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PNEUMOCYSTIS PNEUMONIA IN THE ADULT. REPORT OF CASE ASSOCIATED WITH CORTICOSTEROID THERAPY FOR RHEUMATOID ARTHRITIS

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SUMMARY

A case of pneumonia due to *Pneumocystis carinii* is reported bringing the number of adult cases recorded in the literature up to 31. In this case, it seems likely that the use of large therapeutic doses of corticosteroids in the treatment of the underlying rheumatoid arthritis predisposed to the unusual disease entity, possibly by modifying the patient's resistance, or by reactivating an endogenous and latent infection with an organism which usually behaves as a saprophyte. The case brought up difficult problems of differential diagnosis because its clinical and radiological features resembled chiefly those of pulmonary alveolar proteinosis and of the *Hamman-Rich* syndrome.

A brief review of the literature is presented emphasizing the possible roles of factors commonly incriminated as predisposing causes of *P. carinii* pneumonia.

INTRODUCTION

Pneumocystis carinii or interstitial plasma-cell pneumonia is a peculiar clinical condition chiefly affecting premature and debilitated children [8, 30, 31]. Its peak incidence is found in the second to the fifth month of life [2, 8, 28], and the disease is associated with a high fatality rate [8, 28, 31]. Although the majority of cases has been reported in the European literature, the geographical distribution of the disease seems to be worldwide [8]. Its occurrence has been recorded in Brazil [3, 4, 18].

In adults, the occurrence of *Pneumocystis* pneumonia is rare. In 1960 RUBIN & ZAK [27], in a comprehensive review of the literature were able to find only 13 reported cases and added one of their own. In 4 of these cases the diagnosis of *Pneumocystis* infection was made in retrospect [7, 10]. Since, then, at least 15 new cases were reported [12, 20], indicating an increasing awareness of the condition in the past ten years. Since RUBIN & ZAK [27] apparently missed onde adult case reported by KLEIN [17] in 1958, the total number of reported cases of *Pneumocystis* pneumonia in adults amounts to 30, among which only two or three were considered as primary cases, while the remainder occurred in association with severe and debilitating diseases. The latter [15] were often treated with cytotoxic drugs, radiotherapy, corticosteroids or antibiotics or combination of two or more of these therapeutic agents, for periods of variable lenght, before the clinical manifestations of pulmonary infection were observed.

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In the case herein reported an overwhelming pneumonic process ensued in an adult patient receiving large doses of corticosteroids for rheumatoid arthritis.

CASE REPORT

A twenty-five-year-old *"mestiço"* worker, from Salvador, was first seen in the Outpatient Clinic on July 4th, 1962, with the chief complaints of pain and swelling of joints of three months duration. The history and physical examination were highly suggestive of rheumatoid arthritis. The white-blood-cell count was 9,000 with 44 per cent neutrophils (3 per cent band forms), 5 per cent eosinophils, 46 per cent lymphocytes and 5 per cent monocytes. The hematocrit was 42 per cent, the hemoglobin 11.6 g per 100 ml and the sedimentation rate 11 mm in 1 hr. The C-reative protein was negative. An electrocardiogram was normal and a chest fluorography revealed no abnormal findings.

Aspirin, 4 g a day, orally, and bed rest at home were prescribed. On 7/23, however, because of recurring pain and inflammatory reaction in the lefth wrist, Aspirin was replaced by prednisone, 50 mg a day orally, which was followed by prompt regression of the inflammatory symptoms. Starting on the eight day of therapy, the dose of prednisone was progressively reduced to a daily maintenance dose of 20 mg.

First admission — The patient was admitted on August 6, 1962 with complaints of fever and cough. Two weeks previously he developed fever accompanied by a dry cough which soon became productive of a mucopurulent sputum. Three days later, he noticed the onset of a sharp stabbing-pain in the lower right chest which was related to deep inspiration and to coughing attacks. Three days before entry, prednisone was discontinued with exarcebation of the inflammatory signs in the left ankle. A marked intensification of the chest pain and cough was noticed in the next 24 hours, when the patient began to experience exertional dyspnea of increasing severity.

Physical examination revealed a patient in no acute distress complaining of chest pain. The weight was 48.3 kg, the temperature 37.4°C, the pulse 108, the respirations 24 and the blood pressure 130 systolic, 70 diastolic. There was moderate swelling with localized increase in temperature of the left ankle joint. No subcutaneous nodules were found. Fine moist rales were audible along the right lung base and there was dullness to percussion in the lower third of the posterior right hemithorax.

