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Pneumocystis Carinii Pneumonia in Rhodesia

A CASE REPORT*

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For over 20 years a chronic illness affecting premature or debilitated full-term infants has been prevalent on the continent of Europe. Known first as interstitial plasma cell pneumonia, there is now general agreement that the causative agent is a small protozoon, *pneumocystis carinii,* which is found in large numbers embedded in a protein-rich exudate within the pulmonary alveoli at autopsy. Numerous reports, many dealing with large series of cases, have appeared, particularly from Germany, Czechoslovakia and Switzerland, where the condition was at one time so common that whole wards were reserved to deal with such infants. A comprehensive account of the disease as seen in Europe is that of Gajdusek (1957).

In recent years it has become apparent that *Pneumocystis carinii* pneumonia is of world-wide distribution. Most papers emanating from England and North America indicate, however, that the disease as seen in these countries often affects older children or even adults whose resistance is lowered by hypo- or agammaglobulinaemia, cytomegalic inclusion disease, leukaemia and other reticuloses or blood dyscrazias. Survival is unusual (Marshall *et al.,* 1964). It emerges, therefore, that the disease is seen in two forms: firstly, epidemics occur among young infants, particularly in closed communities such as exist in foundling hospitals; secondly, the disease attacks an older age group where resistance to infection is markedly lowered.

We report here a case of *Pneumocystis carinii* pneumonia in a young infant, the second such case to be reported from Southern Africa (Pepler, 1958) and the first from Rhodesia.

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CASE REPORT

This white female infant, the first-born of an unmarried mother aged 17 years, was delivered in a Bulawayo maternity hospital on the 14th May, 1965, at term, weighing 5 lb. 11 oz. There was no history of drug ingestion, attempts at abortion or febrile illnesses during the pregnancy. On the sixth day after delivery, however, the mother was feverish for a few days. Family history was negative.

The infant cried well after delivery and appeared normal, but after a week showed poor sucking and unsatisfactory weight gain. At that time it was noted that the spleen was palpable, but no other abnormalities were apparent. A urine test was normal.

She continued to do poorly after discharge and various changes in feed formula failed to induce a steady gain in weight. There were no fever, cough or respiratory difficulties, however. She was seen first by one of us (M.A.K.) at two and a half months of age.

Examination showed an under-weight, pale infant weighing 6 lb. 15 oz. Mental and neuromuscular development was judged to be normal, but she was pinched and ill-looking. There was some nasal obstruction. No abnormality could be found in the upper respiratory tract. The heart seemed a little enlarged and there was a blowing grade 2/6 systolic murmur over the whole praecordium. The lung fields were normal. The spleen was palpable two inches and the liver edge one inch below the costal margins.

INVESTIGATIONS

Full blood count was as follows: Erythrocytes were 3.42 million per cu.mm., haemoglobin 66 per cent. (9.8 gm./100 ml.), colour index 0.96, leucocytes 6,000/cu.mm., neutrophils 28.0 per cent., lymphocytes 56.0, monocytes 12.0, eosinophils 3.5, Turk cells 0.5. Red blood cells showed moderate anisocytosis and variation in staining reactions. The reticulocyte count was 11 per cent., ESR 22 mm. in one hour. Urine was normal chemically and on microscopy. No cytomegalic inclusion cells were seen. Lumbar picture showed clear colourless fluid containing two lymphocytes and a total protein of 65 mg. per cent. Globu-

lin showed no increase. Glucose was 50 mg. and chlorides 127 m./Eq. per litre. Kahn and toxoplasma complement fixation tests were negative. Serum potassium was 3.7 mEq./litre; sodium 143.0 mEq./litre; chlorides 95.0 mEq./litre. CO_2 combining power 20.0 mEq./litre, blood urea 44 mg./100 ml. Blood cultures were sterile. Prothrombin index was 90 per cent. and red cell fragility normal. Total proteins were 5.5 gm./100 ml., albumin 3.2 gm./100 ml., globulin 2.3 gm./100 ml., electrophoretic pattern normal. Thymol turbidity 1.0 units, zinc sulphate turbidity 0.5 units, bilirubin glucoronide absent, total bilirubin 0.3 mg./100 ml., serum glutamic pyruvic transaminase 90.0 Cabaud units, blood sugar 65 mg. per 100 ml.

Chest X-ray showed no abnormality in the heart or lungs. X-rays of the skull, long bones and an intravenous pyelogram were also normal. An electrocardiograph was interpreted as normal for her age.

TREATMENT AND PROGRESS

She failed to thrive in hospital, appetite and weight gain being unsatisfactory; 75 c.c.s of whole blood were given to correct progressive anaemia, but there was no clinical improvement. There was intermittent fever which failed to respond to a course of penicillin and streptomycin, and this was later changed to an oral tetracycline and oleandomycin combination. While receiving this her condition suddenly worsened. The temperature rose and there was cough and rapid grunting respirations. The treatment was changed to penicillin and kanamycin by injection and chloramphenicol by mouth, together with prednisolone 2.5 mg. six hourly. Her condition remained stationary for five days, when there was marked deterioration and generalised cyanosis. Lung fields showed moist sounds throughout. She was digitalised, but showed no response and died shortly afterwards at the age of three and a half months. Chest X-ray before death showed "just the slightest increase in shadowing in the right lower lobe." The heart was normal in size.

