Cardiac Rhabdomyoma Causing Progressive Dynamic Severe Right Ventricular Outflow Tract Obstruction in an Infant

Multiple cardiac masses were incidentally detected in a neonate on twelve day of life. Failure to thrive, feeding difficulty and severe dynamic right ventricular outflow tract obstruction developed at 7 months of age. Surgical resection of intracardiac masses relieved symptoms and histological studies confirmed rhabdomyoma. Progressive increase in the size of rhabdomyoma during infancy is an uncommon presentation and surgery can be life-saving.

Keywords: *Cardiac tumor, Echocardiography, Tuberous sclerosis.*

A 12-day-old asymptomatic neonate was detected to have multiple cardiac masses during evaluation of a cardiac murmur. There were multiple lobulated cardiac masses in the left ventricular apical region and interventricular septum (largest 10 x 8 mm) and pedunculated mass (14 × 9 mm) in right ventricular outflow tract (RVOT) **(*Fig.* 1)**. The baby did not have other features of tuberous sclerosis and was kept on close medical follow-up.

At 7 months of life, parents reported failure to thrive and new onset feeding difficulty. The right ventricular mass had increased in size (19×19 mm) and was causing severe RVOT obstruction (peak gradient 86 mmHg) without increase in size of left ventricular masses. In view of symptomatic severe RVOT obstruction, surgical resection of all the masses was done. The largest mass (20×15 mm) was firm in consistency, gray-white and glistening, arising from right ventricular free wall partly attached to the chordae of septal leaflet of tricuspid valve (***Web Fig.* 1a**). Histopathology showed vacuolated tumor cells with clear cytoplasm and characteristic spider cells on Haematoxylin and Eosin staining (***Web Fig.* 1b**) and Desmin expression (***Web Fig.* 1c**) suggestive of cardiac rhabdomyoma.

Neonatal cardiac tumours are rare, rhabdomyomas being commonest among them. Tuberous sclerosis is associated with cardiac rhabdomyomas in 50-60% patients and conversely, rhabomyomas are associated with tuberous sclerosis in 59-80% [1,2]. Rhabdomyomas are generally multiple, well-circumscribed, intramural or pedunculated tumours seen most commonly in the ventricles. They are hamartomas with no malignant potential. Their presentation varies from asymptomatic incidentally detected cardiac murmur, congestive cardiac failure, arrhythmias or sudden infant death depending on the size, number and location of the tumour.

Cardiac rhabdomyomas have a propensity for spontaneous regression [3,4]. Most of them have a benign course and remain static or regress with age, higher chances of spontaneous regression seen at younger age. Complete regression is common in the ûrst 4 years of life [3,4]. Mammalian targets for rapamycin inhibitors have been used to treat large, inoperable or residual rhabdomyomas [5]. Surgical intervention is indicated with haemodynamic compromise or intractable arrhythmia. Progressive severe dynamic outflow tract obstruction is an uncommon presentation and surgery can be life-saving.

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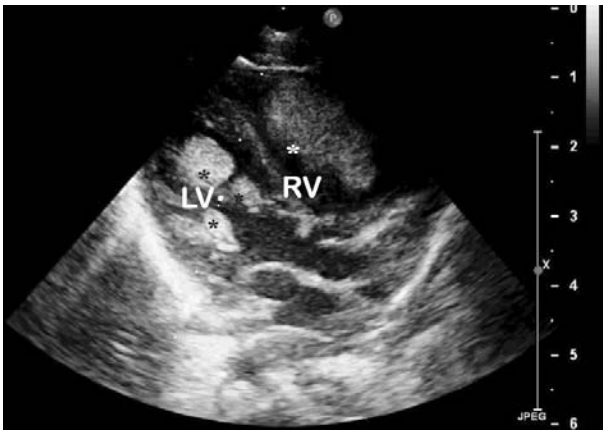

FIG. 1 *Echocardiogr am (parasternal long-axis view) showing multiple cardiac masss in left ventricle (LV) and right ventricle (RV).*

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Mevalonate Kinase Deficiency as Cause of Periodic Fever in Two Siblings

Mevalonate kinase deficiency (MKD) is a rare autosomal recessive autoinflammatory disease caused by mutations in *MVK*. We report two siblings with MKD, presenting with recurrent febrile illnesses, detected to have compound heterozygous variants in *MVK*. MKD mimics common pediatric conditions and should be considered as a differential diagnosis.

