Acquired Immunodeficiency Syndrome (AIDS) with Lymphocytic Interstitial Pneumonitis (LIP) in a Multi Transfused Child with Thalassemia Major

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Pediatric acquired immunodeficiency syndrome(AIDS) manifests clinically in many ways, and one characteristic presentation is with lymphocytic interstitial pneumonitis (LIP) This chronic interstitial lung disease is commonly seen in children with AIDS, and is particularly frequent when AIDS is perinatally acquired, when it occurs in about 50% cases(1).

Routine screening for human immunodeficiency virus (HIV) infection was started for multi-transfused children with thalassemia at the Thalassemia Clinic of the New Delhi Municipal Committee's Charak Palika Hospital, Moti Bagh, New Delhi, in December 1990. Of 203 children screened, 18 (8.9%) were HIV sero-positive. Of these children, 6 could be categorized as AIDS according to the WHO criteria(2). The details of these cases are being published elsewhere.

In this communication, the clinical and the immunological details of a child with AIDS who had features typical of LIP, is described. This is, to the best of our knowledge, the first case report of AIDS and LIP in the pediatric age group in India.

Case Report

A 10-½ years-old girl, was diagnosed a case of thalassemia major at the age of 8 months, and since then had been on regular blood transfusions. All her transfusions had been given at the Charak Palika Hospital, New Delhi where blood from the Indian Red Cross Society Blood Bank is accepted. Donor screening for HIV was started in mid 1988, and thus the child had received unscreened blood for a number of years. Till date, she had received about 150 units, but significantly, had not received any transfusion of commercially donated blood.

Between February 1990 and February 1991, when the child was under regular follow-up of one of us (SS), her pre-transfusion hemoglobin was maintained at 8.5 to 9.5 g/dl on a 3 weekly transfusion regimen. Her height (119 cm, expected 141.5 cm) and weight (19 kg, expected 34.7 kg) were below the 5th percentile for her age. Her liver was 5 cm below costal margin, and spleen 6 cm. Owing to financial constraints, she was receiving inadequate chelation therapy (4 g desferrioxamine/month) and

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her iron studies (done in September 1990) showed evidence of iron overloading (serum iron : 225 μg/dl, normal : 35-140 μg/dl total iron binding capacity (TIBC) : 28.2 μg/dl, normal : 245-400 μg/dl and serum ferritin : 11284 ng/ml, normal : 11-250 ng/ml).

In February 1991, the child presented with a dry persistent cough, moderate grade continuous fever and breathlessness on exertion for over 2 weeks. On examination, the child was pale, tachypneic with bilateral extensive crepitations and occasional rhonchi in the chest. Chest *X*-ray showed bilateral infiltrations. She was started on antimicrobials (penicillin and chloramphenicol) with a provisional diagnosis of bronchopneumonia. Her symptoms deteriorated and in March '91 had to be hospitalized for impending respiratory failure. At this stage her respiratory rate was 50/min, and her chest findings were unchanged. She had mild central cyanosis. She was started on oxygen, intravenous fluids and parenteral antimicrobials (cephaloridine and gentamicin). After 14 days, the child's condition stabilized to some extent, but the chest findings and *X*-ray appearance showed little or no change. Her transfusion requirements had increased considerably, and in spite of 4 transfusions in 14 days, her hemoglobin could be maintained at only 7 g/dl. Investigations done during this period (14.3.91-28.3.91) were as follows: Hb: 6.5 to 7 g/dl, TLC: 5600/mm^3, DLC: $P_{72}L_{20}M_4E_4$, ESR: 84 mm 1st hour, serum bilirubin: 1.2 mg/dl (direct: 0.4, indirect 0.8), SGOT: 114 IU/L, SGPT: 120 IU/L, alkaline phosphates: 96 IU/L, blood urea: 20 mg/dl, serum creatinine: 0.4 mg/dl, blood culture: sterile, sputum culture: sterile, sputum for AFB: negative, and Mantoux test: non-reactive. The child was empirically started on 4 antitubercular drugs (INH, rifampicin, pyrizinamide and ethambutol) and discharged.

