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Pulmonary Alveolar Proteinosis and Histoplasmosis

Report of Three Cases *

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Summary. Pulmonary alveolar proteinosis (PAP), in addition to acute generalized histoplasmosis, was found at autopsy of three adult males, 23, 51, and 52 years of age. All three patients became ill in the same region of Venezuela, south of Lake Maracaibo, an area considered highly endemic for histoplasmosis. The PAP may be due to an environmental factor.

Although the etiopathogenesis of pulmonary alveolar proteinosis (PAP) is not known, more than 15% (Sunderland *et al.*, 1972) of the 200 cases published since the initial report of 1958 (Rosen *et al.*, 1958) have shown an associated fungal, bacterial, or protozoan infection.

Association of acute disseminated histoplasmosis with PAP has not previously been reported. Furthermore, only one case of PAP is known in Venezuela (Angulo and Rodriguez, 1962).

Case Reports

Significant clinical and post mortem data are summarized in Table 1. Case 1 has twice been previously reported (Salfelder, 1960; Salfelder *et al.*, 1970). At that time, diagnosis of PAP was not made and the diffuse alveolar content was interpreted as diffuse edema. Case 1 and 2, involved Italian and Columbian inmigrants, and were observed during different months of the years between 1956 and 1974, respectively.

The second case, that observed in 1973, was a Venezuelan patient who had lived in the Andes, near the capital of the State of Mérida. He had worked for three days in a swampy area, cleaning fields for seeding, prior to becoming ill during the fourth work day.

All three patients had become ill in different States, but in the same region. The location south of Lake Maracaibo, along the Panamerican Highway, was a lowland region, less than 200 meters above sea level. The area can be reached by automobile from Mérida in 2 to 3 hours. It is characterized by a hot and humid tropical climate and has a rich evergreen vegetation with many swamps. There are little or no seasonal (weather) changes and rains are frequent throughout the year.

Two patients were older than 45 years; the third was a young agricultural worker. The initial symptoms, those of an acute respiratory disease with fever, dyspnea, cough, and severe malaise, were similar in all cases. On chest x-ray in Case 1, a diffuse shadowing was noted. In Cases 2 and 3, a constantly progressing bilateral confluent and micronodular infiltration was present (Fig. 1). The duration of the disease varied between three and seven weeks and hospitalization between 9 and 18 days. Skin reaction to histoplasmin was not done in Case 1 and was negative in the other two cases. A scalene lymph node biopsy revealed acute histoplasmosis in Cases 2 and 3, but since this was carried out only a few days prior to the patients demise, no specific treatment could be given.

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Table 1. Clinical and

Case	Month and Year of Autopsy	Age	Nationality	Sex	Occupation	Place of infection	Duration (Disease days)
1	November, 1956	52	Italian	M	Mason	Santa Barbara, Zulia	22
2	October, 1973	51	Venezuelan	M	Agricultural worker	El Vigia Merida	42
3	April, 1974	23	Columbian	M	Agricultural worker	La Tendida, Tachira	51

