Pediatric Rev. Commun., 1990, Vol. 4, pp. 213–222
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Printed in the United Kingdom

PULMONARY ALVEOLAR PROTEINOSIS IN TWO SIBLINGS

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(*Received October 31, 1989*)

Occurrence of Pulmonary Alveolar Proteinosis (PAP) is reported in two siblings. The patients were both females diagnosed at 13 months and 1 month. Gastrointestinal symptoms with vomiting and failure to thrive started in the first weeks of life. Impaired cell-mediated immunity was well documented in both girls. The older sister is at present 12 years old; her clinical evolution is stationary. The youngest died at six months of age due to rapidly progressive respiratory involvement.

Six kindreds with familial occurrence of PAP involving a total of 15 cases including ours, are reviewed. The mortality rate was 73 per cent. We tabulate sex, race, consanguinity, onset of initial symptoms, age of the diagnosis, clinical course, proven immunity disturbances, microbiological findings and health status in all cases. We discuss the clinical features of PAP and therapeutic approaches.

KEY WORDS: Pulmonary alveolar proteinosis, immunodeficiency

INTRODUCTION

In 1958 Rosen[1] described pulmonary alveolar proteinosis (PAP) as a diffuse pulmonary disease with a pathogenic mechanism based on storage of a phospholipidic PAS-positive material inside the alveoli but without interstitial involvement. Since then, isolated cases have been published mainly in adults. In 1971 Colon[2] summarized 23 pediatric cases reported until then and McCook[3] in 1981 reported 40, most with fatal outcome.

Several cases of familial occurrence have been described in the pediatric age group[4] suggesting that a genetic background may be present in PAP with an autosomal recessive pattern of inheritance.

CASE REPORTS

We report two sisters, born of a healthy couple, without history of consanguinity, exposure to external agents or other pathological conditions. First degree relatives, including two brothers and one sister, are free of symptoms. The other six familial cases previously reported in the literature are reviewed (Table 1).

Case 1

The patient, a female, developed feeding difficulties during the first month of life with very little weight gain. There was a history of intermittent diarrhea and repeated respiratory tract infections began at 2 months. Hospital admission occurred at 13

Table 1 Main findings in published pediatric PAP

Reference	*Sex*	*Race*	*Consanguinity*	*Onset of symptoms*	*Age of diagnosis*	*Clinical course*	*Immunity*	*Lung cultures*	*Healthy siblings*	*Siblings with possible PAP*
Teja[27]	♀			NR	6 m.	D. 7 m.				
	♂	Black	Yes	<16 m.	16 y.	D. 19 y.	NR	NR	2	1 (D. 9 m.)
	♂			4 m.	6 m.	D. 9 m.				
Seard[23]	♂			10 m.	18 m.	A. 4 y.	↓ IgG–IgA (transitory)			
Selecky[24]	♂	White	No	3 m.	8 m.	A. $2\frac{1}{2}$ y.	normal	NR	No	NR
	♀			4 d.		D 15 m.				
Wilkinson[29]	♂	White	No	1 m.	$4\frac{1}{2}$ m.	D. $4\frac{1}{2}$ m.	NR	*S. Aureus*	NR	1 (D. 16 m.)
Webster[28]	♂	White	NR	20 y.	21 y.	S. 30 y.	↓ IgA S–IgA (transitory)		NR	NR
	♀			14 y.	14 y.	D. 15 y.	↓ IgA, S–IgA	Nocardia		
Haworth[10]	♂	White	No	2 m.	$4\frac{1}{2}$ m.	D. $4\frac{1}{2}$ m.	Thymic alymphoplasia	CMV	2	No
	♂			$5\frac{1}{2}$ m.	$6\frac{1}{2}$ m.	D. $6\frac{1}{2}$ m.	Thymic alymphoplasia			
	♀	White	Yes	NR	3 m.	D. 3 m.	Thymic alymphoplasia	NR	NR	NR
	♂				5 m.	D. 5 m.	Thymic alymphoplasia			
Propositus	♀	White	No	1 m.	13 m.	S. 13 y.	↓ S–IgA; ↓ FHA			
	♀			10 d.	1 m.	D. 6 m.	↓ T_4	*S. epidermidis*	3	No

NR: not recorded; A: alive with O_2; D: death; S: stable.

months because of this clinical course. On examination the patient appeared malnourished, with a height of 68 cm and a weight of 6.24 kg. Tachypnea and tachycardia were present but the lungs were clear and the heart sounds normal. The extremities were extremely thin, with long fingers and digital clubbing. Slight acrocyanosis was noted.