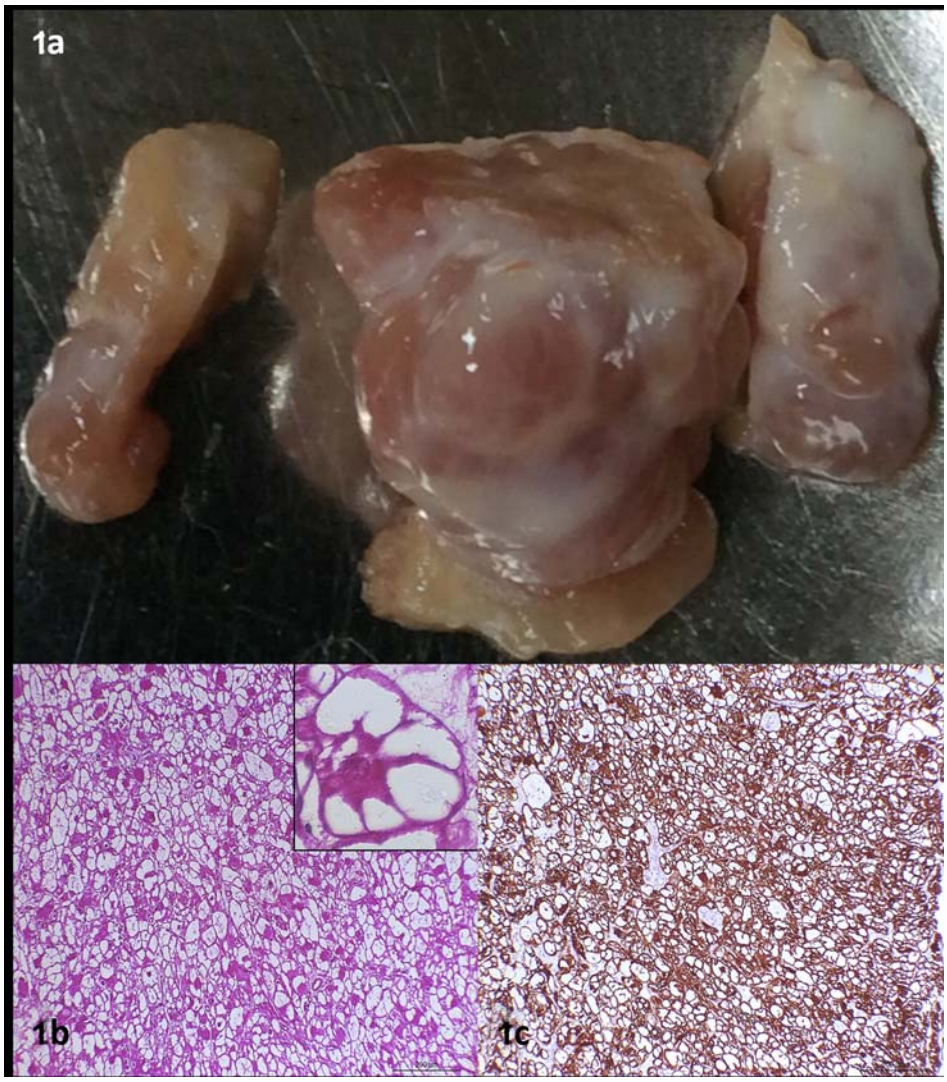
Keywords: *Hyper-IgD syndrome, Pyrexia of unknown origin, Neonatal hepatitis, Periodic fever.*

