Noonan syndrome associated with anomalous left coronary artery from the pulmonary artery in a patient with the rare RAF1 mutation: A case report and review of literature

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ABSTRACT

We present the case of a 7-week-old male infant diagnosed with anomalous left coronary artery from the pulmonary artery (ALCAPA) who underwent repair by left coronary artery reimplantation, followed by an eventful postoperative period including need for venous arterial extracorporeal membrane oxygenation and mitral valve replacement due to mitral calcification and severe insufficiency. He also required heart transplant due to severe rapidly progressive biventricular hypertrophy. The pathology examination of the explanted heart showed massive cardiomegaly. Subsequently, the infant's cardiomyopathy panel was positive for RAF1 mutation, consistent with diagnosis of a rare form of Noonan syndrome. To our knowledge, this autosomal dominant condition in association with ALCAPA has not been previously reported in the literature.

Keywords: Anomalous left coronary artery from the pulmonary artery, Noonan syndrome, hypertrophic cardiomyopathy

INTRODUCTION

We present the case of a patient initially diagnosed as having anomalous left coronary artery from the pulmonary artery (ALCAPA) by echocardiography and confirmed by cardiac catheterization, who ultimately had an additional pathological and genetic diagnosis of Noonan syndrome. To our knowledge, this is the first time such association has been reported in the medical literature.

CASE REPORT

This is a case of a full-term male with no dysmorphic features diagnosed with moderate mitral valve regurgitation in the neonatal period. At 7 weeks old, he presented in cardiogenic shock and after initial resuscitation using volume, intubation, milrinone, and diuretics, an initial echocardiogram revealed ALCAPA, severe mitral valve insufficiency, mildly/moderately dilated left ventricle (LV), and normal LV function; these findings were later confirmed by cardiac catheterization [Figure 1]. He then underwent ALCAPA repair by reimplantation of the left coronary artery into the aorta with the aid of a small pericardial extension to connect the left coronary artery button to the aorta. His postoperative course was remarkable for pulmonary hypertension, moderate dynamic right ventricular (RV) outflow tract obstruction, and severe mitral insufficiency complicated with pulmonary

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hemorrhage and cardiac arrest. On postoperative day 4, he emergently placed on venous arterial extracorporeal membrane oxygenation (V-A ECMO) and required cardiac catheterization for atrial septal defect creation and placement of atrial septal stent due to left atrial hypertension and pulmonary edema. He was unable to wean ECMO support over 6 days; at 10 weeks of age, he underwent mitral valve replacement (15 mm, St Jude), removal of the atrial septal stent, and ECMO decannulation. His immediate postoperative course was complicated by progressive biventricular hypertrophy, bilateral diastolic dysfunction, and marginal cardiac output [Figure 2]. He tested negative for inborn errors of metabolism and infectious causes of cardiomyopathy, and a cardiomyopathy genetic panel was sent. Then, at 11 weeks of age, he had another cardiac arrest for which he was placed back on V-A ECMO support. He then developed worsening biventricular hypertrophy with dynamic RV and left ventricle (LV) outflow obstruction and severe biventricular systolic dysfunction [Figure 3]. He was then emergently listed for heart transplantation. The use of an LV assist device (LVAD) was not a possibility given severe biventricular hypertrophy.

At 12 weeks of age, he underwent heart transplant; however, unfortunately, he remained on V-A ECMO due to acute primary graft failure. Lack of graft recovery leads us to implant a LVAD (10 ml, Berlin Heart) with decannulation from V-A ECMO at 13 weeks of age. He did not tolerate chest closure. Postoperatively, there was inability to provide adequate cardiac output with LVAD filling below 40% and collapse of the failing heart around the LVAD inflow cannula, leading to obstruction and prevention of adequate flow. Furthermore, he developed worsening anasarca, acute kidney injury with anuria, and severe metabolic acidosis. After discussing his poor overall prognosis with the family, they requested withdraw of medical support. Pathological evaluation of his explanted heart revealed cardiomegaly (heart weight 96 g, expected weight 27 g) accompanied by prominent, global hypertrophic changes [Figure 4a and b]. Microscopically, the myocardial fibers showed disarray of the fibers accompanied by vacuolization of the myocytes and regenerative changes [Figure 4c]. Endocardial fibroelastosis and interstitial fibrosis were confirmed by trichrome stain [Figure 4d]. ALCAPA was identified, while genetic testing showed the presence of a pathogenic RAF1 mutation associated with Noonan syndrome.

