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Lymphocytic interstitial pneumonia in children with AIDS: high-resolution CT findings

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Abstract Pulmonary involvement in children with acquired immunodeficiency syndrome (AIDS) represents a wide spectrum of diseases. Among the non-infectious, non-neoplastic affections associated with AIDS, lymphocytic interstitial pneumonia (LIP) is now a well-recognized entity, but its radiological pattern studied with high-resolution computed tomography (HRCT) has rarely been described in children. The aim of this study was to illustrate the HRCT spectrum of pulmonary involvement in children with LIP and to evaluate its usefulness in the early diagnosis of this entity. Twelve children with AIDS, aged 3–9 years (mean age 5 years 7 months), underwent chest radiographs and HRCT. A control group of 7 healthy aged-matched children was also studied in the same conditions. Diagnosis of LIP was based on clinical data and HRCT findings. Eight children of 12 had a reticulonodular pattern on chest radiographs. Two children had normal chest films and two children showed peribronchiolar thickening. High-resolution CT displayed micronodules, 1–3 mm in diameter, with a perilymphatic distribution in all patients. High-resolution CT demonstrated also subpleural nodules in children without reticulonodular opacities on chest radiographs. High-resolution CT is able to define a more specific pattern of abnormalities than conventional chest radiographs in children with LIP, allows an earlier and more confident diagnosis and may be useful for the detection of other pathologies associated with AIDS, such as opportunistic infections or superimposed malignancies.

Key words AIDS · LIP · CT · Chest radiography

Introduction

Lymphocytic interstitial pneumonia (LIP) is an unusual condition, encountered mainly in children infected with the human immuno-deficiency virus (HIV) or with the acquired immunodeficiency syndrome (AIDS) [1, 2, 3, 4, 5]. In the AIDS population LIP represents 25–40 % of pulmonary diseases in children and only 3 % in adults [6].

Furthermore, LIP is considered as an indicator of AIDS when it occurs in HIV-positive patients or before the age of 13 years, unless HIV serologies are negative [7, 8]. It is suggested that LIP represents a lung response to the presence of HIV and Epstein-Barr virus in the lung [9, 10].

Clinical symptoms, when present, consist of cough and dyspnea. Chest radiographs may show a pattern varying from interstitial reticular opacities to alveolar consolidation [11, 12]. In the early stage, LIP must be differentiated from opportunistic infections such as *Pneumocystis carinii* pneumonia (PCP) and tuberculosis, or malignancies such as lymphoma, in order to avoid inappropriate therapy. Recent studies, most of them dealing with the AIDS adult population, have demon-

Table 1 Demographic and clinical data. *CXR* Chest radiographs; *PCP Pneumocystis carinii* pneumonia; *VT* vertical transmission

Child no./ Age (years)/Gender	Mode of HIV transmission	AIDS stage	CD4 Cell Count (cells/mm^3)	PCP prophylaxis
1/3/M	VT	C1	219	+
2/6/F	VT	C3	22	+
3/8/F	VT	C3	833	+
4/7/F	VT	B1	1221	+
5/4/F	VT	C3	364	+
6/7/F	VT	B1	850	+
7/3/M	VT	C3	19	+
8/5/F	VT	B2	217	+
9/9/M	VT	C3	606	+
10/5.3/F	VT	B1	1650	+
11/6/M	VT	B2	414	+
12/9/F	VT	A3	609	+

strated the usefulness of CT and HRCT in the diagnosis of LIP [1, 8, 13, 14, 15, 16, 17]. In a review of the literature, we found only a few papers dealing with HRCT of LIP in the AIDS pediatric population [18, 19]. The aim of this study was therefore to illustrate the HRCT spectrum of pulmonary involvement in children with LIP, and to evaluate its role in the early diagnosis of this entity.

Materials and methods

Our study group comprised 12 consecutive children, 8 girls and 4 boys aged 3–9 years (mean age 5 years 7 months), all vertically infected by the HIV virus, gathered during a 2-year period. Clinical and laboratory data are summarized in Table 1.