Laboratory findings
The white-cell count was 20×10^9/l with 66% neutrophils, 3% band forms, 26% lymphocytes and 5% monocytes. Chest X-ray revealed a diffuse pulmonary infiltrate of nodular or reticulonodular densities more evident in middle lung fields, and with air bronchograms in areas with greatest involvement. Tuberculin skin test was negative. The sweat test reported 30 mEq/l chloride and protein levels of 64 mg/dl. Examination and cultures of stool specimens were negative. A gastrointestinal X-ray survey disclosed slight malabsorption signs. Biopsy specimens revealed chronic, non-specific jejunitis. An open lung biopsy lead to the diagnosis of PAP and excluded viral, bacterial or parasitic infection. The immunological study suggested an impaired response of cell-mediated immunity, with persistent leucocytosis, hypergammaglobulinemia and a secretory IgA deficiency. The results of the immunological screening are summarized in Table 2.

Clinical course
She is at present 12 years old and remains with anorexia, vomiting and persistent cough. Failure to thrive (height 120 cm, weight 19 kg), chronic hypoxia (PaO_2 72 mm Hg at room air) and roentgenographic findings with acquired fibrotic changes remain (Figure 1).

Case 2

A one-month-old girl, sister of the previous case, was admitted to the hospital because failure to thrive and vomiting beginning in the first week of life. Delivery was at term, with a birth weight of 3.25 kg. On examination the infant appeared irritable, ill and very dystrophic. The weight was 3.05 kg and height 52 cm. There was tachypnea and tachycardia without respiratory distress. She had acrocyanosis and mild peripheral edema.

Laboratory findings
The chest X-ray disclosed a bilateral diffuse infiltration of both lungs with small nodules most marked in the center of the lung fields, consistent with alveolar space involvement (Figure 2). Tuberculin test was negative. The sweat test reported 50 mEq/l of chloride and total protein 49 mg/dl. The white-cell count was 22×10^9/l with 35% neutrophils, 3% band forms, 5% eosinophiles, 4% lymphocytes, 6% monocytes and 2% metamyelocytes. In a sample of capillary blood (breathing room air), the PaO_2 was 38 mm Hg and the $PaCO_2$ was 45 mm Hg with a normal pH. Stool specimens were negative for bacteria and parasites. The barium swallow disclosed grade 2 gastroesophageal reflux. A peroral intestinal biopsy showed partial villous atrophy. A pulmonary biopsy demonstrated features compatible with the diagnosis of PAP (Figures 3 and 4) and eliminated viral, bacterial or parasitical infections. An immunological study disclosed impaired cell-mediated immunity with

Table 2 Immunologic and microbiological findings (n.p.: not performed)

	Case 1 (14 months)	*Case 2 (5 months)*
White cell count $\times 10^9$/l	11–30	20–45
Chemotaxis (Boyden) (nv: 75 l/field)	homologue sera: 70 pooled sera: 85	n.p.
Phagocytosis	20%	n.p.
Rebuck's window	normal	n.p.
Complement		
(C3 nv: 80–140 mg/dl)	60	n.p.
(C4 nv: 20–50 mg/dl)	34	
Bone marrow smear	Increased plasma cellularity (0.2%)	Granulopoietic hyperplasia
Immunoglobulins (mg/dl)	IgG = 2360 IgM = 270 IgA = 341 IgAs = <1 IgE = 10	IgG = 1500 IgM = 392 IgA = 241 IgAs = 11.5 IgE = 10
Typhoid antibodies	no response	n.p.
Antibodies		
nuclear	n.p.	negative
DNA	n.p.	negative
mythocondrial	n.p.	negative
smooth muscle	n.p.	positive 1/100
Lymphocytes (nv by IF:		
T = 65–70%	If.: T = 70	T = 55
B = 10–15%	B = 30	B = 16
T4 = 45–60%	Stimul.: T = 62	T4 = 30
T8 = 20–25	B = 15	T8 = 31
PHA response (nv: 12%)	4%	60%
Delayed hypersensitivity skin tests	negative	positive only to Candida antigens
Lung culture	negative	Staph aureus
Blood culture	negative	positive to: Strept pneumoniae Staph epidermidis

(nv: normal value).

persistent leucocytosis and hypergammaglobulinemia. The immunologic findings are shown in Table 2.

