Pulmonary calcification in viral pneumonia

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SYNOPSIS The finding of diffuse pulmonary calcification is reported in a 19-month-old female infant who died from an apparent viral pneumonia with systemic involvement due to varicella or herpes simplex infection. The observation is of interest because of the recently described occurrence of lung calcification following chickenpox in adults.

Varicella pneumonia has recently become recognized as a cause of calcification in the lungs (Mackey and Cairney, 1960; Knyvett, 1966; British Medical Journal, 1968). Radiological investigation in the adult has shown that the calcification tends to occur three to five years after the primary pneumonia (Knyvett, 1966).

The child reported in this paper developed striking pulmonary calcification during the active phase of a pneumonia which was part of a disseminated viral infection.

CASE REPORT

A 19-month-old child developed generalized oedema in September 1966. The nephrotic syndrome was diagnosed and she was treated with corticosteroids and on this she became oedema-free and was discharged. After a remission of seven weeks the oedema reappeared and she did not improve with a second course of corticosteroids. At this stage she was transferred to the Birmingham Children's Hospital. Examination showed gross oedema of the face, legs, and feet. An erythematous rash was noted on the chin, around the mouth, buttocks, and thighs. The blood pressure was 145/100 mm Hg. There was no evidence of heart failure and the lung fields were clear.

INITIAL INVESTIGATIONS The levels of serum sodium were 139 m-equiv/l, potassium 3-2 m-equiv/l, chloride 95 m-equiv/l; blood urea 50 mg per 100 ml; urine protein 2-26 g in 24 hours; total serum proteins 3-9 g per 100 ml (albumin 0-8, globulin 3-1). Electrophoresis revealed an increased alpha, globulin and decreased gamma globulin: haemoglobin 7-0 g/100 ml (48%), WBC 24,000 per cmm, ESR 45 mm in one hour. A swab from the rash on the buttock grew a very heavy mixed growth of Proteus, Escherichia coli, a few haemolytic streptococci, a heavy growth of coagulase-positive staphylococci, and a light growth of Candida. She was treated with prednisone, frusemide, spirolactone, penicillin, and later cyclophosphamide. There was no improvement and three days after admission she had a generalized convulsion and became drowsy and confused; a generalized erythematous rash was noted and she gradually lapsed into coma. A few enlarged occipital lymph nodes were found, and as the child had recently been in contact with measles, a form of steroid-suppressed measles encephalitis was suspected. Complement-fixation tests against influenza A, B, C, parainfluenza 1, respiratory syncytial virus, adenovirus, Q fever, Mycoplasma pneumoniae, psittacosis-lymphogranuloma venereum, and measles were negative at 1/10. Complement-fixation tests against Varicella zoster virus or herpes simplex were not performed.

LATER INVESTIGATIONS The blood urea was 77 mg per 100 ml; blood culture sterile; cerebrospinal fluid sterile, sugar 103 mg/100 ml, protein less than 15 mg per 100 ml. An EEG showed a grossly abnormal record with a generalized bilateral distribution consistent with encephalitis. A chest radiograph showed 'extensive scattered opacities in both lungs with a peribronchial distribution consistent with interstitial bronchopneumonia' (Fig. 1). There was no known history of a recent contact with either varicella or herpes simplex while the child was a patient in either hospital. One month before her admission at the first hospital she received a smallpox vaccination followed by a severe febrile reaction for three to four days when she was ill and irritable. The vaccination healed successfully and was not associated with a generalized vaccinia reaction.

She continued to deteriorate, developed peripheral circulatory failure, and died 10 days after admission.

NECROPSY

The necropsy was performed 29 hours after death. The body was that of a well nourished female child (length 84 cm, head circumference 48 cm) showing oedema of the hands and lower limbs. There were extensive semi-confluent, vesicular, ulcerating lesions around the mouth, chin, perineum, and buttocks.

The trachea and main bronchi were congested and...
FIG. 1. Chest radiograph showing scattered opacities in both lung fields.

FIG. 2. Hyaline membranes lining alveoli. Haematoxylin and eosin. × 150.

FIG. 3. Cubical cell metaplasia of alveolar septal cells with multinucleate giant cells. Haematoxylin and eosin. × 150.
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FIG. 4. Calcification of alveolar walls around vessels and bronchi. Von Kossa. × 35.

FIG. 5. Reticular calcification forming denser deposits. Von Kossa. × 150.

FIG. 6. Intraepidermal vesicle of the skin showing balloonising degeneration of the epidermis. Haematoxylin and eosin. × 150.
contained tenacious mucoid secretion. The lungs were overweight (left 120 g, right 141 g), firm, and the bases showed extensive diffuse nodular induration. The thymus (2.5 g) was markedly atrophied.

The liver (479 g) was enlarged and pale. The cut surface showed fatty change and congestion. The spleen (28 g) showed multiple small greyish white lesions 1 to 2 mm in diameter. The adrenals were small and the cortices thin. The kidneys (left 79 g, right 77 g) were symmetrically enlarged and of a pale, greyish-white colour. The capsules stripped easily to reveal smooth, swollen, oedematous surfaces with multiple small petechial haemorrhages but no scarring or granularity. Corticomedullary differentiation was maintained and the cortex was pale in contrast to the darker medulla. The pelves, ureters, and bladder were normal. A recent adherent antemortem thrombus was found in the left renal vein extending from the hilum of the kidney into the inferior vena cava. The right renal vein was normal. The cranial cavity was normal. There was no evidence of venous sinus thrombosis or meningitis. The brain (880 g) was underweight; it showed generalized oedema but no other external feature of note. Examination after fixation showed no unusual features.