All children had conventional posteroanterior chest radiographs, and a consensus was obtained from two of us (F. G. and P. S.) for the presence or absence of parenchymal reticulonodular or miliary opacities. All children were prospectively studied by HRCT to look for subtle signs of LIP and were asymptomatic. One-second HRCT sections using 1-mm X-ray beam collimation were obtained in all children at 10-mm intervals from the apex to the base of the lungs, without intravenous administration of contrast material or sedation, and reconstruction utilizing a high spatial-frequency algorithm was used. Full-end inspiratory position was employed when feasible, according to the age of the child. The HRCT images were reviewed by two of us (F. G. and P. S.) and the final diagnosis was reached by consensus. The observers assessed the HRCT images for the presence, extent, and distribution of peribronchovascular nodules, bronchial wall thickening, bronchiectasis and bronchiolectasis, pseudocystic air spaces, centrilobular nodules, interlobular septal nodules, subpleural nodules, ground-glass opacities, areas of consolidation, lymph node enlargement, and pleural effusions.

The HRCT images of HIV subjects were compared with the control group HRCT images of the healthy age-matched children referred to our institution for abdominal and pelvic trauma. The HRCT sections of lungs were performed in these children as part of a routine protocol used in our institution to screen for small pneumothorax. This group comprised 7 children aged 1–12 years (mean age 4 years 7 months). Correlation of clinical and HRCT findings were considered diagnostic of LIP and no lung biopsies could be performed for ethical reasons. Clinical and radiological follow-up ranged from 12 to 60 months. The CD4 count (cells/mm^3) and AIDS stages were obtained at the time of the initial radiological examinations. Two children, although their CD4 cell counts were higher than 500 cells/mm^3, where classified in C3 stage because they were receiving an antiretroviral treatment.

Results

Results are summarized in Table 2. Chest radiographs revealed a bilateral reticulonodular or miliary pattern in 8 children, peribronchial thickening without interstitial infiltrates in 2 children, and a normal appearance in 2 children. Children with reticulonodular or miliary infiltrates on plain radiographs were suspected to have LIP before HRCT acquisition (Fig. 1a). High-resolution CT demonstrated interstitial subpleural micronodules with basal predominance in all patients (Fig. 1b), whereas no intestitial abnormalities were observed in the control group. Subpleural micronodules were always demonstrated in the presence of central involvement (children nos. 6, 8, and 9). In 7 children centrilobular micronodules were present (Fig. 2). The size of the nodules ranged from 1 to 3 mm. One child (child no. 2) had an area of confluent centrilobular micronodules in the middle lobe (Fig. 3). Bronchial wall thickening was identified in 4 children. No bronchiectasis could be observed in our cohort. Bronchiolectasis were identified in 3 children at the lung cortex level, in areas particularly involved by micronodules. Bilateral ground-glass opacities, with basal and peripheral distribution, were present in two children (Fig. 4). None of the children in our cohort demonstrated cystic air-space lesions. No mediastinal or hilar adenopathy was observed. Clinical follow-up ranged from 12 to 60 months. During this time, 9 children remained asymptomatic for any pulmonary diseases and 3 children died (nos. 2, 5, and 7). Child no. 2, aged 6 years at the time of LIP diagnosis, died 1 year later from profuse refractory diarrhea and electrolytic disturbances leading to therapeutic abstention. Child no. 5, aged 4 years at the time of LIP diagnosis, re-

