Recurrent Ventricular Tachycardia and Peripheral Gangrene in a Young Child

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A 10-year-old girl presented with sudden onset recurrent ventricular tachycardia and symmetrical distal peripheral gangrene. She also had pulmonary thromboembolism and cerebral sinus venous thrombosis. Investigations revealed anemia, hemolysis, hypocomplementemia, and elevated IgM anti-beta2 glycoprotein antibody levels. Electrocardiogram and echocardiogram suggested features of a rare cardiac anomaly, which was confirmed at autopsy.

Keywords: *Antiphospholipid antibodies (APLA), Arrythmogenic right ventricular dysplasia (ARVD), Thromboembolic manifestations, Ventricular tachycardia.*

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Ventricular tachycardia in children is a life-threatening emergency that needs prompt recognition and treatment. When immediate correctable causes like dyselectrolytemia and drug overdosages are not found, underlying structural defects of the heart need to be looked for [1]. Thromboembolic manifestations in a child with ventricular tachycardia are more likely to be due to underlying cardiac pathology. We describe a child with ventricular tachycardia and extensive thromboembolic features, where the final autopsy yielded a rare cardiac anomaly. The etiology of thrombus was not only cardiac but also an associated thrombophilic condition.

CLINICAL PROTOCOL

History: A 10-years-old girl presented with intermittent fever and cough of 12 days duration. She started developing pain and bluish discoloration of fingers and toes on day 3 of illness which progressed over the next few days to involve bilateral hands and feet. She started developing difficulty in breathing on day 8 of illness. This was associated with decreased urine output and generalized swelling beginning from lower limbs and progressing to abdomen and face. She had altered sensorium in the form of irritability and incoherent speech for three days prior to presentation. Past history and family history were unremarkable. She was a product of non-consanguineous marriage. Her four other siblings were alive and healthy.

Examination: Her anthropometry was normal. At admission, she was noted to have increased work of breathing with tachypnea (respiratory rate 30/min), tachycardia (heart rate 170/min), prolonged capillary refill and cold peripheries. All peripheral pulses were palpable but feeble. Blood pressure in right arm was 90/68 mm Hg. She had gangrene and edema of all fingers and toes extending to dorsum of hands and feet, respectively (***Fig.* 1*a*** and **1*b***). Pallor, periorbital puffiness and peripheral cyanosis were also noted. Chest and cardiovascular

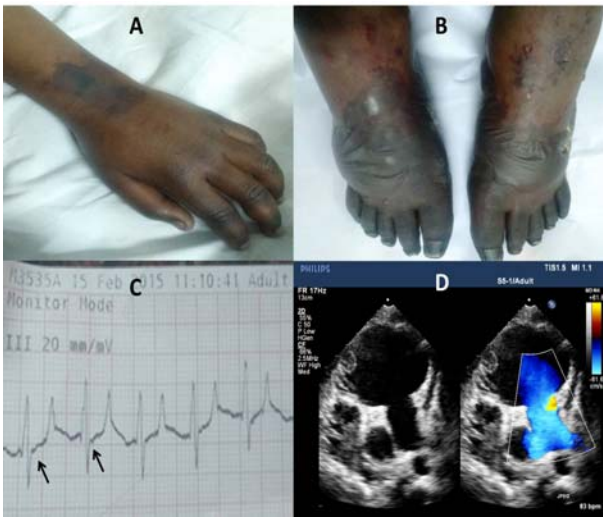

FIG. 1 *(a and b) Upper and lower limbs of the index child showing bilateral symmetric distal gangrene (c) Electrocardiogram lead III of the index child showing epsilon waves and tall p waves (d) B mode echocardiography with doppler - apical four chamber view showing grossly dilated right ventricle (RV) with sacculations and a RV clot.*

examination revealed poorly localized apical impulse, muffled heart sounds, S3 gallop and bilateral basal crepitations. Soft, tender hepatomegaly with a span of 12 cm was also found. She was conscious, oriented and obeyed commands but had occasional aggressive behavior and incoherent speech. There were no meningeal signs.