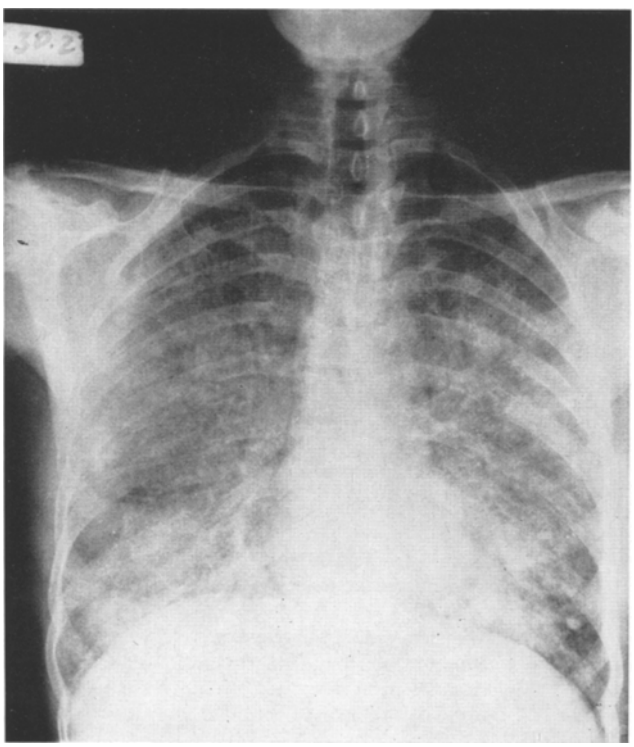

Fig. 1. Case 2. Five days before death. Diffuse dense bilateral shadows. Faintly visible small infiltrates

In all three cases, the lungs were heavy, weighing 2000 grams or more. From the cut surfaces of the lungs in Cases 1 and 2, a milky, viscous, and greyish liquid was easily obtained by pressure. These firm cut surfaces appeared uniformly consolidated with faintly recognizable small foci. In case 3, multiple greyish miliary granules were present on the firm cut surfaces

post mortem data

Hospital days	Histo-plasmin	Lymph node biopsy	Lungs		Organs involved by Disseminated Histoplasmosis
			Weight (grams)	Cut surface	
10			2500	Milky, viscous liquid	Lungs, mediastinal lymph nodes, trachea, liver, spleen, kidneys, adrenals, bone marrow, myocardium
18	negative	+	3300	Milky, viscous fluid	Lungs, mediastinal lymph nodes, liver, spleen, adrenals
9	negative	+	1950	Diffuse consolidated miliary foci	Lungs, mediastinal lymph nodes, liver, spleen, adrenals, kidneys, pancreas

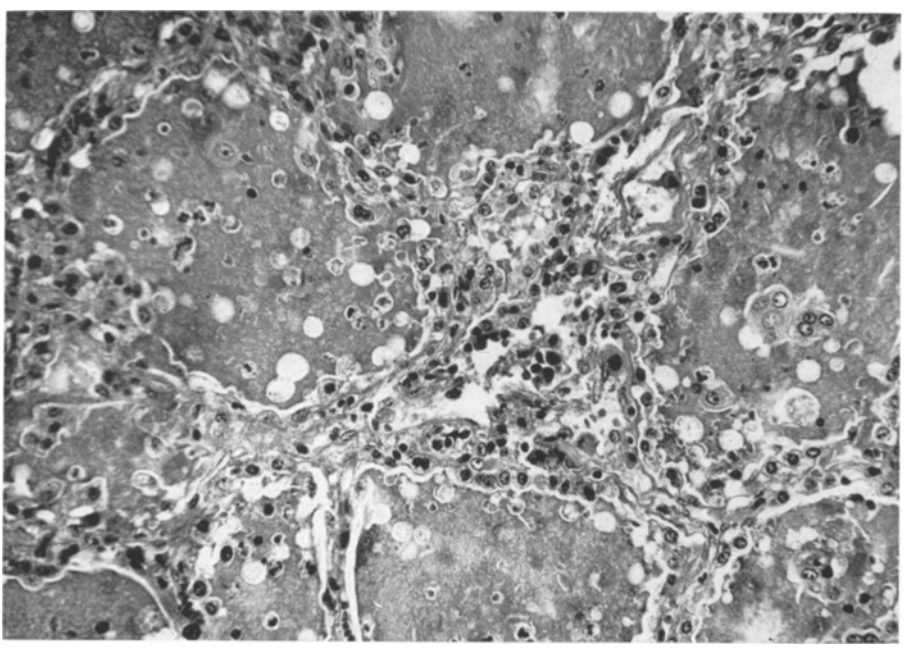

Fig. 2. Case 2. Alveoli and bronchi diffusely filled with PAS positive substance and alveolar cells. Interstitial cell infiltrates. (H&E×190)

of both lungs. Enlarged mediastinal lymph nodes, hepatomegaly, and splenomegaly were observed in all three cases.