Table 2 Plain radiographs and HRCT findings

Child no.	Chest radiograph findings	Peribronchovascular nodules	Bronchial wall thickening	Bronchiectasies	Bronchiolectasies	Pseudocystic air space	HRCT Centrilobular nodules	findings Interlobular septal nodules	Subpleural nodules	Ground-glass opacities	Air-space consolidation/atelectasis	Adenopathies	Pleural effusion
1	Bilateral miliary infiltrates	–	+	–	+	–	+	–	+	+	–	–	–
2	Bilateral reticulonodular infiltrates	–	+	–	+	–	+	–	+	+	+ (focal)	–	–
3	Bilateral miliary infiltrates	–	+	–	–	–	–	+	+	–	–	–	–
4	Normal	–	+	–	–	–	+	–	+	–	–	–	–
5	Bilateral reticulonodular infiltrates	–	–	–	+	–	+	–	+	–	+ (atelectasis)	–	+
6	Peribronchial thickening	+	–	–	–	–	+	+	+	–	–	–	–
7	Normal	–	–	–	–	–	–	+	+	–	+	–	–
8	Bilateral reticulonodular infiltrates	+	–	–	–	–	+	+	+	–	–	–	–
9	Bilateral reticulonodular infitrates	+	–	–	–	–	+	+	+	–	–	–	–
10	Bilateral reticulonodular infiltrates	–	–	–	–	–	–	+	+	–	–	–	–
11	Bilateral miliary infiltrates	–	–	–	–	–	–	+	+	–	–	–	–
12	Peribronchial thickening	–	–	–	–	–	–	+	+	–	–	–	–

mained asymptomatic during 2 years and died aged 6 years from a rapidly progressive extranodal high-grade non-Hodgkin's B-lymphoma with diffuse multiorganic involvement, including the lungs, as demonstrated at autopsy. This condition was considered as a new disease without relationship to the preexisting LIP. Child no. 7, aged 3 years at the time of LIP diagnosis, died 6 months later from cardiac failure in relation to severe HIV cardiomyopathy. No autopsy was obtained for patient nos. 2 and 7.

Discussion

Lymphoproliferative disorders of the lung are more common in the immunosuppressed and are therefore frequently seen in the AIDS population. They consist of many complex diseases, ranging from benign to malignant conditions. In adults, LIP, atypical lymphoproliferative disorder (ALD), and mucosa-associated lymphoid tissue lymphoma (maltoma) form a group of interstitial pneumonias in patients with AIDS [13]. Lym-

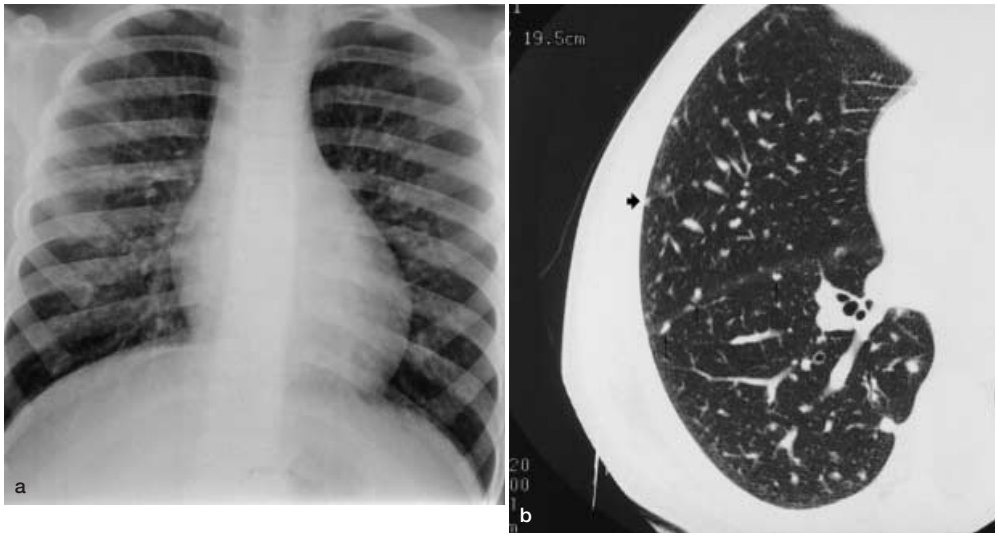

Fig. 1 **a** Chest radiograph (posteroanterior view) of patient no. 3. A diffuse micronodular infiltrate is present on both lungs. **b** High-resolution CT sections show numerous subpleural micronodules, adjacent to the fissures *(arrows)*. Rare interlobular septal micronodules are also present *(large arrow)*

