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Original Article

Cardiac complications in children following infection with varicella zoster virus

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Abstract Infection with varicella zoster virus, leading to chicken pox in susceptible hosts, is usually a benign self-limiting disease conferring immunity in those affected. Cardiac complications are rare, but when present may lead to severe morbidity or mortality.

We have recently encountered three children, all of whom developed significant cardiac complications secondary to infection with varicella. Myocarditis has long been associated with such infection. The pathological mechanism is presumed similar to other cardiotropic viruses, where both direct cytopathic and secondary auto-immune effects contribute to myocardial cellular destruction and ventricular dysfunction. Complications include arrhythmias and progression to dilated cardiomyopathy.

Pericarditis, and secondary pericardial effusion, related to infection with the virus is most commonly associated with secondary bacterial infiltration. Both cardiac tamponade and chronic pericardial constriction may result.

Endocarditis complicating varicella has only been described in the last fifteen years, and is associated with the emergence of virulent strains of both streptococcus and staphylococcus, the two organisms most commonly associated with endocarditis. The exact mechanism by which varicella causes secondary bacterial endocarditis remains unclear.

Whilst cardiac complications of infection with the varicella zoster virus are rare, the resulting complications are potentially life threatening. Evidence of varicella-induced carditis must be aggressively pursued in any child with signs of acute cardiac decompensation in whom chicken pox is confirmed or suspected.

Keywords: Varicella; endocarditis; myocarditis; pericarditis

THE VIRUS PRODUCING VARICELLA AND HERPES zoster is highly contagious. In susceptible children, it causes chicken pox. Chicken pox itself is usually a benign and self-limiting disease, and infection probably confers life-long immunity.[1] Complications are rare, but very severe pulmonary, neurological, and cardiac sequels have been reported.

Myocarditis was the first cardiac complication, described in 1953,[2] and since then there have been scattered reports of both myocarditis and isolated pericarditis. More recently, secondary infective endocarditis with virulent strains of staphylococcus and streptococcus has been described. We have recently encountered three children suffering cardiac complications of infection with the varicella virus. We review the underlying mechanisms by which these may occur.

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Cases

Case 1

A 9-month-old girl was referred with a 5-day history of increasing dyspnoea and irritability. Her elder brother had developed chicken pox 1 week prior to the onset of her symptoms. On examination she was pale and irritable. She had a tachycardia, with easily felt pulses. A fourth heart sound was audible at the left sternal edge, but no murmurs were present.

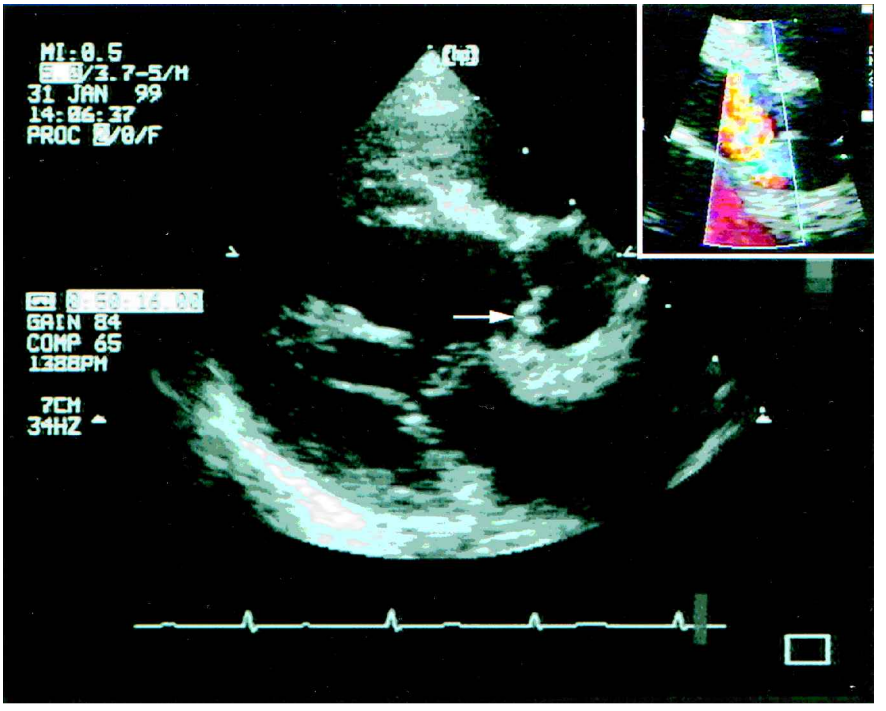

Figure 1.
Parasternal long axis view from patient #2. There is a perforation of the non-coronary leaflet of the aortic valve (arrowed). On colour flow imaging (inset), there is severe regurgitation through this perforation.

