrombus.

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The patient was treated with IV gentamicin, flucloxacillin, and rifampicin per the susceptibilities in our region and on the advice of our infectious disease specialists for prosthetic valve endocarditis.

She was transferred to the quaternary center for the country for consideration of a redo operation, but this was declined because of the extremely high surgical risk. Subsequently she was transferred back to our center for further medical management.

DISCUSSION

As is the case around the world, within New Zealand there is significant geographic and ethnic variation in the incidence of ARF. Maori and Pacific Islanders are disproportionately affected by ARF and chronic RHD. Most cases of ARF occur in children aged 5 to 14 years, and about one third of cases occur in older teens and young adults. A genetic predisposition has thus far not been proved. Causative risk factors that have been identified include economic deprivation, household crowding, poor health literacy, and lack of access to health care.¹ These factors prevent swift investigation and effective treatment of group A *Streptococcus* (GAS; *Streptococcus pyogenes*) pharyngitis and access to secondary prevention of recurrences. They also increase the

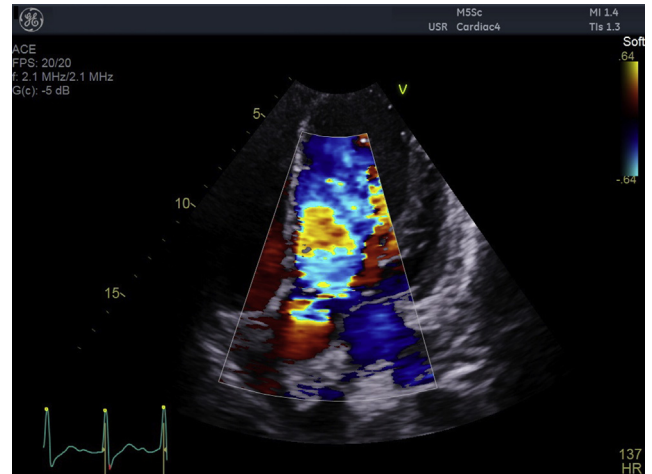


Figure 1 Case 1: transthoracic echocardiography, apical five-chamber view. Still image of color Doppler demonstrating severe aortic regurgitation.

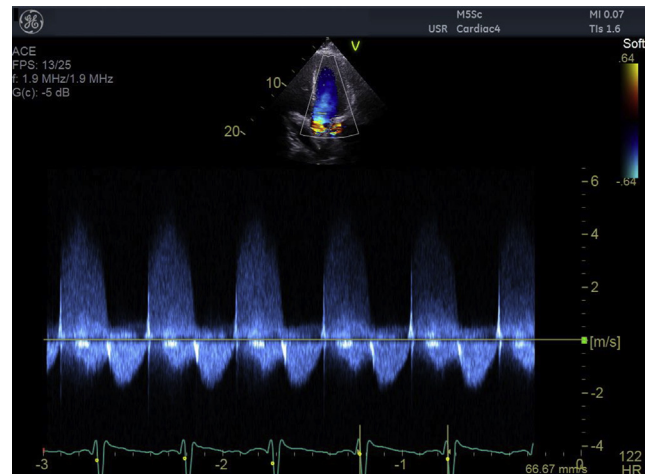


Figure 2 Case 1: transthoracic echocardiography, apical five-chamber view, continuous-wave Doppler through aortic valve. Severe aortic regurgitation.

risk for repeated exposure to GAS and therefore the development of symptomatic ARF and consequent chronic RHD.

ARF is an autoimmune consequence of GAS pharyngitis mediated by molecular mimicry.¹ Until recently there have only been case reports of ARF following GAS skin infection (impetigo) without obvious pharyngitis, but there is emerging epidemiologic evidence supporting the association between high rates of impetigo and RHD in some Pacifica communities with a comparatively normal rate of GAS pharyngitis.²

Following a latent period of 2 to 3 weeks, there is an acute generalized inflammatory response that typically affects the heart (carditis, valvulitis, pericarditis, and/or myocarditis), joints (arthritis), central nervous system (Sydenham chorea, motor impersistence, and behavioral symptoms), and skin (erythema marginatum and subcutaneous nodules).¹

One episode of rheumatic fever significantly increases the risk for further episodes and further cardiac damage. Usually several episodes of GAS, which may be subclinical, are required to develop the sequela