Histologic examination of the lungs from Cases 1 and 2 demonstrated the same pattern. The alveoli were diffusely filled with a partly homogeneous, partly granular, PAS-positive, eosinophilic substance and different amounts of Sudan-positive granules. Few alveolar cells were found. Some of the alveolar walls were thinned andi n other parts were thickened, with mononuclear cell infiltrates (Fig. 2).

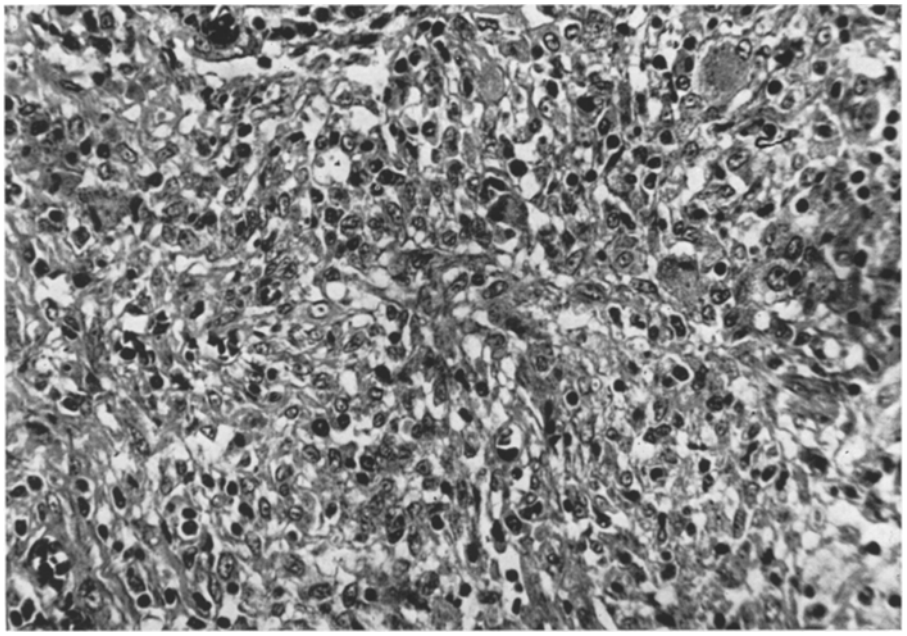

Fig. 3. Case 3. Pulmonary nodule. Alveoli and interstitial spaces filled with mononuclear cells, histiocytes, and some epithelioid cells. No clear granuloma formation; no organisms visible. (H&E ×300)

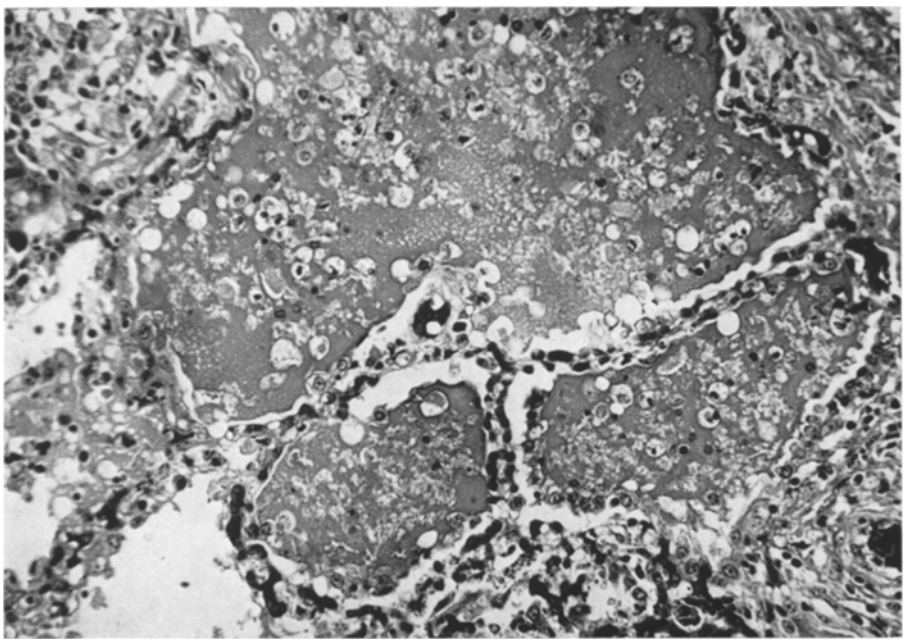

Fig. 4. Case 3. Lung tissue outside of the nodule of Fig. 5. Area with alveoli filled with the same content as in Case 2. Compare with Fig. 2. (H&E ×190)