Course and management: At admission, she was started on nasal prong oxygen support, and inotropic support for shock. Immediate cardioversion was done for electrocardiogram (ECG) -proven ventricular tachycardia. Low molecular weight heparin (LMWH) infusion was started for peripheral gangrene. Chest *X*-ray revealed cardiomegaly and counts showed polymorphonuclear leucocytosis, normocytic anemia and thrombocytopenia (***Table* I**). Peripheral smear was suggestive of hemolysis and reticulocyte count was 8.14%. Serum lactate dehydrogenase was elevated to 1707.6 U/L (Normal: 140-280 U/L). Complement C3 and C4 levels were low at admission. Lung perfusion scintigraphy suggested intermediate probability of pulmonary thromboembolism. Initial coagulogram showed prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT) with low fibrinogen and elevated d-dimer values. Considering her age, sex, thrombocytopenia, hemolytic anemia and low complements at admission, a possibility of systemic lupus erythematosus (SLE) with antiphospholipid antibody syndrome (APS) was considered and she was given intravenous methylprednisolone at a dose of 30 mg/kg/day for 3 days.

Extensive infection work-up done during hospital stay was not contributory. Immunological work up revealed immune complex vasculitis in skin biopsy and elevated IgM anti-beta2 glycoprotein antibody levels. Other investigations including procoagulant work-up are summarized in ***Table* II**. Protein C, protein S, antithrombin III levels and lupus anticoagulant activity could not be done as the child was already on LMWH. Contrast enhanced Magnetic resonance imaging (MRI) of the brain showed ill-defined hyperintense foci in bilateral cerebral hemisphere that showed diffusion restriction suggestive of ischemic foci of acute or subacute nature. MR venography of brain revealed features of chronic sinus venous thrombosis in parietal region. Epsilon waves were detected in subsequent ECGs done during hospital stay (***Fig.* 1*c***). Severely dilated right atrium and ventricle with sacculations and aneurysms of the right ventricle (RV) were noted in the echocardiogram suggesting a diagnosis of arrhythmogenic right ventricular cardiomyopathy/ dysplasia (ARVC/D) (***Fig.* 1*d***). Clot was noted in RV with severe RV dysfunction. There was no patent foramen ovale to explain systemic thrombo-embolic tendency. There was no evidence of pulmonary arterial hypertension. On day 9 of hospital stay, she developed recurrent episodes of ventricular tachycardia needing repeated cardioversions and amiodarone infusion. Permanent pacing or implantable defibrillator was planned and supportive

TABLE I BLOOD COUNTS, BIOCHEMISTRY AND COAGULOGRAM OF THE INDEX CHILD

Investigations	*Day1*	*Day6*	*Day 12*	*Day16*	*Day 19*
Hemoglobin (g/dL)	10.1	10.8	8.9	8.1	10.5
White cell counts (/mm^3)	16,400	17,800	19,600	14,400	11,300
Differential counts*	P_{76},L_{20}	P_{90},L_{06}	P_{84},L_{11}	P_{88},L_{08}	P_{86},L_{10}
Platelets (/mm^3)	63,000	88,000	1,13,000	94,000	1,40,000
Serum sodium/potassium (mEq/L)	130/5.4	141/2.8	140/5.6	138/4.1	134/4.1
Blood urea/creatinine (mg%)	149/1.0	29/0.5	40/0.6	48/0.9	45/0.5
Serum total proteins/albumin (g/dL)	-	5.2/2.7	6.2/3.8	6.1/3.8	7.0/3.5
Serum total/conjugated bilirubin (mg/dL)	2.05/1.01	0.99/0.43	1.23/0.46	1.25/0.36	0.7/-
Serum AST/ALT (U/L)	-	188/195	57/101	58/96	34/72
Alkaline phosphatase (U/L)	-	169	159	165	146
Serum calcium/phosphorous (mg/dL)	-	7.6/2.3	8.4/3.3	7.8 /2.7	8.7/2.3
C-reactive protein (mg/dL)	58.5	12.6	6.5	66.8	-
Prothrombin time (s)	40	33	23	19	15
International normalized ratio	2.8	2.3	1.7	1.3	1.1
APTT (s)	40	39	48	32	30
Fibrinogen (mg/dL)	-	0.90	-	-	4.8

**P: Polymorphonuclear leucocytes %, L: Lymphocytes %; AST: Aspartate transaminase, ALT: Alanine transaminase, APTT: Activated partial thromboplastin time.*