A chest X-ray revealed a homogeneous area of increased density in the lower third of the right lung and obliteration of the right costophrenic angle (Fig. 1A). The white-cell count was 8,500 with 75 per cent neutrophils (7 per cent band forms), 17 per cent lymphocytes and 8 per cent monocytes. An L.E. test was negative. The urea nitrogen was 23 mg per 100 ml. The total serum protein was 6.5 g with 3.8 g of albumin and 2.7 g of globulins per 100 ml. A sputum smear was positive for Gram-positive cocci, and a sputum culture grew *Staphylococcus pyogenes aureus* resistant to penicillin. Penicillin, two million units every eight hours, intramuscularly, and dexamethasone 1.5 mg every eight hrs, orally, were given with no improvement. On the third hospital day penicillin was replaced by erithromycin R and chloramphenicol, 2 g of each a day, orally, which was followed by progressive improvement. On the eleventh hospital day a new chest plate showed complete resolution of the pneumonic process. The antibiotics were discontinued and, starting on the twentieth hospital day, the daily dose of dexamethasone was reduced to 3 mg. He was discharged on dexamethasone on the twenty-fourth hospital day.

Second admission — After discharge he was well during the first two weeks after which time, in spite of the use of 3 mg of dexamethasone a day, the pain and joint swelling recurred several times in the ankles and he noticed sporadic stiffness of the interphalangeal joints. About two weeks before admission, he experienced a rapidly-progressive dyspnea and a cough which was productive of a muco-purulent sputum. He was readmitted on March 30, 1963.

On physical examination the patient was in acute distress, with marked orthopnea and frequent coughing attacks. The pulse was 112, the temperature 37.4°C. The blood pressure 100 systolic, 60 diastolic, and the respirations 36. There was a slight degree of cyanosis in the extremities. The skin was darkly pigmented over the ankles. No swelling nor stiffness of joints were found. Fine rales were heard along both lung bases. The heart was normal.

The C-reative protein was positive (+++), the blood urea nitrogen 29 mg per 100 ml, the hematocrit 52 per cent, the hemoglobin 17.1 g per 100 ml, the sedimentation rate 6 mm in 1 hr. An L.E. test was negative. The carbon dioxide was 25.7 milliequiv. and the chloride 104 milliequiv. per liter. A sputum culture disclosed no significant growth and the urinalysis was negative. X-ray films of the chest revealed extensive areas of consolidation extending from both hilar areas into the mid-lung fields leaving the bases and apices remarkably freen of the infiltrate (Fig. 1B). Penicillin 1 million units, every 2 hours, intramuscularly and oxygen were given with apparent significant improvement in the first