Fever of unknown origin is often a diagnostic challenge in children. Etiology includes infections, malignancy, autoimmune and autoinflammatory diseases. Autoinflammatory diseases are multisystem disorders characterized by periodic attacks of fever and systemic inflammation. Mevalonate kinase deficiency (MKD) is an autosomal recessive autoinflammatory disease caused by mutations in the *mevalonate kinase* (*MVK*) gene which encodes for mevalonate kinase, a key enzyme in the mevalonic acid pathway [1]. The clinical spectrum ranges from Hyper-IgD syndrome (HIDS) (MIM 260920) to the more severe mevalonic aciduria (MIM 610377). This paper reports two siblings with MKD.

A five-year-old male child born to nonconsanguineous parents was symptomatic from 2 months of age with history of recurrent febrile illnesses associated with diarrhea, icterus, hepatosplenomegaly, along with thrombocytopenia and severe anemia requiring repeated blood and platelet transfusions. From 3 months of age he developed febrile episodes recurring weekly without any systemic focus, which subsided by 8 months of age. At 1.5 years of age, he developed frequent constipation with abdominal distention and pain which continued till 2.5 years of age. He developed recurrent tonsillitis and lymphadenopathy from four years of age. At five years, his height was 92 cm (-3.95 SD), weight 11.5 kg (-3.55 SD) and head circumference 46cm (-3.19 SD). He had a triangular face, open anterior fontanelle, blue sclera, cervical lymphadenopathy and hepatosplenomegaly (liver 4.5 cm and spleen tip palpable). Investigative work-up detected raised C-reactive protein (CRP) but other tests for infectious etiologies, immunodeficiency, chronic liver disease and storage disorders were negative. The proband's younger brother was also symptomatic at 1 month of age with fever, neonatal hepatitis, cholestasis and severe anemia. He also had elevated CRP levels even during asymptomatic periods. At 1 year of age he developed episodes of subacute intestinal obstruction and one episode of acute lymphadenitis. At 18 months of age his length was 68 cm (-5.3 SD), weight 6.5kg (-4.4 SD) and head circumference 43.5cm (-2.9 SD). He had a facial phenotype resumbling his brother's, cervical lymphadenopathy, hepatosplenomegaly (liver 5.5 cm and spleen 3.5 cm below costal margin) and motor and speech delay.

Repeated febrile episodes with elevated inflammatory markers raised the possibility of periodic fever syndrome. Urine organic acid analysis using gas chromatography and mass spectrometry (GCMS) showed elevated levels of mevalonolactone. Genetic testing using clinical exome panel by next generation sequencing in the proband revealed previously reported compound heterozygous variants, c.803T>C (p.Ile268Thr) on exon 9 and c.976G>A (p.Gly326Arg) on exon 10 in *MVK* gene (***Web Fig.* 1a**). Both the variants were confirmed in the second sibling (***Web Fig.* 1b**). Segregation analysis in parents could not be done. Both siblings were treated with tocilizumab. There was reduction in frequency of febrile episodes and normalization of CRP levels. Tocilizumab was discontinued due to adverse drug reactions and patients were shifted to nonsteroidal anti-inflammatory drugs (NSAID) and corticosteroids.

Approximately 300 cases of MKD have been reported with the vast majority having European ancestry (median age at diagnosis, 8 to 10 years) [2]. HIDS is characterized by recurrent febrile inflammatory episodes associated with diarrhea, abdominal pain, vomiting, lymphadenopathy, splenomegaly, macular papular rash, and arthritis. Additionally patients with mevalonic aciduria have intrauterine growth reduction, failure to thrive, facial



WEB FIG. 1 *(a) Gross specimen of the cardiac mass. (b) Histopathology showing vacuolated tumour cells with clear cytoplasm and characteristic spider cells on Haematoxylin and Eosin staining (spider cell in inset). (c) Immunohistochemistry demonstrating desmin expression by rhabdomyoma cells.*