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Quadrivalvar Rheumatic Cardiopathy in Tetralogy of Fallot in an Adult—A Case Report

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Abstract

Rheumatic involvement of all four heart valves is uncommon and its association with congenital heart disease is very rare. Tetralogy of Fallot is a frequent cyanotic congenital heart disease with a survival beyond middle age. Background of this case report described the rheumatic involvement of all four heart valves (quadrivalvar rheumatic cardiopathy) with stenotic lesions of semilunar valves (aortic and pulmonary valves) and regurgitant lesions of atrioventricular valves (mitral and tricuspid valves) in Tetralogy of Fallot in a 48-year old asymptomatic female, detected by transthoracic two dimensional echocardiography in Thoothukudi region of India.

Keywords

Tetralogy of Fallot, Rheumatic Cardiopathy, All Four Heart Valves, Echocardiography, Current Research Status

1. Introduction

Incidence of valvular involvement in rheumatic heart disease (RHD) is the function of hemodynamic pressures and shear stresses on the exposed valves. The sparing of pulmonary valve in rheumatic process is usually attributed to low pressure and shear stress on this valve, but it does not explain in patients with severe pulmonary hypertension secondary to left sided valvular disease and lack of pulmonary involvement. When the transplanted pulmonary valve is placed in aortic position in pulmonary valve autograft Ross' procedure, it is susceptible to rheumatic valvulitis similar to the native aortic valve [1]. This reinforces the theory that no valve is immune to rheumatic process.

Involvement of all four valves is an uncommon feature of rheumatic heart disease [2]. There is a high inci-

dence of multivalvar damage when Aschoff bodies are identified at necropsy [3]. There are few reports available in the literature describing the rheumatic lesions of all four heart valves [4]. When all the four valves are affected by rheumatic disease, the lesion is usually one of stenosis and the majority of the reported cases are females. Kumar *et al.* [5] have quoted only 10 cases of quadrivalvar rheumatic heart disease in the English literature in 1985. In 1987, Hossack *et al.* [6] reported the case of a patient with rheumatic involvement of all valves treated with quadruple valve replacement and 12 cases have been reported upto 2005. In 2012, Cao and colleagues reported a 11-year follow-up study of a patient with subacute rheumatic endocarditis who underwent quadruple valve replacement [7]. Coexistent rheumatic disease in patients with congenital heart disease was known to occur [8] [9]. Tetralogy of Fallot (TOF) is the most common congenital heart disease seen beyond infancy and childhood with about 5% of patients surviving to the age of 40 years.

Rheumatic involvement of all four heart valves (quadrivalvar rheumatic cardiopathy) is uncommon in tetralogy of Fallot and so this case had been reported.

2. Case Report

A 48-year old asymptomatic female was referred for echocardiographic evaluation with a history of cyanosis from early childhood and a precordial murmur. Her pulse rate was 96 bpm and blood pressure was 110/70 mmHg. She had some frequent episodes of upper respiratory infection during childhood and treated with antibiotics, but penicillin prophylaxis was not given. She had delivered two healthy children normally, aged 10 and 13 years. General examination revealed central cyanosis and clubbing. Physical examination revealed a grade 3/6 systolic murmur in the left second intercostal space and a soft, single second heart sound. ECG and X-ray chest revealed right ventricular hypertrophy, consistent with Tetralogy of Fallot. Blood chemistry revealed a positive ASO (anti-streptolysin O) test suggesting the reactivation of rheumatic process following a recurrent episode of streptococcal infection. She was advised penicillin prophylaxis and periodic follow up. Transthoracic 2D echocardiography revealed a large malaligned ventricular septal defect (VSD) with valvular pulmonary stenosis suggesting tetralogy of Fallot and a thickened, calcified pulmonary and aortic valves with stenosis, thickened and calcified mitral and tricuspid valves with regurgitation suggesting quadrivalvar rheumatic cardiopathy as shown in **Figures 1-8**.

3. Discussion

The prevalence rate of rheumatic heart disease (RHD) is 0.5 - 0.67 per thousand in India [10]. The risk of coincident rheumatic disease in patients with tetralogy of Fallot was described in the literature. Rheumatic mitral stenosis was reported in an adult male, aged 35 years with tetralogy of Fallot at Visakhapatnam in India [11] and rheumatic involvement of all four valves in tetralogy of Fallot was also reported in a 14-year-old male [12].

3.1. Echocardiography

Transthoracic echocardiography provides an early diagnosis of rheumatic involvement of all four heart valves (quadrivalvar rheumatic cardiopathy). There are only few reports of echocardiographic diagnosis of stenotic involvement of all four heart valves due to rheumatic etiology [13] [14]. Bandin *et al.* stated that 3.6% of hearts with rheumatic disease show organic lesions of the pulmonary valve based on autopsy series and reported one patient having quadrivalvar rheumatic disease, diagnosed preoperatively by echocardiography [15]. Thus, echocardiography is useful for confirming clinical findings and allows assessment of the severity of valvular stenosis and regurgitation [16].

In this case, transthoracic 2D echocardiography revealed a large malaligned ventricular septal defect as shown in **Figure 1** and Color Doppler imaging in **Figure 5**, with valvular pulmonary stenosis as in **Figure 6** and **Figure 7**, suggesting the tetralogy of Fallot. The classical echocardiographic features of rheumatic involvement of valves such as thickened leaflets, commissural fusion with calcific deposits noticed in pulmonary and aortic valves as shown in **Figure 3**, thickened mitral and tricuspid valves as in **Figure 4**, valvular regurgitation involving the thickened mitral and tricuspid valves as in **Figure 8**, suggesting the quadrivalvar rheumatic cardiopathy in tetralogy of Fallot. Stenotic lesions are predominant and severe in semilunar valves (aortic and pulmonary valves) due to simultaneous exposure of semilunar valves to the equal pressure gradients in the ventricles and regurgitant lesions are predominant in atrioventricular valves (mitral and tricuspid valves) is a characteristic feature of rheumatic involvement in tetralogy of Fallot of this patient.

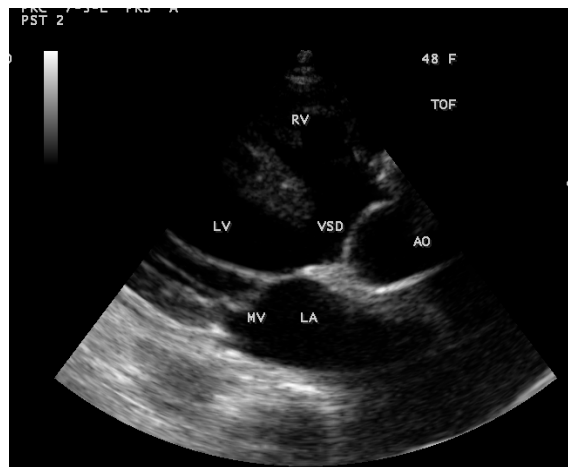


Figure 1. Parasternal long axis view showing the large malaligned ventricular septal defect (VSD).



Figure 2. Parasternal long axis view showing the thickened and calcified mitral valve.

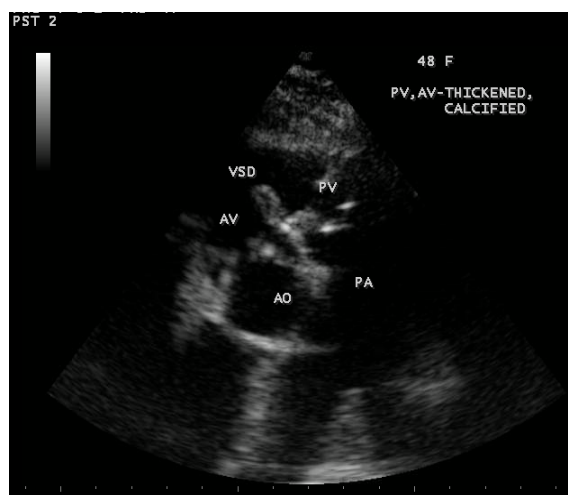


Figure 3. Short axis view showing the thickened and calcified pulmonary and aortic valves.