TABLE II INVESTIGATIONS FOR PROTHROMBOTIC AND VASCULITIC CONDITIONS IN THE INDEX CHILD

Investigations	*Results*
Radiology	
Lung perfusion scintigraphy	Segmental wedge shaped mismatch defect in the right lower lobe– intermediate probability of pulmonary thromboembolism
Ultrasound doppler	Normal flow demonstrated in both carotid, subclavian, axillary, brachial, radial, renal, common femoral, popliteal, and anterior tibial arteries. Flow could not be demonstrated in posterior tibial arteries.
CE-MRI* Brain with MRA* and MRV*	MRV* showed obliterated straight sinus/proximal transverse sinuses with venous collaterals in high parietal region ? sequelae of chronic sinovenous thrombosis. MRA*- normal.
Immunology	
Anti-nuclear antibody by IIF*, anti-double stranded DNA, anti-neutrophil cytoplasmic antibodies by IIF*, anti-cardiolipin antibodies	Negative
Serum complements-C3/ C4 levels	47/ 4 (Normal C3- 50 to 150 mg/dL, C4- 20 to 50 mg/dL)
Anti- β2 glycoprotein 1 antibodies	IgG- 2.8 U/mL, IgM- 11.6 U/mL (Normal <5 U/mL)
Skin immunofluorescence	IgM patchy band noted in blood vessels. IgG, IgA, C3 negative.
Infectious diseases	
Blood cultures	Sterile- repeated thrice
Tuberculosis work up	Negative (Tuberculin testing, gastric aspirates for AFB* staining × 3)
IgM Mycoplasma, IgM EBV VCA*, IgM CMV*, IgM anti-Hepatitis C, HIV* serologies	Negative
Hepatitis B surface antigen	Negative
Hematology	
Direct Coombs test	Negative for C3d and IgG
Peripheral smear for sickling, factor V Leiden mutation, flow cytometry based immuno-phenotyping for PNH*	Negative
Serum homocysteine levels	7.22 micromol/ L (Normal- 4.6 to 8.1)

**CE-MRI: Contrast enhanced magnetic resonance imaging, MRV-Magnetic resonance venography, MRA-Magnetic resonance arteriography, IIF-Indirect immunofluorescence, AFB-Acid fast bacilli, EBV VCA-Epstein Barr virus viral capsid antigen, CMV- Cytomegalovirus, HIV-Human Immunodeficiency Virus, PNH-Paroxysmal Nocturnal Hemoglobinuria.*

measures were continued. On day 20 of illness, she succumbed to refractory ventricular tachycardia and cardiogenic shock.

Unit's final diagnosis: ARVC/D with RV failure, RV clot and pulmonary embolism, ? Underlying prothrombotic condition, ? Infection related or immune vasculitis, Disseminated intravascular coagulation (DIC).

Clinical Discussion

The index child had features of cardiac involvement (RV failure, ventricular tachycardia and shock) and thrombotic manifestations at admission. In view of distinct right sided cardiomyopathy with sacculations, ventricular tachycardia and epsilon waves in ECG, diagnosis of ARVC/D appears likely [2-5]. Pulmonary embolism and RV clots could be explained by right sided cardiac pathology.

The index child had thrombotic manifestations both in systemic and peripheral circulation- pulmonary embolus, symmetrical peripheral gangrene and chronic sinovenous thrombosis on brain imaging. She also had features of DIC- thrombocytopenia and prolonged PT and aPTT. Recurrent ventricular tachycardia due to ARVC/D resulting in systemic hypoperfusion and gangrene could explain symmetric peripheral gangrene. However, it is impossible to explain preterminal febrile illness, hemolysis, MRI evidence of chronic sinovenous thrombosis and low complement levels with this diagnosis. Hence, thrombophilia (congenital and acquired) is a strong possibility. Coming to the inherited thrombophilias, serum homocysteine levels were normal

and factor V Leiden mutation was negative. Other inherited thrombophilias are protein C deficiency, protein S deficiency, anti-thrombin deficiency, dysfibrinogenemia, factor VIII mutations or prothrombin gene mutation, for which the child could not be evaluated antemortem. The index child had elevated IgM anti-beta2 GP1 antibody levels which may point to APS. APS is an important acquired risk factor for both arterial and venous thromboses. However, diagnosis of APS requires evidence of thrombosis with elevated antibody titers (one of the three: lupus anticoagulant (LA), anti-cardiolipin antibody (ACA), anti-beta2 GP1 antibody) on two occasions at least 12 weeks apart. Diagnosis of catastrophic APS (CAPS) requires demonstration of small vessel thrombotic manifestations of at least three organs occurring within a week. APS is also known to cause cardiomyopathy by causing multiple small vessel thrombosis and this is one of the most important causes of death in APS [6,7].

