

One week after discharge, the patient visited our outpatient department for follow-up; the serum CK level, renal and liver function had returned to normal.

## DISCUSSION

Rhabdomyolysis is defined as a clinical and laboratory syndrome resulting from skeletal muscle breakdown with leakage of muscle cell contents into the systemic circulation. It is characterized by an elevated serum creatine kinase level and myoglobinuria, and may lead to renal dysfunction [2]. Rhabdomyolysis can cause life-threatening complications, including hypovolemia, hyperkalemia, metabolic acidosis, acute renal failure (ARF) and DIC [3]. ARF often results from the nephrotoxic effects of lytic myocyte components and usually presents as oligouric pigment-induced intrinsic renal failure [4]. The early and aggressive fluid repletion and bicarbonate therapy are the standard treatment to prevent ARF in such cases.

Influenza B-associated rhabdomyolysis is an infrequent and little-known complication of influenza B virus infection in children. In 2010, Wu, *et al.* [5] reviewed hospitalized children with influenza B virus infection at a university children's hospital in North Taiwan during 2000–2007 and found that 24 had presented with rhabdomyolysis; none had renal involvement. A recent review suggests that the risk of acute kidney injury in rhabdomyolysis is usually low when CK level at admission is <15,000 to 20,000 IU/L [3]. Our patient had high level CK 407,421 IU/L. Because limited data indicate that administering

oseltamivir via a gastric tube can provide systemic absorption in critically ill patients [6], our patient was treated with intravenous peramivir. It is, a neuraminidase inhibitor, authorized for emergency use for the treatment of hospitalized patients with known or suspected 2009 H1N1 influenza. Clinicians should be alert to patients with flu-like symptoms with severe muscle pain and dark brown urine (to rule out rhabdomyolysis). The high level of CK could be an indicator for the fatal complication of ARF. The early diagnosis and appropriate therapy should decrease mortality and restore renal function.

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## Naxos Disease and Carvajal Variant

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An 11-yr-old girl, born out of a consanguineous marriage presented with recurrent exertional syncope due to ventricular tachycardia. She had woolly hair, palmoplantar hyperkeratosis and mild cardiomegaly. Echocardiogram revealed mild left ventricular dysfunction. Features were consistent with Carvajal variant of Naxos disease, an arrhythmogenic cardiomyopathy with autosomal recessive inheritance.

**Key words:** *Cardiomyopathy, Palmoplantar keratoderma, Ventricular tachycardia, Woolly Hair.*

**N**axos disease is a recessive form of arrhythmogenic right ventricular dysplasia/cardiomyopathy associated with a cutaneous phenotype characterized by

palmoplantar keratosis and woolly hair. It is caused by mutations of the genes encoding desmosomal proteins [1]. Cardiac disease has 100% penetrance by adolescence, manifested as symptomatic arrhythmias,

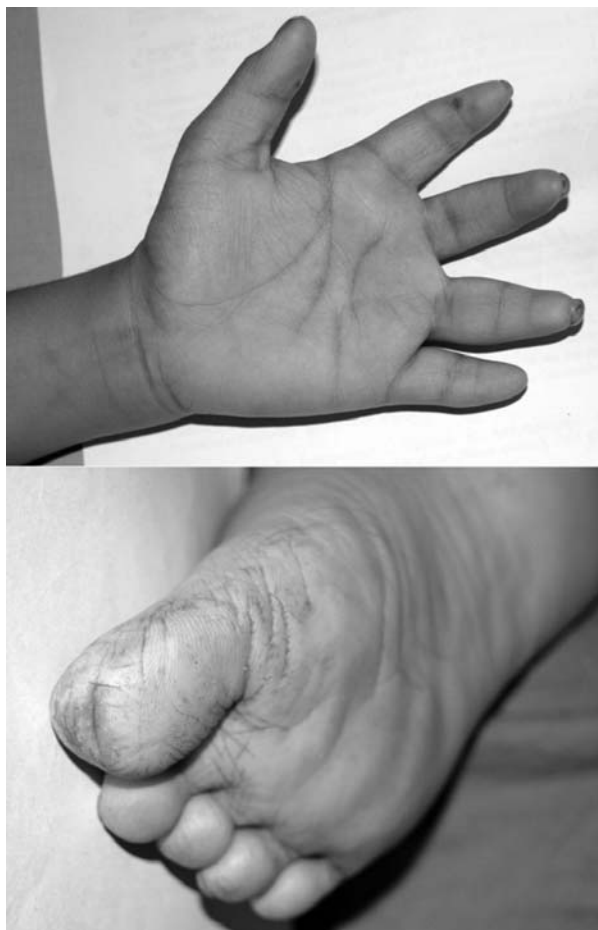
heart failure and sudden death. The variant, Carvajal syndrome is characterized by younger age at presentation and more pronounced left ventricular involvement.

