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Corticosteroid Treatment for Pulmonary Lymphoid Hyperplasia in Children With the Acquired Immune Deficiency Syndrome

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Summary. Five children with positive serology for human immunodeficiency virus (HIV) infection by enzyme-linked immunosorbent assay and Western blot were followed for chronic pulmonary disease. Lung biopsies were performed in all patients, and confirmed the diagnosis of pulmonary lymphoid hyperplasia. All children demonstrated progressive hypoxia and increasing alveolar capillary oxygen gradients over at least 1 year of follow-up. All children were on periodic intravenous gamma globulin treatment for a B-cell defect prior to the initiation of corticosteroid therapy. Prednisone was initially given at a dose of 2 mg/kg daily and was subsequently tapered to an alternate day regimen. All children showed improvement in oxygenation. No deterioration in immune function was noted, and there was no increase in bacterial infection. This study indicates that corticosteroids can successfully reverse the severe hypoxia that may result from pulmonary lymphoid hyperplasia in pediatric AIDS patients. **Pediatr Pulmonol 1988; 4:13–17.**

Key words: Daily (short-term), alternate day (long-term) regimen; gamma globulin pretreatment; effect on oxygenation; roentgenographic results; complication; mycobacterium avium infection.

INTRODUCTION

We have previously described two distinct lung disorders in children with the acquired immunodeficiency syndrome (AIDS); acute *Pneumocystis carinii* pneumonia and nodular pulmonary lymphoid hyperplasia (PLH).[1,2] In PLH nodules that contain aggregates of lymphocytes and plasma cells are found surrounding bronchiolar epithelium and in adjacent alveolar septa.[2] These cells essentially represent an excessive proliferation of bronchial-associated lymphoid tissue. A variable diffuse linear lymphocytic interstitial infiltrate may be seen as well, but this is not as prominent as the peribronchial aggregates.[3] Progressive hypoxia is accompanied by significant morbidity. Corticosteroid therapy has been used with variable success in interstitial pneumonia, especially when the infiltrate is lymphocytic in nature.[4–11] Because of this experience we initiated corticosteroid therapy in several children with pulmonary lymphoid hyperplasia. Our first experience was reported in 1985.[12] Similar results were observed in two patients in 1986 by Kornstein, et al.[13] The present paper deals with a long-term follow-up of five patients.

MATERIALS AND METHODS

Patients

Five patients were defined as having AIDS according to the revised criteria of the Center for Disease Control (CDC).[14] All had serological evidence of exposure to the human immunodeficiency virus (HIV). All had been followed for at least 1 year prior to initiation of corticoste-

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TABLE 1—Clinical Profiles Prior to Corticosteroid Therapy

Pt	Age at initial PLH evaluation (months)	Initial Pa_{O_2} (torr)	Initial P_A-a_{O_2} (torr)	Age at lung biopsy (months)	Pa_{O_2} at steroid initiation (torr)	P_A-a_{O_2} at steroid initiation (torr)	IV gamma globulin
1	38	62	37	67	57	49	Yes
2	41	81	29	66	48	42	Yes
3	15	69	31	33	52	42	Yes[c]
4	44	101	3	56	60	40	Yes[c]
5	11	81[a]	19	18[b]	47	43	Yes[c]

[a]Prior episode of *Pneumocystis carinii* infection.
[b]Steroid therapy begun at 23 months.
[c]Begun ⩽ three weeks before initiation of corticosteroid.

roid treatment. The diagnosis of PLH was confirmed in all patients by histological analysis of specimens obtained by open lung biopsy. Routine stains and cultures established the absence of an infectious agent. All patients received periodic intravenous gamma globulin therapy (300 mg/kg every other week) for at least 3 weeks prior to the institution of corticosteroid treatment. Two children (patients 1 and 2) had received gamma globulin for 2 years and for 6 months, respectively, prior to being placed on steroid therapy. In these two patients progressive hypoxia occurred despite being maintained on gamma globulin. The other three patients had received gamma globulin for more than 3 weeks prior to initiating corticosteroids. Arterial blood oxygen tension (Pa_{O_2}) below 65 torr and alveolar arterial gradient (P_A-a_{O_2}) above 40 torr were documented on three separate determinations over a period of at least 3 months in all patients receiving corticosteroids. Ten additional patients of similar ages also had PLH documented by open lung biopsy. Two of them received periodic intravenous gamma globulin for more than 6 months, but none received steroids during a 1-year follow-up. In all of these control patients the chest X-ray findings were suggestive of PLH.