Figure 4. Apical four chamber view showing the thickened and calcified mitral and tricuspid valves.

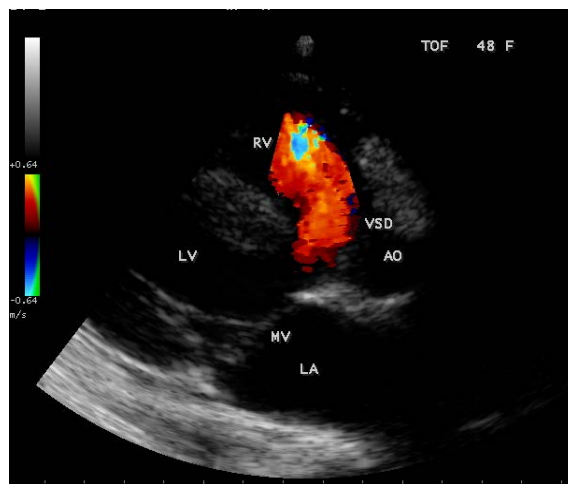


Figure 5. Color-Doppler imaging showing the malaligned VSD.

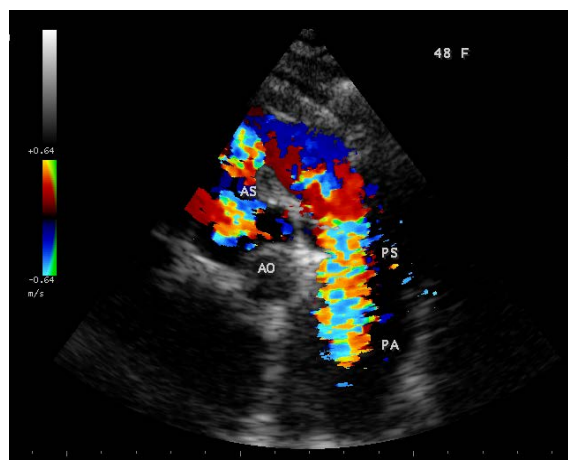


Figure 6. Color Doppler imaging showing the pulmonary and aortic stenosis in short axis view.

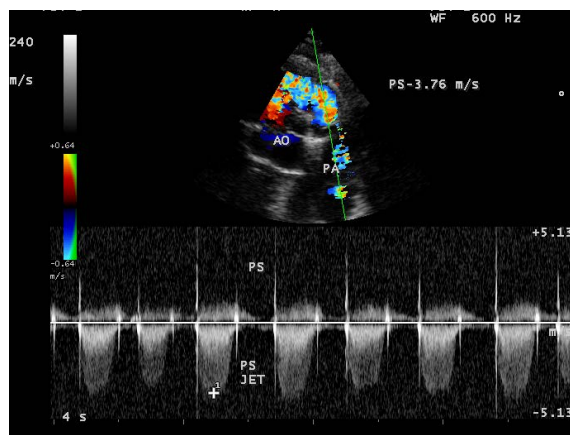


Figure 7. Continuous wave Doppler (CW) imaging showing the pulmonary stenosis jet.

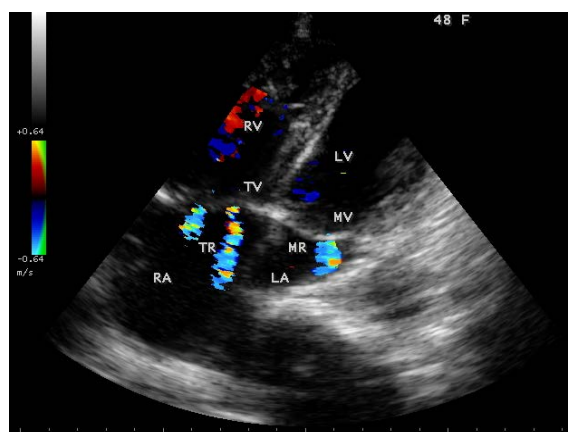


Figure 8. Color Doppler imaging showing the mitral and tricuspid regurgitation in apical four chamber view.

3.2. Penicillin Prophylaxis

Primary prophylaxis to eradicate the streptococcal infection and secondary prophylaxis to prevent the recurrent episodes are indicated as a therapeutic and preventive measures for RHD (Rheumatic Heart Disease) patients. Primary prophylaxis also serves as the first course of secondary prophylaxis. Ideally, continue prophylaxis indefinitely and sometimes life long, because recurrent streptococcal infections and rheumatic fever cases occur at any age in endemic areas and it should be maintained for those with clinically significant RHD for at least ten years after the last episode. Long-acting penicillin is of particular value in patients with a high risk of recurrence of rheumatic fever. An injection of 1.2 million units of benzathine penicillin G intramuscularly every 3 weeks [17] is recommended for this patient at least for ten years and preferably life long.

Thus, the recognition of rheumatic involvement of heart valves in tetralogy of Fallot is significant in endemic areas of RHD and the penicillin prophylaxis may prevent further deterioration in this case.

3.3. Current Research Status

3.3.1. In Pathogenesis

The organism group A beta-hemolytic streptococcus (*streptococcus pyogenes*), attach the epithelial cells of the upper respiratory tract and produce battery of enzymes, allowing them to damage and invade human tissues. Only infections of the pharynx have been shown to initiate or reactivate rheumatic fever in 0.3% - 3% of cases. However, epidemiological association in certain population have shown that group A streptococcus impetigo could predispose to or cause rheumatic fever as well [18]. Streptococcal proteins display molecular mimicry

recognized by the immune system, especially bacterial M-proteins and human cardiac antigens such as myosin [19] and valvular endothelium. Currently *emm* typing is felt to be more discriminating than M typing [20]. Anti-myosin antibody recognizes laminin, an extracellular matrix alpha-helix coiled protein, which is part of the valve basement membrane structure. T-cells that are responsive to the streptococcal M-protein infiltrate the valve through the valvular endothelium, activated by the binding of anti-streptococcal carbohydrate with the release of tumor necrosis factor (TNF) and interleukins [21]. Thus, cross-reactive antibodies bind to cardiac tissue, facilitate infiltration of streptococcal-primed CD4+T cells, which then triggers an autoimmune reaction and releasing inflammatory cytokines (TNF- α and IFN-gamma). Because few IL-4 producing cells are present in valvular tissue, inflammation persists, leading to valvular lesion. A study reported that the increased expression of Th 17 cell-associated cytokines might play an important role in the pathogenesis and development of rheumatic heart disease [22]. In chronic disease, there is thickening and fibrosis of the valve resulting in stenosis, or less commonly regurgitation.

In utero precursors predisposing to rheumatic heart disease have also been proposed [23] [24]. Eriksson *et al.* suggest increased spiraling of the umbilical cord may increase the risk of rheumatic heart disease secondary to presumed changes in hemodynamic conditions during the formation of the mitral valve [25].

Familial studies of rheumatic heart disease suggest a vulnerable population with increased risk of having relationship between the development of rheumatic fever and human leukocyte antigens (HLA)-DR subtypes have been found [26]. HL-DR3 was present more frequently in rheumatic fever patients in India, DR-1 in South Africa, DR-2 in African-American population, DR-4 in Caucasian and DQW2 in Asian Patients.