The child was readmitted on 10.4.91 with complaints of difficulty in swallowing and weight loss. At this time her chest signs persisted, and she had in addition developed severe oro-pharyngeal candidasis with ulcerations in the palate, tonsils and the posterior pharyngeal wall. She had also lost 2 kg weight (10.5%), had developed alopecia, a generalized lymphadenopathy, digital clubbing and bilateral parotid enlargement. Her liver size had increased to 8 cm and spleen to 12 cm. Candidiasis responded to vigorous therapy with clotrimazole. *X*-ray of the chest at this stage showed hilar adenopathy, bilateral extensive parenchymal infiltrates with a diffuse reticular pattern (*Fig. 1*). Fine needle aspiration of lymph node showed a reactive hyperplasia. It was at this stage that HIV antibodies were detected in the serum by ELISA and confirmed by West-

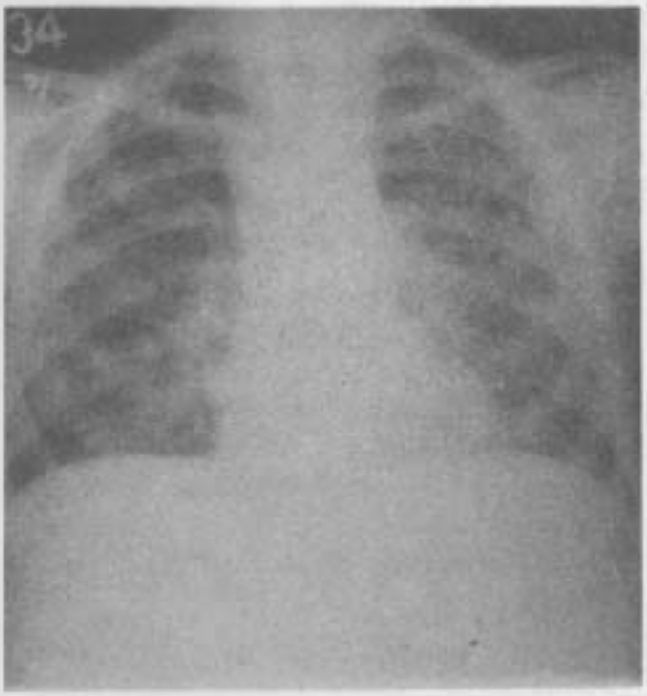

Fig. 1.X-ray chest (10.4.91) showing extensive bilateral reticulonodular parenchymal opacities and hilar and mediastinal adenopathy.

ern Blot. A sputum induction test by hypertonic (3%) saline, done on a number of occasions, failed to demonstrate *Pneumocystis carinii* or any other pathogenic organism.

Immonologic tests done on the child showed evidence of severe immuno-deficiency (*Table I*), with 3 of the 4 immunologic parameters being abnormal. The 'Multitest CMI' (Institute Merieux, Lyon, France) which simultaneously tests delayed skin hypersensitivity to 7 common recall antigens (tetanus toxoid, diphtheria toxoid, streptococcus (Group C), tuberculin (old), *Candida albicans, Trichophyton mentagrophytes* and *Proteus mirabilis*) was totally non-reactive. The immunoglobin values showed a low IgG, a marginally raised IgM and a raised IgA (*Table I*).

The child was thus classified as having AIDS according to WHO criteria for children under 13 years of age(2). With the characteristic clinical and radiologic features of an interstitial lung disease, clubbing, lymphadenopathy and parotid gland enlargement, a diagnosis of LIP was made. The child was given oral prednisolone 2 mg/kg/day in 3 divided doses for a month and this was then tapered. The response was excellent: her cough, dyspnea showed great improvement, and the paroid swellings disappeared; lymphadenopathy, clubbing and alopecia however persisted. The chest findings and the *X*-ray picture showed improvement (*Fig. 2*). The child is currently on maintenance doses of prednisolone (0.5 mg/kg/day in a single dose), and on alternate day co-trimoxazole (2 mg/kg) for prophylaxis against *P. carinii* infection.

Discussion

Lymphocytic interstitial pneumonitis is a very common complication among children with perinatally acquired AIDS, but also occurs in transfusion associated AIDS. It was simply our inexperience with this entity that prevented us from making a diagnosis earlier. LIP is a chronic interstitial lung disease that manifests clinically with chronic cough, progressive dyspnea and

TABLE I—*Results of Immunological Test (15.4.91)*

Test	Value	Normal value
Absolute lymphocyte count (ALC)	1691/mm^3	> 1500/mm^3
CD4+ cell count	152/mm^3	> 1000/mm^3
% CD4+ cell count	9%	
CD8+ cell count	1116/mm^3	
% CD8+ cell count	66%	
CD4+/CD8+ ratio	0.14	> 1
CMI multitest score	0 mm	> 10 mm
IgG	146 mg/dl	923 ± 256 mg/dl
IgM	169 mg/dl	65 ± 25 mg/dl
IgA	301 mg/dl	124 ± 45 mg/dl

Immunodeficiency present if: ALC <1500/mm^3, CD4+ <1000/mm^3, CD4+/CD8+ <1, CMI multitest <10 mm.