Etiology of APS could be primary or secondary to infections, autoimmune causes and malignancy. Extensive infectious disease panel did not reveal any underlying infections. When we look at autoimmune causes, the index child had two clinical criteria (hemolytic anemia and thrombocytopenia) and two laboratory criteria (low complements and elevated IgG anti-beta2 GP1 titres), which fulfils the Systemic Lupus International Collaborating Clinics (SLICC 2012) criteria for diagnosis of SLE. She also had evidence of immune complex mediated vasculitis in skin biopsy. However, ANA and anti-dsDNA were negative, making this diagnosis less likely.

Hypocomplementemia, immune complex mediated vasculitis and embolic phenomenon can occur in infective endocarditis; however, multiple blood cultures were sterile so this possibility does not seem likely. The preterminal febrile illness with DIC, hemolysis and low complement levels could be explained by an immune- or infection-related vasculitis. So our final diagnosis would be

- Right sided cardiomyopathy ?ARVC/D ?APS related
- Pulmonary thromboembolism: related to RV cardiomyopathy
- Systemic thrombotic manifestations ?APS related

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Pediatric Rheumatologist: There is no going away from the diagnosis of ARVC/D in this child as the index child had refractory ventricular tachycardia and multiple sacculations and dilatations of RV in echocardiogram. Histopathology of the heart may show fibrofatty replacement of RV myocardium [2]. Though the clot in the RV can explain the pulmonary embolism, the index child had features of systemic microvascular/venous thrombosis, which prompted a procoagulant work-up.

Adult Physician: The lesions in the extremities are like purpura fulminans. The condition looks like CAPS and there may be multiple thrombi in the cerebral, renal and extremity veins though ARVC/D appears to be the primary heart disease.

Adult Rheumatologist: CAPS looks highly likely as all the events in the index child occurred within a week.

Pediatric Rheumatologist 2: ARVC/D is distinctly rare in pediatric population. Primary APS which caused the coronary thrombosis and changes in RV appears more likely here.

Immunopathologist 1: Skin is the largest organ in the body and looking at its biopsy helps in making diagnosis. We had a very faint band test with occasional IgM deposits in the vessels suggestive of immune complex vasculitis. I feel that APS related vasculitis is likely in this child.

Pediatrician 1: Given the typical ECG and echo findings, there is no doubt in the diagnosis of ARVC/D. This child developed recurrent episodes of ventricular tachycardia which ultimately took away the child. Pulmonary embolism can be explained by ARVC/D itself; however to explain past sinovenous thrombosis and symmetric peripheral gangrene with preserved pulses, prothrombotic state was thought of. Preterminal illness could be infection related vasculitis.

Pediatrician 2: Index child fulfilled the SLICC criteria for diagnosis of lupus. Yet, I think this child did not have lupus as there was absence of ANA positivity by indirect immuno-fluorescence testing on human cell lines. Though a question of semantics, strictly speaking, we cannot use the term APS here because to call it as a syndrome, we should repeat the antibody testing after 12 weeks [6].

Radiologist 1: What we found striking was the enlarged veins in the posterior fossa that can be due to collaterals due to chronic sinovenous thrombosis.

Adult physician 2: If cardiac MRI was done in this child, it could have picked up the fibrofatty changes of the myocardium in ARVD.

Cardiologist: We are dealing with two conditions: procoagulant state and ARVC/D. Myocardial infarction related to right coronary artery cannot cause such huge dilation of right atrium (RA) and RV. Dilatation of RV secondary to pulmonary embolus is also less likely as there was low pressure tricuspid regurgitation.

Adult Rheumatologist 2: This child had symmetrical

peripheral gangrene, low fibrinogen and prolonged PT and aPTT. This looks more like DIC triggered by an infection which had a focus in the heart like an infected clot.

Chairperson: There is no doubt that this child had gangrene which was predominantly related to smaller vessels as the peripheral pulses were palpable and this would bring in the possibility of pro-coagulant disorders. Pathologist may clarify whether right heart changes are related to the primary heart disease or it is secondarily involved.

PATHOLOGY PROTOCOL

A complete autopsy was carried out and the prosector noted gangrene of both feet.

