Varicella zoster myocarditis progressing to cardiomyopathy and cardiac transplantation

Andrew Tsintsof, Warwick J Delprado, Anne M Keogh

Abstract
The case of a 12 year old schoolgirl with heart failure due to varicella myocarditis is reported. Heart failure and cardiogenic shock were evident 21 days after the appearance of the rash, and cardiac transplantation was performed two weeks later. Myocarditis is a serious complication of varicella zoster infection and heart failure may be fulminant. Endomyocardial biopsy changes consistent with myocarditis were documented six days after the start of heart failure. The histological changes, however, developed into those of idiopathic dilated cardiomyopathy (with anisokinesis and fibre width variation) over a seven day period. This case provides further evidence for the link between viral myocarditis and idiopathic cardiomyopathy and underlines the value of immediate endomyocardial biopsy in heart failure of recent onset. Cardiac transplantation led to a rapid and full recovery.

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Primary infection with varicella zoster virus (chickenpox) is characterised by a generalised pruritic vesicular rash, usually without significant systemic illness. Serious complications such as encephalitis, pneumonia, pancreatitis, and nephritis may occur, however, particularly in neonates, immunocompromised patients, and sometimes normal adults.¹ Myocarditis is an uncommon but serious complication. We report on a previously healthy child who developed biopsy-proven myocarditis after a primary infection with varicella zoster virus. This rapidly developed into a dilated cardiomyopathy (with histological changes consistent with this diagnosis) and the girl then needed cardiac transplantation.

Case report
A 51 kg, 12 year old schoolgirl presented with a five day history of vomiting, exertional dyspnoea, cough, and extreme lethargy that started 21 days after the start of an itchy, vesiculopapular rash diagnosed as chicken pox. Initial treatment comprised salicylates and two weeks isolation. Previously the patient had experienced no major illness. There was no relevant family history of heart disease. On presentation she was pale, peripherally cool, unwell, and lethargic. Heart rate was 145 beats/minute, blood pressure was 95/60 mm Hg, and she was febrile. Jugular venous pressure was elevated to the jaw, the apex beat was displaced laterally, and a third heart sound was audible. Lung fields were clear and there was no hepatomegaly or peripheral oedema.

A chest radiograph showed cardiomegaly, pulmonary venous congestion, interstitial oedema, and small bilateral pleural effusions. The electrocardiogram showed sinus tachycardia, a nonspecific intraventricular conduction defect, poor anterior R wave progression and inferolateral ST-T wave changes. The white cell count was 12.7 x 10⁹/l (normal 4–11 x 10⁹/l) with a neutrophilia (neutrophils 71%, lymphocytes 14%, monocytes 15%). Serum potassium (3.2 mmol/l) and magnesium (0.74 mmol/l) concentrations were subnormal. Serum albumin, creatinine, and urea concentrations, and hepatic transaminase activities were normal. Serological studies confirmed a recent primary varicella zoster infection with positive IgM and viral antibody titre of 32 (complement fixation test). Coxsackie, echo, influenza A and B, measles, cytomegalovirus, and Epstein Barr viral titres were all negative. Thyroid function testing was consistent with a sick euthyroid state. Echocardiography showed a considerably dilated, diffusely hypokinetic left ventricle with end diastolic diameter 73 mm (normal 35–56 mm) and dilated left atrium (47 mm, normal < 40 mm). There was moderate mitral regurgitation, mild tricuspid regurgitation, and a large apical thrombus. Left ventricular ejection fraction was 22% on radionuclide ventriculography. Endomyocardial biopsy performed 28 days after the start of the rash showed focal aggregates of mononuclear cells (> 5 lymphocytes/high power field), anisokinesis, variation in fibre diameter and scattered necrotic myocytes with lymphocyte "cuffing" (fig).