3.3.2. Probiotic Treatment

To find a solution to outbreaks of group A streptococcal (GAS) sore throat, a probiotic treatment was developed at Otago University. The BLIS K 12 probiotic specific to the throat and mouth, sold as “BLIS throat guard” was trialled in selected primary schools in Whakatane and Kawerau where the rheumatic fever has been an increasing problem and a school sore throat rheumatic fever programme has been running since 2010. The term antibiotics points to treatments which kill the microbes and the term probiotic refers to being “in support of life” as the mechanism supports the re-setting of the microbial biome, through growing beneficial microbes. BLIS K 12 populate the mouth and throat with a beneficial strains of streptococcus salivarius. When antibiotics were followed by taking the BLIS K 12 probiotic lozenges daily for 30 days, encouraging results were seen in school children with clearance of streptococcal infection from the throat up to 3 months [27].

3.3.3. Group A Streptococcal Vaccine Development

Efforts to produce a vaccine against streptococcus pyogenes began several decades ago, and different models have been proposed as M-protein based vaccines (N-and C-terminal portion), the major antigen of streptococcus pyogenes, the non-M protein based vaccine and other potential GAS vaccines such as Spe (streptococcal pyrogenic exotoxin) A and C.

StreptAvax is a M-protein based, multivalent type-specific vaccine, consists of a sequence of short peptides from the N terminal region of multiple different *emm* type strains in tandem, linked together using unique restriction sites. It may not produce sufficient and long-lasting protection in countries with highly endemic GAS diseases.

StreptIncor, a vaccine candidate peptide, comprising 55 aminoacid residues of the C-terminal portion of the M protein and encompassing both the T-and B-cell protective epitopes. StreptIncor overlapping peptides induced cellular and humoral immune responses of individuals bearing different HLA class II molecules of the macrophage to T lymphocytes via the T-cell receptor (TCR) and it could be considered as an immunogenic and safe vaccine. The safety of this vaccine was assessed using DR2, DR4, DQ6 and DQ 8 HLA class II transgenic mice.

StreptAnova^(R) multivalent vaccine is composed of four recombinant proteins containing protective peptides from 30 streptococcal serotypes that account for the vast majority of infections in North America and Europe. Phase I trial is ongoing as 3 injections over 6 months, with a one-year follow-up to assess the immune response to the vaccine [28].

3.3.4. Global Research Priorities

It is universally accepted that the most cost-effective approach to RHD (Rheumatic heart disease) control is delivery of secondary prophylaxis and improved clinical care of patients, using register-based RHD control pro-

grams as in New Zealand and Australia. An implantable form of penicillin could be a major advance. Naltrexone penicillin implants provide a promising model, given that the equivalent daily dose is similar to what would be required for penicillin [29]. Genetic studies to identify the nature of host susceptibility to detect the vulnerable groups and development of vaccine, screening echocardiography to detect subclinical carditis and to implement secondary prophylaxis are the priority measures in endemic areas.

3.3.5 Role of Statins

Early medical therapy with statins in patients with rheumatic heart disease showed a significantly slower progression of the disease as found in a recent study done in Europe on 315 patients with rheumatic mitral stenosis in 2010 [30] and reducing LDL-C (low-density lipoprotein cholesterol) may help to prevent aortic valve disease [31] as found by Smith *et al.* in 2014.

4. Conclusion

Quadrivalvar rheumatic cardiopathy with stenotic lesions in semilunar valves and regurgitant lesions in atrio-ventricular valves is a characterized feature detected by 2D echocardiography in a 48-year old female with tetralogy of Fallot in the tropical district of Thoothukudi in India in the year 2016.

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Ischaemic Monomelic Neuropathy in a Diabetic Patient after Brachio-Basilic Arteriovenous Fistula Creation

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Abstract

Introduction: The number of people with diabetes is increasing in every country. Recent estimates put the prevalence at 8.3% of adults, with a predicted rise to 10.1 in 2035 [1]. Although less than 1% of patients with diabetes require definitive haemodialysis, this still represents a significant number who may require arteriovenous fistula creation. **Presentation:** We report a case of IMN occurring in a patient with end stage diabetic nephropathy following brachio-basilic arteriovenous fistula creation for chronic maintenance haemodialysis. **Discussion:** Ischaemic monomelic neuropathy (IMN) has developed as a distinct clinical entity involving dysfunction of multiple peripheral nerves following vascular access. Symptom onset is usually immediate, and neurological symptoms are dominant, generally in the absence of significant clinical ischaemia. Acute neurological symptoms may be disabling and irreversible, but prompt ligation of arteriovenous fistula can prevent permanent disability. **Conclusion:** Ischaemic monomelic neuropathy (IMN) is a rare but serious complication of vascular access for arteriovenous fistula for haemodialysis and should be considered in the differential diagnosis of hand dysfunction following such surgery. While the condition is not preventable or predictable, prompt recognition and treatment can lead to prevention of permanent disability.

Keywords

Diabetes, Vascular, Neuropathy

1. Introduction

The number of people with diabetes is increasing in every country. Recent estimates put the prevalence at 8.3%

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of adults, with a predicted rise to 10.1% in 2035 [1]. Although less than 1% of patients with diabetes require renal replacement therapy, this still represents a significant number who may require arteriovenous fistula creation.

We highlight ischaemic monomelic neuropathy (IMN) as a rare but serious complication which should be considered in the differential diagnosis of hand dysfunction following vascular access. While the condition is not preventable or predictable, prompt recognition and treatment is essential, and can prevent permanent disability from rapid onset nerve damage.

Presentation of Case

A patient with diabetes mellitus presented with shortness of breath, abdominal distension and lower limb swelling for one week due to acute kidney injury secondary to sepsis from infection of a poorly healing wound post right patella fracture repair six months prior to presentation. Additional past history was notable for poorly controlled diabetes, hyperlipidaemia, anaemia of chronic disease, and chronic renal impairment. Surgical history was significant for an infected left toe ulcer for which the patient underwent debridement. On examination, blood pressure was 148/85, and pulse rate was 82/minute and regular. Jugular venous pressure was noted to be elevated and bilateral pedal oedema was present up to the knees. Coarse crepitations were noted in the bases of both lungs and gross ascites was present. Laboratory investigations revealed a haemoglobin level of 9.7 [14.0 - 18.0 G/DL] with a white cell count of 11.33 [4.0 - 10.0 $\times 10^9/L$]. Platelet count was 214 [140 - 440 $\times 10^9/L$]. Serum creatinine was 376 [54 - 101 $\mu\text{Mol/L}$], and serum urea, bicarbonate and potassium levels were 17.2 [2.7 - 6.9 $\mu\text{Mol/L}$], 20.1 [19.0 - 29.0 $\mu\text{Mol/L}$] and 3.8 [3.6 - 5.0 $\mu\text{Mol/L}$] respectively. Chest x-ray was consistent with acute pulmonary oedema. The patient was started on diuretics including intravenous furosemide and oral metazone. Hemodialysis was commenced via a tunnelled vascular catheter and planned for the creation of an arterio-venous fistula as a form of a permanent access for dialysis.

79 days after initial admission, a brachio-basilic arteriovenous fistula was created in the ambulatory surgical unit. Within hours after the surgery, the patient developed numbness of the right 4th and 5th fingers and thumb. The right upper limb was swollen, with reduced range of motion of the right wrist and fingers. The patient was unable to make a fist and exhibited clawing (**Figure 1**). Radial pulses were present bilaterally, capillary refill was < 2 seconds and the hands were noted to be warm. The neurological deficits persisted over the next two hours and were noted to be worsening as reported by the patient.

A clinical diagnosis of IMN with signs of sensorimotoric dysfunction of the nerves of the hand was made based on neurological symptoms out of proportion to physical findings, good pulse and warm peripheries. Reoperation with ligation of the AVF was performed within 24 hours of the fistula creation. Post-operatively an improvement in sensation and range of motion of the limb was noted. Over the next couple of weeks a complete recovery was made.