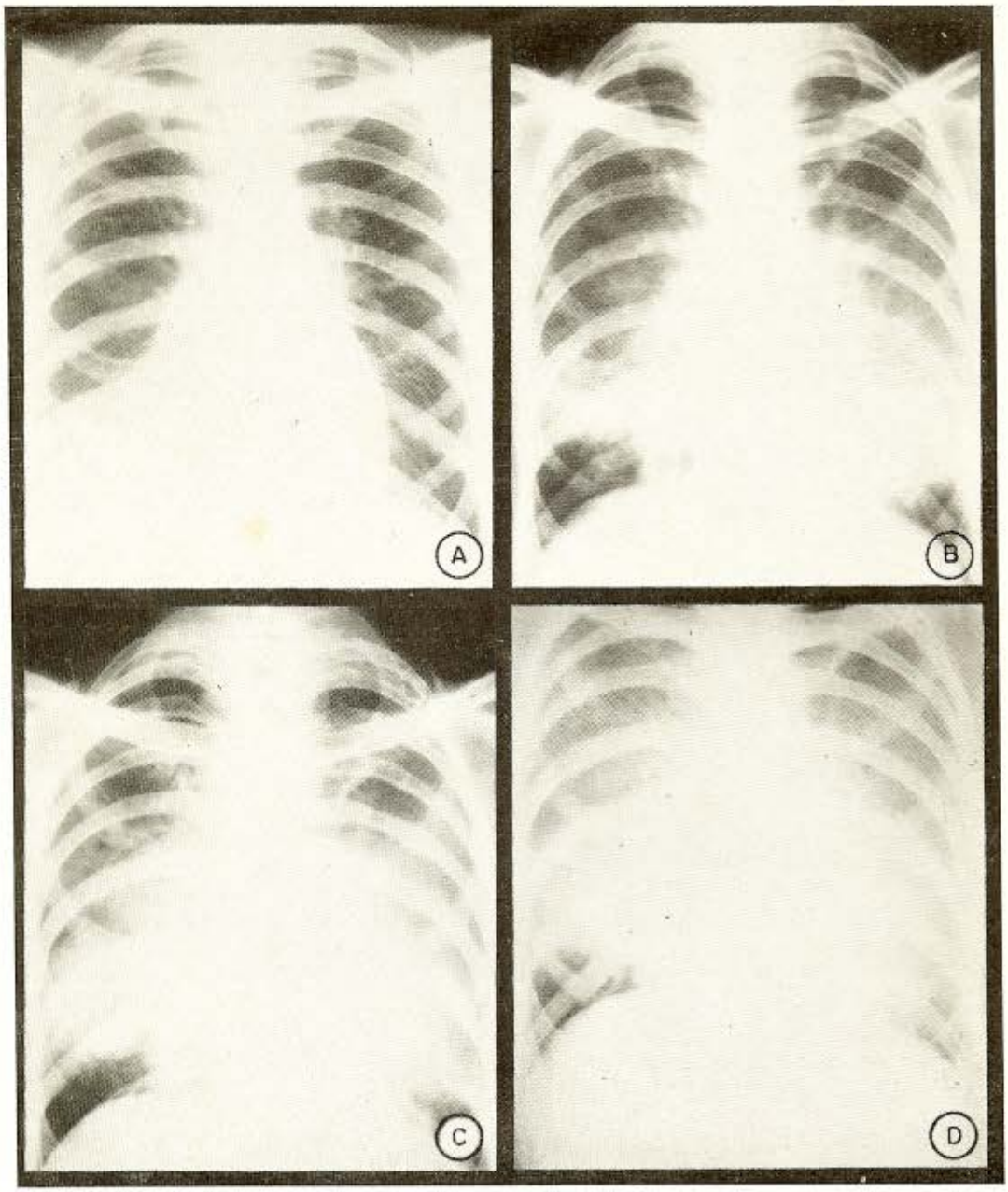

Fig. 1 — A) Roentgenogram of the chest taken on August 6, 1962 showing an homogeneous area of increased density in the lower third of the right lung and obliteration of the right costophrenic angle. B) Film of the chest taken on March 29, 1963 revealing extensive, bilateral areas of consolidation of the pneumonic type extending from both hilar areas into the medium lung fields. The bases, infraclavicular areas and apices are free of the infiltrate which assumes a "butterfly" appearance. Peripherically, the infiltrate appears to have a somewhat nodular character. C) Chest film taken on April 1, 1963 showing an increase in the densities in both lung fields. The peripherical nodular appearance is now easily observed. There are areas of emphysema in the upper and lower lung fields, bilaterally. The apices and bases are remarkably free of the infiltrate. D) Chest film obtained on April 10, 1963, six days before death, showing diffuse infiltrate throughout both lung fields, resembling the pattern of pulmonary edema.

two or three days. On the third hospital day prednisone was re-introduced. The daily dose was 60 mg up to the twelfth day when the dose was increased to 150 mg a day. There was a progressive intensification of the dyspnea. On the sixth hospital day the carbon dioxide was 20.3 milliequiv., the chloride 92 milliequiv. per liter, and the blood urea nitrogen 34 mg per 100 ml. Subsequent chest-films obtained on the third (Fig. 1C) and on the twelfth hospital day (Fig. 1D) showed an increase in the consolidation in both lung fields. The temperature chart showed sporadic peakes of temperature rise not exceeding 38°C. On the eighteenth hospital day there was a sudden increase in severity of the dyspnea and marked cyanosis developed. The pulse was 120 and the blood preassure 120 systolic, 70 diastolic at 8:00 a.m., after which time, the pulse frequency increased and the blood pressure decreased progressivily. At 11 a.m. the blood pressure could not be recorded and the patient died at 13:30 p.m. The presumptive clinical diagnosis were Hamman Rich syndrome and rheumatoid arthritis.

Pathological findings — Fibrinous adhesions between the pleurae were found in the lateral aspects of the right lung and in the apical region of the left lung. Such adhesions were also found between the external surface of the pericardium and the lower lobe of the left lung. The lungs were enlarged, distend and heavy (the right lung weighed 1,320 g. the left 1,610 g). They showed no retraction after opening the thoraxic cavities and were shown to sink in water. They had a blush hue and an elastic consistency. There was some resistance to cutting and the cut surfaces showed consolidated areas and marked edema and congestion. Neither alveolar or mediastinal emphysema or abscess were seen. The trachea and bronchi were patent, depicting a congested mucosa covered with a slight amount of mucinous secretion. Mediastinal lymph nodes showed no changes.

