The Diagnosis of Atypical Varicella*

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SUMMARY

Atypical varicella often poses diagnostic problems to the clinician and to the virologist. Five case reports are presented to draw attention to the difficulties that may be encountered and reference is made to some of the procedures which may be used. The variety and type of specimens required for investigation and the time of their collection are important considerations in efforts to establish a definitive diagnosis.

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In the great majority of cases of varicella the medical practitioner is able to make a confident clinical diagnosis without resorting to laboratory tests for confirmation. However, the manifestations are occasionally so atypical that a certain diagnosis may only be established by laboratory investigation. These atypical cases vary from the very mild with few vesicles and little constitutional disturbance, to the very severe which require differentiation from generalized herpes simplex or variola virus infections.

Atypical varicella may show widespread bullous or haemorrhagic cutaneous lesions and visceral involvement may occur with lesions in practically every tissue of the body. A feature of varicella is the affinity for epithelial tissues and the early involvement of the endothelium of capillaries and arterioles leading to necrosis of the vessels. Severe varicella infections tend to occur in newborn infants, in adults, in patients with an immunological defect, in children with kwashiorkor, or in children following acute infectious diseases such as measles or rubella. Patients with Hodgkin's disease or leukaemia, or patients on long-term steroid therapy or receiving immunosuppressive drugs run a high risk of the complications of varicella whether they have contracted a primary infection or are suffering from reactivation of latent infection.

The laboratory diagnosis is not always easy. Material submitted for examination is often unsuitable or insufficient, making it important to decide which tests should be applied to give the maximum information. The 5 cases described below draw attention to the clinical and laboratory problems arising in the diagnosis of atypical, severe, or fatal varicella.

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CASE REPORTS

Case 1

A Coloured female, aged 11 years, was admitted to hospital with a generalized rash most prominent on the trunk and face and consisting of macules, papules and vesicles. Vesicles were present on the fauces, pharynx and tongue as well as on the soles of the feet and the palms of the hands. She was extremely ill with a temperature of 39·4 °C and a respiration rate of 50/minute.

The diagnosis of varicella pneumonia was supported by diffuse bilateral patchy opacities in the lungs on X-ray examination. The appearance of the rash and the vesicular stomatitis, however, demanded that generalized Herpes simplex virus infection be considered.

Neither Herpes simplex virus nor varicella virus was grown from vesicle fluid harvested from some of the larger vesicles on the fifth day of the rash. Serum samples gathered on the 5th and 34th day after the appearance of the rash contained the same titre of Herpes simplex virus neutralizing antibodies, but the titre of antibodies to varicella virus tested by complement fixation and by indirect immunofluorescence was <10 in the early serum samples, whereas the titre was 100 by both procedures in the second serum sample.

The pulmonary lesions resolved slowly and the patient was discharged well and happy after 10 weeks in hospital.

Case 2

A 44-year-old White female patient was admitted to hospital with a generalized, haemorrhagic, bullous eruption over almost the entire body. Immediately preceding her illness the patient

had a severe intractable yeast infection of the mouth suggesting mucocutaneous candidiasis. During the 7 days in hospital before her death she developed an obstructive laryngo-tracheo-bronchitis with a widespread bronchopneumonia.

Varicella virus was isolated from the vesicle fluid, from the blood and from a sample of faeces on the day of admission. The viraemia was surprising since she was known to have had varicella at the age of 3 years and an attack of zoster 3 years before admission and she should have been immune to the disseminated form of varicella virus infection. However, her immune responses were grossly defective since she showed an extreme hypogammaglobulinaemia with no detectable alpha- or betaglobulins and only a trace of gammaglobulin.

Postmortem samples taken from the liver, the skin and the intestinal contents yielded varicella virus in cell culture. It is interesting that a mixed infection was present since Herpes simplex virus was isolated from the lungs and the hilar lymph nodes, and was probably responsible for the obstructive laryngitis.

Case 3

A non-White adult male, after travelling from Johannesburg to the Cape by train, was admitted to a country hospital with a widespread vesicular eruption on the skin and mucous membranes. The distribution of the rash was mainly peripheral involving the arms and legs, the soles and palms, and the buccal mucosa. The lesions appeared to be at the same stage of evolution, and many of them were umbilicated. On clinical grounds alone, it was uncertain whether this was a case of variola or one of severe varicella.

