Necropsy findings in a case of progressive vaccinia

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SYNOPSIS A case of progressive vaccinia complicating chronic lymphocytic leukaemia is reported. At necropsy a vaccinia pneumonia, focal pancreatitis, and evidence of disseminated intravascular coagulation were found. Epithelial proliferation was noted in sweat glands, bronchi, and pancreatic ducts associated with lesions in these sites. The significance of these findings is discussed.

Progressive vaccinia is a rare but often lethal complication of smallpox vaccination. In this condition the lesion at the site of the inoculation fails to heal and becomes a progressively enlarging ulcer. New satellite vesicles often appear round this ulcer and secondary vesicles, thought to be due to haematogenous spread of the virus (Kempe, 1960), may arise in mucosal surfaces and distant areas of the skin. In some cases visceral lesions have been found at necropsy. In children the commonest underlying cause of this complication is congenital hypogammaglobulinaemia (Kempe, 1960) and in adults the immunological deficiency often associated with leukaemias or lymphomas (Dixon, 1970).

Case Report

A 69-year-old American woman had been found to have chronic lymphocytic leukaemia in 1963 but she was free of symptoms and no treatment was given. In 1965 she had been revaccinated against smallpox without any untoward reaction. In February 1969 and before a trip to Europe she had smallpox vaccination on the left upper arm. At this time she was taking 80 mg of prednisone and 12 mg of chlorambucil daily (Fig. 1).

On arrival in the UK she became febrile (102° F) and weak. When examined in hospital she had multiple bruises and petechiae. On the left upper arm there was a 10 × 8 cm reddened area with a raised border and a central black necrotic slough surrounded by a ring of vesicles (Fig. 2). One vesicle was present on the forehead. The left axillary and supraclavicular lymph nodes were enlarged and tender. The liver and spleen were palpable. Non-tender nodes were felt in the right axilla and both groins. No abnor-

malities were found in the cardiovascular system (BP 120/75 mm Hg), respiratory system (the chest radiograph was clear), or central nervous system. The blood urea was 92 mg/100 ml; haemoglobin 13.2 g/100 ml; WBC 23,000 per cmm with 19,000 lymphocytes per cmm; platelets 100,000 per cmm; serum immunoglobulins; IgG 190 mg/100 ml, IgA 130 mg/100 ml, IgM 29 mg/100 ml. Vaccinia virus was isolated from the fluid of a vesicle in the arm.

TREATMENT AND PROGRESS

Chlorambucil was discontinued and the dose of prednisone was gradually reduced. Antivaccinia gammaglobulin and methisazone were given immediately. Because of the low absolute neutrophilic count (Fig. 1) reverse barrier nursing was used during the first 23 days in hospital.

In spite of this treatment new vesicles appeared in distant areas of the skin (Fig. 1) and the patient developed a generalized erythematous rash. Seventeen days after admission the erythema had subsided but new vesicles continued to appear and the haemoglobin fell to 10 g/100 ml. By the 25th day in hospital she was very weak and experienced sudden intermittent attacks of dyspnoea accompanied by falls in blood pressure. The blood urea was 46 mg/100 ml and a chest radiograph showed scattered small shadows in both lung fields. Virus was again isolated from vesicles in the palate and right elbow. It was thought that the attacks of dyspnoea were due to pulmonary embolism and the patient was therefore given an intravenous infusion of heparin which was continued for two days. On the 35th day she collapsed, her blood urea rose to 134 mg/100 ml, and multiple vesicles appeared on the sacral region, right groin, and abdomen. She was treated with antibiotics, dextran, and a further heparin infusion, but she died next morning, 56 days after vaccination.

Fig. 1 Treatment and clinical course from the beginning of January until the patient's death.

Fig. 2 Appearance of the vaccination lesion on admission.

Necropsy Findings

The necropsy was performed 12 hours after death and permission was obtained for a limited internal examination only. As well as the skin lesions already described there was generalized skin oedema. Fresh ecchymoses and petechiae were present on the face, shoulders, and arms. The surface of the right lung was covered by fibrinous exudate. Scattered throughout the parenchyma of the lower lobes there were areas of grey consolidation up to 1.5 cm in diameter. The liver, spleen, and abdominal lymph nodes were enlarged. The pancreas was hard and showed foci of necrosis up to 0.3 cm in diameter. Other abdominal organs appeared normal.