Fragments of several organs were fixed in ten per cent formalin and paraffin sections were stained with hematoxylin and eosin, Mc MANUS *P.A.S.* method, GOMORI's trichrome, WEIGERT's fucsin-resorcin, MALLORY's trichrome, MEYER's muci-carmin, Mac CALLUM — GOODPASTURE's method for bacteria and GOMORI's silver methenamine impregnation. Frozen sections were stained by the Sudan-black B for fat. Unfortunately, articular tissue was not removed for histological examination. Also pulmonary tissue was not cultured.

Microscopically, alveolar spaces were filled with a foamy eosinophilic material while the alveolar septa showed congestion and cellular infiltration (Fig. 2A). The intra-alveolar material had a peculiar honey-combed appearance, was *P.A.S.* positive and presented a higher density in the central part (Fig. 2C). The foamy material could not be observed and the fibrin staining yielded negative results. Cellular infiltration in the alveolar wall was moderate or marked and made up by lymphocytes, histiocytes and a few plasma-cells (Fig. 2B).

There were extensive areas of bronchopneumonia with many polymorpho-nuclear leukocytes, both within the alveoli and interstitial tissue. A few Gram-negative organisms were seen in some alveoli. Septal cells were prominent in the alveolar wall, sometimes appearing within the alveolar space as large macrophages with a foamy cytoplasm. A few scattered droplets were seen free or within the cytoplasm of the macrophages.

Pneumocystis carinii was evidenced by the *P.A.S.* and the silver methenamine methods which strongly stained the capsules of the cystic forms. Within some of these cysts one or more deeply impregnated corpuscular structures were seen and interpreted as spores (Fig. 2D).

DISCUSSION

Recent reviews of the literature on *P. carinii* pneumonia are available [3, 8, 21, 27, 31]. The spread of the infection leading to severe and progressive disease in man is possibly related to decreased defense mechanisms [28, 29]. The age distribution of *Pneumocystis* pneumonia in infants corresponds to that of the transient, physiological low-levels of gamma-globulin which is observed from one week after birth to three to six months of age. In a few cases, the association of the diseases with hypo or agammaglobulinemia, has been observed [28]. In adults, the pathogenesis of the disease is by no means well defined. Sub-clinical infection as a terminal event in the course of certain diseases has been the usual finding in the majority of reported cases in adults. The relative role of associated diseases such as lymphosarcoma, Hodgkin's disease, multiple myeloma, leukemia, etc., or that of the therapeutic agents such as radiotherapy, corticosteroids, cytotoxic drugs and antibiotics which are frequently used in the treatment of these patients cannot be comparatively assessed as predisposing factors in the light of information presently available. It is noteworthy, however, that in about 45 per cent of the adult cases reported in the literature the underlying disease was either leukemia lymphoma, or