Clinical course

The patient had a stationary clinical course until 6 months. Attempts to improve the nutritional status were unsuccessful. There was a progressive impairment in the roentgenographic features (Figure 5). The hypoxia worsened and supplementary oxygen was required. The patient died at six-and-a-half months of life because of sepsis. Necropsy was not authorized.

Pathological findings

The histopathology of the lung was similar in both sisters. Parenchymal architecture

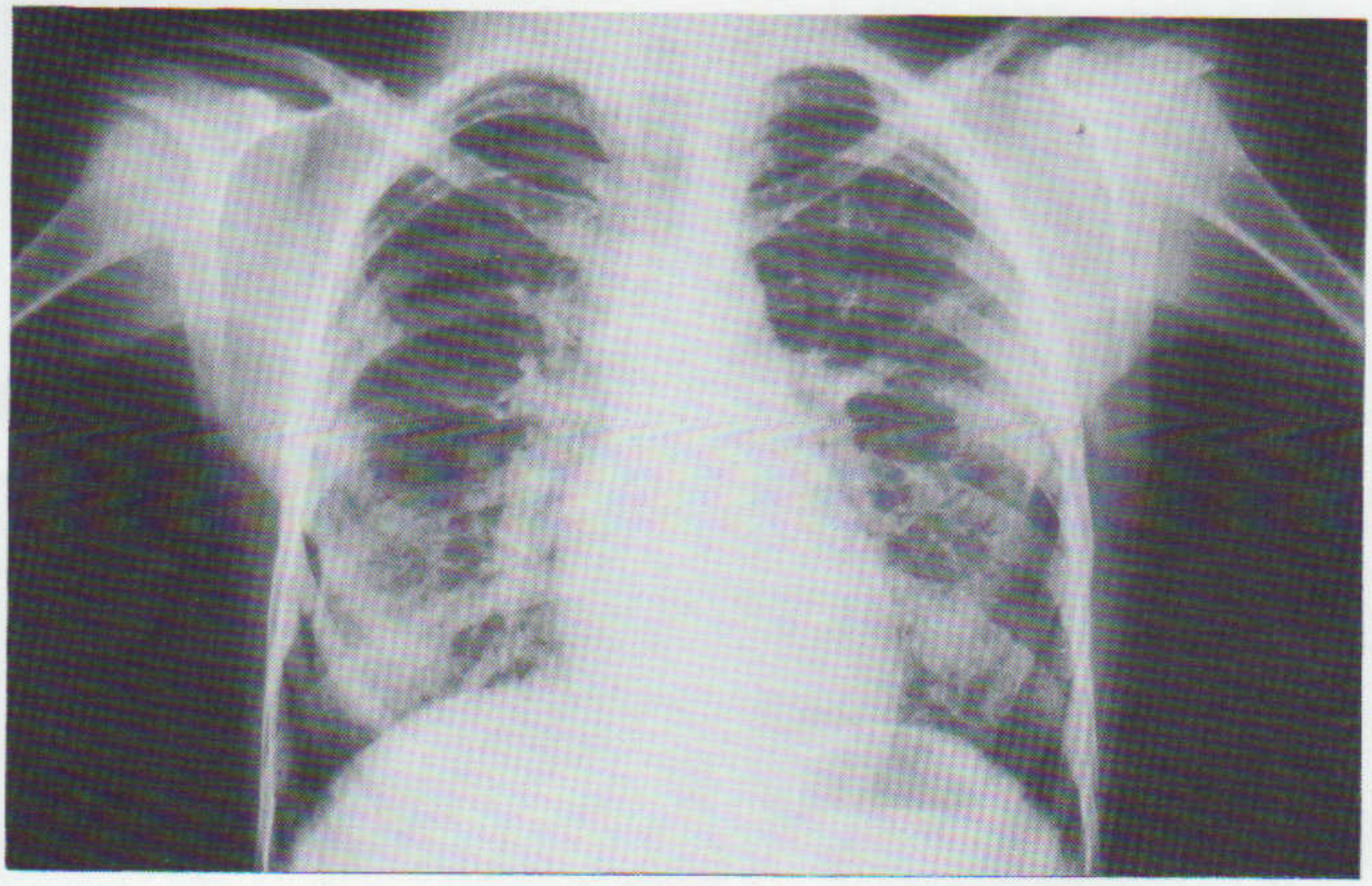

Figure 1 Chest X-ray of Case 1.