#### CASE REPORT

An 11-year-old girl of Indian origin born out of 3<sup>rd</sup> degree consanguineous marriage presented with 2 transient episodes of syncope during exertion within a period of three months. Both the times she recovered spontaneously before reaching the hospital. She was previously asymptomatic except for thickening of palmar and plantar skin with fissures noticed since early childhood. None of her family members had a similar illness. General examination revealed woolly hair and hyperkeratosis of palms and soles. In the palms, hyperkeratosis was most marked in the subungual areas. There were fissures on the plantar aspect of big toe. In addition, distal phalanges of hands appeared shorter than normal (**Fig. 1**). Rest of the general examination including anthropometry was normal. Clinical examination of cardiovascular system revealed a resting pulse rate of 80/minute with normal volume and character of the peripheral pulses. Blood pressure was 96/44 mm Hg in the left upper limb in the sitting position. Cardiac apex was in the 5<sup>th</sup> left intercostal space in the midclavicular line with normal character, indicating cardiomegaly. First and second heart sounds were normal and there were no additional sounds or murmur.

She was evaluated further to find out the etiology of syncope. Baseline electrocardiogram (ECG) showed complete right bundle branch block with left posterior hemiblock indicating advanced myocardial disease. Transthoracic echocardiogram showed mild ventricular dysfunction. Left ventricle (LV) was predominantly involved with significant chamber dilatation and the ejection fraction was 45%. ECG obtained during subsequent episode showed ventricular tachycardia (VT) at a rate of 150/minute (regular wide QRS tachycardia with north-west axis and deep S in V5 and V6) suggesting VT as the etiology of syncope. Magnetic resonance imaging did not reveal any fat deposits in the myocardium.

The phenotypical features and cardiac manifestations along with history of consanguinity are suggestive of arrhythmogenic cardiomyopathy with autosomal recessive inheritance. These features are consistent with Naxos disease, probably Carvajal variant. Family was counseled regarding the disease and poor prognosis. She is being managed with amiodarone and antifailure medications including carvedilol. Two years from the initial diagnosis, her disease continues to worsen with recurrent refractory episodes of ventricular tachycardia and progressive cardiac failure.



**FIG. 1** Palmoplantar keratosis. Note the subungual keratosis in the hands and fissures in the sole. Short distal phalanges of fingers are also obvious.

#### DISCUSSION

Naxos disease was first reported in 1986 by Protonotarios, *et al.* [1] in patients from the Greek island of Naxos. Apart from Naxos, cases have also been reported from Italy, Turkey, Israel, Saudi Arabia and India. The variant with more pronounced left ventricular involvement and clinical overlap with dilated cardiomyopathy has been described in families from Ecuador (Carvajal syndrome) [2].

Genetic studies have located two causative genes, encoding for the desmosomal proteins plakoglobin and desmoplakin. Homozygous mutation of the *plakoglobin* gene truncating the C terminal of the protein causes Naxos disease which maps to 17q21 [3]. Homozygous mutations of another desmosomal component, desmoplakin which truncates the C terminal of the protein and maps to 6p24 is identified in involved patients from Ecuador [4]. The disease pathogenesis is linked to the specific tissue characteristics of cardiac muscle. Cardiac

muscle consists of single myocytes connected by complex intercellular contact sites called intercalated discs. Three different types of intercellular junctions are located in intercalated discs, namely adherence junctions, gap junctions and desmosomes. Adherence junctions and desmosomes secure mechanical coupling enabling synergistic contraction while gap junctions serve electrical coupling allowing rapid spread of action potentials. Plakoglobin is a common component of both adherence junctions and desmosomes. At the adherence junctions, it is connected to the actin cytoskeleton and at desmosomes to the intermediate filaments of desmin. Desmoplakin is another desmosomal protein that interlinks plakoglobin or plakophilin with desmin intermediate filaments. Defects in linking sites (C terminal) of these proteins interrupts cell to cell adhesion, particularly under conditions of increased mechanical stress leading to cell isolation and death. The result is progressive loss of myocardium and fibro-fatty replacement. Surviving myocardial fibers within fibro-fatty tissue provide a slow conduction substrate inducing re-entrant ventricular arrhythmias [5]. The degree of fatty replacement is variable.

Desmosomes are abundant in epidermis too, explaining the cutaneous manifestations. Cutaneous disease is confined to areas most exposed to pressure like the palmar and plantar surfaces, indicating the role of mechanical stress in disease expression.

In patients with Naxos-Carvajal disease, woolly hair was apparent from birth while palmoplantar keratoderma developed during the first year of life [5]. The symptomatic presentation was usually with syncope and/or sustained ventricular tachycardia during adolescence. Disease is progressive with death occurring from arrhythmia or congestive heart failure [6]. Treatment options are limited and include antiarrhythmic therapy, medical therapy for congestive heart failure, implantable cardioverter defibrillator (ICD) implantation and cardiac transplantation.

There are a few reports of Naxos disease from India earlier [7-10]. Features of this patient including presentation at younger age and left ventricular

involvement are more suggestive of the Carvajal variant. However, hypoplasia of distal phalanges seen in our patient is not reported earlier.

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