DISCUSSION

The presence of an ALCAPA has an incidence of 1:300,000 live births.[1] Usually asymptomatic at birth, patients start showing symptoms of myocardial ischemia once the pulmonary vascular resistance drops and the coronary artery steel phenomenon occurs around 6–10 weeks of life.[1] Furthermore, Noonan syndrome has an estimated incidence of 1:1000–1:2500 live births, although milder cases may be more common.[2] The syndrome is inherited in an autosomal dominant pattern or may arise through *de novo* mutations. The most common mutation, occurring approximately half of all cases is in the PTPN11 gene, although other genes such as KRAS, SOS1, and RAF1 have also been involved in the pathogenesis.[2-4] RAF1
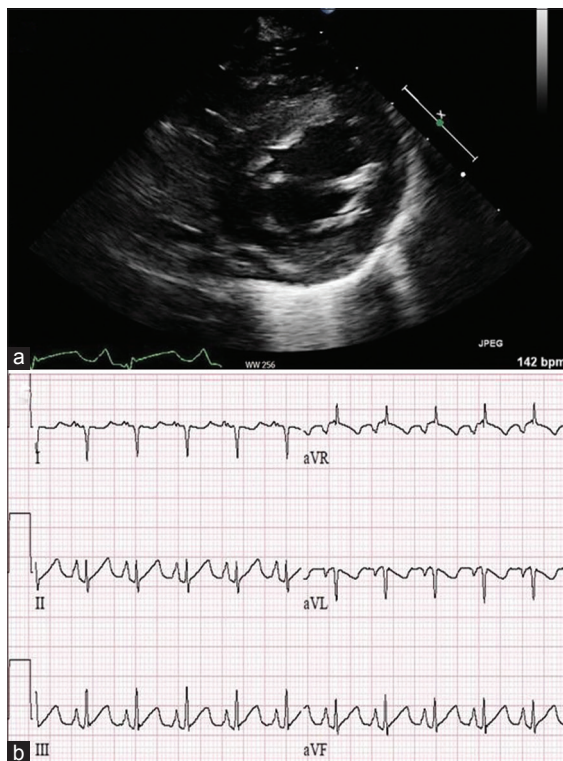

Figure 1: (a) (Transthoracic parasternal short-axis view) moderate left ventricular dilation and normal right ventricular size; 7 weeks of age; (b) Q waves in leads I and AVL suggestive of anomalous left coronary artery from the pulmonary artery; 7 weeks of age
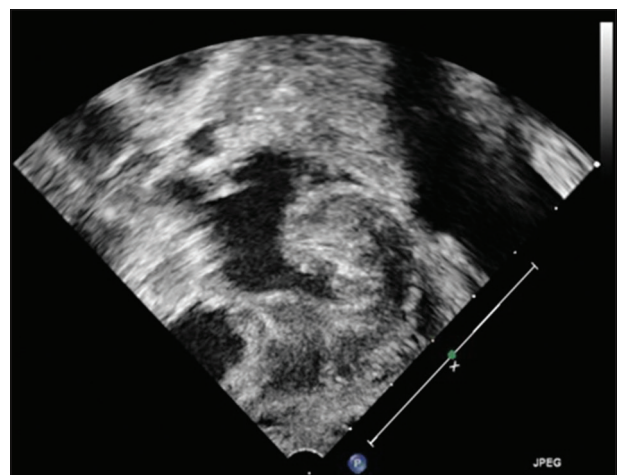