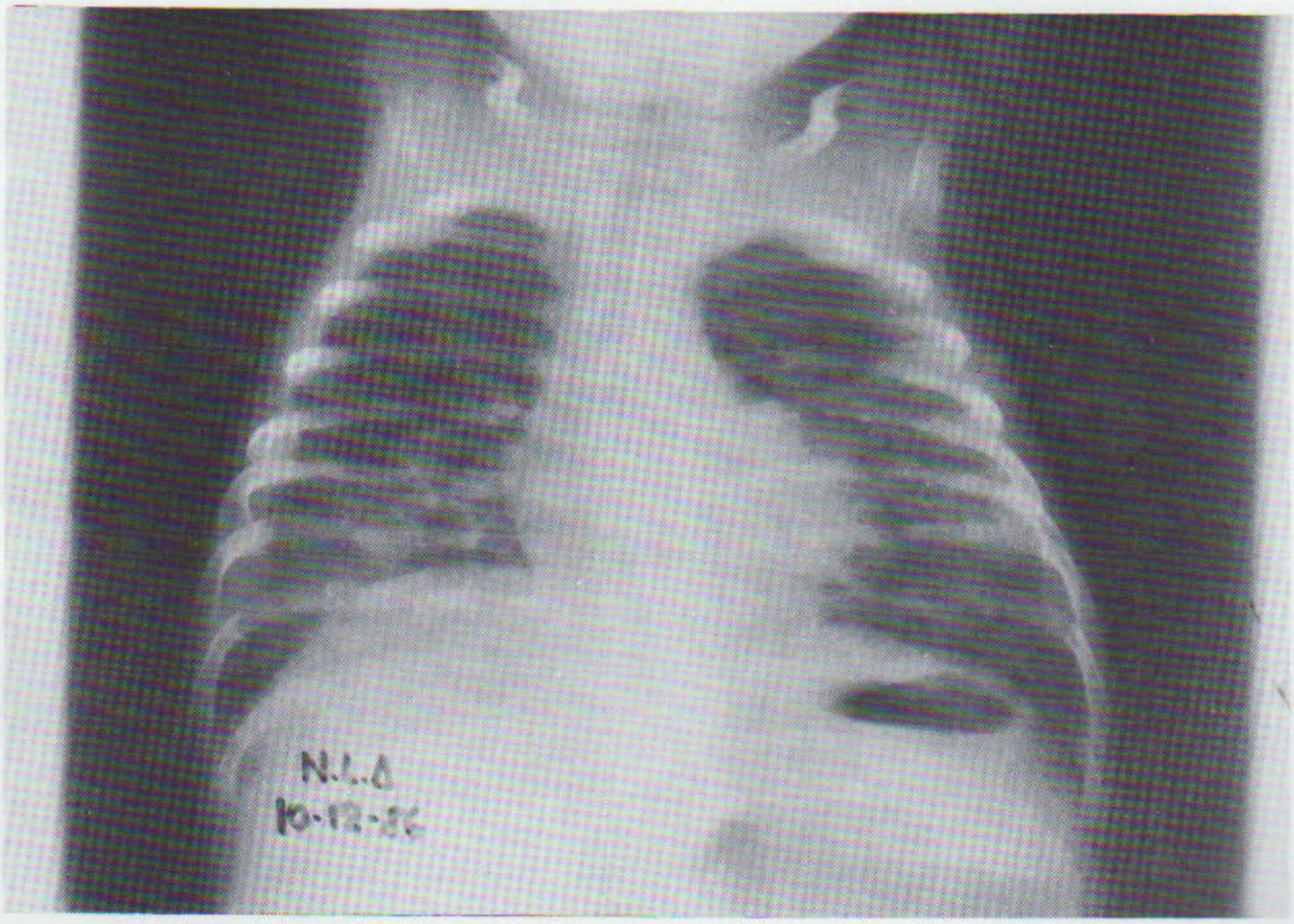

Figure 2 Chest X-ray of Case 2 on admission.