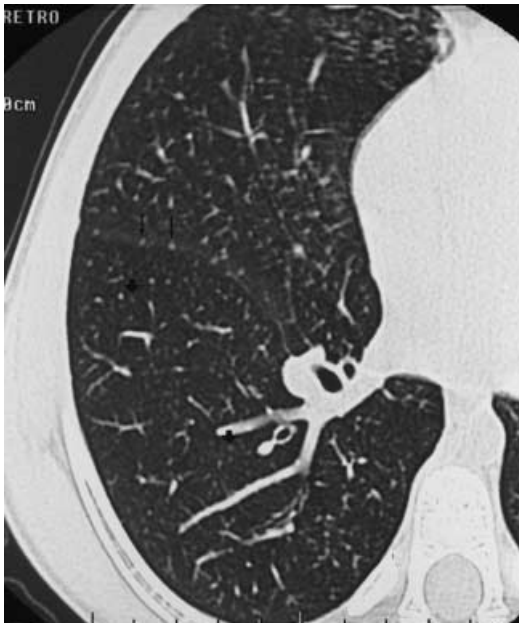

Fig. 2 High-resolution CT section of patient no. 4, carrying a normal chest radiograph, displays few intrascissural micronodules *(arrows)* and tiny ill-defined centrilobular micronodules *(large arrows)*

phocytic interstitial pneumonia is a frequent lung disease in children with AIDS, representing 25–40 % of lung involvement [6], and is considered as an indicator of AIDS in any child before the age of 13 years, unless HIV serology is negative. The diagnosis of LIP is infrequently made before the age of 1 year [6, 20, 21, 22, 23]. The suggested etiopathogenic factor of LIP in AIDS patients is the simultaneous presence of both HIV and Epstein-Barr virus in the lung, LIP representing the lung response to this presence. No progression into lymphoma is observed in pediatric AIDS patients, whereas LIP is a prelymphomatous condition in the HIV-negative adult population [4, 24]. Clinically, children usually have no respiratory complaints and diagnosis is suspected on an asymptomatic reticulonodular infiltrate on chest radiographs. Conventional radiographic patterns of LIP have been frequently described [2, 3, 8, 11, 19, 25, 26, 27, 28, 29, 30], and Oldham described four types of chest abnormalities in patients with LIP [12]. The usual presentation is a nonspecific diffuse reticulonodular infiltration of both lungs, allowing a large differential diagnosis, including opportunistic infections and early forms of neoplastic disorders.

The CT and HRCT descriptions of LIP have been made since the end of the 1980s. The most frequent HRCT findings consist in a diffuse micronodular infiltration of the interstitium, with nodules ranging from 2 to 4 mm in diameter. Bronchiectasis and bronchiolectasies have also been described and, in a recent study, 15, 8 % of children with AIDS had bronchiectasies with a frequency of 34 % in children with LIP [31]. Potential for spontaneous rupture of peripheral cyst with secondary pneumothoraces exists and can be responsible for acute respiratory failure [32, 33, 34]. Ground-glass opacities, air-space consolidation, lymphadenopathy, and pleural effusion are less frequently observed. Although infrequently observed, ground-glass opacities were described in two recent studies with a high frequency in adults [13, 16]. In the latter study, the only two patients presenting without lymphadenopathy were patients with AIDS.