Changes were present in the T waves of the lateral chest leads of the electrocardiogram, and cross-sectional echocardiography showed a dilated, poorly functioning left ventricle, with a shortening fraction of only 18%, associated with mild mitral incompetence.

She was treated with diuretics and digoxin, and later an inhibitor of angiotensin converting enzyme. Three days after admission, she developed the typical rash of chicken pox.

Her cardiac function improved over the following 2 weeks, and she was discharged home. She remains asymptomatic despite trivial mitral regurgitation.

Case 2

A 3-year-old boy was referred for assessment of possible endocarditis. Two weeks before he had developed the typical vascular rash of chicken pox. Over a period of 1 week, he had suffered pyrexia, arthralgia, and haematuria and exhibited a prominent vesicular rash. Twenty-four hours prior to transfer, he suffered an acute arterial occlusion of his left leg and, during transfer from the referring hospital, he suffered a cerebrovascular accident complicated by a prolonged seizure.

On examination, he remained pyrexial and was irritable, with peripheral stigmas of infective endocarditis. The left leg was pulseless below the femoral artery. An ejection click was heard in early systole, but there were no murmurs. A dense left hemiparesis was evident, although bulbar and facial function was preserved.

Cross-sectional echocardiography demonstrated an abscess of the aortic root, which involved the left and non-coronary leaflets of the aortic valve. In addition, the non-coronary leaflet was perforated (Figs 1 and 2). Replacement of the aortic root was performed using a 20 mm aortic homograft. The post-operative course was complicated by transient complete heart block requiring a temporary pacemaker, but his early post-operative recovery was essentially uncomplicated.

Streptococcus pyogenes were isolated from blood cultures taken prior to the operation, and from pericardial fluid and tissue samples taken during surgery. He was treated with teicoplanin, benzyl penicillin and rifampicin for 6 weeks and has subsequently improved with minimal neurological impairment.

Case 3

A 21-month-old boy was transferred after a 3-day history of pyrexia, lethargy, and respiratory compromise, having developed chicken pox 11 days previously. He had received cefuroxime and acyclovir by intravenous injection for 2 days.

On examination, he had tachycardia, evidence of low cardiac output, and had quiet heart sounds on auscultation. The chest radiograph revealed an enlarged heart, while cross-sectional echocardiography showed a large pericardial effusion with poor systolic ventricular function (Fig. 3). Pericardiocentesis yielded 150 ml of turbid, straw-coloured fluid which contained gram positive cocci. The pericardial fluid and blood cultures were negative for both varicella zoster and bacterial growth. He was treated

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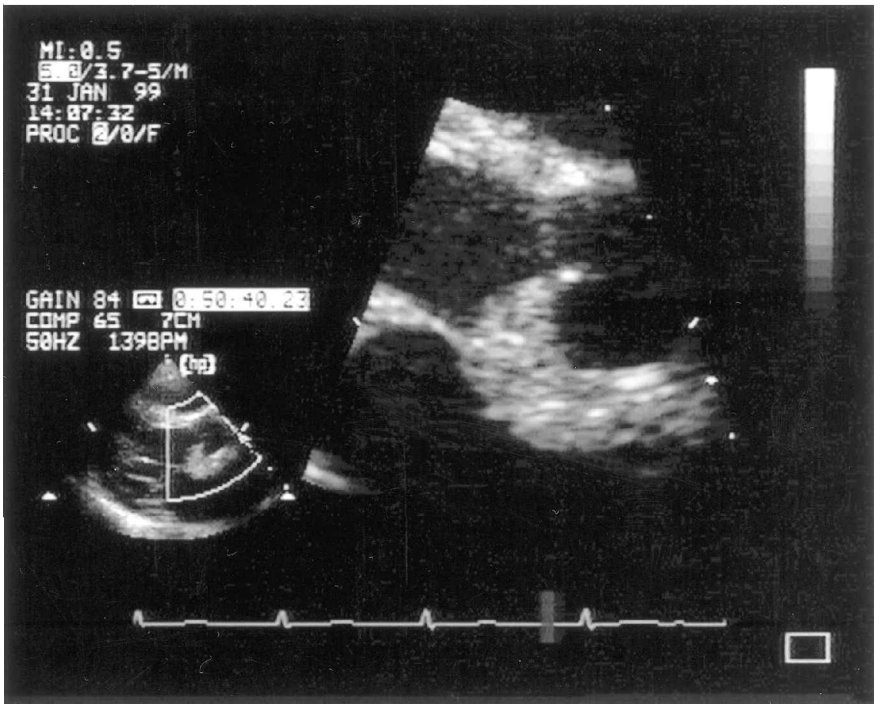

