FATAL VARICELLA INFECTIONS IN SINGAPORE

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ABSTRACT

Varicella (chickenpox) is common in Singapore. The annual incidence of reported cases for the period 1977-1990 ranged from 790 to 18,934, with a mean of 4,747. Mortality from chickenpox is rare. However, failure to recognise the severity and the potential complications of the disease, especially in immunocompetent patients, exists because of the common knowledge that chickenpox is a mild and self-limiting illness. We report six cases of fatal varicella in immunocompetent patients during the period 1988 to 1990.

Keywords: *varicella-zoster virus, chickenpox, epidemiology, clinical, mortality*

SINGAPORE MED J 1993; Vol 34:213-215

INTRODUCTION

Varcella-zoster virus (VZV) infection is a relatively benign infection in immunocompetent individuals and occurs commonly in childhood, typically between the ages of 2 to 8 years[1]. In Singapore, the annual incidence of reported cases of chickenpox for the period 1977-1990 ranged from 790 to 18,934, with a mean of 4,747[2]. The incidence rate per 100,000 population increased from 34.2 in 1977 to 705.1 in 1990. The male-to-female ratio is 1.4:1. The disease was seen more frequently in adolescents and young adults which constituted 70% of the cases.

The annual mortality rates varied from 0 to 0.08 per 100,000 population and the case fatality rate, 0% to 0.11%[2]. The commonest cause of death was encephalitis. Other causes included pneumonia, septicaemia and disseminated intravascular coagulation. While morbidity in chickenpox included secondary bacterial infections, pneumonitis, myocarditis, hepatitis, arthritis, and neurological and haematological complications, varicella pneumonitis was reported to have the highest mortality, particularly in the immunocompromised[3,4]. Varicella pneumonia[5], acute cerebellar ataxia[6] and radiculomyelopathy[6] had been reported as non-fatal complications of VZV infection in Singapore. We reviewed six cases of fatal varicella infections admitted to the Communicable Disease Centre during the period 1988 to 1990.

CASE REPORTS

Case 1

A previously healthy 17-year-old Chinese male presented with fever and a vesiculopapular rash of chickenpox. He also complained of epigastric discomfort of three days' duration before admission and was treated symptomatically by a private practitioner. On admission, his general condition was satisfactory. His body temperature was 38°C. A profuse vesicular haemorrhagic rash was noted on his face, trunk and abdomen. There was also petechial rashes on the trunk. Haematoma formation was noted over venepuncture sites. Abdominal examination was unremarkable. Laboratory results showed coagulopathy with thrombocytopenia of 30,000/ul, a white cell count of 35,000/ul and a prolonged prothromin and partial thromboplastin time. The serum creatinine was 4.8 mg/dl. He collapsed eight hours after admission. Post-mortem examination revealed haemorrhages on the lungs, liver and gastric mucosa. The cause of death was disseminated intravascular coagulation.

Case 2

A 53-year-old Indian man was admitted for dry cough and shortness of breath of two days' duration on the sixth day of symptomatic chickenpox. He had an underlying history of hypertension and type II diabetes mellitus. Clinically, he was febrile (38.5°C) and tachypnoeic. Bilateral pleural rubs were detected on auscultation. There was an extensive vesiculopustular rash of chickenpox on his body with secondary *Staphylococcus aureus* infection. Arterial blood gases showed hypoxaemia (pO_2 49mmHg; pCO_2 30mmHg). Chest X-rays showed bilateral reticulonodular opacities consistent with varicella pneumonia. He was intubated and mechanically ventilated. Intravenous acyclovir and cloxacillin were started on admission. However, he collapsed and died 18 hours later.

Case 3

A 11-year-old previously healthy Chinese girl developed a typical exanthem of chickenpox with fever and backache and was admitted on the 4th day of her rash. She was febrile (38°C) with a generalised vesicular rash on the face, trunk and limbs. Spinal and neurological examinations were normal. A spot of tenderness was noted on her left paraspinal region at the level of the fourth lumbar vertebra. On the second hospital day, her rash was noted to have progressed to a profuse vesicular eruption. She also developed a cough and rales in her left lung base. Chest X-rays showed nodular opacities in the left lung. Arterial blood gases showed hypoxaemia (pO_2 51mmHg; O_2 saturation 84%). She was started on intravenous acyclovir and intubated. She remained persistently hypoxaemic and died on the third hospital day.