In our series, HRCT demonstrated interstitial micronodules with a perilymphatic distribution and a basal predominance in all children. Compared with chest ra-

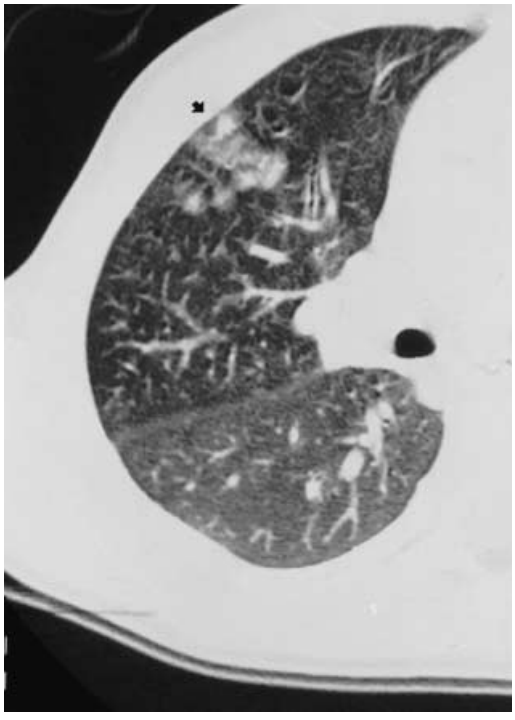

Fig. 3 High-resolution CT of patient no. 2. Confluent nodules realizing a patchy ill-defined area in the middle lobe *(large arrow)*. Bronchial wall thickening and ground-glass opacities are present in the lower lobe

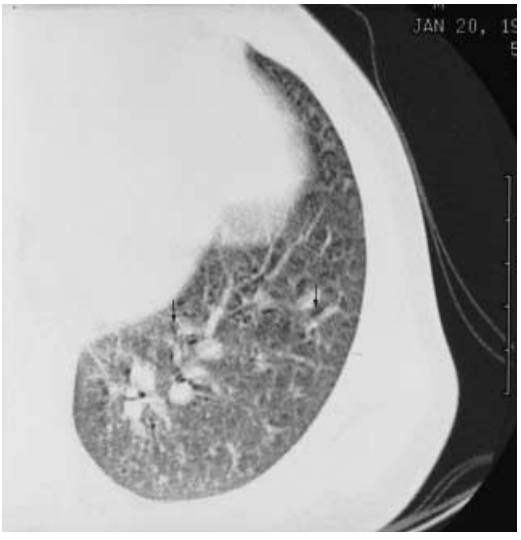

Fig. 4 High-resolution CT of patient no. 1. Diffuse ground-glass opacities and bronchiolectasies *(arrows)* in the left lower lobe

diographs, HRCT demonstrated an unsuspected interstitial involvement in 4 of 12 children. Subpleural, interlobular septal, centrilobular, and peribronchovascular micronodules were observed in decreasing order of frequency, suggesting a peripheral onset of the disease. Bronchiolectasis (children nos. 1, 2, and 5) and ground-glass opacities (children nos. 1 and 2) were infrequently observed and, when present, always associated with micronodular infiltrates. Pleural effusions were associated with superimposed lung disease. Lymphadenopathy was not seen in our series as is commonly reported in the literature.

Differential diagnosis of micronodular interstitial infiltration with perilymphatic distribution consists of pathologies not seen in the pediatric population such as sarcoidosis, silicosis, and coal worker pneumoconiosis, amyloidosis, and lymphangitic carcinomatosis. An important differential diagnosis is lymphoma. Comparing LIP and malignant lymphoma with HRCT, Honda et al. [16] observed that air-space consolidation, large nodules (11–30 mm) and pleural effusions were characteristic for malignant lymphoma and that cysts were characteristic for LIP. Presence of lymphadenopathy was not a significant feature to allow their differentiation. No children in our series presented with pulmonary cysts.

Conclusion

High-resolution CT of the lung provides a more specific pattern of abnormalities than chest radiographs in children with LIP and allows an earlier diagnosis. The correlation of HRCT findings with clinical and laboratory data allows the diagnosis of LIP without further invasive investigations. Furthermore, HRCT is useful in ruling out other pathologies such as opportunistic infections or malignancies in immunocompromised patients.

We think therefore that HRCT of the lung should be part of the initial staging and follow-up of HIV-positive children.

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