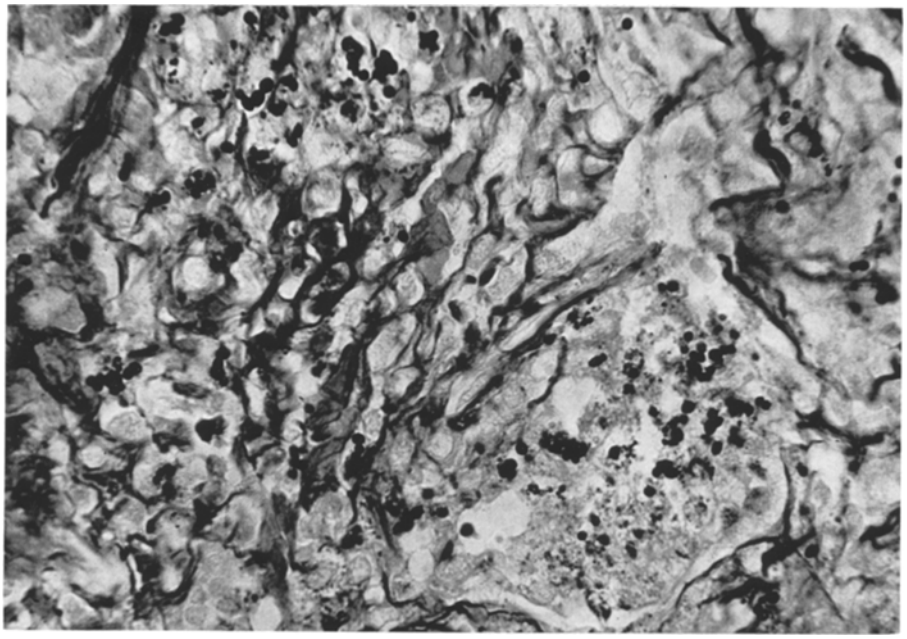

Fig. 5. Case 2. Small yeast-like fungus cells in the alveolar content and in interstitial spaces. (Grocott method ×450)

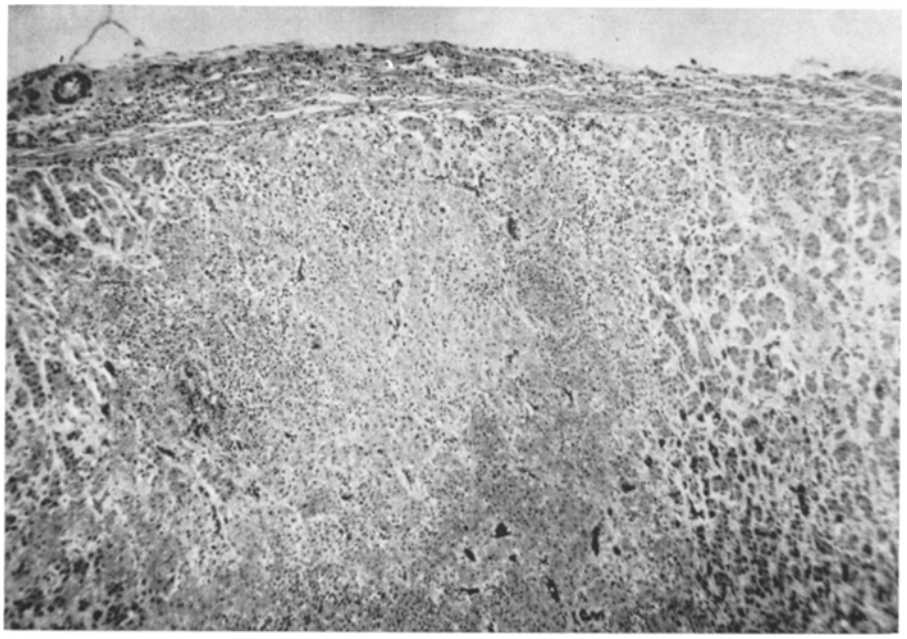

Fig. 6. Case 3. Adrenal gland. Large area of histoplasmic caseous necrosis in cortex. Organisms not visible with this staining method and magnification. (H&E ×60)