Figure 2.
Detail from a parasternal long axis image from patient #2 demonstrating an abscess of the aortic root.

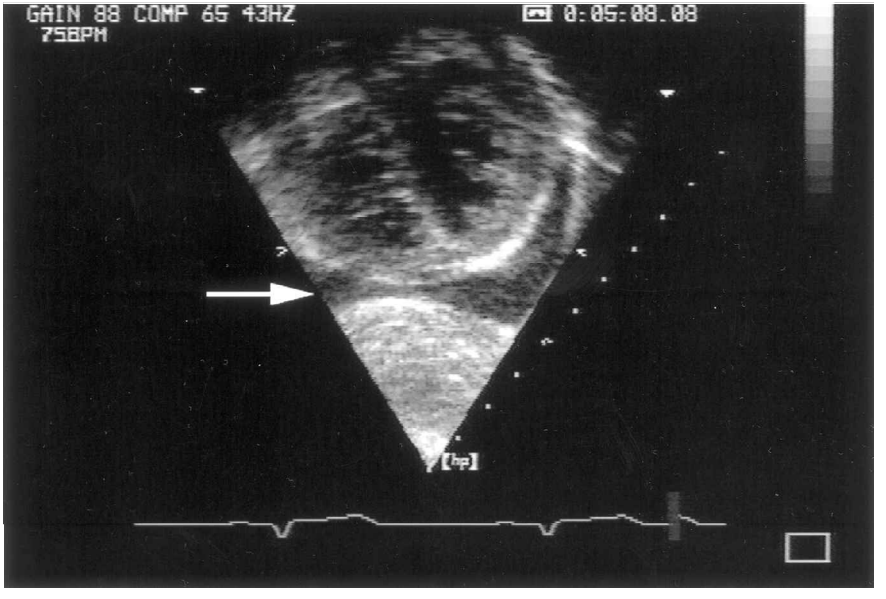

Figure 3.
Subcostal four-chamber view from patient #3 demonstrating a large pericardial effusion.

for 2 weeks with intravenous antibiotics and acyclovir and discharged home well.

A follow-up echocardiogram, performed 3 months later, showed recovery of ventricular function and no evidence of pericardial constriction.

Discussion

Primary infection with the virus producing varicella and herpes zoster is characterised by a generalised vesicular rash with relatively insignificant systemic effects. The major symptoms are pyrexia, irritability, and a widespread pruritic exanthem.[1] Complications are rare, occurring in no more than 2 cases per thousand,[3] of which secondary bacterial infection of the skin, soft tissues, and lower respiratory tract predominate. Cardiac complications are much less common, but when present may cause significant morbidity and mortality.

Myocarditis

The virus is one of many known to cause myocarditis, although the reported incidence is much less than for

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many other organisms, such as coxsackie B and echovirus. Myocarditis following varicella was first described by Hackel[2] in 1953. In his series, later confirmed by others,[4] interstitial myocarditis was present in a significant number of patients who died during an acute infection of chicken pox, even in those with no clinical evidence of cardiac involvement.

The exact mechanism of varicella-associated myocarditis has not been elucidated, but is probably similar to that related to other viral infections. Coxsackie B has been shown not only to cause direct viral-mediated cell lysis, but also to induce a cytotoxic response of the T cells against both virus-infected and non-infected myocytes, persisting as an auto-immune phenomenon. Natural killer cells have also been implicated in the destruction of non-infected cells.[5–7]

Patients may present with heart failure secondary to myocardial dysfunction,[8–12] or arrhythmias, including supraventricular tachycardia,[11] ventricular tachycardia and fibrillation,[12–13] and complete heart block requiring treatment with a permanent pacemeker.[14] Our patient is the only case described where cardiac symptoms preceded the appearance of the rash.