Case 4

A 12-year-old Chinese girl with red cell aplasia on regular packed cell transfusion was admitted with a history of fever and rash of four days' duration. Clinically, she was febrile (39.5°C) with a profuse vesicular rash of chickenpox. Hepatosplenomegaly was noted but her lungs were clear. She complained of palpitations 12 hours after admission. A regular tachycardia of between 100 to 120/min was noted. Haemodynamically, she was stable and not in heart failure. On the sixth hospital day, she suddenly turned pale and started gasping. Right basal rales were detected in her lungs. She collapsed and died despite resuscitative efforts.

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Case 5

A 58-year-old man without significant past medical history was admitted with a five-day history of fever and rash. Clinically, he was febrile (38°C) with a profuse vesicular rash of chickenpox over the face, trunk and limbs associated with swelling of the face and eyelids. His lungs were normal on auscultation. On the second hospital day, he complained of severe abdominal pain and was treated conservatively after surgical consultation. There was no evidence of pancreatitis or free gas under the diaphragm on abdominal X-rays. On the fourth hospital day, he became oliguric and the previous normal serum creatinine climbed to 124 mg/dl. He became progressively hypotensive and collapsed.

Case 6

A 28-year-old Chinese woman was admitted on the 8th day of chickenpox rash with a 2-day history of weakness of the lower limbs and difficulty in micturition. Clinical examination revealed low grade fever and a drying vesiculopapular rash of chickenpox. Examination of the heart and lungs were normal. Neurological examination revealed a drowsy but responsive patient without cranial nerve involvement or nuchal rigidity. There were a grade 3/5 power of the lower limbs, a second thoracic vertebra dermatome sensory level with hyperreflexia of both lower limbs and bilateral Babinski responses. The clinical diagnosis was varicella encephalomyelitis. CT scan of the brain showed a low attenuation area in the right parietal region consistent with viral encephalitis. Intravenous acyclovir was administered. She continued to be febrile and developed increasing drowsiness while being monitored in the intensive care unit. She deteriorated on the 14th hospital day. Her clinical course was complicated by nosocomial urinary tract infection and pneumonia. These were compounded by hypotension and intermittent tachyarrhythmias. Her neurological deficits did not improve and she succumbed on the 21st hospital day. The cause of death was varicella encephalomyelopathy complicated by multiple nosocomial infections.

DISCUSSION

Haematological complications associated with VZV infections include thrombocytopaenia, neutropaenia, haemolytic anaemia and disseminated intravascular coagulation (DIC). DIC, resulting in extensive haemorrhage into the viscera and death, is one of the rarest haematological complications of VZV infection[1]. This rare complication occurred in our first case. The clinical course of this patient was acute and fulminant and reflected the high mortality associated with this unfortunate complication.

Varicella pneumonia is the most common complication of chickenpox and it also has the highest mortality[3,4]. It appears both in immunocomptetent and immunocompromised individuals. Our second and third case presented with varicella pneumonia. The typical history is that of an insidious onset, one to 6 days following the appearance of the rash, with cough and dyspnea. This may be associated with haemoptysis. There is a poor correlation between the physical findings and the severity of the pneumonia. While Weinstein and Meade[4] reported that the severity could be correlated with the diffuseness of the rash, Triebwasser et al[3] did not find any link between the two. It has been estimated that 15% of adults with chickenpox will have radiographic evidence of varicella pneumonia, the majority of whom will be asymptomatic. Chest X-rays typically reveal diffuse infiltrates, either interstitial or reticulonodular[7]. Less commonly, pleural effusion[3], haemothorax[8], spontaneous subcutaneous emphysema[9], the adult respiratory distress syndrome (ARDS)[10-12], and pulmonary calcifications[13,14] have been reported. Mortality has been reported to be between 20 to 30% and even higher in immunocompromised patients.