The heart weighed 208 g (normal range for this age 65-122 g) and was grossly enlarged. There was gross dilatation of the right auricle, RA and RV with fresh auricular thrombus. RV anterior wall was papery thin with marked endocardial sclerosis (***Fig.* 2*a***). Histology of the RV myocardium confirmed the gross thinning (just about one mm) and replacement by collagenized tissue with dense collagenisation of the endocardium with abundant elastic tissue deposition and degeneration of cardiac myocytes (***Fig.* 2*b***). Remaining RV myocardium was discoloured due to ischemic myonecrosis. There were multiple mural thrombi both in RA and RV. Endocardium overlying the interventricular septum along outflow tract of RV was thickened and it also showed collagenisation. Pulmonary valve and artery were dilated. Left atrium was of normal morphology. Left ventricle (LV); however, was hypertrophied and discolored. Aortic valves, aorta and coronaries were within normal limits. Histology of LV myocardium showed diffuse subendocardial myocytolysis, sparse inflammatory cell infiltration and focal myofibre disarray. Sections studied from the atrioventricular (AV) nodal system showed total collagenisation. No thrombus was identified in intra-abdominal or intra-thoracic vessels.

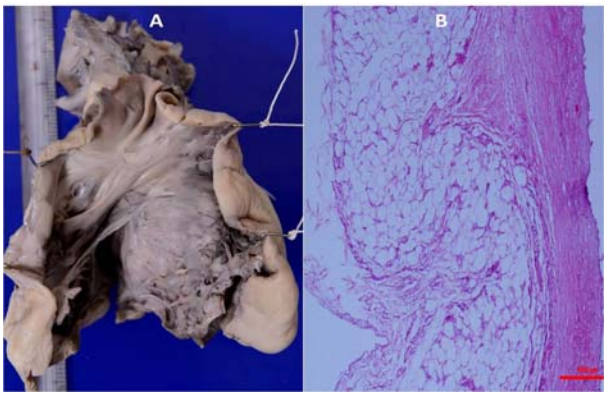

FIG. 2 *(a) Gross photograph of the right side of the heart along the outflow tract showing grossly thinned out right ventricular anterior wall and endocardial sclerosis overlying the interventricular septum and (b) Low power photomicrograph of the anterior right ventricular wall showing totally fibrotic myocardium with no visible myocardial fibres and thickened and elastisized endocardium. The red coloured scale measure 1000 micron. (H&E, ×50).*

Liver weighed 1032 g (normal range for this age 422-574 g) indicating gross enlargement. Capsular and cut surfaces of the liver were grossly nodular and mottled due to bile staining. Normal lobular architecture was lost and there was centro-central and occasional centro-portal bridging fibrosis with many complete and incomplete regenerative nodules. There was prominent centrizonal sinuosoidal dilatation and congestion along with intra-sinusoidal collagenisation. Larger sized portal tracts showed multiple dilated intercommunicating portal venous channels. The scarred areas showed deposition of excess hemosiderin pigment deposition.

Lungs showed evidences for aspiration and pulmonary thromboembolism. Histology revealed pulmonary edema and fresh intra-alveolar hemorrhages. Kidneys were swollen with marked medullary congestion. Microscopic examination showed acute tubular necrosis and granular, red blood cell and proteinaceous casts. Glomeruli and blood vessels were within normal limits. There were multiple enlarged lymph nodes in hilar, peri-pancreatic and mesentery regions measuring 10-15 mm. Sections showed reactive lymphoid follicles and sinus histiocytosis with erythrophagocytosis. The spleen was of normal weight, and histology showed depleted lymphoid follicle and evidence of extra-medullary hematopoiesis in the sinusoids. The gastrointestinal tract (GIT) showed mild mucosal congestion and histology showed changes of reflux esophagitis and diffuse submucosal fibrosis along the entire length of the intestine. The remaining organs were within normal limits. Post-mortem bone marrow showed normal to mild hypercellularity with presence of all the three hematopoietic cell lineages.

Final Autopsy Diagnosis

- Heart: ARVC/D associated with AV node fibrosis and fresh mural thrombi of RA and RV
- Liver: Chronic passive venous congestion with diffuse nodular regenerative hyperplasia
- Lungs: Pulmonary edema, thromboemboli and aspiration.
- Kidneys: Acute tubular necrosis.
- GIT: Reflux esophagitis with diffuse sub-mucosal fibrosis.