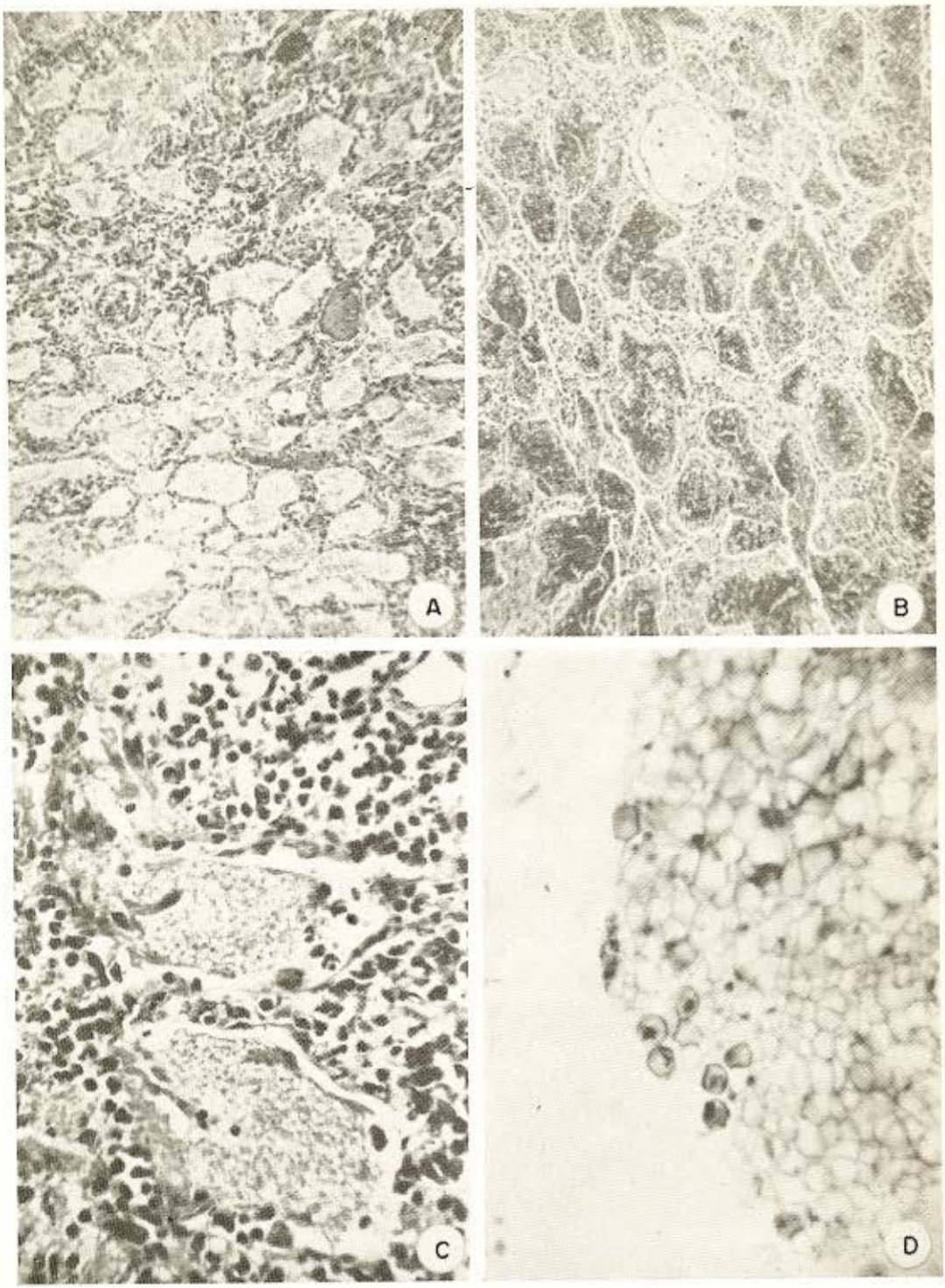

Fig. 2 — Histological sections of the lungs showing: A) Intra-alveolar foamy material and interstitial infiltration of the septa with mononuclear cells. H.E. 120 ×. B) In contrast with the findings in the majority of the histological sections, a discrete area in which the septal infiltrate is of a polymorphonuclear character. H.E. 430 ×. C) The honey-combed appearance of the intra-alveolar material which is P.A.S. positive. P.A.S. 120 ×. D) Several cysts of *Pneumocystis carinii* immersed into the intra-alveolar material. One or more deeply-stained punctate structures can be seen within some of the cysts. Gomori's silver methenamine method. 1.200 ×.

lymphosarcoma. On the other hand, among 25 reported cases with recorded information on treatment only three apparently did not receive any of the therapeutic agents which are commonly incriminated as predisposing factors; five patients received corticosteroids, radiotherapy and cytotoxic drugs; six were treated with association of two of these agents; three with cytotoxic drugs alone, while eight received only corticosteroids. Seventeen patients in this group received corticosteroids while in thirteen cases cytotoxic agents were administered either as a single drug or in combination with other agents.

The increasing incidence in recent years of infections due to the so-called endogenous bacteria, fungi and related agents is believed by some workers [16, 33] to be associated with the use of modern therapeutic agents among which are those frequently used in such diseases as leukemia and the lymphomas. *P. carinii* pneumonia can possibly be included in that category of diseases of increasing incidence. Certainly the diseases which predispose to some other uncommon infections such as cryptococcosis, mucormycosis, aspergillosis, histoplasmosis, etc.

The experimental evidence that administration of corticosteroids predisposes to *P. carinii* infection [33] adds weight to some clinical observations [1, 11, 12, 25, 27, 33]. It is likely that the corticosteroid which was given at high doses to our patient contributed to a decreased host resistance in this case, thus allowing the saprophytic organism to adopt a pathogenic role. The first episode of lung involvement leading to the first admission of the patient is difficult to interpret in retrospect, since the short course, and the prompt response to therapy, as well as the roentgen picture make the possibility of staphylococcal pneumonia unlikely.