Corticosteroid Therapy

Prednisone was started at 2 mg/kg/day for 2–4 weeks until an increase of Pa_{O_2} of at least 20 torr was noted. It was then tapered gradually to 0.5 to 0.75 mg/kg every other day, provided that the Pa_{O_2} remained over 70 torr. All patients were followed for at least 16 months. Arterial blood gases and chest roentgenographs were obtained prior to therapy and serially thereafter. In vitro lymphocyte responses to phytohemagglutinin were measured by incorporation of tritiated thymidine. T4 cells were quantitated on a fluorescent-activated cell sorter as previously reported.[1]

RESULTS

In all five patients treated with corticosteroids significant hypoxemia was recorded prior to the initiation of therapy. Age at diagnoses and biopsy and corresponding arterial Pa_{O_2} and P_A-a_{O_2} are noted in Table 1. Patient 1 demonstrated no improvement in Pa_{O_2} while on gamma globulin infusions for 2 years. Patient 2 had a decrease in Pa_{O_2} of approximately 15–20 torr during the 6 months when he was on gamma globulin treatments alone.

Results of prednisone treatment are presented in Figure 1. After 1 month of prednisone therapy, three of five patients (patients 1, 3, 4) demonstrated a Pa_{O_2} of greater than 70 torr (P_A-a_{O_2}: 30 torr). In the other two patients (2, 5) Pa_{O_2} was 70 torr or more after 3 months of treatment (Fig. 1). Further improvement was noted at follow-up. Two patients (2, 5) achieved normal Pa_{O_2} and a normal P_A-a_{O_2} over the period of follow-up, and in two others Pa_{O_2} values reached 90 torr or more.

Patient 4 was taken off steroids after 18 months of therapy because compliance could no longer be guaranteed. Gamma globulin infusions were continued. At that time Pa_{O_2} was 85 torr (P_A-a_{O_2}: 19 torr). Five months later, his Pa_{O_2} decreased to 76 torr (P_A-a_{O_2}: 28 torr), and 7 months after having stopped taking corticosteroids, the Pa_{O_2} was 64 torr.

Chest roentgenographs of all treated patients showed a nodular pattern throughout the lung fields, including the periphery (Fig. 2). As the disease progressed, the nodules increased in size, and hilar and upper mediastinal lymphadenopathy became evident. Following steroid treatment, three patients (2, 3, 5) showed dramatic roentgenographic improvement. Only minimal residual nodularity was evident. The other two patients (1, 4) showed almost complete resolution of hilar and mediastinal lymphadenopathy with only a moderate decrease in the size and number of nodules on roentgenograph.

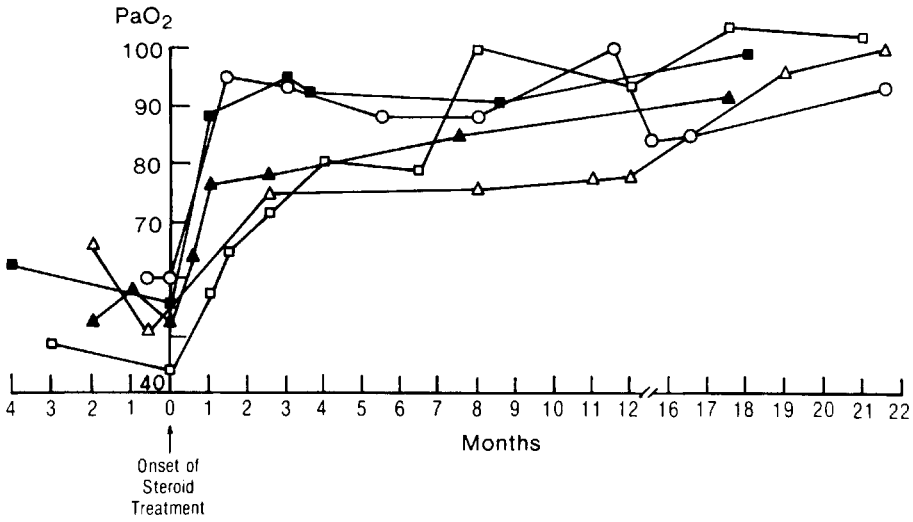

Fig. 1. Pa_{O_2} in children with AIDS and PLH before and after corticosteroid treatment. ■, patient 1; △, patient 2; ▲, patient 3; ○, patient 4; □, patient 5.

While four of five treated patients had developmental delay, this was not affected in either a positive or negative way by corticosteroid therapy. No corticosteroid effects on growth pattern or on the musculoskeletal and vascular system were noted.

Total lymphocyte counts remained unchanged during treatment. In four children a gradual decrease in T4 cells was noted, but it was similar to that observed in other patients with HIV infection not on steroids. Mitogenic responses to phytohemagglutinin were not significantly different from other children with PLH who did not receive corticosteroids. No episodes of *Pneumocystis* or disseminated fungal infection was documented during follow-up. One patient (2) developed abdominal distention and recurrent fevers 2 years after initiation of corticosteroids. At that time he was on 0.2 mg/kg q.o.d. of prednisone. The presence of disseminated mycobacterium avium infection (MAI) was demonstrated.

