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CASE REPORT

Fatal Varicella Myocarditis in a Child with Down Syndrome—A Case Report

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ABSTRACT

A 12-year-old male child with Down syndrome, who had recovered from congenital heart disease, succumbed to severe varicella myocarditis. His clinical presentation at admission mimicked acute coronary syndrome. Analysis of this case throws insight into several aspects of varicella myocarditis.

KEYWORDS: varicella, myocarditis, acute coronary syndrome, cardiac biomarkers, Down syndrome.

INTRODUCTION

Varicella (chicken pox) caused by varicella zoster virus (VZV) is an extremely common illness in childhood and usually results in complete recovery and lifelong immunity. Cardiac complications are exceedingly rare [1], but myocarditis due to VZV is a severe, potentially life-threatening disorder. In immunocompromised children, varicella can be a severe disease and can result in serious complications and death [2]. We report a case of fatal varicella myocarditis in a child with Down syndrome.

CASE REPORT

A 12-year-old male child with Down syndrome was referred to the Pediatric Emergency Services of Nizwa Hospital, Oman, with history of fever and cough of three-day duration and severe chest discomfort, orthopnea and progressive dyspnea of one-day duration. He had been diagnosed at birth as Down syndrome with severe congenital heart disease (atrioventricular septal defect—AVSD), leading to congestive heart failure by the end of the first week of life. He had improved after treatment for heart failure, and had undergone successful corrective cardiac surgery for AVSD at four months of age at a tertiary cardiology service. Subsequently, with regular follow-up visits, his medications for heart failure had been gradually tapered and withdrawn. By one year of age, his cardiomegaly had disappeared and he had normal hemodynamic status and effort tolerance. During the past 10 years, he had been regularly monitored, whereby his growth parameters were in the normal centiles as per Down syndrome-specific growth charts and his thyroid status was normal. He had intermittent asthma. There was no history of systemic vasculitis or family history of ischemic heart disease or premature death. His immunization status

was up-to-date, except that he had not received varicella vaccine, as it was not part of the National Immunization Programme (NIP) in Oman until 2011.

On examination, he was afebrile, extremely restless and diaphoretic. He had cool extremities; his heart rate was 120 beats/min, respiratory rate 40 breaths/min and blood pressure 86/44 mm Hg; and the capillary refill time was more than three seconds. On auscultation, S_1 and S_2 were muffled and S_3 gallop was heard at the apex. A Grade 2/6 systolic murmur was audible along the left sternal border with no pericardial rub. There was no wheeze, but a few bilateral basal rales were heard. The liver edge was palpable 5 cm below the right costal margin. After resuscitation in the paediatric emergency room, he was admitted to the paediatric intensive care unit under the differential diagnosis of acute coronary syndrome and acute myocarditis.

His chest radiograph showed cardiomegaly and pulmonary edema. His electrocardiogram (ECG) showed right bundle branch block, left ventricular hypertrophy, Q waves in leads V3–V4 and ST-T wave changes in the chest leads. Transthoracic echocardiography performed on the next day of admission showed mild-to-moderate mitral and tricuspid regurgitation, dilation of both ventricles, decreased myocardial contractility (ejection fraction 45%), no pericardial effusion and normal coronary arteries.

Laboratory results (reference range in parentheses) showed total leucocyte count $22.23 \times 10^3/\mu l$ (4.5–14.5) and neutrophils $20.30 \times 10^3/\mu l$ (1.4–9). Platelet count was $81.05 \times 10^3/\mu l$ (140–400). Serum calcium and electrolytes and urine analysis were within normal limits. The coagulation profile and metabolic screen were normal. Serum C-reactive protein (CRP) was significantly elevated, 113.5 mg/l (0–5). Serum total creatine kinase (CK) was 4070 U/l (normal 0–190) at presentation but decreased to 834.44 U/l on the third day. Serum cardiac Troponin T (cTnT) was 10 ng/ml (normal 0–0.014 ng/ml) and remained elevated throughout the hospital course. Serum alanine aminotransferase was 439 U/l (10–60) at admission and increased to 1319.40 U/l on the second day. Serum aspartate aminotransferase was 2160 U/l (0–38), and lactate dehydrogenase was 4135 IU/l (125–240). Throat

swab and blood culture were negative for bacterial growth. His respiratory viral panel test for all common viruses including pandemic influenza (H1N1) and Middle East Respiratory Syndrome Coronavirus (MERS – CoV) was negative.