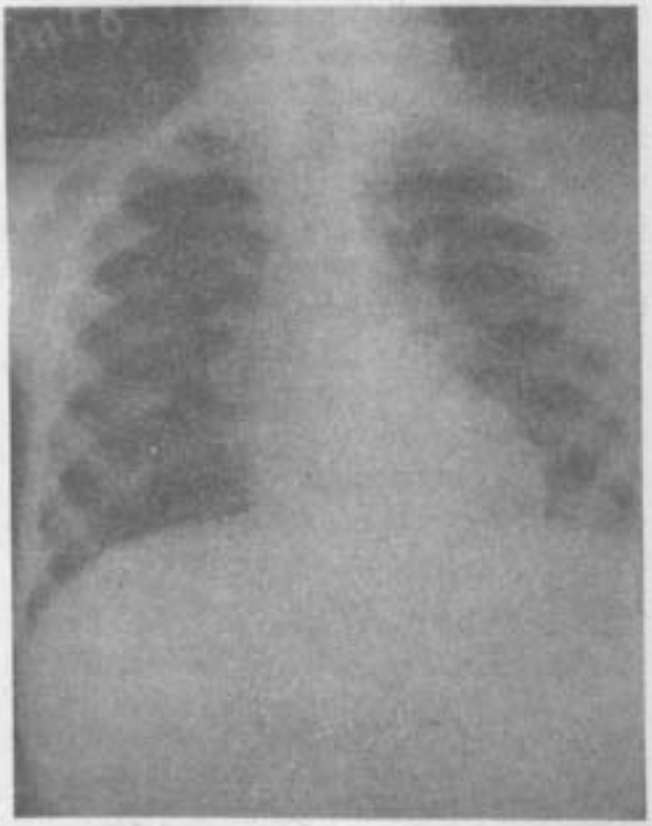

Fig. 2. X-ray chest (21.5.91) showing partial clearing of paranchymal lesions after 4 weeks of steroid therapy.

hypoxemia, variable auscultatory findings, generalized lymphadenopathy, digital clubbing and salivary gland enlargement(3). Radiologically, there are bilateral diffuse reticulo-nodular infiltrates sometimes associated with hilar and mediastinal adenopathy(4).

Definitive diagnosis is usually made on biopsy, but the clinical and the radiological features in this case were so characteristic that histological confirmation was not considered necessary. On biopsy, LIP-affected lungs contain nodular peribronchiolar lymphoid aggregates, some with germinal centres, or a diffuse infiltration of the alveolar septa of the peribronchilar areas by lymphocytes and plasma cells(5).

Though hypergamma-globulinemia is a characteristic finding of pediatric AIDS(6), this feature has been uniformly absent in all our children, including this child. Values of immunoglobulins have been similar (a low IgG, and slightly raised IgM and IgA) in our children with AIDS, HIV positive asymptomatic, and in HIV negative thalassemics. We can only speculate, that multiple blood transfusions, by repeated antigenic challenges have blunted the immunologic responses of the B-cells, and thus hypergammaglobinemia has not occurred. Hypogamaglobinemia in AIDS has previously been described in a few children(7,8).

Pneumocystis carinii pneumonia (PCP) is the closest differential diagnosis of LIP in a child with AIDS, but typically, a child with PCP presents more acutely with sudden onset of dyspnea, cyanosis and a rapidly downhill course unless specifically treated(3). PCP may however sometimes present as a subacute illness(9). In our case, however, the clinical and the radiologic features were so typical and the response to therapy so good, that the diagnosis of LIP is not in doubt. The factors that predispose one child to LIP and another child to PCP are not known, although HIV strain differences may play a role(10).

Therapy for LIP is expectant. Superimposed infections must be vigorously treated, and in children with progressive LIP, the use of corticosteroids has been advocated(4), and there are reports of good response to this form of therapy(6). The toxicity of long term use of steroids in HIV infected patients is not known, but there are serious concerns about this.

Children with LIP have a median survival of 91 months which is better than those with PCP who have a median survival of only 14 months(11). Since immunologic abnormalities correlate best with the stage of AIDS(12) and as our patient has grossly deranged immunologic parameters, she is obviously in a very advanced stage of the disease, and her prognosis will be poor.

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Nesidioblastosis: Ultrastructural and Immunohistochemical Observations

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Although hypoglycemia is a frequent occurrence in the newborn, persistent hypoglycemia due to hyperinsulinemia is rare. An early diagnosis goes a long way in

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