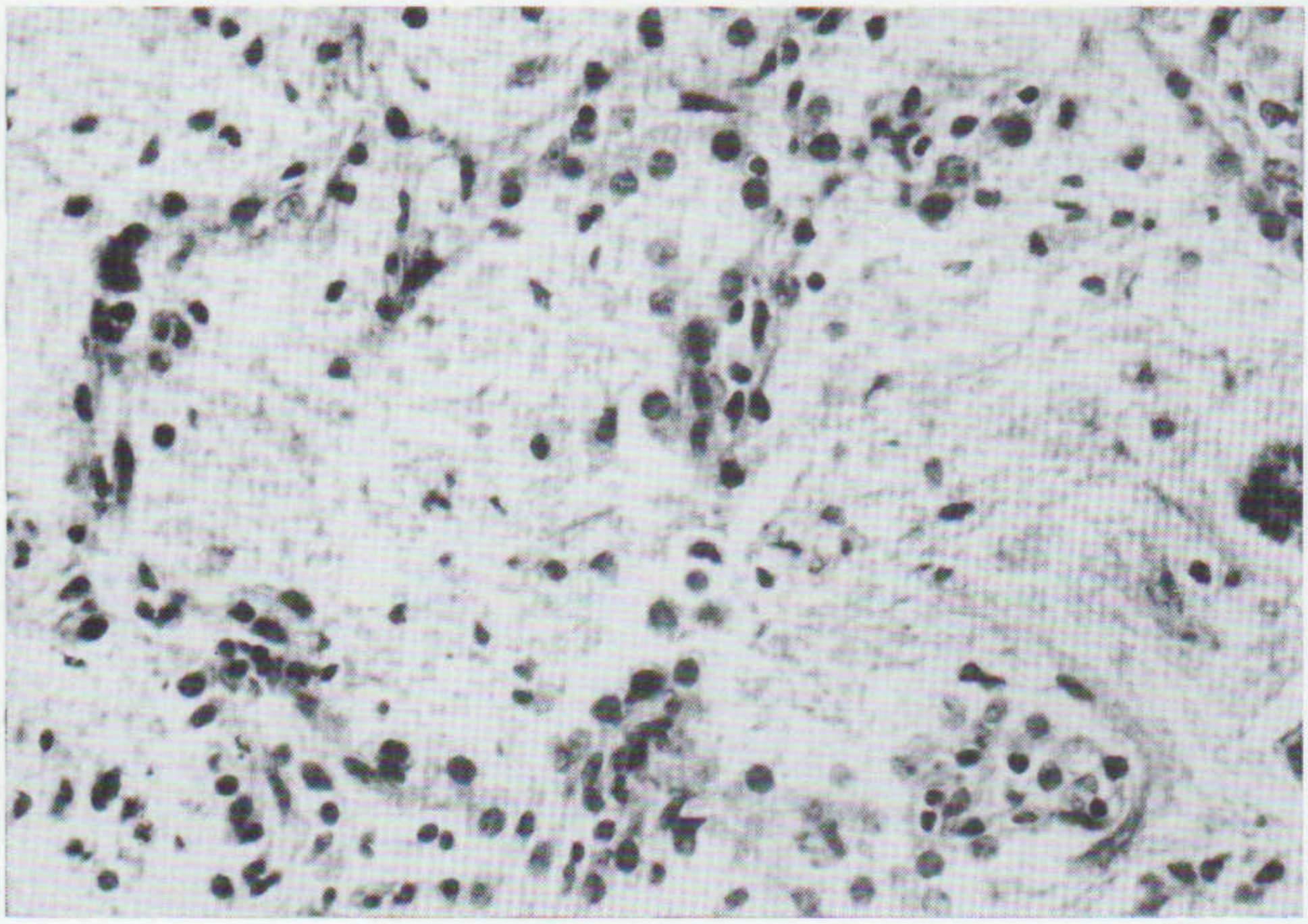

Figure 3 Two alveolar spaces are filled by a granular material, with cellular remnants and aciculary spaces. Septa are normal. (HE 400×)

of the lung was preserved. The alveolar space and the bronchioli were filled partly by a granular, PAS-positive eosinophilic material that included cellular remnants of mainly macrophages. Occasionally clefts were seen, corresponding to small cholesterol crystals which have been dissolved in alcohol (Figure 3). Slices specially stained to detect fungi or other pathogens were negative. The interstitial space and vascular structures were morphologically normal. In Case 2, an electron microscopic examination was performed and revealed the composition of the alveolar material which contained cell remnants mainly of type II pneumocytes with lamellar bodies partially destroyed (Figure 4). This appearance is distinctive of PAP.