He was started on inotropes, namely, dopamine and dobutamine, measures to combat heart failure and broad-spectrum antibiotics, and was electively ventilated. After 18 h of admission, a few erythematous areas with vesicular eruption, 15–20 in number, were noted on his abdomen, buttocks and legs, thereby raising the suspicion of varicella. On enquiry, his parents revealed that one sibling had suffered from varicella 2 weeks before the patient's admission. The patient was started on intravenous acyclovir (30 mg/kg/day every 8 h) and the inotropic support was sequentially upgraded. Milrinone could not be administered in view of co-existing thrombocytopenia, which also precluded an emergency coronary angiography. He was treated as a case of severe varicella myocarditis with heart failure and cardiogenic shock. His condition was unstable to undertake cardiac magnetic resonance imaging (MRI), and N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) assay was not available at our hospital at that time. He had a relentless downhill course, developed ventricular arrhythmias and expired after 80 h of admission. Autopsy to confirm the histopathological diagnosis of varicella myocarditis was not possible, as it is not permitted in Oman except for medico-legal issues. Blood that had been sent for real-time polymerase chain reaction (PCR), after noting vesicular eruptions, subsequently demonstrated presence of VZV DNA in plasma.

DISCUSSION

The clinical diagnosis of myocarditis was based on an acute presentation with severe heart failure and cardiogenic shock, highly elevated CK and cTnT [3], radiological findings of cardiomegaly and pulmonary edema and myocardial hypokinesia and left ventricular dysfunction on echocardiography. Skin lesions suggestive of varicella and subsequent detection of VZV DNA in plasma confirmed the diagnosis of varicella infection.

In a review of the English literature from 1955 through 1988 for reports of varicella myocarditis in patients below 18 years of age, Waagner and Murphy [4] reported that all patients had presented with myocarditis after the exanthem. However, diagnosis of varicella myocarditis becomes challenging when cardiac manifestations precede skin rash, as seen in our patient, and which has also been reported by Abrams *et al.* [1] (2001). Following varicella infection, visceral involvement occurs during the primary low-grade viremic phase and skin involvement later during the secondary viremic phase. Varicella may have a severe course with complications in children with Down syndrome, as observed in our case, possibly due to immunodeficiency commonly described in this disorder [5]. In fact, our report is the first case of fatal varicella myocarditis in Down syndrome reported in the English literature.

The child's presentation mimicked an acute coronary syndrome at admission, because of history of sudden onset of severe effort intolerance; markedly elevated CRP, CK and cTnT; and ST-T wave changes observed in the ECG. Had varicella eruption not been observed subsequently, this diagnosis would have remained as the main provisional diagnosis. In comparison with CK (a non-specific marker), cTnT assay may provide higher sensitivity for detecting myocardial cell damage in myocarditis because of a proportionally higher and longer-lasting elevation of serum levels [6]. Soongswang *et al.* [7] suggested that cTnT level of 0.052 ng/ml is an appropriate cutoff point for the diagnosis of acute myocarditis in children. When elevated cTnT levels were detected in adult patients with clinically suspected myocarditis, histologic and immunohistologic analysis of the endomyocardial biopsy specimen showed evidence of myocarditis in 93% [8]. However, cTnT and CK may not rise when myocardial involvement in varicella is restricted only to the conduction system, such as in complete AV block [9]. Our patient also had marked neutrophilic leucocytosis and highly elevated CRP levels, suggesting VZV caused significant myocardial inflammation, giving rise to elevation of positive acute-phase reactants. Cardiac MRI using gadolinium is an extremely useful non-invasive method for diagnosis of acute myocarditis. Another biochemical marker gaining interest in the evaluation of myocarditis is plasma NT-proBNP, especially with respect to prognosis and recovery [6].