Histology

The bone marrow and lymph nodes showed evidence of chronic lymphocytic leukaemia. The skin vesicles (Fig. 3) were intraepidermal and had the reticulating

Fig. 3 *Histology of a metastatic vesicle at necropsy. Reticulating degeneration is present in the superficial layers and ballooning degeneration in the deep layers of the epidermis. H & E $\times 100$.*

and ballooning types of degeneration typical of poxvirus lesions. Many epithelial cells contained round, circumscribed eosinophilic inclusions (Fig. 4). Ballooning degeneration was also present in sweat glands and hair follicles. In addition there was stratification of the epithelium in some of the sweat glands (Fig. 5). The areas of consolidation in the lung consisted of partially collapsed alveoli containing abundant fibrinous exudate, some red cells and a few neutrophils. In the middle the alveolar walls were necrotic and towards the periphery they were lined by swollen cells. Very occasionally one of these cells contained cytoplasmic eosinophilic inclusions. Several bronchi were lined by markedly hyperplastic epithelium (Fig. 6). Many small arterioles showed necrosis and oedema of the wall and the intima was coated by a layer of fibrin (Fig. 7). Alveolar capillaries, small arteries, and bronchial veins contained spheroidal aggregations of fibrin surrounded by one or several cells apparently derived from endothelium. In the pancreas there were areas of recent necrosis surrounded by a few neutrophils. In older lesions a few surviving acini were surrounded by many young fibroblasts, lymphocytes, and neutrophils. The pancreatic ducts in these areas showed numerous

mitoses and in a few of them there was stratification of the epithelium (Fig. 8). A few small arterioles contained fibrin thrombi. Focal deposition of fibrin was prominent in the spleen. In the kidney several glomerular and intertubular capillaries and arterioles contained delicate fibrin thrombi (Fig. 9). In the liver there was congestion and focal fatty change. No necrosis was seen.

Discussion

The association of progressive vaccinia with various leukaemias and lymphomas is well documented (Dixon, 1970). It is noticeable that our patient was vaccinated on two different occasions after a diagnosis of chronic lymphocytic leukaemia had been made, and that at the time of the second vaccination she was receiving large doses of two powerful immunosuppressants.

SKIN LESIONS

In this case, the histological features of the vesicles correspond closely with those previously described in human progressive vaccinia (Dible and Gleave, 1934). Proliferation of the sweat gland epithelium

Fig. 4 *Cytoplasmic inclusions in a skin lesion. H & E $\times 600$.*

Fig. 5.

Fig. 7.

Fig. 6.

Fig. 5 *Stratification of sweat gland epithelium beneath a skin vesicle. H & E $\times 240$.*

Fig. 6 *Stratification of epithelium in a medium-size bronchus at the periphery of an area of consolidation. H & E $\times 400$.*

Fig. 7 *Arteriolar oedema and necrosis in the lung. H & E $\times 250$.*

Fig. 8 Area of focal pancreatitis with stratification of the epithelium in one duct. *H & E* $\times 100$.

Fig. 9 Delicate fibrin thrombi in a glomerulus. *PTAH* $\times 375$.

does not appear to have been previously noted. However, intraepidermal proliferation is often present quite early in the development of the vesicles both in vaccinia and in smallpox (Bras, 1952) and has been observed in experimental lesions in animals (Lillie and Armstrong, 1930; Downie and Dumbell, 1947). Since there is no evidence that cells infected by poxviruses are capable of mitotic division, it has been postulated that mitoses occur in uninfected cells when they are stimulated by neighbouring infected cells either by disturbances in their nutritional mechanisms or by breakdown of contact inhibition (Joklik, 1966).

It has been said that the inclusion bodies of vaccinia are basophilic and irregular in outline (B type) and that round eosinophilic inclusions (A type) are rare, occurring only if the strain is from cowpox rather than from variola (Dixon, 1970). However, A type inclusions were present in this case and are also mentioned in seven of 17 cases of human progressive vaccinia in which histological

descriptions of the lesions are available (Table). In no case were basophilic inclusions mentioned. This may be due to difficult identification in histological sections or, more probably, a reflection of the fact that the majority of lymphs used for human vaccination are derived from cowpox and not from variola (Horsfall and Tamm, 1965).

VISCERAL LESIONS

Haematogenous dissemination of the virus is thought to occur in most cases of progressive vaccinia, but only in very severe cases, with new vesicles appearing almost daily, has the virus been isolated from the blood during life (Keidan, MacCarthy, and Haworth, 1953; Sédallian, Badon, Fayolle, and Rouchon, 1957). This is due to the speed with which the relatively large poxviruses are removed from the circulation by the reticuloendothelial system (Mims, 1964).