DISCUSSION

Several hypotheses have been proposed about the pathogenesis of PAP and all of them consider an intrinsic alveolar mechanism. Possible related factors are overgrowth and desquamation of type II pneumocytes, disturbances in surfactant turnover or dysfunction of alveolar macrophages.[5] *In vitro* studies with macrophages from patients with PAP disclosed impaired phagocytosis and decreased intracellular killer activity, specially against Candida and Staphylococcus. Inactivation of lysosomal enzymes could be a possible explanation for the storage of lipoprotein remainders. This condition would be independent of previous immunological deficiencies, immuno-

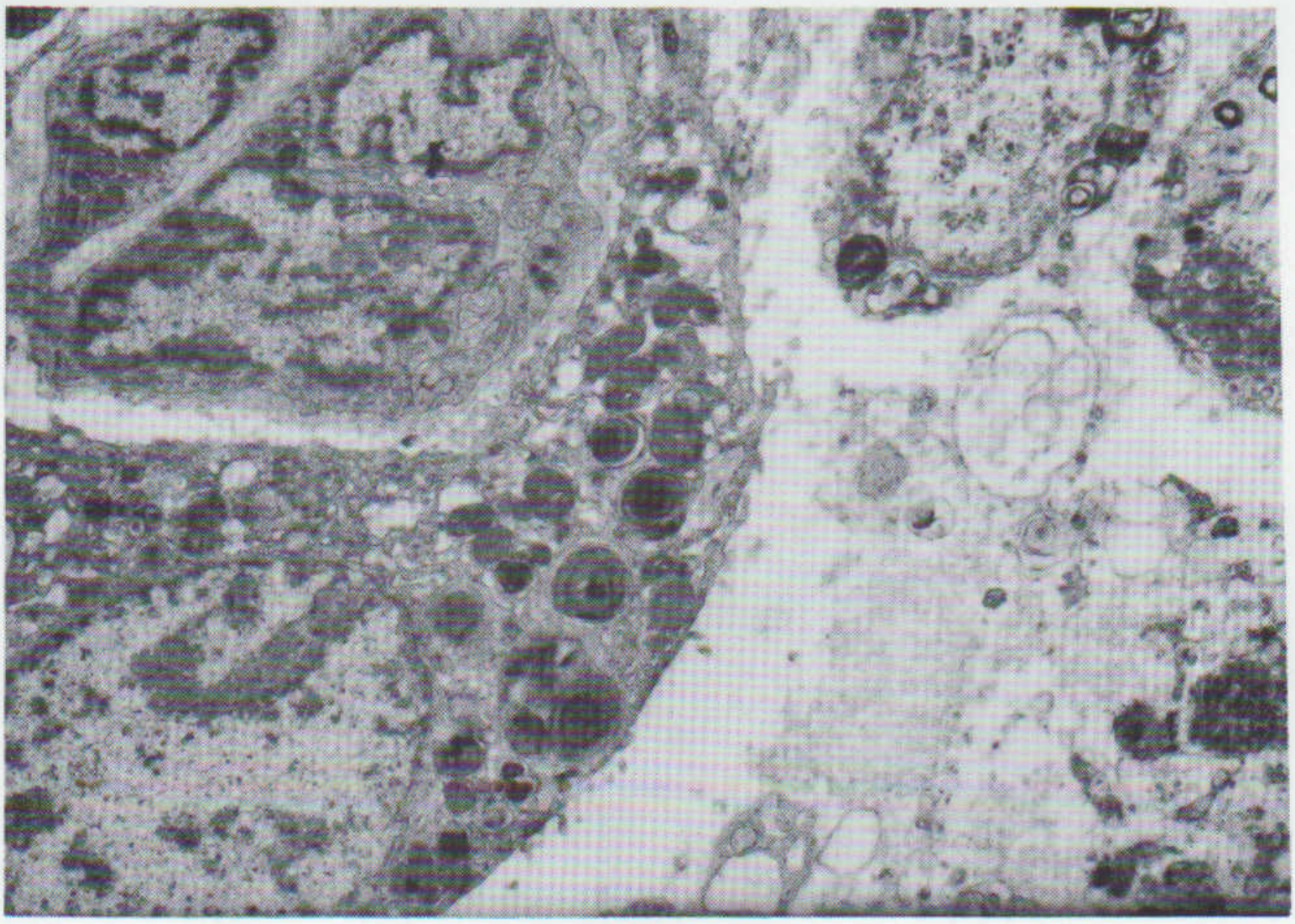

Figure 4 Ultrastructural appearance of the alveolar material. Membranous, lamellar bodies and fragments of cytoplasm from type II pneumocytes fill the alveoli.

suppression or chronic alveolar aggression. There are some reports on the inhibition of phagocytes in normal mouse by these remnants.[6]

It is important to recognise the differences between child and adult PAP. Adult or secondary PAP is found in patients with general acquired immunodeficiency, leukemia, lymphomas,[7] Hodgkin disease,[8] histiocytic disorders, immunosuppressive therapies, AIDS[9] or in patients with local acquired immunodeficiency by alveolar involvement (silicosis). Pediatric or primary PAP coexists with congenital immunodeficiencies (thymic alymphoplasia,[10] IgA deficiency[11] and non-specific cell-mediated deficits[12]).