Although many cases with varicella myocarditis in immunocompetent children recover [4], our patient had a fatal outcome, possibly owing to a combination of poor prognostic factors such as refractory hypotension; thrombocytopenia; markedly elevated CK, cTnT and CRP levels; conduction abnormalities; and echocardiographic findings suggestive of severe cardiac dysfunction. It has been reported that presence of Q waves or bundle branch block is associated with increased rates of heart transplant or death [10].

Myocarditis caused by VZV in children was first described by Hackel [11] (1953) at postmortem in six children dying with unequivocal clinical diagnosis of varicella but without significant clinical evidence of myocarditis. Hackel postulated that focal inflammatory lesions may develop in the myocardium in non-fatal cases of varicella not severe enough to produce clinical manifestations. Noren *et al.* [12] (1982) reported a retrospective study of 17 children dying with active varicella, and 11 of 17 cases had unsuspected interstitial myocarditis at the time of their death. Osama *et al.* [13] (1979) found no symptomatic cases of myocarditis but only transient ECG changes in 5.6% of patients hospitalized for varicella, two of whom were children. This implies that it may not be possible to know the true incidence of myocarditis in varicella, as some cases may be subclinical and resolve without sequelae [4]. A wide spectrum of cardiovascular presentations has been documented in varicella myocarditis such as arrhythmias, junctional ectopic tachycardia, transient AV conduction disorder, complete heart block, chest pain with features mimicking myocardial infarction, acute heart failure and sudden death [4, 9, 14, 15]. Tsintsof *et al.* [16] reported varicella myocarditis in a 12-year-old girl, who presented with heart failure and cardiogenic shock 3 weeks after the appearance of skin rash. Histological changes consistent with myocarditis, documented by endomyocardial biopsy, rapidly developed into those of idiopathic dilated cardiomyopathy over a 7-day period and cardiac transplantation led to a rapid, full recovery. It is pertinent to note that pericarditis and endocarditis in varicella are reported to

be most commonly associated with secondary bacterial infection [1].

In the pre-vaccine era, varicella with its highly characteristic features used to be readily recognized clinically by most clinicians. However, with decrease in the incidence of the disease as a result of vaccination, coupled with modified presentations among vaccinated individuals, laboratory testing is becoming increasingly important for a definite diagnosis of varicella [17, 18]. Routine laboratory confirmation is recommended for severe and unusual presentations, hospitalizations and deaths due to varicella [17]. Detection of VZV DNA by PCR testing of skin lesion specimens (ideally vesicles, scabs or cells from the base of a lesion) provides convenient, reliable, rapid and accurate evidence of varicella [17, 18]. Whole blood, plasma or serum is also a convenient biological matrix for PCR testing and diagnosis of VZV viremia [19] especially in cases involving severe complications and death. Serologic tests for detection of IgM and IgG antibodies to VZV are less sensitive than VZV DNA detection methods and culture, and the latter are the laboratory methods of choice for confirmation of varicella infection in both vaccinated and unvaccinated persons [17].

CONCLUSION

Health-care providers must be aware of atypical presentations and uncommon complications of varicella and perform appropriate diagnostic tests [20]. In Oman, introduction of the varicella vaccine in the NIP will most likely reduce mortality due to the disease, as evidenced in the USA [21]. Though it is a notifiable disease, further studies with active surveillance of varicella-related complications, hospitalizations and deaths would be necessary to monitor the impact and effectiveness of the vaccine programme and changes in the epidemiology of varicella [17]. Also, this case highlights the need to commence a 'catch-up' vaccination schedule for children and adolescents who have not received varicella vaccine scheduled in the NIP appropriate for his/her age [22]. Prevention of varicella in immunocompromised persons through vaccination of their susceptible household contacts cannot be overemphasized [2].

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