Of the ten patients who were not on corticosteroids, all developed clubbing of their fingers and progressive chest X-ray nodularity. In nine patients, progressive hypoxia was also documented, with Pa_{O_2} less than 75 torr in all. One patient's condition remained stable with a normal Pa_{O_2} over a 1-year follow-up. One patient developed disseminated MAI.

DISCUSSION

Pulmonary lymphoid hyperplasia (PLH) is characterized by insidiously progressive mild-to-moderate hypoxemia, digital clubbing, and a recticulonodular pattern on roentgenographs. Although the initial cellular response is mostly confined to the bronchial-associated lymphoid tissues (BALT), cellular infiltrates may also occupy interstitial spaces[4] leading to lymphocytic interstitial pneumonitis (LIP) with subsequent ventilation perfusion imbalances.[1,2] In classical LIP, which is not associated with AIDS, progressive diffuse scarring and honeycombing with respiratory compromise may occur. In a series of ten patients treated with steroids, Leibow and Carrington[5] reported roentgenographic responses ranging from no changes, to arrest of progression, to definite improvement. Seven of 13 cases of LIP reported by Strimlan et al[6] improved on corticosteroid treatment. Kohler et al[7] described the beneficial effect of alternate-day steroid therapy in a patient with common variable immunodeficiency with predominantly T cell LIP. Over the period of analysis, alterations of peripheral blood B cells and T cell subsets were not documented in this patient.

Our results show a favorable clinical and radiographic response of PLH to corticosteroid treatment in five children with HIV infection. The beneficial effect could be sustained on low-dose, alternate-day therapy resulting in a marked increase of arterial Pa_{O_2} and a decrease of P_A-a_{O_2}. In three patients this improvement was corroborated by an almost complete clearing of the roentgenographic lung findings (Fig. 2). These results confirm earlier observed improvement in a small number of children with PLH on corticosteroids by us[12] and by Kornstein et al.[13]

It is, however, imperative to compare the effects of corticosteroids on PLH to the natural course of the disease. Our five corticosteroid-treated patients were fol-