Postmortem bacteriological examination of the lung yielded a heavy growth of Pseudomonas pyocyanea, moderate numbers of Klebsiella, and a small number of Proteus mirabilis.

Postmortem virological examination of the ileal contents was negative. No other virological studies were undertaken.

**HISTOLOGY**

The lungs showed areas of bronchopneumonia, pulmonary oedema, and congestion. Many alveoli were filled with amorphous basophilic debris. In some areas there was alveolar emphysema due to destruction of alveolar walls by eosinophilic fibrinoid necrosis. Many alveoli were lined by eosinophilic hyaline membranes (Fig. 2), and contained numerous swollen, lipid-containing macrophages. Cubical cell metaplasia was frequent and multinucleate giant cells were common (Fig. 3). The walls of many peripheral alveoli bordering the interlobular septa were impregnated by dark basophilic deposits of calcium (Fig. 4). In other areas the calcification was more extensive, forming a reticular pattern within the lobules and occasional denser masses of calcification (Fig. 5). Throughout the lung there was marked infiltration with polymorphs and macrophages. A few alveolar cells showed pale intranuclear inclusions.

The skin showed intraepidermal vesicles formed by extensive acantholysis and 'ballooning degeneration' of the epidermal cells (Fig. 6). The balloon cells were swollen and had a homogeneous eosinophilic cytoplasm. Most of the nuclei had disappeared but some pyknotic forms remained. A few cells had eosinophilic intranuclear inclusions. The most superficial region of the epidermis and edge of the vesicle showed 'reticular degeneration'. The upper dermis showed a mild mononuclear inflammatory cell infiltrate.

The liver showed centrilobular fatty change and well demarcated, punctate areas of necrosis up to 2 mm in diameter (Fig. 7). Their central portion consisted of necrotic debris and the periphery was congested. No intranuclear inclusions were detected.

The spleen (Fig. 8) and adrenals (Fig. 9) showed similar small punctate areas of necrosis. A few intranuclear inclusions were identified in the cells of the zona fasciculata.

The kidneys showed no abnormality of the glomeruli apart from one with an intercapillary thrombus and lobular infarction. The tubules contained 'colloid' casts and the proximal tubular epithelium showed hydropic change, and infiltration with lipid.

The remaining organs were unremarkable.

**DISCUSSION**

Radiological evidence of pulmonary calcification following varicella pneumonia was first described by Mackey and Cairney (1960), and the account by Knyvett (1966) has attracted further interest in the condition. Darke and Middleton (1967) described two patients with multiple calcified lesions who had an attack of chickenpox five and 23 years previously, respectively. A recent leading article (British Medical Journal, 1968) further emphasizes the condition and makes the point that some 16 to 33% of adults with chickenpox develop pneumonia with an estimated
mortality rate of 20% (Weinstein and Meade, 1956; Krugman, Goodrich, and Ward, 1957; Mermelstein and Freireich, 1961). The histological features consist of areas of fibrinoid necrosis, mononuclear inflammatory cell infiltration, giant cells, and intranuclear inclusion bodies in the cells of the alveolar septa (Frank, 1950). There are also rare fatal cases of disseminated chickenpox in which focal areas of necrosis containing intranuclear inclusion bodies are found in the adrenals, liver, spleen, and kidney as well as in the lungs (Eisenbud, 1952).

In the paediatric age group chickenpox rarely causes pneumonia but primary varicella pneumonia has been reported as a necropsy finding in infants with varicella neonatorum and congenital chickenpox. Lucchesi, la Bocetta, and Peale (1947) described two infants who developed the condition eight and nine days postnatally. A premature child (2,155 g) showed widely distributed varicella lesions in the lungs, liver, and gastrointestinal tract associated with the usual cutaneous changes. The lesions were characterized by multiple areas of focal necrosis and the presence of intranuclear inclusions.

In the newborn and in young infants, the virus of herpes simplex can cause a fatal viraemia with numerous focal necroses in the visceral organs. This was first recognized as a specific entity by Hass in 1935. Eruption may occur anywhere on the skin but is found most commonly about the face and genitalia. In older infants herpetic stomatitis may give rise to a specific herpetic hepatitis (Zuelzer and Stulberg, 1952). Macroscopically the lesions of herpes simplex may be visible in the adrenal, liver, lung, and brain. Microscopically the lesions in all parts are essentially the same and consist of discrete areas of necrosis with or without surrounding inflammatory cell infiltration. Intranuclear eosinophilic homogeneous inclusions are present in the parenchymal cells in the edge of the lesions.

In our particular case specific viral studies were not performed other than the routine culture of a loop of ileum at necropsy. However, the histological findings were so strikingly similar to the described lesions that we feel there is good presumptive evidence for a systemic viral infection, either herpes simplex or varicella. The oral and genital distribution of the vesicles in this case more closely resembled herpes simplex infection.

The findings of diffuse calcification in the lungs following an apparent viral pneumonia is interesting because hitherto this occurrence has only been reported in varicella infections and then some years after the attack.
To the best of our knowledge this is the first report of histological calcification of the lung associated with a primary viral pneumonia.

The authors wish to thank Dr White for permission to record clinical details of this case.

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The following reports and bulletins are published by the Association of Clinical Biochemists. They may be obtained from The Administrative Office, Association of Clinical Biochemists, 7 Warwick Court, Holborn, London, W.C.1. The prices include postage, but airmail will be charged extra. Overseas readers should remit by British Postal or Money Order. If this is not possible, the equivalent of 10s. is the minimum amount that can be accepted.

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