ARDS has been reported as a terminal event in most patients with respiratory complications. The persistent hypoxaemia in our second patient suggests that he had ARDS as a terminal event. Management includes the timely introduction of continuous positive alveolar pressure ventilation and positive end-expiratory pressure to prevent atelectasis and alleviate shunting. The use of anti-virals, previously reserved for immunocompromised patients with VZV infections, now appears justified in patients with symptomatic varicella pneumonitis. Early therapy with acyclovir leads to a dramatic decrease in the morbidity and mortality[15-17].

In our fourth case, the patient's main complaint was palpitations which were not associated with haemodynamic compromise. Although no tachyarrhythmia was documented, her sudden collapse was very suggestive of this. The probable terminal events could be due either to varicella pneumonia, pulmonary haemorrhage or varicella myocarditis leading to fatal arrhythmia. The last postulation seems more likely as the collapse was too sudden to be explained by the earlier diagnoses. However, no autopsy was carried out. Varicella myocarditis is a recognised, although little known and rarely encountered complication of chickenpox infection[18]. Most often, it is diagnosed at post-mortem[19,20]. This is because firstly, the presentation is occult in many cases, and secondly, the importance of cardiac involvement has not been emphasised widely enough. Furthermore, cardiac monitoring in such patients is not a routine procedure. Sudden deaths in varicella have been attributed to arrhythmias[21,22]. The hallmarks of infectious myocarditis are an inflammatory infiltrate and injury to adjacent myocardial cells. The mechanism of injury is thought to be from direct invasion and infection by the virus with cytolysis of the myocytes[1]. In the fifth case, our patient presented with extensive chickenpox with possible visceral involvement. He deteriorated rapidly and became oliguric. He probably died of disseminated varicella infection. Varicella nephritis was the likely cause of his acute renal failure.

Complications following varicella infections are rare and neurological complications are even rarer. Clinical neurological syndromes that have been described include encephalitis, encephalopathy, cerebellar ataxia, meningitis, myelitis, neuritis, radiculitis, and extrapyramidal involvement. Cerebellar ataxia is the commonest and usually affects children. The frequency of encephalitis following chickenpox has been reported to be less than 1 per 1000 and mainly affecting children[1]. The average latent period for appearance of encephalitic symptoms following varicella rash is 6 days, but can vary from 3 days before appearance of the rash to 21 days post-rash[23]. Varicella-associated neurological disease without skin lesions have also been described[24,25]. Our sixth patient had a clinical picture of encephalomyelopathy presenting with altered sensorium and a transverse thoracic myelopathy on the sixth day following a varicella rash. Myelopathy is the rarest neurological complication of varicella[6,26,27]. However, good prognosis has been reported with patients achieving complete or almost complete recovery within weeks to months. The pathogenetic mechanisms of these neurologic syndromes are poorly understood and have been thought to be either related to direct viral invasion of the nervous system or to an immune-mediated complication similar to experimental allergic encephalitis[23,28,29]. Specific therapy is currently not available although steroids have been reported to be of use in acute disseminated encephalitis[30,31]. Our patient was started on intravenous acyclovir on the eighth day of the rash. However, she succumbed to nosocomial infections.

CONCLUSION

Varicella is often considered a mild, self-limiting disease rarely associated with complications. Mortality is low and complications are uncommon in immunocompetent individuals. Mortality rises appreciably when it affects immunocompromised patients in whom varicella can be associated with visceral dissemination leading to death. Acyclovir has been demonstrated to be a safe and effective agent for use in early VZV infections, particularly in the immunocompromised[32,33]. Unfortunately there exists a small group of apparently immunocompetent patients who present with a severe form of varicella and in whom potential complications of the disease are not recognised. Efforts to improve the outcome of immunocompetent individuals will come from early recognition of the uncommon manifestations of severe varicella and prompt institution of effective anti-viral therapy.

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