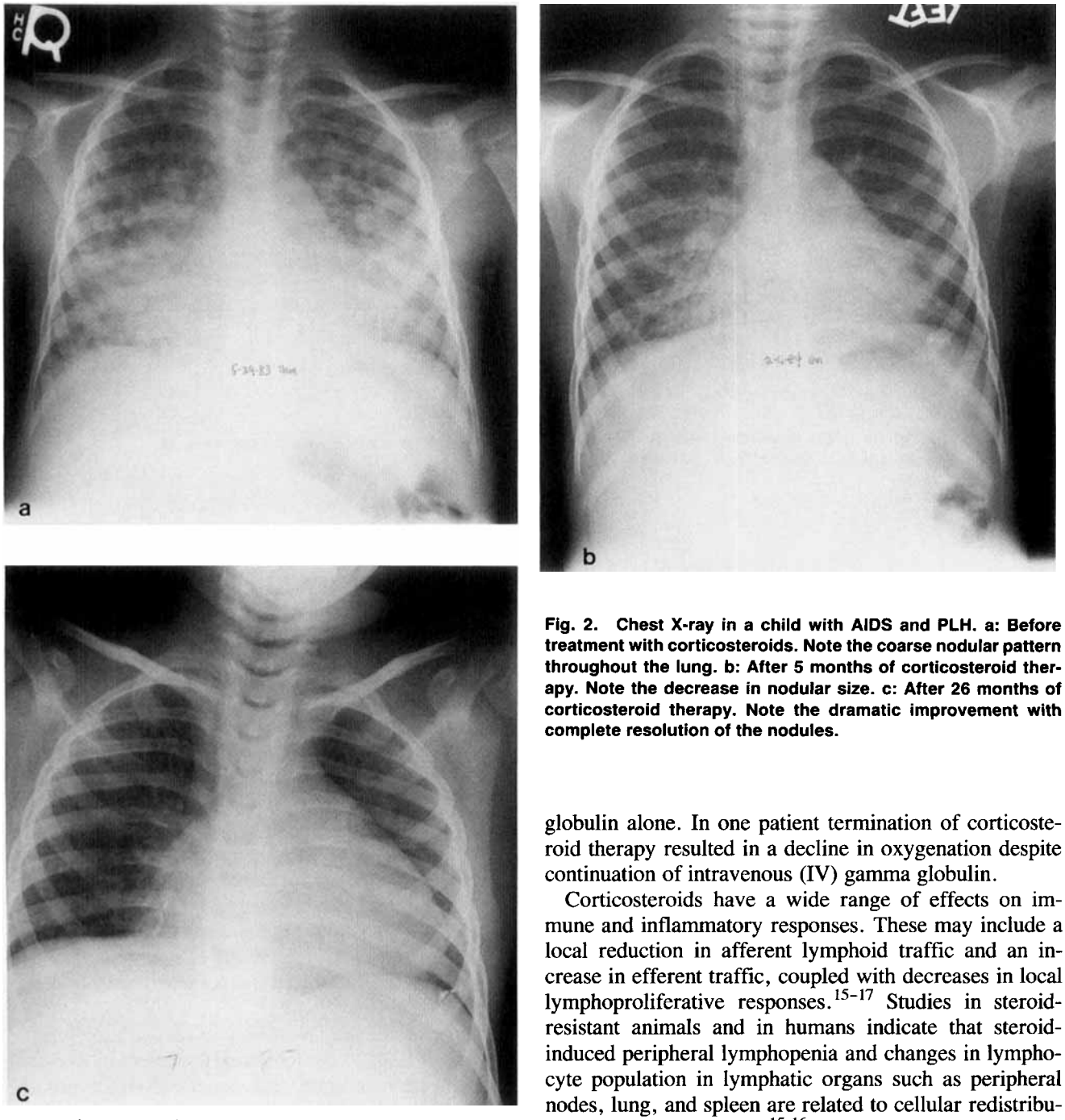

Fig. 2. Chest X-ray in a child with AIDS and PLH. a: Before treatment with corticosteroids. Note the coarse nodular pattern throughout the lung. b: After 5 months of corticosteroid therapy. Note the decrease in nodular size. c: After 26 months of corticosteroid therapy. Note the dramatic improvement with complete resolution of the nodules.

lowed for 7 to 36 months before initiation of therapy. None of these patients showed improvement of Pa_{O_2}. Ten control patients with PLH confirmed by biopsy were followed for at least 1 year. Nine of these patients developed progressive hypoxemia. Two of the corticosteroid-treated patients and two of those not on steroids (4 of a total of 14) received long-term intravenous gamma globulin. In the absence of concomitant corticosteroid therapy, improvement of PLH has not been noted with gamma globulin alone. In one patient termination of corticosteroid therapy resulted in a decline in oxygenation despite continuation of intravenous (IV) gamma globulin.

Corticosteroids have a wide range of effects on immune and inflammatory responses. These may include a local reduction in afferent lymphoid traffic and an increase in efferent traffic, coupled with decreases in local lymphoproliferative responses.[15-17] Studies in steroid-resistant animals and in humans indicate that steroid-induced peripheral lymphopenia and changes in lymphocyte population in lymphatic organs such as peripheral nodes, lung, and spleen are related to cellular redistribution to the bone marrow.[15,16] In general, T cells are more steroid sensitive than B cells, and T helper (T4) cells are more sensitive than T suppressor (T8) cells.[16,17] In our patients, alternate-day corticosteroids had no effect on lymphocyte counts and on T4 cell numbers, as compared to the corticosteroid untreated control group.

Pediatric patients with AIDS have a profound functional B cell defect[18] and a tendency to develop recurrent bacterial infections with sepsis.[19] Prolonged courses of

daily corticosteroids in these patients may further increase the risk for bacterial infections. Since 1981 we have elected to treat these patients prophylactically with periodic intravenous gamma globulin. Consequently, all patients on the corticosteroid regimen and some control patients received IV gamma globulin. Whether the use of gamma globulin has averted infectious complications related to corticosteroid treatment has yet to be determined. However, in the present study no patient with concomitant steroid and IV gamma globulin therapy demonstrated an increase in the rate and severity of bacterial infections. We have also not recorded any musculoskeletal side-effects or additional growth failure in treated patients. This favorable outcome may further be attributed to the regimen used, in which daily corticosteroids were only administered for a short period of time, at most for 4 weeks, until an increase in Pa_{O_2} of 20 torr was achieved. Subsequently, an alternate-day treatment program was instituted. It has been previously shown that untoward immunologic effects of corticosteroids are by and large preventable by alternate day treatment. For example, recovery of lymphocyte distribution and of bactericidal monocyte functions are noted on the off-steroid day.[15-17,20] The alternate-day treatment modality is, therefore, preferable in pediatric and adult patients who have T cell and monocyte defects.

The development of MAI in one child is obviously of concern with regard to potential cell-mediated immunosuppression by corticosteroid therapy. The overall incidence rate of this disease in our patients with AIDS is approximately 10%. One patient in the control group also developed MAI. Preliminary data suggest that alternate-day corticosteroid treatment does not increase the risk of opportunistic infection. However, longer follow-up in a larger number of patients is necessary to resolve this question.

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