TABLE III CRITERIA FOR DIAGNOSIS OF ARVC/D

Major criteria	*Minor criteria*
Global or regional dysfunction and structural alterations	Global or regional dysfunction and structural alterations
• Severe dilatation and reduction of RV ejection fraction with no (or only mild) LV impairment	• Mild global RV dilatation and/or ejection fraction reduction with normal LV
• Localized RV aneurysms (akinetic or dyskinetic areas with diastolic bulging)	• Mild segmental dilatation of the RV
• Severe segmental dilatation of the RV	• Regional RV hypokinesia
Tissue characterization of wall	
• Fibrofatty replacement of myocardium on endomyocardial biopsy	
Repolarization abnormalities	Repolarization abnormalities
	• Inverted T waves in right precordial leads (V_2 and V_3) (people age >12 years, in absence of right bundle-branch block)
Depolarization/conduction abnormalities	Depolarization/conduction abnormalities
• Epsilon waves or localized prolongation (>110 ms) of the QRS complex in right precordial leads (V_1 to V_3)	• Late potentials (SAECG)
Arrhythmias	Arrhythmias
	• Left bundle-branch block-type ventricular tachycardia (sustained and nonsustained) (ECG, Holter, exercise)
	• Frequent ventricular extrasystoles (>1000 per 24 hours) (Holter)
Family history	Family history
• Familial disease confirmed at necropsy or surgery	• Family history of premature sudden death (<35 years of age) due to suspected ARVC/D
	• Familial history (clinical diagnosis based on present criteria)

Adapted from References 3 and 4; SAECG: Signal averaged electrocardiogram; Diagnosis is fulfilled by the presence of 2 major, or 1 major plus 2 minor criteria or 4 minor criteria from different groups.

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Immunopathologist 2: Most of the patients with ANA negative lupus are positive for anti-Ro and anti-La, and even Hep2 cells can sometimes fail to detect these antibodies, sometimes necessitating ELISA. These autoantibodies are known to cause heart blocks and the pathology had shown fibrosed AV node. The index child could have had this condition and the mother might be tested for those antibodies.

Chairperson: It is beyond doubt that the child had primary heart disease (ARVC/D). Distal gangrene cannot be explained completely by the heart disease alone unless there was a communication between right and left side, which has been negated by autopsy findings. DIC precipitated by a different event or APS might have played part in the presentation. The platelet counts never went below 80,000 cells/mm^3, which is a little unusual for purpura fulminans.

Adult physician 1: Are the changes in ARVD due to apoptosis or due to infiltration with inflammatory cells?

Pathologist: Apoptosis is part of the degenerative process and especially in the pediatric age group, one related condition - Uhl's anomaly should be considered in the differential diagnosis of RV failure and enlarged RV in echocardiogram. However, the pathology is not suggestive of the same.

DISCUSSION

ARVC/D is a cardiomyopathy characterized by anatomical and functional abnormalities of predominantly RV. Genetic origin is found in 30-50% individuals and is most commonly inherited as autosomal dominant trait. Disease pathogenesis results from dysfunction of desmosomes which are essential for electric conductivity and contractility of myocardium. Most patients are men and it usually presents between the ages of 20 and 40 [2]. In a large autopsy series of ARVC/

D, only 13% of cases were identified at less than 18 years [3]. Clinical phenotype evolves over a period of time. Common clinical presentations are syncope, palpitations and ventricular tachycardia. Arrhythmias are primarily a result of re-entry electrical circuits generated from fibrofatty tissue in ARVC/D and can be triggered by adrenergic stimulation such as exercise. Moreover, arrhythmias in ARVC/D tend to be refractory to drugs [4]. Sudden death can be an initial manifestation. In a large autopsy series of 1400 unexplained sudden cardiac deaths, 200 (10.4%) cases had ARVC/D [3]. In the same series, most cases of ARVC/D had abnormal Bundle of His and its branches because of fat or fibrous tissue infiltration [3]. Disease progression in ARVD might occur as periodic bursts rather than a continuous process. Disease exacerbations can sometimes lead to life-threatening arrhythmias.

Definitive diagnosis of ARVC/D requires histopathological demonstration of fibrofatty replacement of RV myocardium. Expert consensus criteria requires either two major criteria, one major plus two minor criteria or four minor criteria from different groups for diagnosis (***Table* III**) [4,5]. Index child had histopathologically confirmed ARVC/D and many other features of the consensus criteria.