In Case 3, the histologic features were different. There was a diffuse hyperemia, and in foci of different sizes and shapes, the alveoli were either filled with mononuclear, histiocytic, and epithelioid elements or they were broken up and replaced by the same cellular elements (Fig. 3). The rest of the noninfiltrated lung parenchyma showed alveoli filled with the same content as in Cases 1 and 2, but containing more alveolar cells (Fig. 4). Only a few alveoli were optically empty.

Organisms were not clearly seen in any of the cases with H&E staining. PAS-positive granules, which appeared in the alveolar cellular content and histiocytes in the alveolar interstitium of only Case 2 were thought suspicious for organisms. In contrast, Grocott staining revealed in all three cases numerous small intracellular yeast-like elements morphologically resembling *Histoplasma capsulatum* (Fig. 5).

Other organs involved by the disseminated fungal infection are noted in Table 1. In the organs listed, yeast cells were found by the Grocott method. Various sized, partially necrotic foci without granuloma formation were also seen (Fig. 6).

Discussion

Only one case of PAP (which occurs worldwide) has been reported from Venezuela. This involved a young adult from Caracas (Angulo and Rodriguez, 1962). Since the etiology of this entity is unknown, the observation of the three cases herein from the same region may point to an environmental factor. The constant humid and hot atmosphere south of Lake Maracaibo alone may influence intra-alveolar conditions by altering the surfactant substance and/or intrapulmonary circulation.

The confirmed infections associated with PAP are considered fortuitous or secondary to PAP, the alveolar content constituting an ideal culture medium for inhaled infectious agents. In the 26 cases with fungal infections, Aspergillus, fungi of the Phycomycetes, Cryptococcus, and Candida were found. In addition, Nocardia now classified as bacteria, and *Pneumocystis carinii*, apparently a protozoan (Sunderland *et al.*, 1972) were frequently seen. The infection with *H. capsulatum* has not yet been reported associated with PAP, but it is not surprising in an area considered highly endemic for histoplasmosis. There is, however, no evidence to assume that infection with *H. capsulatum* occurred first and played a predisposing role eliciting PAP.

In two of our cases, PAP was diffuse and massive, while in the third the same alveolar content was present only focally. Apparently, partial or focal PAP, as described in the third case, occurs more frequently when associated with other conditions. PAS and Sudan positive intra-alveolar substances in circumscribed areas were observed in inflammatory pulmonary lesions of different types in our routine autopsy material. Hence, a differentiation seems appropriate between the massive, diffuse, and symptomatic form of PAP, with an overwhelming quantity of this enigmatic intra-alveolar substance and a focal, circumscribed associated and asymptomatic form. A similar situation seems to exist regarding the so called hyaline membrane disease; in premature babies where numerous hyaline membranes occur diffusely without other changes. Conversely, single or discrete hyaline membranes are seen frequently in patients with various pulmonary injuries.

Regarding the infection with *H. capsulatum*, three other features require comment. The disseminated fatal form is exceptional in young adults. A massive infection and the simultaneous PAP may have played a role leading to a fatal

form in a person of this age group. Further, massive infection and the PAP may also be the predominant factors in producing multiple primary lung foci in all the three cases, instead of the usual single lung focus in the benign primary infection (Salfelder *et al.*, 1970). Finally, the formation of larger pneumonic foci in Case 3 may be explained by a longer duration of infection with *H. capsulatum* than in the other cases. This is in accordance with the clinical observations.

Differential diagnosis between miliary tuberculosis, histoplasmosis with multiple lung foci, and massive PAP or the association of the two latter conditions only on the basis of x-rays, may be extremely difficult, as shown in two of our cases.

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