Clinical diagnosis was possible cytomegalic inclusion disease with terminal broncho-pneumonia.

AUTOPSY

Gross Findings

The body was that of a marasmic three months old white female infant showing slight cyanosis of the mucous membranes and nail beds. The trachea and bronchi contained quantities of thick, slightly frothy tenacious sputum. The thymus was present and appeared normal. The lungs were uniformly pink in colour and gave a diffuse rubbery feeling throughout their substance. There was no pleural reaction. The heart was quite normal apart from dilatation of the right ventricle and the ductus arteriosus was closed. The spleen was firm and slightly enlarged, but the liver not definitely so, the lower edge being easily palpable due to depression of the right dome of the diaphragm. There were no other abnormalities.

Microscopic Findings

The pulmonary alveoli were filled with an eosinophilic honeycomb-like granular precipitate which contained a variable number of desquamated alveolar cells. Many alveoli were lined with hyaline membranes (Fig. 1). Staining with toluidine Blue O and the Gomori methenamine silver technique showed many oval *Pneumocystis carinii* organisms (Figs. 2 and 3). These organisms were usually arranged in clusters like bunches of grapes and were not found outside the alveoli. The alveolar walls were thickened and infiltrated with small round cells, plasma cells and macrophages.

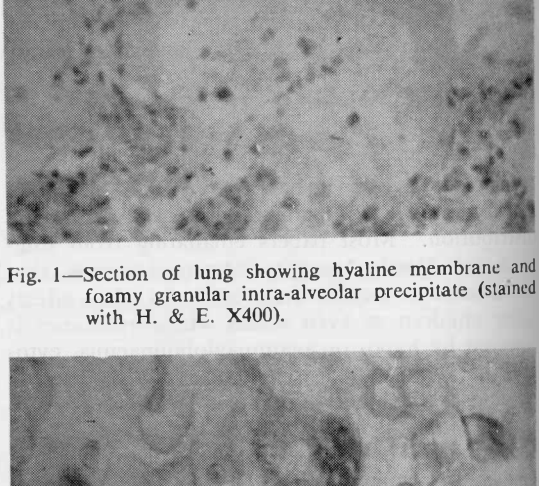

Fig. 1—Section of lung showing hyaline membrane and foamy granular intra-alveolar precipitate (stained with H. & E. X400).

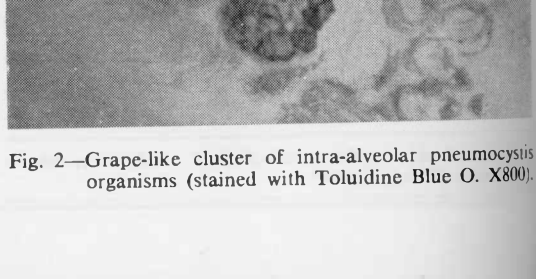

Fig. 2—Grape-like cluster of intra-alveolar pneumocystis organisms (stained with Toluidine Blue O. X800).

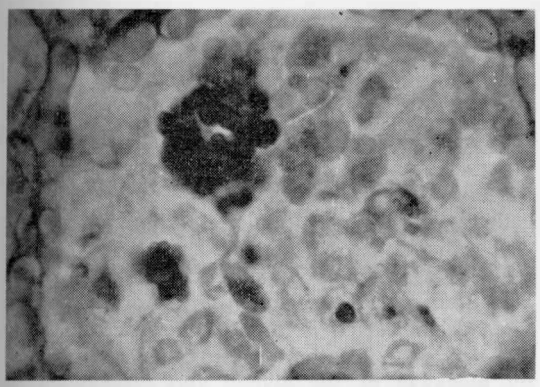

Fig. 3—*Pneumocystis carinii* (stained with Methenamine Silver X800).

Examination of many sections taken from various organs failed to show any evidence of cytomegalic inclusion disease or any other abnormality.

DISCUSSION

Clinical Aspects

In retrospect the symptomatology and clinical course in our case were typical. The disease usually has its onset between the second and the fifth month of life. It is rare in older children and adults, usually complicating an underlying disease such as agammaglobulinaemia or leukaemia. Some 40 per cent. of infants affected have been born prematurely. It is contagious and many epidemics of the disease have been reported. The incubation period is thought to be 20 to 40 days. The onset is insidious, the initial symptoms being feeding difficulties and failure to thrive. To these are added tachypnoea and a dry, unproductive but persistent cough. Cyanosis then becomes evident, and though the infant appears alert, he has an anxious, distressed facies (Gerrard, 1958). There is usually little or no fever unless secondary infection occurs. The alae nasi are active and there are retractions of the chest wall on inspiration, but clinical findings on auscultation are usually remarkably absent, contrasting with the dramatic radiological appearances. Cyanosis is eventually only relieved by high concentrations of oxygen.

The disease may run a rapid course and the infant may die within a few days of the onset; more commonly he suffers for three to four weeks before succumbing. Death is not inevitable, mortality varying in reported series from 10 to 100 per cent.