Thromboembolic phenomena are observed in 4% of patients with ARVD and it predominantly occurs in the right heart cavity and pulmonary circulation [8]. Systemic thromboembolism in this condition has been reported in only a few case reports [9,10]. Attenhoffer, *et al*. [9] reported a 36 year-old-woman with ARVC/D and multiple large vein thromboses, where prothrombin gene mutation G20210A was identified.

Anti-phospholipid antibodies (APLA) are identified in 4.2% of pediatric patients with thrombosis and it is the commonest autoimmune etiology for acquired hyper-coagulable state [6]. Pathogenesis of thrombosis in APS is mainly due to activation of platelets, monocytes and endothelium along with complement cascade trigger by APLA. Around 50% of APS in children are associated with autoimmune conditions, especially SLE [7]. Nearly 20% of patients with primary APS can develop features of SLE in follow up. Presence of APS is considered as a significant predictor for organ damage and mortality in lupus patients [11]. Presence of LA correlates more with the thromboembolic events in APS than the ACA or anti-beta2 GP1 assay. Though anti-beta2 GP1 antibodies are more specific for thrombosis than ACA, elevated titers of IgG anti-beta2GP1 antibody are much more specific than elevated IgM which was observed in the index child [12]. Transient elevations of APLA are also found in association with various infections and malignancies [13].

REFERENCES

1. Pfammatter JP, Paul T. Idiopathic ventricular tachycardia in infancy and childhood. J Am Coll Cardiol. 1999;33:2067-72.
2. Marcus F, Towbin JA. The mystery of arrhythmogenic right ventricular dysplasia / cardiomyopathy. Circulation. 2006;114:1794-5.
3. Tabib A, Loire R, Chalabreysse L, Meyronnet D, Miras A, Malicier D, *et al*. Circumstances of death and gross and microscopic observations in a series of 200 cases of sudden death associated with arrhythmogenic right ventricular cardiomyopathy and/or dysplasia. Circulation. 2003;108: 3000-5.
4. Gemayel C, Pelliccia A, Thompson PD. Arrhythmogenic right ventricular cardiomyopathy. J Am Coll Cardiol. 2001;38:1773-81.
5. Basso C, Corrado D, Marcus FI, Nava A, Thiene G. Arrhythmogenic right ventricular cardiomyopathy. Lancet. 2009;373:1289-300.
6. Ahluwalia J, Sreedharanunni S, Kumar N, Masih J, Bose SK, Varma N, *et al*. Thrombotic primary antiphospholipid syndrome: The profile of antibody positivity in patients from North India. Int J Rheum Dis. 2014 Oct 8. [Epub ahead of print] doi: 10.1111/1756-185X.12479.
7. Avcin T, Cimaz R, Silverman ED, Cervera R, Gattorno M, Garay S, *et al*. Pediatric antiphospholipid syndrome: clinical and immunologic features of 121 patients in an international registry. Pediatrics. 2008;122:e1100-07.
8. Wlodarska EK, Wozniak O, Konka M, Rydlewska-Sadowska W, Biederman A, Hoffman P. Thromboembolic complications in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy. Europace. 2006;8: 596-600.
9. Attenhoffer Jost CH, Bombeli T, Schrimpf C, Oechlin E, Kiowski W, Jenni R. Extensive thrombus formation in the right ventricle due to a rare combination of arrhythmogenic right ventricular cardiomyopathy and heterozygous prothrombin gene mutation G20210 A. Cardiology. 2000;93:127-30.
10. Basso C, Thiene G, Corrado D, Angelini A, Nava A, Valente M. Arrhythmogenic right ventricular cardiomyopathy. Dysplasia, dystrophy, or myocarditis? Circulation. 1996;94:983-91.
11. Descloux E, Durieu I, Cochat P, Vital-Durand D, Ninet J, Fabien N, *et al*. Paediatric systemic lupus erythematosus: prognostic impact of antiphospholipid antibodies. Rheumatology (Oxford). 2008;47;183-7.
12. De Groot PG, Urbanus RT. The significance of autoantibodies against β2-glycoprotein I. Blood. 2012;120:266-74.
13. Kratz C, Mauz-Körholz C, Kruck H, Körholz D, Göbel U. Detection of antiphospholipid antibodies in children and adolescents. Pediatr Hematol Oncol. 1998;15:325-32.