A diagnosis of varicella myocarditis was made. Fluid and salt restriction, frusemide, digoxin, captopril, and anticoagulation with heparin were started. In an attempt to limit myocardial destruction, 500 mg/day methylprednisolone was given intravenously for three consecutive days followed by a tapered dose of oral prednisolone (1 mg/kg/day reducing over 14 days to 0.2 mg/kg/day), and 1 mg/kg/day asazthioprine orally was started. She also received acyclovir (500 mg eight hourly) intravenously. By 30 days after the...
start of the rash, intravenous dopamine (4 
μg/kg/min) was required for persistent sinus
tachycardia and hypotension (70/50 mm Hg).
Left anterior pleuritic chest pain led to a ven-
tilation perfusion scan that reported low
probability of a pulmonary embolus.
Right heart catheterisation showed right
atrial pressure to be 3 mm Hg, mean pul-
monary artery pressure 20 mm Hg, pul-
monary capillary wedge pressure 15 mm Hg,
cardiac index 2.1 litres/min/m² (on
dopamine) and pulmonary vascular resistance
1.6 Wood units. An electrocardiogram on day
31 of the illness showed transient 2 mm ST
elevation in the anterior chest leads, resolving
after four hours without Q wave develop-
ment. Serum creatine kinase and its myocar-
dial subfraction were normal. Frequent
multifocal ventricular extrasystoles and salvoes
of ventricular tachycardia occurred and there
was progressive broadening of the intraven-
tricular conduction defect on electrocardiog-
raphy. It was decided to perform an urgent
cardiac transplant as lack of response to treat-
ment was obvious. On the 35th day after
development of the rash, a suitable donor
became available. Orthotopic transplantation
was performed with an unremarkable postope-
راتive course. The patient resumed school
four months later and remains well two years
after transplantation.
Examination of the explanted heart showed
a very dilated, thin walled left ventricle and
thickened epicardial surface anteriorly with
numerous petechial haemorrhages. There
were areas of fibrosis at the bases of the right
ventricular papillary muscles. The epicardial
arteries were normal. Histological examina-
tion showed features consistent with a dilated
cardiomyopathy with anisonucleosis and fibre
width variation. There was no evidence of
lymphocytic or mononuclear cell infiltration,
or of myocyte necrosis, and little or no
fibrous tissue.

Discussion
Clinically evident chickenpox myocarditis is
rare, yet in this case was severe enough to
require cardiac transplantation. Vomiting was
initially misdiagnosed as gastroenteritis before
heart failure was correctly identified. RNA
probe techniques were not available to assess
the presence of virus in the myocardium, but
serological evidence of a recent infection was
shown.
The diagnosis of myocarditis was based on
the histological changes of an inflammatory
mononuclear conduction defect near necrotic
myocytes. The inflammatory infiltration was
not intense and the myocyte necrosis not
widespread, yet the clinical picture of severely
impaired systolic function was irrefutable.
This is in keeping with the well reported lack
of correlation between the severity of histo-
logical changes in the myocardium and the
degree of myocardial dysfunction. This may
be partly explained by the effects of cytokines
released from lymphocytes, which can be
functional depressants to the myocardium.
Seven days after cardiac biopsy, the
explanted heart was indistinguishable from
one with idiopathic cardiomyopathy. The
lack of development of fibrosis probably
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reflects the short time of illness. This rapid change in histological appearance adds to other evidence linking acute myocarditis with idiopathic dilated cardiomyopathy. It also shows the potentially rapid transition of myocarditis to postmyocarditic cardiomyopathy and the need to biopsy as early as possible in cases of heart failure of recent onset. Repeat endomyocardial biopsy has been advocated between three weeks and three months after the initiation of treatment for myocarditis. Other reports, however indicate that early repeat endomyocardial biopsy (within four days) may show remarkable changes in histopathology.

Chickenpox affects 90% of children during the first decade of life. It seems possible that subclinical varicella myocarditis may underlie entities previously classified as idiopathic cardiomyopathy and such a myocardial insult could leave the heart more prone to dysfunction when stressed in later life.

Acyclovir was given after the varicelliform skin manifestations had resolved. We are aware of three reports in which acyclovir has been used in varicella myocarditis. These patients received acyclovir within five days of the start of exanthem. One patient recovered fully, another was left with heart block and left ventricular impairment, and third patient died. It seems certain that our patient would have died had a donor not become available.

The use of acyclovir did not appear to be beneficial. Acyclovir may be useful against Varicella in normal adults, in preventing dissemination in immunocompromised children and in shortening the duration of fever and skin manifestations in normal children when given orally within 24 hours of developing the rash. Acyclovir may thus be potentially beneficial in varicella myocarditis if presentation occurs during the stage of viral replication within the myocardium. This is more likely early in the course of the illness when new skin lesions are still appearing.

Steroid treatment and azathioprine were also given in an attempt to prevent further myocardial destruction. The place of immunosuppression, however, in the treatment of myocarditis, particularly that mediated by viruses, remains controversial. In this case, there was deterioration in clinical state despite reduction in inflammatory infiltrate.

In conclusion, the histopathological changes seen in this case are evidence that acute chickenpox myocarditis can progress rapidly to dilated cardiomyopathy. Such a transition may occur within a seven day period. Chickenpox is a common condition and it is conceivable that subclinical infection or myocarditis may contribute to some cases of idiopathic dilated cardiomyopathy.