The clinical features show overt differences between adults and children. Although PAP may be the cause of neonatal distress, usually it begins as a gastrointestinal disorder with vomiting, diarrhea and striking failure to thrive. Later, tachypnea, tachycardia and acrocyanosis become apparent. Clinical features in adults are those of a chronic lung disease from the onset.

Lung biopsy is the definitive diagnostic procedure for PAP. Open lung biopsy offers the most accurate results but closed techniques such as "needle" biopsy or cytologic examination of bronchial lavage-aspirate are also employed. Bronchial aspirate is reported to show an increased amount of immunoglobulins and C-reactive protein.[13]

In children, radiological features of PAP are more obvious than clinical findings. X-ray changes are initially similar to diffuse interstitial involvement;[3,14] later alveolar opacities become evident usually with small areas of confluence and consolidation

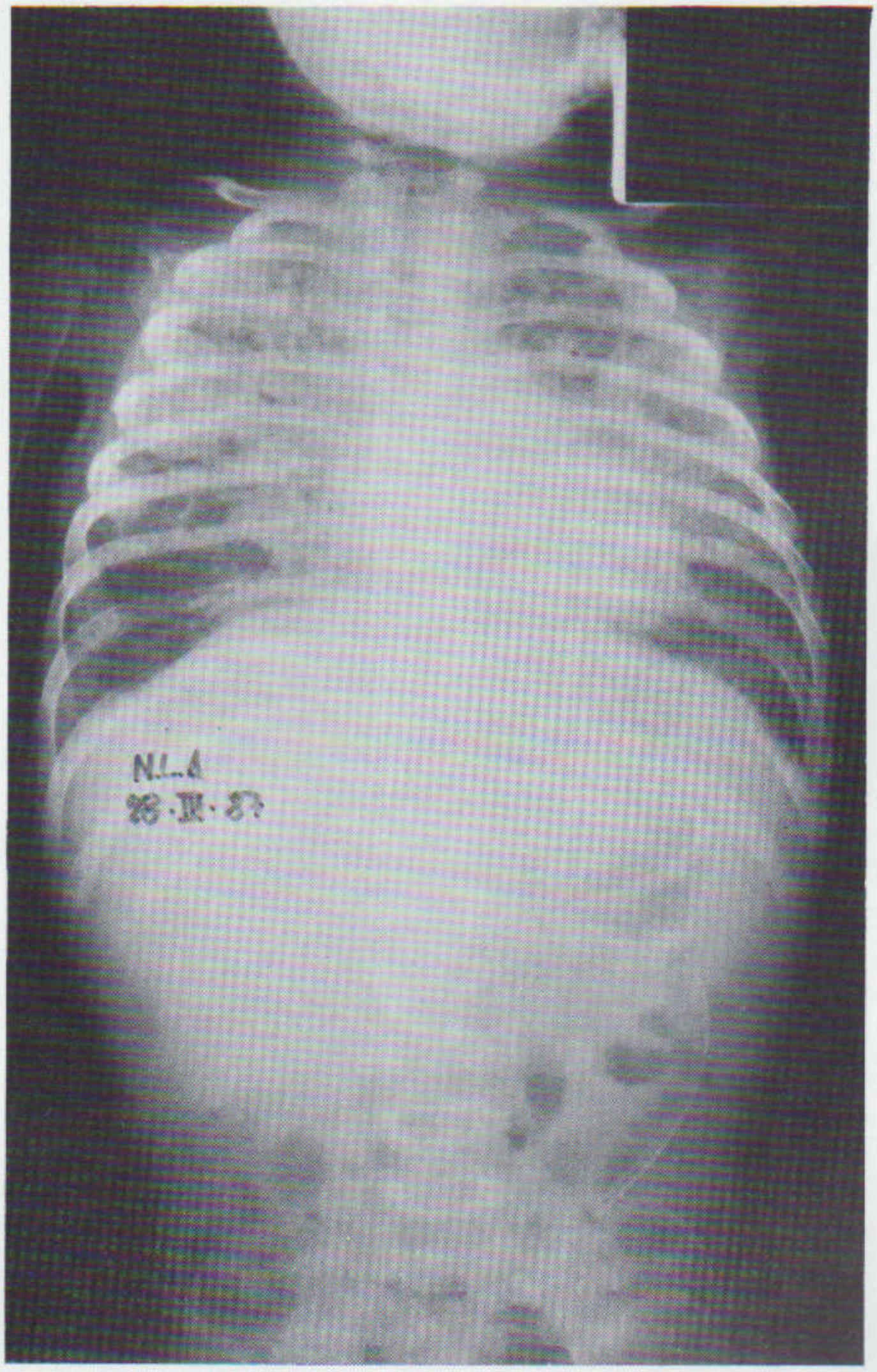

Figure 5 Chest X-ray of Case 2 aged 6 months.

mimicking a pseudomilliary pattern. Diffuse reticular densities, fibrosis and sometimes patchy atelectasis are seen in chronic patients.

The differential diagnosis of newborn and infants with PAP includes disorders that produce chronic respiratory distress[15] or similar roentgenographic changes, like bronchopulmonary dysplasia, cystic fibrosis, histiocytosis, pulmonary lymphangiectasia and hemosiderosis. Extrapulmonary disorders such as congenital heart disease or central hypoventilation need to be considered. The diagnosis of PAP in older children and especially in adults is difficult and finally depends on pathological examination. Frequently, other disorders are considered before PAP is diagnosed, such as pulmonary tuberculosis, idiopathic lung fibrosis, cor pulmonale, Good-

pasture's syndrome, lymphomas, chronic occupational lung diseases and sarcoidosis.

Pathological features of PAP must be differentiated from alveolar edema and the early stages of acute bacterial pneumonia. Ultrastructural examination reveals the relationship between surfactant and the stored material in the alveoli which corresponds to type II pneumocyte fragments, remnants of lamellar bodies and lipidic or cholesterol inclusions.[16] Infections must be ruled out in both children and adults. The association of PAP with hematological malignancies is well known in adults and has to be considered in children.