Figure 2: (Transthoracic subcostal long-axis view) severe biventricular hypertrophy with small intracavitary volumes; 10 weeks of age

Figure 3: (Transthoracic parasternal short-axis view) worsening severe biventricular hypertrophy; 11 weeks of age
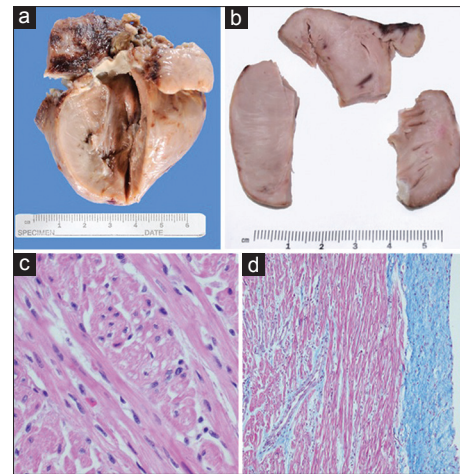

Figure 4: (a) Massive global hypertrophic changes; (b) massively thickened right and left ventricular walls and septum (top); (c) prominent disarray of the myocardial fibers accompanied by hypertrophic changes (H and E, ×400); (d) extensive endocardial fibroelastosis and interstitial fibrosis (trichrome, ×200)

has been implicated in only 4.7% of cases, according to a broad review in 2010 by Romano *et al.*[2]

Our patient presented initially with signs and symptoms consistent with the diagnosis of ALCAPA and given the widely variable phenotypical presentation of patients with Noonan syndrome there was delay in recognizing the cardiomyopathy. Moreover, it is not uncommon for patients to require V-A ECMO for some days after ALCAPA repair, making the diagnosis further challenging. In hindsight, when patients develop dynamic outflow tract obstruction associated with significant myocardial hypertrophy after ALCAPA repair, the differential diagnosis should include Noonan syndrome.

The RAF1 mutation identified in our patient has a significantly higher incidence of hypertrophic cardiomyopathy (80%–95%) as compared to the general incidence of hypertrophic cardiomyopathy in the rest of Noonan syndrome patients (18%–26%).[4-7] Interestingly, pulmonic stenosis was noted to be significantly less frequent in RAF1 mutation when compared to other Noonan syndrome mutations (particularly PTPN11 and SOS1). Furthermore, Pandit *et al.* stated that expressed RAF1 mutants enhance mitogen-activated protein kinases which can lead to increased intracellular signaling toward pathological cardiomyocyte hypertrophy.[4] In our patient, this pathological signaling pathway may have been enhanced by myocardial stress. The end result was the accelerated pathological adaptation response of progressively worsening biventricular hypertrophy, leading to his need for heart transplantation. In an animal model, cyclosporine has been shown to attenuate the specific myocyte hypertrophy response induced by RAF1 mutants.[8]

Finally, this case provides evidence toward a potential trend of earlier presentation among Noonan syndrome patients with RAF1 mutation when compared to others.

In the literature, RAF1 is often implicated in Noonan syndrome cases diagnosed prenatally, in the first several weeks after birth, or on fetal autopsy.[5,7,9,10] The trend in earlier diagnosis could point toward RAF1 mutations being either more severe or more clinically apparent than other forms of Noonan syndrome. Furthermore, mortality rate has been documented to be higher among this same set.[5,7,10] Kobayashi *et al.* have suggested that the remarkably higher incidence of heart conditions—including hypertrophic cardiomyopathy and biventricular hypertrophy—is likely responsible for this finding.[7]

CONCLUSION

We present this case as a unique incidence of Noonan syndrome-associated ALCAPA. Our case also highlights the early-onset massive cardiomegaly in association with RAF1 mutation.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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