A focal necrotizing pneumonitis with little inflammation has been previously noted (Hall, Cunliffe,

Author and Year	Site	Position	Staining Reaction
Dible and Gleave (1934)	Skin	Cytoplasm and nuclei	Not stated
Bigler and Slotkowski (1951)	Skin	Cytoplasm	Not stated
Hall <i>et al</i> (1953)	Not seen		
Keidan <i>et al</i> (1953)	Skin	Cytoplasm	Eosinophilic
Kozinn <i>et al</i> (1955)	Bronchi and kidney	Cytoplasm	Eosinophilic
Barbero <i>et al</i> (1955)	Periostium	Cytoplasm	Eosinophilic
Somers (1957)	Skin, tongue, and oesophagus	'Intracellular'	Eosinophilic
Sédallian <i>et al</i> (1957)	Skin	Not stated	Not stated
Lewis and Johnson (1957)	Skin	Cytoplasm	Eosinophilic
Galloway and MacBean (1958)	Not seen		
Medansky <i>et al</i> (1960)	Not mentioned		
Kozłowska and Sztymela (1962)	Not mentioned		
Flewett and Ker (1963)	Skin	Cytoplasm and nuclei	Eosinophilic
White (1963)	Not mentioned		
O'Connell <i>et al</i> (1964)	Skin	Cytoplasm	Eosinophilic
Van Rooyen <i>et al</i> (1967)	Not seen		
Dixon (1970)	Not seen		

Table Inclusion bodies in human cases of progressive vaccinia

and Dudgeon, 1953; Kozinn, Sigel, and Gorrie, 1955; Flewett and Ker, 1963; Dixon, 1970). In other instances purulent inflammation was also seen (Bigler and Slotkowski, 1951; Lewis and Johnson, 1957; Somers, 1957) but the presence of bacteria in the lesions in two of these cases suggests that this was due to secondary infection.

Proliferative changes of the bronchial or bronchiolar epithelium have also been noted previously (Bigler and Slotkowski, 1951; Lewis and Johnson, 1957; Flewett and Ker, 1963; Dixon, 1970). This change, although not specific, may be useful in the histological diagnosis of the lesions. The proliferation seen in pancreatic ducts in the present case could be interpreted in the same way. We have not found a description of similar pancreatic lesions in the literature, but the pancreas is mentioned in only two instances: areas of focal necrosis were present in one case (Hall *et al*, 1953) and the organ was macroscopically normal in the other (Shortt, 1933).

There is no previous reference to arteriolar necrosis or thrombosis in human vaccinia lesions. This is surprising, since they are not uncommonly found in smallpox (Bras, 1952) and are often described in experimental vaccinia lesions in rabbits (Ledingham and Barratt, 1929; McIntosh and Scarff, 1929; Lillie and Armstrong, 1930). McIntosh and Scarff thought that vascular lesions were of cardinal importance in the subsequent development of focal necrosis. However, the more detailed descriptions of Lillie and Armstrong show that tissue necrosis usually precedes arteriolar lesions. The electron microscopical observations of Montasir, Rabin, and Phillips (1966) in vaccinia pneumonia of mice confirm that necrosis is essentially due to a cytopathic effect, but they also show that the virus can infect the vascular endothelium. It is therefore possible that ischaemia resulting from vascular

lesions may be a contributory factor in the necrosis.

The intravascular fibrin thrombi seen in this case in the lungs, kidneys, pancreas, and spleen suggest disseminated intravascular coagulation, which was never severe enough to produce frank haemorrhagic manifestations. It has been postulated that disseminated intravascular coagulation secondary to endothelial damage by the virus is the cause of the haemorrhagic symptoms which occur in some cases of smallpox, progressive vaccinia, and other viral diseases (McKay, 1965; McKay and Margaretten, 1967). In vaccinia the evidence for this rests mainly on the experimental production of the localized Shwartzman reaction in rabbits with vaccinia virus (Koplik, 1935). A frankly haemorrhagic picture in human progressive vaccinia is rare (Kozłowska and Sztymela, 1962) and ours appears to be the only case in which widespread intravascular thrombi have been seen histologically. However, it remains undecided whether in this case disseminated intravascular coagulation was due to direct endothelial damage by the virus or a result of the anoxia secondary to the terminal state of shock.

It is difficult to evaluate the relative importance of the visceral lesions in causing the death of patients with progressive vaccinia. Bacterial pneumonia and bacterial septicaemia are common terminal complications, but in our case no bacteria were demonstrated in any of the lesions or tissues histologically. It is therefore possible that the vaccinia pneumonia and the intravascular coagulation may have been directly responsible for the otherwise unexplained irreversible shock.

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