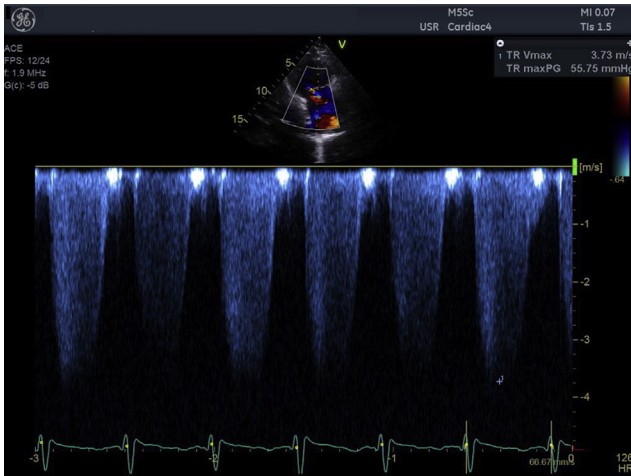


Figure 3 Case 1: transthoracic echocardiography, parasternal long-axis view, tricuspid valve. Continuous-wave Doppler through tricuspid valve demonstrating pulmonary hypertension.

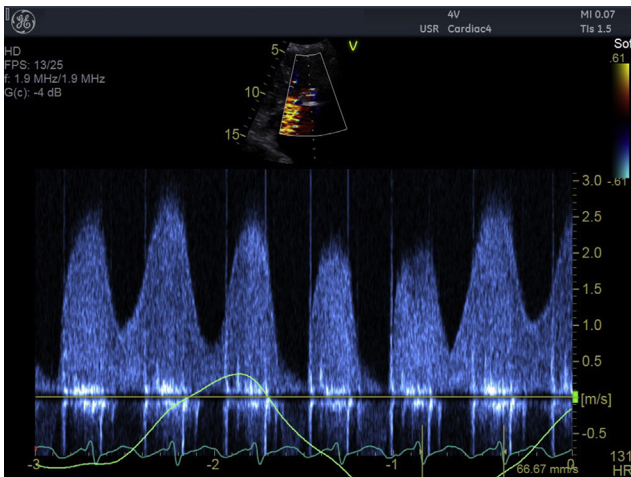


Figure 4 Case 2: transthoracic echocardiography, parasternal long-axis view, tricuspid valve. Continuous-wave Doppler through tricuspid valve demonstrating almost continuous forward flow.

of ARF. The risk for ARF after the first attack of GAS pharyngitis is approximately 0.3% to 3%, but with subsequent infections this risk rises to 25% to 75%.³ This helps demonstrate the importance of long-term preventive antibiotic therapy, as often episodes of pharyngitis are only mildly symptomatic but contribute to the progression of RHD.

There is no one diagnostic test to confirm the diagnosis of ARF. Worldwide, the diagnosis is based largely on the Jones criteria, which date to 1944 and were modified in 1992, reconfirmed in 2004 by the World Health Organization, and then further revised in 2015 by the American Heart Association.⁴ They consist of major and minor criteria, and scoring determines the certainty of diagnosis as possible, probable, or definite.

In New Zealand, rheumatic fever has been a notifiable disease since 1986. Regional registries have been established, and a national registry is currently in development. Since 2009, the government of New Zealand has made rheumatic fever a health priority. The New

Zealand guidelines were updated in 2014 with diagnostic criteria modified to represent the presenting characteristics within New Zealand. One such distinction of note is that aseptic monoarthritis is a major criterion even in the absence of nonsteroidal anti-inflammatory drugs, in contrast to the American guidelines, in which it is a minor criterion. Epidemiologic data would suggest that in Auckland, New Zealand, monoarthritis is a presenting symptom in up to 85% of cases of ARF.³ Despite variation in the categorization of signs and symptoms as major or minor, the diagnostic algorithm is the same around the world.

A probable diagnosis is made when there is evidence of a preceding GAS infection (throat culture or rapid antigen test) or serologic evidence of GAS infection (antistreptolysin O or anti-DNAse B) and one major and one other minor criteria. Definite diagnosis is made with serological evidence of GAS infection and two major or one major and two minor criteria or chorea. Because chorea is pathognomonic, other major manifestations or evidence of GAS infection is not required.

In New Zealand, there is a higher incidence of rheumatic fever than in comparable countries and regions such as North America and the United Kingdom. Because of these higher rates of RHD, especially with marked ethnic differences, New Zealand statistics are quoted in the American Heart Association scientific statement regarding rheumatic fever and RHD. The overall mean incidence of ARF in New Zealand rose by 55% over the past two decades, but the incidence of ARF among the non-Maori/Pacific Islander New Zealand populations declined by 70% over the same period.⁴ In 2018, 161 cases met the definition for first episode rheumatic fever.⁵ This gives a rate of 3.3 per 100,000 population. Pacific Islander children aged 5 to 14 years had the highest rate at 83.2 per 100,000, followed by Pacific Islanders aged 15 to 24 years, at 54.5 per 100,000. Maori children aged 5 to 14 years had a rate of 28.6 per 100,000. There were very small numbers among European and other ethnicities, with an overall rate of 0.2 per 100,000, for a total of only six cases in this group.⁵ This ethnic variation is also observed in other countries such as Australia, where the indigenous population has one of the world's highest reported incidence rates at 153 to 380 cases per 100,000 people per year in the 5-to-14 age group.⁴