The final episode was characterized by massive consolidation of the lungs with increasing pulmonary disfunction which was the immediate cause of death. Unfortunately no pulmonary function studies were performed to define precisely what clinically appeared to be a severe alveolar capillary block. The lack of response to antibiotics as well as the progressive deterioration on large dose of corticosteroids suggested the possibility of an unusual clinical condition. The X-ray picture brought up the possibility of pulmonary alveolar proteinosis. The possible relation of *Pneumocystis carinii* infection to alveolar proteinosis is not clear. A certain similarity between the disease entities has been noted [23, 26]. The X-ray pictures in alveolar proteinosis and *Pneumocystis* pneumonia are remarkably similar and ressemble pulmonary edema and Boeck's sarcoid. Changes are usually diffuse and bilateral. PLENK et al. [23] were able to demonstrate the presence of *P. carinii* complement-fixing antibodies in four out of nine surviving cases of proven alveolar proteinosis while in Central Europe, where *Pneumocystis* pneumonia is endemic, few healthy adults react positively to the antigen [32]. These findings, however, do not necessarily indicate a cause-and-effect relationship between alveolar proteinosis and *P. carinii* infection, inusmuch as tissue invasion by a saprophytic organism as a final event in the course of a debilitating disease may possibly propiciate an antibody response. Fungal infections superimposed on alveolar proteinosis have been observed [14, 26]. It would certainly be of some interest to search also for antibodies against these organisms in cases of pulmonary alveolar proteinosis. The clinical course in this case as well as the histological findings differed from those described in alveolar proteinosis [26].

Because the disease underlying the pneumonic process in this case was thought to be rheumatoid arthritis, the HAMMAN-RICH syndrome [9] was considered as a possibility in the differential diagnosis. Histologically there was no evidence suggesting idiopathic interstitial fibrosis of lungs.

The diagnosis of *Pneumocystis* pneumonia was made microscopically. It is of interest to note that in the majority of cases of *P. carinii* pneumonitis in adults, little or no inflammatory reaction and no plasma-cell infiltration of the alveolar septa are found although the alveoli may be filled with the characteristic spongy and eosinophilic material and with organisms [11, 24, 27, 29]. The pathological findings in some adult cases like those in most of the infant cases contrast with such a lack of tissue reaction. A

widespread pneumonia with infiltration of the alveolar septa with chronic inflammatory cells, predominantly plasma-cells and distention of the alveoli by a characteristic "honey-combed", P.A.S. positive material containing large numbers of parasites [1, 11, 12] are the histological features in these cases of true *Pneumocystis* pneumonia. The pathological findings in our case was of the latter type.

In two instances the disease was recorded in association with collagen diseases [29]. This is the first case, to our knowledge, of *Pneumocystis* pneumonia possibly preceded by rheumatoid arthritis. This fact and evidences in the literature [1, 8, 11, 12, 25, 33], suggested a significant role of corticosteroid therapy as a predisposing factor to the *Pneumocystis* pneumonia, in this case. Since no joint tissues were examined microscopically, the nature of the articular process must in fact, remain a matter of conjecture. There is need for further clinical and epidemiologic studies of *Pneumocystis* infection and for investigation of the possible role which therapy with corticosteroids, antibiotics, cytotoxic agents and ionizing radiation may play as predisposing causes.

RESUMO

Pneumonia pneumocística no adulto. Registro de um caso associado à terapêutica por corticosteróide, em paciente com artrite reumatóide

Com êste relato, de um caso de pneumonia por *P. carinii* observado em paciente adulto, o número de casos na literatura atinge a 31. Neste caso de pneumonia generalizada e bilateral, parece provável que o uso de corticosteróides em altas doses, no tratamento da doença básica apresentada pelo paciente — artrite reumatóide — tenha atuado como fator predisponente ao desenvolvimento da doença de rara ocorrência, possìvelmente induzindo modificações na capacidade reacional do paciente ou talvez ativando, pela ação sôbre o microrganismo, a infecção endógena latente que parece ser bastante freqüente em animais e possìvelmente no homem. O caso suscitou problemas de diagnóstico diferencial bastante difícil, principalmente porque apresentava características clínicas semelhantes às descritas na proteinose alveolar e na síndrome de HAMMAN-RICH.

Em breve revisão da literatura, procura-se salientar a possível ação de fatôres comumente considerados como prováveis causas predisponentes da pneumonia pneumocística do adulto.

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