2. Discussion

Differential diagnosis of hand dysfunction following AV access include neurological complications of axillary



Figure 1. Photograph of right hand demonstrating clawing and absence of ischaemic pallor.

block or as a result of incorrect positioning during surgery, peripheral nerve compression as a result of acute compartment syndrome, functional deficit secondary to surgical trauma, postoperative pain or postoperative swelling. Vascular differentials include arterial emboli or thrombi, vascular steal syndrome, and ischaemic-monomelic neuropathy. In vascular steal syndrome there is distal ischaemia, manifesting as numbness, pain and paraesthesia. Clinical findings include reduced peripheral temperatures, diminished or absent pulses, and delayed capillary refill. Reduced digital pressure and absent Doppler signal can be used to support the diagnosis. Symptoms may occur immediately after vascular access, but can also be delayed, and may develop up to several months later.

Ischaemic monomelic neuropathy (IMN) has developed as a distinct clinical entity involving dysfunction of multiple peripheral nerves. Symptom onset is usually immediate, and neurological symptoms are dominant, generally in the absence of significant clinical ischaemia. Typically the hand is warm, pulses are present, and capillary refill is preserved. Mildly reduced or normal digital pressures and audible Doppler signal can support the diagnosis. Features supporting IMN over a vascular steal syndrome are brachial artery based fistula, presence of a radial pulse, and limited evidence of clinical ischaemia. Positive arterial Doppler studies and normal or slightly decreased digital pressures can aid in differentiating between the 2 conditions.

An initial description of IMN was made by Bolton *et al.* in 1979 [2], but it was not until 1983 when Wilbourn *et al.* formalised the term IMN [3]. The initial report described a clinical entity with arterial insufficiency (ischaemic), involving a single extremity (monomelic) and causing selective dysfunction (neuropathy) of multiple peripheral nerves. In his subsequent report, Wilbourn described three patients, two with acute arterial occlusions, and one with creation of an AVF for permanent access for hemodialysis. Following this Riggs *et al.* in 1989 described upper extremity IMN occurring after shunt placement in diabetic patients with end stage renal disease and evidence of peripheral vascular disease [4]. The pathophysiology of IMN has been attributed to a decrease in arterial blood flow secondary to diversion of large amount of blood away from the distal forearm and hand following arterio-venous shunt formation in the proximal forearm, or as a result of acute noncompressive major arterial occlusion. Under-perfusion of vasa nervosum results in acute axonal loss in multiple peripheral nerve fibres. Acute neurological symptoms may be disabling and irreversible, but there is not sufficient ischaemia to cause muscle or skin necrosis. It is thought that previous neuropathy results in a lower threshold to ischaemic injury leading to an increased risk of IMN in patients with diabetes mellitus, atherosclerotic peripheral vascular disease and women [5]-[8]. Raheb *et al.* reviewed 12 cases of IMN that occurred in 273 patients (4.4%) undergoing placement of PTFE brachial artery based loop graft and reported that all patients who developed IMN were diabetic and female [9].

Brachial artery based vascular access is most commonly associated with IMN due to lack of collateral blood supply to the distal arm. Zanow *et al.* reviewed a personal experience of 4853 procedures and found the incidence of ischaemia in patients with arteriovenous access to be 0.3% for wrist fistulas, 1.8% (0.9% - 5.2%) for elbow fistulas and 2.2% for upper extremity PTFE grafts [10].

Electrophysiological findings can be used to confirm a diagnosis and include axonal loss, low amplitude or absent responses to sensory and motor nerve stimulation with relatively preserved conduction velocities, and fibrillations and reduced motor unit requirement on needle EMG, but treatment should not be delayed when clinical suspicion is high. Kaku *et al.* reported in 1993 that conduction block occurs early in the course of upper extremity IMN, but this may not be present later in the disease [11].

Prognosis depends largely on the amount of initial nerve damage. Functional improvement may be seen as the nerve regenerates at a rate of approximately 2.5 cm per month. In the hand disability may result from weakness of the thenar and intrinsic muscles as well as sensory loss in all fingers which may extend into the palm and hand. Contractures of joints may also develop. For some patients pain is the most disabling aspect of this disease.

In the case presented here a clinical diagnosis of IMN with signs of sensorimotor dysfunction of the nerves of the hand was made based on neurological symptoms out of proportion to physical findings, good pulse and warm peripheries. Based on high clinical suspicion and the urgency of treatment further electrophysiological testing was not carried out to avoid any delay in treatment. Reoperation with ligation of the AVF was performed within 24 hours of the fistula creation. Post-operatively an improvement in sensation and range of motion of the limb was noted. Over the next couple of weeks a complete recovery was made. Although permanent damage can result as a result of IMN, in this patient early reoperation to ligate the fistula allowed complete recovery within a month. This case highlights the importance of prompt diagnosis and treatment in this condition as well as high-

highlighting the differential in patients with diabetes undergoing vascular access given the increasing number of such patients.

3. Conclusion

The distinction between vascular steal syndrome and IMN is important as vascular steal syndrome and is readily treated with access revision while treatment of IMN requires immediate closure of the AVF (NKF K/DOQI 2006 guideline 5.6). In Singapore, the rate of new diagnoses of diabetes was increasing, currently affecting 11.3% of the population, up from 8.2% in 2004 [12]. It is estimated that by 2030, 14% - 15% of the adult Singaporean population will be diabetic [13]. Moreover, diabetic nephropathy (DN) is the main cause of Stage 5 Chronic Kidney Disease (CKD 5) in Singapore. Haemodialysis is the main dialysis modality and 86.6% of incident CKD 5 patients in 2014 are on hemodialysis [1]. Arteriovenous fistula is the preferred vascular access modality and with the increasing incidence of stage 5 CKD secondary to DM nephropathy, the incidence of ischaemic monomelic neuropathy may increase with increased number of haemodialysis vascular access creation. It is critical that IMN is considered in the differential diagnosis of hand dysfunction following vascular access as it is potentially reversible and prompt recognition and treatment can lead to prevention of permanent disability.

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Contact Urticaria Syndrome from Tofu

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Abstract

A-52-year-old woman ate dinner after preening roses in her garden. Immediately, she developed oralaryngeal malaise and pruritic rash. Nasal obstruction and increase of cutaneous lesions were seen although she took betamethasone, 2 mg, orally. Physical examination revealed geographic wheal on trunk and extremities, and no overt mucosal lesions. History demonstrated that she had developed such reactions four times before: three of the four were seen shortly after eating soybean. Tofu was examined by prick-by-prick testing, and prick testing was performed with a petal, a piece of stem and rose leaf, positive and negative control. Positive reactions to tofu (wheal, 5 × 7 mm) and positive control (wheal 5 × 5 mm) and negative ones to others were noted. Although sensitization to soybean seemed to antedate pollen allergy on the basis of interview, oral allergy syndrome could be complicated because of various pollens-specific IgE. Since soy-bean specific IgE was class 2, such titer was not an effective predictor of clinical severity. This case should be classified into stage 3 of contact urticaria syndrome (CUS). Since CUS can be fatal, we must be careful in management for such patients.

Keywords

Contact Urticaria Syndrome, Prick Testing, Tofu, Soybean

1. Introduction

Tofu is soy milk curdled by some coagulating agents called “nigari”. It is widely used in cooking often instead of meat, and regarded as being good for health. However, soy is an allergen that can cause cellulites and dermatitis around lips [1], and late-onset anaphylaxis [2]. In addition, anaphylaxis to tofu is reported [3].