The white blood count is often elevated, with polymorphonuclear leucocytes preponderating, and eosinophilia has often been present.

In suspected cases, particularly in males, the serum gammaglobulin levels should be estimated in view of the occurrence of this disease as a complication in the immunological deficiency syndromes.

An interesting feature of *Pneumocystis carinii* pneumonia is the presence in some cases of disordered calcium metabolism. Since the early reports in 1950 and 1951, some authors have mentioned the presence of hypercalcaemia, whereas others have reported normal calcium values. The reason for this discrepancy and the nature of the abnormality are not understood.

Radiological Aspects

Chest radiograms typically show a ground-glass cloudiness and areas of emphysema. Bilateral infiltration spreads from the hilum in radial striations with small and confluent patches of increasing density. The radiological features have been reviewed by Falkenbach, Bachman and O'Loughlin. In our case, the normal X-ray initially, followed by one showing only equivocal changes in the right lung, did not suggest *Pneumocystis carinii* pneumonia and we were led to explore other diagnostic avenues. Negative findings, however, have been reported by others, notably Krama *et al.* (1962).

Pathology

Ever since Chagas (1909) first described the presence of this organism in smears of the lungs of guinea pigs infected with *Trypanosoma cruzii*, observers have argued over its nature and classification. It is now generally agreed that *P. carinii* is probably a protozoon of uncertain relationship. The organism is common in animals, but it was not until 33 years after the report by Chagas that Van Der Meer and Brug (1942) described three cases in man. Since then, cases have been reported from central Europe, the United States, Canada, Australia, Chile, South Africa and Melanesia.

Vanek and Jirovec (1952), describing the appearance of the organisms in human lung tissue, state that the parasites "are small, unicellular, roundish or longish bodies, reproducing by biniary fission and finishing by forming eight germinal sporozaries about five to seven microns in size." Westphal (1953) considered the octonucleate cysts to be the most important diagnostic criterion.

The organisms are readily stained by the periodic acid-Schiff method and the Gomori methenamine silver technique. More recently a method described by Chalvardjian and Grawe

using toluidine Blue O show the organisms as distinctive violet or purple bodies against a light to dark green background. This method is said to be of value in detecting *P. carinii* in the sputum in suspected cases during life.

The pathological changes in *P. carinii* have been well described (Hamperl, 1957; Bird and Thomson, 1957). The predominant changes are thickening of the alveolar walls which are infiltrated with round cells, macrophages and plasma cells, and the alveoli themselves are filled with a foamy, granular, eosinophilic precipitate in which masses of pneumocystis are found.

The diagnosis has been made during life by examination of nasopharyngeal aspirates (Le Tan-Vinh *et al.*, 1963). The organisms have also been found in lung biopsy specimens and at autopsy they are most easily demonstrated by taking smears of the fresh-cut lung. A complement fixation test is widely used for diagnosis in Europe (Navratil *et al.*, 1954; Vivell, 1955).

Differential Diagnosis

This will include congenital heart disease, cystic fibrosis of the pancreas, a large range of infective causes and such less well-known entities as lipid and talc pneumonitis, pulmonary haemosiderosis and histiocytosis X. The Hamman-Rich syndrome of idiopathic progressive pulmonary fibrosis is not seen in infancy, although a rare but similar condition affecting infants with a hereditary transmission has been described by Donohue *et al.* (1959).

A further form of chronic respiratory disease in premature infants was described by Wilson and Mikity (1960). Respiratory symptoms commenced insidiously in infants of one to five weeks of age. There was gradually worsening cyanosis and dyspnoea with an over-expanded chest, wheezing and coughing. Cor pulmonale tended to develop. General growth and development were not necessarily interfered with, but only two infants out of five survived. Chest X-ray showed bilateral diffuse pulmonary infiltration of a coarsely nodular or reticularly streaked pattern. A striking degree of involvement was always found on the initial X-ray. Clinically the disease resembles *Pneumocystis carinii* pneumonia, but histological examination of the lungs unequivocally differentiates the two. A further outbreak of this disease involving eight premature infants was described by Butterfield *et al.* (1963). In one case only *post-mortem* cultures of lung, brain and other organs revealed Echo Virus Type 19. High concentrations of oxygen administered to these infants in the first weeks of life have been incriminated as a cause of the syndrome (Feingold, 1965).

Treatment and Course

No treatment is of proven benefit. There is no response whatsoever to antibiotics and many other agents have been used without success. Recently the administration of Pentamidine, together with gammaglobulin, is thought to have cured the disease in a male child of two years with hypogammaglobulinaemia (Marshall, Weston and Bodian, 1964). The overall mortality of the disease has varied in reported series from 10 to 100 per cent. Death is due to asphyxia produced by blockage of the alveoli and bronchioles by proliferating masses of parasites. The occurrence of outbreaks amongst young infants has recently been markedly reduced in Europe by the use of artificial ultra-violet light in nurseries.

SUMMARY

A case of *Pneumocystis carinii* pneumonia in a white female infant is reported. No predisposing cause for this infection could be found.

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