Lung infections are frequent and generally produced by opportunistic pathogens. Fifteen per cent of positive lung cultures have been reported.[8] Etiology in secondary adult PAP is most frequently due to Nocardia,[17,11] Cryptococcus,[18] Aspergillus and M. tuberculosis. In primary PAP, Staphylococcus,[19] Cytomegalovirus,[10] Pneumocystis carinii and herpes virus infections[19] are more frequent.

The best therapy in PAP is selective bronchial lavage, well tested in adults,[20] but poor results have been reported in children and in infants because of technical problems.[21] Some attempts to remove alveolar detritus have used a Swan–Ganz catheter to occlude a bronchus and lavage the other,[22] or by extracorporeal membrane oxygenation and total bronchial lavage.[23,24] Clinical course of these children was unfavourable mainly for the common associated immunological deficiencies. Most children diagnosed as PAP survive without requiring bronchial lavage but these patients were immunologically normal and the diagnosis of PAP was late. This may mean a less extensive disease or secondary PAP with an early beginning.

Three groups of patients may be differentiated according to evolution. Some children deteriorate in spite of bronchial lavage with development of pulmonary fibrosis and cor pulmonale (generally in adult age). Others die in the first years of life, corresponding to primary PAP. The third group of patients show a stabilization and, in some cases, a disappearance of symptoms. Kariman[25] reported 24 per cent of remissions without treatment in a group of adult patients although roentgenographic features remain. These patients remain moderate hypoxic. For that reason, he does not advise bronchial lavage to PAP patients whose arterial PaO_2 is greater or equal to 70 mm Hg or P(A-G) O_2 lower than 40. If marked hypoxia and progressive deterioration in ventilatory function occurs, bronchial lavage[26] may be reconsidered.

Our two patients reinforce the hypothesis of recessive autosomic inheritance with a variable penetrance which is expressed as different patterns of the clinical course in both cases. Case 1, after an onset with frequent digestive and respiratory involvement, is now stabilized with chronic hypoxia and growth delay. In Case 2, the main problem was malnutrition which was resistant to all feeding techniques. The second case is more typical of the pediatric clinical picture, while the first had an adult appearance with early beginning.

Many questions are still open about PAP and need to be solved[27] since the true pathogenic mechanism,[28] systemic implications, genetic background and treatment are unknown.

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