2. Case Report

A-52-year-old woman presented at the Dermatology Department with pruritic lesions in November 2011. Past

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medical history included asthma infantum (from 3 to 12 years old), and pollen allergy (from 50 years old). She took lunch after taking care of roses in her garden. Immediately, she developed oralaryngeal malaise and pruritic rash. Nasal obstruction and increase of cutaneous lesions were seen although she took betamethasone, 2 mg, orally. When she examined the emergency clinic of Dermatology, physical examination revealed geographic wheal on trunk and extremities, and no overt mucosal lesions. As olopatadine hydrochloride, 10 mg per day could not prevent new rash, she was admitted to identify the cause of those behaviors. History taken after admission demonstrated that she had developed such reactions four times before: three of the four were seen shortly after taking food (**Table 1**). The white blood cell and eosinophils count were 6900/ μ l and 610/ μ l. Serum IgE level was 621 IU/ml, and antigens specific IgE were detected not only to soybean but to various pollens (**Table 2**).

Tofu was examined by prick-by-prick testing. In addition, prick testing was performed with a petal, a piece of stem, and a leaf of rose, positive control (histamine chlorhydrate solution, 10 mg·ml⁻¹) and negative control (saline) [4]. Those were applied to the volar aspect of left forearm, and were pierced with Prick-Lancetter (Ewo Care AB, Sweden). After 15 minutes, those were wiped off with soft paper tissue, and reading performed. Positive reactions to tofu (wheal, 5 × 7 mm) and positive control (wheal 5 × 5 mm) (**Figure 1**), and negative ones to others were noted. All of 10 normal controls were prick-by-prick test-negative to tofu.

Table 1. Episodes of contact urticaria syndrome.

	Age	Meal contents	Onset	Symptoms
1	30 (22 years prior)	loquat tofu	immediately	oral malaise
2	46 (6 years prior)	vegetarian diet	unclear	swelling of face
3	51 (5 months prior)	sichuan style bean curd (Mapo tofu)	15 minutes after	respiratory discomfort nausea generalized urticaria
4	51 (4 months prior)	ginger-flavored slices of grilled pork stir-fried vegetables (bean sprouts, pepper, eggplant)	15 minutes after	respiratory discomfort nasal obstruction generalized urticaria
5	52 (initial visit day)	fried soba with soybean sprouts apple pie	immediately	oralaryngeal malaise nasal obstruction generalized urticaria

Table 2. Results of antigen-specific IgE.

Antigen-specific IgE	UA/ml	class
birch	>100	6
Japanese alder	97.1	5
hazel	54.6	5
beech	48.8	4
oak	48.9	4
peach	18.50	4
apple	9.45	3
pear	3.54	3
peanut	5.74	3
soybean	1.72	2
buckwheat	<0.34	0



Figure 1. Results of prick-by-prick and prick testing: positive reactions to tofu (5 × 7 mm wheal in diameter) and histamine chlorhydrate solution.

3. Discussion

Allergic reactions to soybean embrace various clinical behaviors: contact urticaria syndrome, food-dependent exercise-induced anaphylaxis, and oral allergy syndrome. Classic food allergy is that perioral intake of the same allergen plays a role in sensitization and elicitation. Yagami suggested another type of food allergy: sensitization was established through direct contact to latex or inhalation of allergen-containing particle, and allergic reactions were provoked by not only same allergen but ingestion of vegetables containing the cross-reactive allergens [5]. Such reactions have been called as oral allergy syndrome or latex-fruits syndrome. In this case, although sensitization to soybean seems to antedate pollen allergy on the basis of interview, oral allergy syndrome can be complicated because of various pollens-specific IgE. On the other hand, Lack demonstrated dual-allergen exposure hypothesis for pathogenesis of food allergy: sensitization results from cutaneous exposure and tolerance occurred as a result of oral exposure [6]. It is unclear whether percutaneous or peroral sensitization occurs to soybean in our case. In this case, soybean-specific IgE is class 2 whereas class 5 or 6 to pollens (Table 2). As Sato *et al.* pointed out, soy-bean specific titer was not an effective predictor of clinical severity [7].

Contact urticaria syndrome (CUS) is classified to 4 stages: from stage 1 (localized urticaria) to stage 4 (anaphylactic symptoms) [8] [9]. This case should be classified into stage 3 of CUS because the patient developed rhinoconjunctivitis and orolaryngeal symptoms as well as generalized urticaria [4] [5]. Since CUS can be fatal, we have to be careful in management for patients with this syndrome.

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Isolated Rheumatic Pulmonary Valve Disease—Case Reports

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Abstract

Rheumatic heart disease (RHD) is the most common cause of acquired heart disease in children and young adults worldwide and particularly developing countries continuing to experience a high incidence of this disease. The unexpected increase in the incidence of the disease in certain areas may explain the clinical and epidemiological characteristics of this disease. The key manifestation of RHD is the cardiac valvular abnormalities characterized principally by deforming the layered and avascular leaflet architecture due to inflammation and subsequent diffuse fibrosis. Mitral valve is mostly involved and pulmonary valve is rarely affected. Background of these case reports highlighted the increased incidence of rheumatic pulmonary valve disease in Thoothukudi region of India in Tamil Nadu state.

Keywords

Rheumatic Fever, Pulmonary Valve, Echocardiography, ASO Screening Test

1. Introduction

Rheumatic fever is the commonest form of heart disease in many developing countries of tropics and subtropics including Southern states of India. There are relatively few countries in the world without any data on rheumatic fever [1]. The information on the incidence of rheumatic fever and rheumatic heart disease (RHD) mortality is unsatisfactory because the reliable incidence data are very difficult to obtain [2] and hospital statistics give a biased picture of occurrence, since admissions depend on a host of different factors.

The literature has been reviewed repeatedly and recent reviews [3] point out that the prevalence of rheumatic heart disease in school children seems to be about 0 - 1 per thousand in developed countries, and is much higher in developing countries. Thus rheumatic heart disease prevalence rates are as high as 22 per thousand [4] and even 33 per thousand have been reported in school-age children in urban slums of some developing countries. House-to-house surveys have also been carried out, such as Berry's survey in Northern India [5]. Worldwide,

there are only 15 million cases of rheumatic heart diseases (RHD), with 282,000 new cases and 233,000 deaths from this disease each year [6]. In contrast to trend in United States, rheumatic fever and RHD have not decreased in developing countries. Retrospective studies in developing countries showed the highest predilection for cardiac involvement and highest recurrence rate of rheumatic fever [7].

Rheumatic fever often produces a pancarditis, characterized by endocarditis, myocarditis and pericarditis. Endocarditis is manifested as valvular insufficiency and severe scarring of the valve develops during a period of months to years after an episode of acute rheumatic fever, and recurrent episodes may cause progressive damage to the valves. The mitral valve is affected most commonly and severely in 65% - 70 % of patients and the aortic valve is affected in 25%. The tricuspid valve is involved in only 10% of patients, almost always in association with mitral and aortic lesions. RHD is responsible to 99% of mitral valve stenosis in adults and the pulmonary valve is rarely affected.

An isolated rheumatic involvement of pulmonary valve is uncommon in literature and so it had been reported.

2. Case Reports

2.1. Case-1

A 9 year old asymptomatic male child, having precordial murmur was referred for echocardiographic evaluation. The child had 2 to 3 episodes of febrile illness with joint pains at the age of 3 - 4 years and not taken penicillin prophylaxis thereafter. His pulse rate was 80 bpm. Blood chemistry revealed a positive ASO titer suggesting an antecedent streptococcal infection. ECG revealed the persistent juvenile pattern of T inversion in V1-V3 and X-ray chest revealed mild prominence of main pulmonary artery. Physical examination revealed normal general appearance with a grade 3/6 systolic murmur over the precordium, most prominent in the left second intercostal space and a phasic ejection click which was loudest during expiration and diminished in intensity during inspiration. The second heart sound was soft and single. These features were consistent with valvular pulmonary stenosis. Echocardiography revealed a thickened pulmonary valve as shown in **Figure 1** with commissural fusion as shown in **Figure 2**, moderate to severe pulmonary stenosis as in **Figure 3** and a moderate pulmonary regurgitation as in **Figure 4** suggesting the rheumatic pulmonary valve disease. **Figure 9** revealed the pulmonary stenosis and regurgitant jets and their velocities. **Figure 5** and **Figure 6** revealed the normal mitral, aortic and tricuspid valves. The child is advised penicillin prophylaxis and periodic follow-up.