Treatment of an episode of ARF aims to reduce the inflammatory response, decreasing damage to the heart and joints, eradicate the GAS from the pharynx, and provide symptomatic relief. This is usually managed with anti-inflammatory medications for symptom management, especially arthralgias, and penicillin antibiotic therapy to treat the causative organism. Glucocorticoid therapy can be considered for severe carditis, but there is a paucity of evidence demonstrating any benefit over placebo when studied in two meta-analyses.³ Despite this, many clinicians still believe that glucocorticoids may have a role in severe acute carditis and may lead to more rapid resolution of cardiac compromise, especially in patients in whom surgery is not indicated. However, this therapy must be considered in the context of the potential major adverse effects, such as gastrointestinal bleeding and worsening heart failure because of fluid retention.³ Of the available evidence, salicylates do not appear to decrease the incidence of residual RHD and are therefore not recommended in the treatment of carditis.³

Prevention of recurrent episodes after an episode of ARF is important. This is usually done with a 1.2 million International Units intramuscular injection of benzylpenicillin every 3 to 4 weeks to improve compliance. There is evidence that more frequent dosing (every 2–3 weeks) reduces the risk for recurrence further, but this often proves impractical with poorer adherence.^{1,3} The majority,

but not all, episodes of recurrences occur when there has been poor compliance with prophylaxis.³ Duration of prophylaxis is not fully known, but depending on the degree of carditis, it is often recommended into adulthood or for life. The New Zealand guidelines recommend that if there is no or mild evidence of RHD, prophylaxis should continue until the 21 years of age or 10 years after the last attack, whichever is later. If RHD is moderate, prophylaxis should continue until 30 years of age, and risk should then be reassessed. If RHD is severe, prophylaxis should continue until 40 years of age with reassessment.³

Follow-up, surveillance, and management of patients after valve surgery for RHD is similar to that for any patient after valve surgery. Apart from ongoing antibiotic prophylaxis, as noted earlier, there are no other alterations to standard care. Factors that make managing these patients difficult are their age and ethnic and socioeconomic characteristics. The same challenges are faced with standard valve replacement follow-up as are seen with adherence to ongoing antibiotic therapy. Nonadherence to anticoagulation and heart failure medications can significantly affect the immediate, intermediate, and long-term prognoses of these patients. Management of complications of valve surgery is the same as for any other patient after valve surgery.

CONCLUSION

These cases highlight the severity of ARF and the long-term consequences associated with managing these, often young, patients. Both cases demonstrate the utility of echocardiography in confirming the diagnosis and determining the severity of valve involvement and dysfunction. They also bring into perspective the complex nature of RHD and its ongoing sequelae, especially in young patients.

The first patient is progressing well after his cardiac surgery, with recovery of both left and right ventricular function, improvement in pulmonary pressures, and stable valve function on clinical and echocardiographic assessment. He will be on monthly prophylactic intramuscular antibiotics until the 40 years of age with benzylpenicillin and warfarin therapy to prevent thrombosis associated with his mechanical valves. The family has been given a strict plan for assessment if any members develop sore throats. This includes a throat swab and antibiotic therapy with oral amoxicillin for any family member if it is positive for GAS. Our patient is undergoing regular clinical and echocardiographic follow-up, with intervals determined by his progress.

The second patient continued on IV antibiotic therapy and was eventually discharged from the hospital to live with her parents. She

initially attended her appointments, was clinically well, and seemed to have improved cardiac function. She then missed several outpatient appointments, but with ongoing input from community and Tongan support workers, she has started attending appointments again. She has completed her IV antibiotics and is now on oral penicillin only. She has managed to maintain an INR of 2.5 to 3, with only one INR as low as 2.0. She is currently being followed up regularly and awaiting repeat echocardiography to assess her ventricular and valvular function. This case adds some support to medical management as an option for the treatment of prosthetic multivalve endocarditis in patients with prohibitively high immediate surgical mortality risk. Her intermediate and long-term mortality risk remains high given her underlying cardiac pathology. In the meantime she is also being supported with a weight loss and cardiovascular fitness regime to improve her risk should she be a candidate for and require cardiac surgery in the future, as she is progressing favorably.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.case.2020.01.010>.

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