In view of the important public health implications an early diagnosis was essential. A minimal amount of vesicle fluid in a capillary tube was submitted to the laboratory. Electron-microscopic examination completed within an hour of receipt of the specimen revealed many herpes virus particles and no pox virus particles. Variola could therefore be excluded.

Case 4

A 15-year-old White male had Hodgkin's disease for which he received radiotherapy, cytotoxic drugs and steroids over a period of 18 months.

At the time of his death he had a few petechial haemorrhages over the dorsum of both feet but no vesicular lesions anywhere on the body surface. At autopsy the liver was enlarged and jaundiced. Under the capsule there were many rounded haemorrhages, some of which had a pale yellow central area of necrosis. Histologically, apart from the lesions of Hodgkin's disease, there were other necrotic areas resembling those seen in disseminated Herpes simplex or varicella virus infection. Varicella virus was isolated from the liver, the only tissue submitted for virological examination.

Case 5

A 9-year-old Coloured female had a severe blood dyscrasia of more than 12 months' duration which was diagnosed as eosinophilic leukaemia. During the last few weeks of life the child developed staphylococcal septicaemia and a few days before death a haemorrhagic rash appeared on the chest, trunk, arms and legs. The lesions were mainly petechial but some larger haemorrhages had central necrotic spots which could have been haemorrhagic varicella lesions.

At postmortem examination there was frank subarachnoid haemorrhage over the right cortex. Histologically, many tissues showed septic embolic lesions with clusters of Gram-positive cocci. Although necrotic lesions associated with intranuclear inclusion bodies were scant, the few scattered haemorrhagic lesions in the liver were very suggestive of disseminated varicella. Varicella viraemia was confirmed by culture of the blood. There were no cases of varicella or zoster in the ward immediately before or during the few days she was in hospital.

DISCUSSION

In cases 2, 4 and 5 the diagnosis was confirmed by the isolation of varicella virus. In case 1 the vesicle fluids were taken at least 5 days after onset of the rash and this may explain why no virus could be cultured. Gold[1] found that in varicella virus was only isolated from vesicles when the rash had been present for up to 3 days and in no instances when varicella antibody was present in the serum. In zoster, on the other hand, the vesicles often persist longer and virus may be isolated as late as the 7th day even when varicella antibodies are present in the serum in high titre.

Early and convalescent serum samples were available only in case 1. The rising titre of varicella antibodies from <10 to 100 in the presence of unchanged Herpes simplex antibody levels left no doubt about the differentiation of the two possible causal agents.

It is interesting that one patient (case 2) suffered a disseminated varicella virus infection which was a reactivation of a latent infection. This, and the ready isolation of varicella virus from several different sites as long as 14 days after the onset of the rash could be explained on the basis of immunological deficiency.

Mild primary varicella infection with very few skin vesicles is well known, but visceral varicella without cutaneous lesions must be very rare. Scheinman and Stamler[2] were unable to find a report of fatal varicella without typical cutaneous lesions in the literature, but their 7-year-old child on cyclophosphamide therapy seems to be a likely example, even although they were unsuccessful in isolating the varicella-zoster virus. There are many reported instances of fatal varicella infection in patients on immunosuppressive, cytotoxic or long-term steroid therapy, particularly when associated with malignant lymphomatous disease. But these are the very cases in which zoster is a common complication resulting from activation of latent varicella-zoster virus infection. In patients without typical varicella skin lesions as in the patient with Hodgkin's disease who had received intensive therapy (case 4) and in the patient with leukaemia under treatment with prednisone (case 5) and where there is no apparent source of infection it appears that reactivation of a latent varicella infection may occur and lead to dissemination and visceral lesions.

Immunofluorescence was used to titrate serum antibodies in case 1 but could be applied to identifying antigen in suspected varicella lesions. At the moment, however, the raising of a satisfactory specific immune serum in experimental animals remains a problem. Serum from convalescent cases must be used with an acute phase serum from the same patient as a control.

The usefulness of electron-microscopy in obtaining an urgent diagnosis is illustrated by case 3.

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