2.2. Case-2

A 3 year old female child having grade 2/6 systolic murmur over the precordium was referred for screening echocardiography with a positive serum ASO titer. The child had a history of febrile illness during the neonatal period and the nature of illness was unknown. Pulse rate was 90 bpm. General appearance was normal and cardiac auscultation revealed 2/6 systolic murmur in the left second intercostal space. ECG and X-ray chest were normal. Transthoracic echocardiographic imaging revealed bright echoes on the tip of pulmonary valve with mild thickening suggest rheumatic inflammation as shown in **Figure 7** and a mild pulmonary valve stenosis as in **Figure 8**. The child is advised penicillin prophylaxis and periodic follow-up.

3. Discussion

3.1. Etiological Aspects

3.1.1. Congenital

Diseases of the pulmonary valve are most often congenital, and only rarely due to acquired disorders such as carcinoid, rheumatic and infective endocarditis [8]. Pulmonary stenosis represents 8% - 12% of all congenital heart defects in children [9] and 15% in adults [10]. The morphological features of pulmonary valve disease have been well described. Stenotic pulmonary valves are always anatomically abnormal (fibrous thickening and rarely calcific deposits [11]). Congenital type of pulmonary stenosis include acommisural dome-shaped, dysplastic, and bicuspid. The most common cause of isolated pulmonary valve stenosis is the congenital dome-shaped acommisural valve. It is stated that stenotic pulmonary valve may be associated with some element of regurgitation. The acommisural stenotic pulmonic valve usually is a dome-shaped structure with central aperture. Ridges are usually visible that mark sites of apparently malformed commissures [12]. The second major

type of isolated congenital pulmonary stenosis is a tricuspid pulmonary valve in which all the three cusps are greatly thickened and rubbery. This form of congenital abnormal pulmonary valve has been termed “dysplastic pulmonic stenosis” [13]. In such dysplastic valves, there usually is no commissural fusion but the valve annulus is small and histologically, the valve cusps contain extensive amount of acid mucopolysaccharide-stained material and fibrous tissue and lack of poststenotic dilatation of the pulmonary artery. The pulmonary valves in patients with Noonan’s syndrome characterized by “moon’s facies” are genetically dysplastic. In patients with Tetralogy of Fallot, pulmonic valve stenosis is frequently associated with bicuspid pulmonary valve. All congenital forms had thickened cusps with (bicuspid, tricuspid) commissural fusion [14] or without (domed, unicommissural, dysplastic).

3.1.2. Rheumatic

Rheumatic disease causing pulmonary valve stenosis is quite uncommon and, when it occurs, it is invariably associated with rheumatic disease of other cardiac valves. Vela and colleagues [15] reported frequent and more severe pulmonic valve lesions in patients with rheumatic heart disease in Mexico city. These authors suggested that pulmonary hypertension associated with the altitude of Mexico city, increased the stress on the pulmonary valve and making it more prone to damage. Rheumatic forms also had thickening and commissural fusion which are more evident at leaflet tips and subvalvular apparatus.

Isolated rheumatic involvement of pulmonary valve is observed in children < 15 years of age at the tropical zone of Thoothukudi in India. Majority are presented with mild to moderate pulmonic stenosis without the involvement of other cardiac valves. Earliest rheumatic involvement of the pulmonic valve is noticed frequently among school referral cases in this region.

3.2. Screening Test

Rheumatic fever is a non-suppurative sequelae to the rheumatogenic strains of Lancifield group A β hemolytic streptococcal infection of tonsillopharynx after a latent period of approximately 3 weeks and causing exudative and proliferative inflammatory reaction which in turn damage to collagen fibrils and ground substance of connective tissue. These rheumatogenic strains are often encapsulated mucoid strains, rich in M proteins and resistant to phagocytosis. These strains are strongly immunogenic and immunologic cross-reactions between the streptococcal carbohydrate and valvular glycoprotein, resulting damage to heart valves. Group A streptococci (GAS) elaborate the cytolytic exotoxins, streptolysins S and O that act as antigens and the affected individuals produce specific antibodies against these antigens. Of these two toxins, streptolysin O induces persistently high antibody titers that provide a useful marker of GAS infection and its nonsuppurative complications. The antibodies to the extracellular streptococcal antigens rise during the first month after infection and then plateau for 3 - 6 months before returning to normal levels after 6 - 12 months. When the ASO titer peaks (2 - 3 weeks after the onset of rheumatic fever), the sensitivity of the test is 80% - 85%. Several serological tests are now available to determine the occurrence of an antecedent streptococcal infection. Most of these tests assay for neutralizing antibodies to streptococcal extracellular enzymes. The first such test, described by Todd in 1932 [16] determines the titers of serum antibodies that neutralize streptolysin O. This test, the anti-streptolysin O (ASO) test, is still the most standardized and universally used of the streptococcal antibody tests. ASO titers may vary with age, geographic area, and other factors influencing the frequency of streptococcal infection. Titers of 200 to 300 units/ml are common in healthy children 5 to 14 years of age who live in crowded cities at the temperate zone of United States. Surveys of healthy school children 6 - 10 years of age, found anti-streptolysin-O titers > 200 Todd units in 15% - 70% of children [17]. ASO titers greater than 200 to 250 Todd units per ml are generally considered elevated. Titers > 333 Todd units in children and > 200 Todd units in adults are taken as positive for streptococcal infection. In this region of Thoothukudi, titers > 200 IU/ml is taken as positive for both adults and children.

Serum ASO titer (a non-type-specific antibody test) was positive in these children, suggesting the laboratory evidence of antecedent Group A streptococcal infection.

3.3. Echocardiography

In individuals with rheumatic heart disease (RHD), echocardiography is useful to identify and quantify the valvular lesions. Studies in Cambodia and Mozambique have demonstrated a 10-fold increase in the prevalence of

RHD when echocardiography is used for clinical screening compared with strictly clinical findings [18]. In individuals with chronic RHD, echocardiography tracks the progression of valve stenosis and may help to determine the time for surgical intervention. The leaflets of affected valves become thickened diffusely, with fusion of commissures and chordae tendineae. Increased echo density of the valve may signify calcification. World Heart Federation has published guidelines to identify individuals with RHD without a clear history of acute rheumatic fever. Based on 2D and color Doppler imaging, patients are divided into 3 categories—definite, borderline and normal. For pediatric patients (defined as age < 20 years), definite echo features include pathological regurgitation and at least two morphological features of rheumatic involvement of the valve such as commissural fusion, leaflet thickening, calcification and restrictive mobility of the valve.

Most children with pulmonary stenosis do not require evaluation beyond echocardiography. Two dimensional and Doppler imaging is the sine qua non of its diagnosis and a thickened pulmonary valve with restricted systolic motion (doming) in the parasternal short axis view is the characteristic feature [19] as shown in **Figure 1**. The main pulmonary artery is dilated in almost all cases as shown in **Figure 1** and **Figure 2**. This dilatation is independent of the severity of the pulmonary valve obstruction and presumably related to a high-velocity jet across the stenotic valve [20]. The commonly occurring dilatation of the main pulmonary artery distal to the stenotic orifice (post stenotic dilatation) is remarkably absent in patients with dysplastic pulmonary valve, characterized by markedly thickened, nodular, and immobile valve leaflets. Pulmonary valve annular measurements is useful in selecting the diameter of the balloon to be used during valvuloplasty and can be compared with normal values to determine if the annulus is hypoplastic.