Cardiac transplantation was needed in the 12-year-old girl reported by Tsintof et al.[12] She suffered varicella myocarditis which resulted in severe ventricular dysfunction refractory to medical management. The authors noted two interesting histological features. Multiple petechial haemorrhages were seen on the surface of the explanted heart, a feature usually associated with coxsackie B myocarditis,[5] and no evidence of a myocarditic process was found 35 days after the onset of the varicella exanthem, which had been present in an endomyocardial biopsy specimen taken 1 week earlier. This would appear to support theories that the transition from myocarditis to dilated cardiomyopathy is rapid, and as such the incidence of infective myocarditis may be under estimated.[15–17]

Endocarditis

As far as we know, only four cases of acute bacterial endocarditis have been reported in the literature following varicella infection, with the first being seen by Harnden et al.[18] in 1988. This case involved a young Polynesian girl who developed fatal sepsis produced by the Group A β-haemolytic streptococcus, with echocardiographically proven endocarditis, 7 days after developing the typical rash of varicella. The three further cases have all involved infection with staphylococcus aureus.[19,20] In all four patients, clinical and bacteriological evidence of staphylococcal sepsis was present prior to the echocardiographic demonstration of vegetations. Only one child had clinical evidence of initial cellulitic infection. Two children survived despite multiple embolic complications, one of whom underwent a Ross procedure because of the development of significant aortic incompetence. None of the patients had prior evidence of a structurally abnormal heart.

Bacterial infections are well documented as a complication of infection with chicken pox, particularly in children under the age of 5 years. The majority of cases,[3,21,22] although not all,[23] are caused by the group A β-haemolytic streptococcus, or staphylococcus aureus, the two organisms most commonly associated with endocarditis.[24,25] An increased incidence of infection by the invasive group A β-haemolytic streptococcus has recently been recognised in association with varicella,[26,27] accounting for one quarter of all bacterial complications in one study.[28] This has coincided with the emergence over the last 10 years of more virulent M-serotypes of the β-haemolytic streptococcus, which cause severe and often fatal infections.[29–32] The production of toxins leads to a toxic shock syndrome, characterised by severe hypotension and multi-system failure, similar to that already described in conjunction with staphylococcus.[33]

Both streptococcal and staphylococcal toxic shock have been described in association with varicella infection.[34–36] Pollard et al.[36] described 13 children who suffered potentially lethal bacterial infection associated with such infection, addressing the issue as to why varicella leaves children susceptible to secondary bacterial infection.

One obvious explanation is the breakdown of the cutaneous barrier by the viral exanthem, thereby facilitating transdermal bacterial passage, particularly of staphylococcus. This cannot be the explanation in our case or one of the cases of sepsis described by Pollard et al.[36] where secondary infection occurred 2 weeks after the onset of varicella. An alternative hypothesis is that the infection lowers the natural immunity to these organisms. A granulocyte killing defect was reported by one group,[37] although the exact mechanism by which varicella may cause transient immunodepression has been much discussed but remains unproven.

Pericarditis

Pericarditis associated with infection with the virus is usually the result of secondary bacterial infiltration of the pericardial sack, presumably via haematogenous spread.[38] Direct viral pericarditis may occur,[39] although it is less common. The clinical picture, as well as the electrocardiographic and echocardiographic findings, are often very similar, necessitating microscopy and culture of pericardial fluid to differentiate the two entities.

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Staphylococcus aureus is the most common organism to cause purulent pericarditis, being isolated from three quarters of fatal cases.[40] This is also the case in association with varicella, having been reported in three cases to date,[41–43] although meningococcus type C,[41] and streptococcus[44] have also been found.

As gram positive cocci were seen in the pericardial fluid of our case, staphylococcus aureus would appear to be the most likely organism, although streptococcus cannot be excluded.

More importantly, the clinical picture was dominated by life-threatening pericardial tamponade. This patient emphasises the need for prompt recognition and treatment if morbidity and mortality are to be avoided. Furthermore, as in any patient with purulent pericarditis, diligent long-term follow-up for the development of pericardial constriction will be required.

Cardiac complications following chicken pox, therefore, are rare. The potential sequels, nonetheless, may be severe, and early detection and treatment may be life-saving. Any child with chicken pox showing signs of cardiovascular compromise must have carditis actively excluded. The exact mechanism by which the virus modulates the immune system facilitating bacterial complications remains uncertain.

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