Color Doppler imaging shows smooth, laminar subpulmonary flow (blue) and some flow acceleration (red) immediately beneath the pulmonary valve with turbulent (mosaic) flow beginning immediately distal to the pulmonary valve leaflets as shown in **Figure 3**. Doppler studies can be used to accurately determine the velocity of flow at single or multiple levels, which then can be converted to reproducible pressure gradients by applying the modified Bernoulli equation-pressure gradient (mmHg) = $4 \times V^2$ (m/s) [21]. The sample volume moved across the pulmonary valve demonstrates an abrupt increase in peak Doppler flow velocity, which suggests pulmonary valve obstruction as shown in **Figure 9**. A gradients of > 50 mmHg, as diagnosed using a continuous-wave Doppler recording through the pulmonary valve indicate severe stenosis. This Doppler measurement represent peak instantaneous gradient which overestimates the peak-to-peak systolic catheterization gradient, presumably because of a pressure-recovery phenomenon [22]. In this child, the peak Doppler flow velocity of pulmonary stenotic jet 3.45 m/s as shown in **Figure 9** and the gradient 48 mmHg suggest a moderate to severe pulmonary stenosis. Pulmonary regurgitation is easily seen during Doppler imaging but is unlikely to be present without previous surgical or balloon valvuloplasty in valvular pulmonary stenosis.

Valvular thickening has been demonstrated to be a feature of RHD on echocardiography and is often most marked at leaflet tips [23]. The thickened pulmonary valve with commissural fusion as shown in **Figure 1** and **Figure 2**, a moderate to severe pulmonary stenosis as in **Figure 3**, associated with moderate pulmonary regurgitation as in **Figure 4** with a positive ASO titer indicating the antecedent streptococcal infection, suggesting the rheumatic pulmonary valve disease in this male child aged 9 years.

Figure 7 illustrate bright echo density on the tips of the pulmonary valve suggest a rheumatic inflammation associated with mild pulmonary valve stenosis as in **Figure 8** in a 3-year old female child.

3.4. Treatment

Therapy is directed towards preventing recurrent rheumatic heart disease in children and monitoring for the complications and sequelae of chronic rheumatic heart disease in adults. The importance of preventing recurrences of rheumatic fever is evident. The incidence of residual rheumatic heart disease at ten years is 34% in patients without recurrence and 60% in patients with recurrent rheumatic fever. Disappearance of the murmur, when it occurs, happens within 5 years in 50% of patients. Thus, significant number of patients experience resolution of valve abnormalities even 5 - 10 years after the episode of rheumatic fever. Oral penicillin V remains the drug of choice for treatment of streptococcal pharyngitis. Oral penicillin 250 mg for children and 500 mg for adults, given 3 times daily for 10 days is the primary recommended regimen. For recurrent pharyngitis, a second 10-day course of the same antibiotic may be repeated. GABHS (Group A beta hemolytic streptococcus) carriage is difficult to eradicate with conventional penicillin therapy. Thus, oral clindamycin (20 mg/kg/day) in 3 divided doses for 10 days is recommended. Although oral penicillin prophylaxis is also effective to prevent recurrent



Figure 1. Short axis view showing the thickened pulmonary valve, well seen at leaflet tips, AO-aorta, PA-pulmonary artery, PV-pulmonary valve.

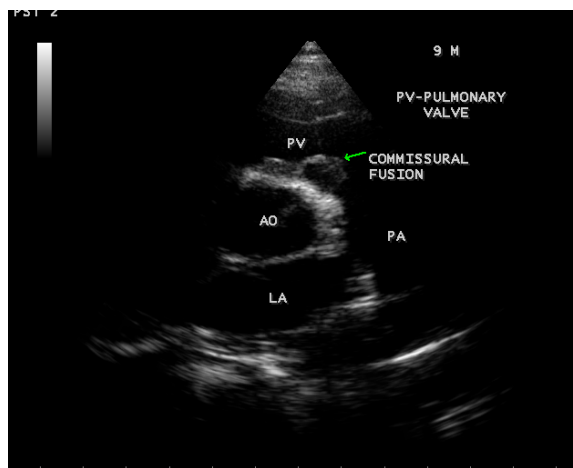


Figure 2. short axis view showing the commissural fusion of pulmonary valve, AO-aorta, PV-pulmonary valve, LA-left atrium, PA-pulmonary artery.

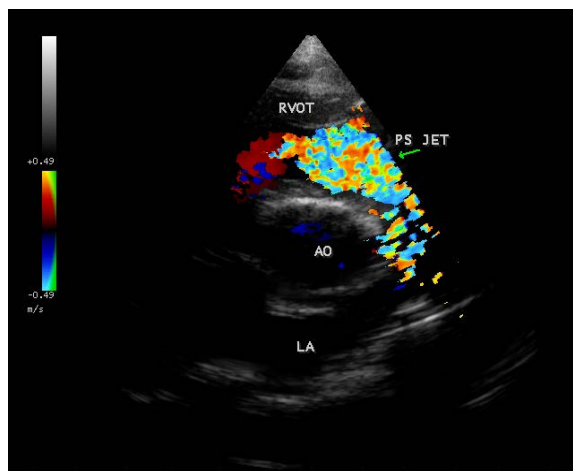


Figure 3. Short axis view-color Doppler imaging showing pulmonary stenosis jet, AO-aorta, PS-pulmonary valve stenosis, LA-left atrium, RVOT-right ventricular outflow tract.

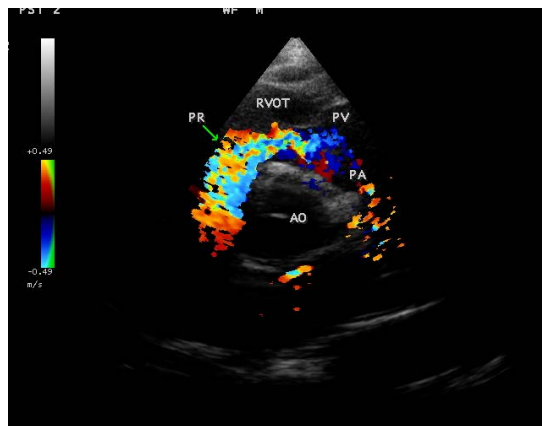


Figure 4. Short axis view-color Doppler imaging showing pulmonary regurgitant jet, AO-aorta, PR-pulmonary valve regurgitation, PV-pulmonary valve, PA-pulmonary artery, RVOT-right ventricular outflow tract.

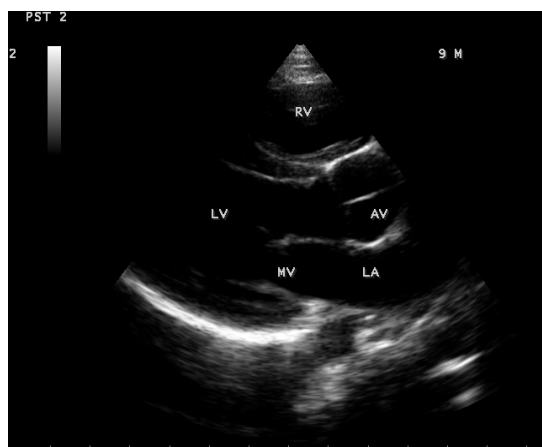


Figure 5. Parasternal long axis view showing the normal mitral and aortic valves. LA-left atrium, LV-left ventricle, MV-mitral valve, AV-aortic valve, RV-right ventricle.

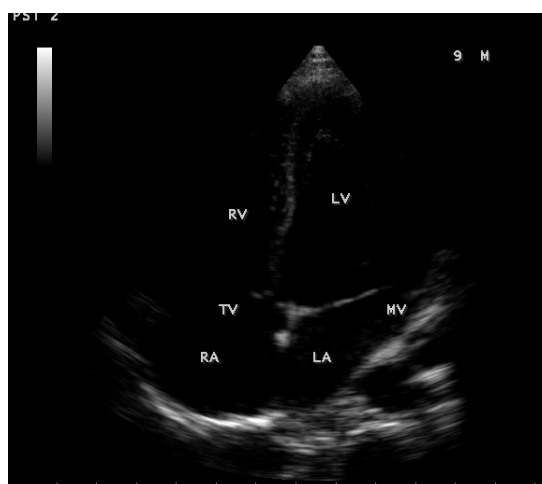


Figure 6. Apical four chamber view showing the normal mitral and tricuspid valves, MV-mitral valve, TV-tricuspid valve, LA-left atrium, RA-right atrium, LV-left ventricle, RV-right ventricle.

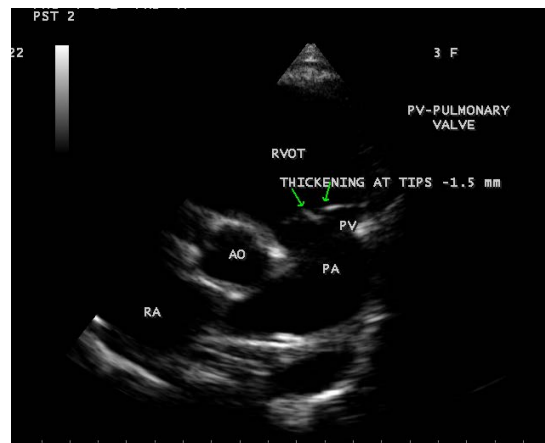


Figure 7. Short Axis view showing bright echoes on the tips of pulmonary valve suggesting Rheumatic inflammation, AO-aorta, PA-pulmonary artery, PV-pulmonary valve, RA-right atrium, RVOT-right ventricular outflow tract.

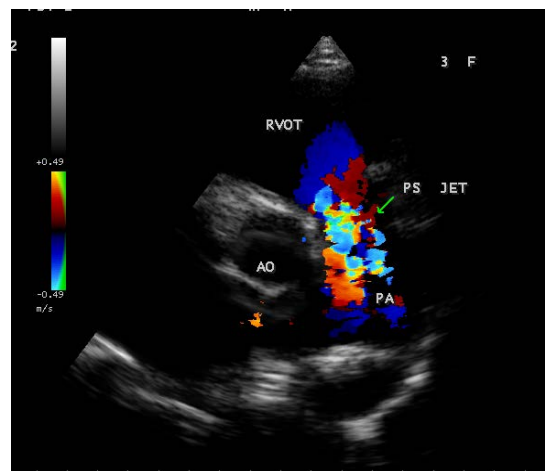


Figure 8. Short Axis view showing the pulmonary stenosis jet, AO-aorta, PA-pulmonary artery, PS-pulmonary valve stenosis, RVOT-right ventricular outflow tract.

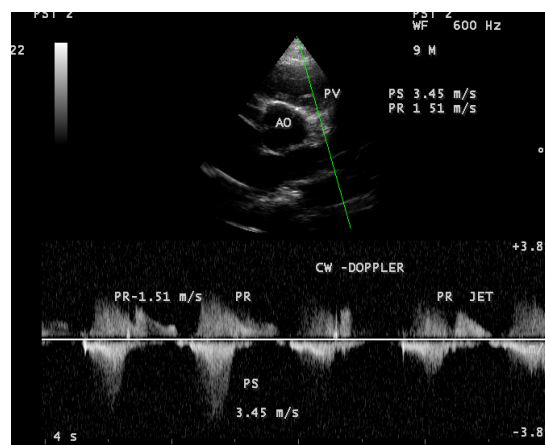


Figure 9. Continuous Wave (CW) Doppler imaging showing the velocities of pulmonary stenosis and regurgitation, AO-aorta, PS-pulmonary valve stenosis, PR-pulmonary valve regurgitation, RVOT-right ventricular outflow tract.

episodes, data from the World Health Organization (WHO) indicate that the recurrence rate of GABHS pharyngitis is lower when penicillin is administered parentally.

In case-1, an injection of 1.2 million units of benzathine penicillin G intramuscularly every 3 weeks for this 9-year old boy and in case-2, 0.6 million units for this 3-year old female child are advised as a preventive and prophylactic therapy for a duration well into adulthood and preferably for life. Tompkin *et al.* [24] reported that signs of rheumatic valvular disease resolve in 70% - 80% of patients with rheumatic carditis who adhere to prophylaxis. Thus, emphasis should be placed on the importance of prophylaxis in affording a good prognosis for recovery even in patients with severe heart disease and prevention of recurrence to reduce cardiac morbidity from this disease.

In acute rheumatic heart disease, heart catheterization is not indicated. With chronic disease, heart catheterization has been performed to evaluate the valve disease and to balloon the stenotic valve. More recently, the interventional procedures are increasingly performed under general anaesthesia and the gradients are usually lower than those with conscious sedation. Therefore, the Doppler-echocardiography gradients should be used in making the decision regarding balloon pulmonary valvuloplasty and balloon dilation should be performed only in patients with peak-to-peak gradient of more than 50 mmHg. Patients with echocardiographic evidence of clinically significant pulmonary stenosis (50 - 60 mmHg) should undergo diagnostic and therapeutic cardiac catheterization with preparation for balloon dilation of the pulmonary valve [25].

The positive ASO titers of these cases indicate the recent streptococcal infection suggesting the recurrent episodes, both preventive and prophylactic therapies are indicated. A peak gradient of 48 mmHg (PS velocity - 3.45 m/s) across the pulmonary valve suggesting moderate to severe stenosis and a pulmonary diastolic pressure of 9 mmHg (PR velocity - 1.51 m/s) on Doppler-echocardiography which is similar to catheter-based pressure in the pulmonary veins (PCWP = LA pressure) suggest an isolated pulmonary valve disease of rheumatic etiology as shown in **Figure 9**. Adherence of prophylaxis may resolve valve damage and so these patients are advised periodic follow up. Since there is a significant pulmonary regurgitation associated with stenosis in case-1, balloon valvuloplasty is not preferred at this moment.

3.5. Echocardiographic Screening

Handheld echocardiography has been investigated as a screening tool and found to be 90% sensitive and 92% specific for identifying patients with rheumatic heart disease in Uganda children [26]. A study by Goodwin *et al.* assessed the value of handheld echocardiography over auscultation to identify rheumatic heart disease. The study found that auscultation alone is a poor screening test for rheumatic heart disease and that handheld echocardiography significantly improves detection of rheumatic heart disease in resource-limited settings [27].

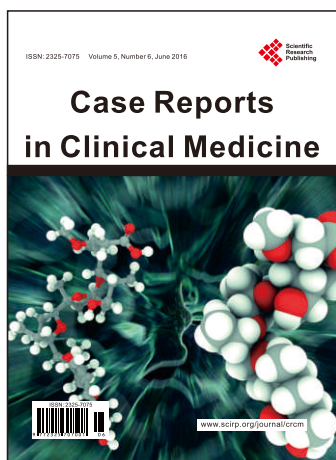
4. Conclusion

Rheumatic involvement of pulmonary valve is frequently observed in the coastal district of Thoothukudi in India and an isolated rheumatic pulmonary valve disease in a 9 year old male and in a 3 year old female child is detected by Transthoracic echocardiographic imaging. Both echocardiography and ASO screening test, which are adapted to detect rheumatic cases and early administration of penicillin prophylaxis is practiced in positive cases as a preventive measure and penicillin therapy is given to treat any episodes of streptococcal pharyngitis which is endemic in this tropical region. From these case reports, it is known that a possibility of rheumatic pulmonary valve disease is more common similar to congenital etiology and more frequent like rheumatic mitral, aortic and tricuspid valve diseases in this region.

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