CASE REPORT
CASO CLINICO

A boy with idiopathic interstitial lung disease

Un bambino con polmonite interstiziale idiopatica

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Summary

We present the case of a child with idiopathic interstitial lung disease unresponsive to steroids, diagnosed by biopsy. Recurrent respiratory infections contraindicated more aggressive immunosuppressive treatment. Physical growth was markedly unsatisfactory. Because of the progressive deterioration of lung function, and of the continuous need for oxygen administration, a heart/double-lung transplantation was performed. At present, 4 years after the procedure, the patient appears clinically stable, with normal spirometry parameters.

Riassunto

Descriviamo il caso di un bambino con polmonite interstiziale idiopatica diagnosticata con la biopsia polmonare e non responsiva al trattamento cortisonico. L'aggiunta di altra terapia immunosoppressiva era controindicata dalla elevata frequenza di infezioni respiratorie ricorrenti. L'accrescimento staturo-ponderale era marcatamente compromesso. A causa del progressivo peggioramento clinico respiratorio e della continua necessità di ossigeno abbiamo effettuato un trapianto cuore-polmone. Attualmente, a distanza di 4 anni, il paziente è in buone condizioni cliniche e la funzionalità respiratoria è nella norma.

Key words

Interstitial lung disease • Lung transplantation

Parole chiave

Polmonite interstiziale • Trapianto polmonare

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Introduction

The term interstitial lung disease (ILD) encompasses a wide range of conditions in which the clinical symptoms primarily include dyspnea or breathlessness on exertion and/or at rest, and cough. Main histological findings consist of the infiltration of inflammatory cells, associated with fibrotic changes characterized by fibroblast proliferation and excessive collagen deposition [1].
ILD in children represents a real challenge for physicians because of difficulties in making the diagnosis and because treatment is sometimes less than optimal [2]. Indeed, although most pediatric ILD are caused by infectious agents and are characterized by a quite good outcome the cases reported are similar to adult idiopathic interstitial pneumonias, in whom the etiology is hard to identify, the response to treatment sometimes poor, and worsening of lung function may lead to respiratory failure [3].
We herein report the case of a child with ILD unresponsive to steroids in whom lung transplantation was performed with good results.

Case report

A four year-old Caucasian boy, whose parents are first-degree cousins, was referred to our unit with a 1-year history of cyanosis and dyspnea on exertion. The family history was negative for respiratory diseases. He was free of respi-

ratory symptoms, and physical growth had been satisfactory until age 3 years, when progressive shortness of breath on exertion, cyanosis and fatigability began. His parents had noted the development of clubbing of the fingers six months earlier. In the year prior to admission in our unit he had experienced a few episodes of upper respiratory tract infections with fever and cough.

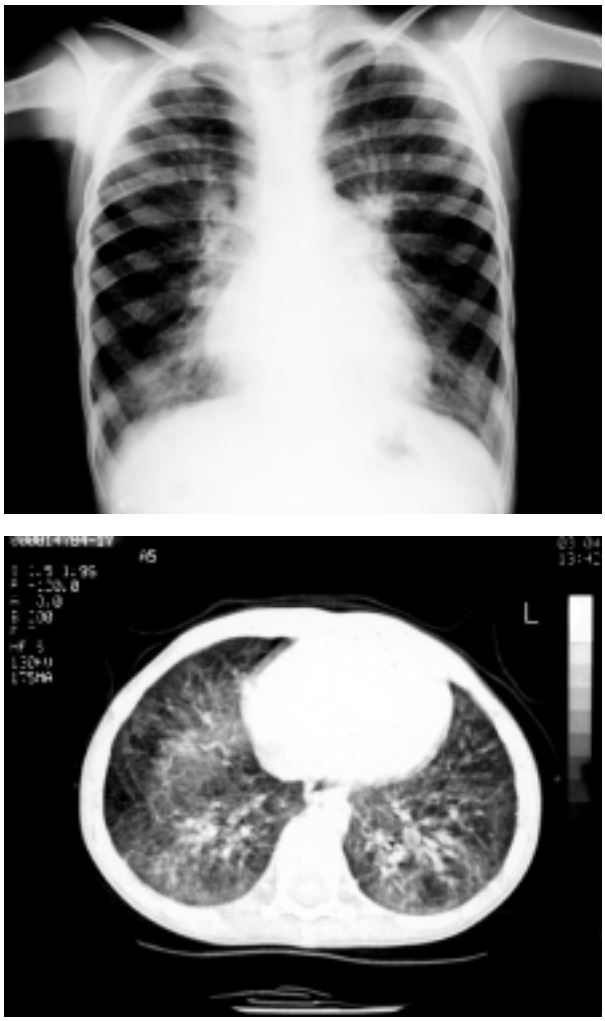
At presentation the examination revealed fine, crackling rales audible over both lung fields. The patient had dry cough. There was prominent clubbing and moderate to severe labial and limb cyanosis. Room air resting blood gases indicated an arterial oxygen tension (PaO_2) of 48 mm Hg, a carbon dioxide tension ($PaCO_2$) of 36 mm Hg, a pH of 7,35, and an oxygen saturation (SaO_2) of 70%.

Cardiac evaluation excluded heart failure. However, the electrocardiogram showed right ventricular hypertrophy. B-mode and Doppler echocardiography showed dilatation of the right heart cavities and pulmonary artery; a high speed tricuspid regurgitation was also evident. Estimated pulmonary systolic pressure was 50 mm Hg while breathing 21% FiO_2, and dropped to 25 mmHg when breathing 100% oxygen.

The chest x-ray and the high resolution computed tomography (HRCT) of the lung revealed bilateral interstitial linear and reticular opacities with areas of ground glass appearance mostly at the base (Fig. 1A, B). Immunodeficiency and malignancy were excluded. Exposure to pets, metals or organic dusts, and atopy were excluded. Diagnostic tests for gastroesophageal reflux and swallowing disorders were negative. Cultures obtained by nasal wash, and infectious titers were negative. Connective tissue diseases, including rheumatoid arthritis, systemic lupus erythematosus, polymyosite and scleroderma were excluded. The sweat test was negative and the patient had never received drugs associated with pulmonary toxicity. Gallium-67 scintiscan showed diffuse, mildly increased uptake in both lungs. Bronchoalveolar lavage (BAL) count showed 350 x 10^3 cells x mm^{-3} with 30% macrophages, 1% lymphocytes, 38,5% neutrophils, 30% eosinophils. No pathogens were identified. The thoracoscopic lung biopsy demonstrated uniform intense to moderate fibrosis. Uniform thickening of the alveolar wall due to expansion of the cellular matrix, with large numbers of proliferating fibroblasts and dense deposits of collagen and elastin fibers were evident. Cells infiltrating the alveolar septa were mainly fibroblasts and monocytes. Hyperplasia of type II pneumocytes covering the surface of most alveoli was also present (Fig. 2A, B).

Continuous oxygen and oral prednisone (2 mg/kg/day) therapy were started. After 6 months of treatment, the Gallium-67 scan and the HRCT of the chest appeared substantially unchanged. Room air blood gases analysis revealed a PaO_2 of 58 mmHg and a CO_2 of 43 mmHg. The results of the physical examination and cardiac evaluation were unchanged. Recurrent respiratory tract infections requiring antibiotic treatment occurred, contraindicating treatment with immunosuppressive agents. Exercise tolerance was minimal and physical growth was markedly unsatisfactory. A heart/double-lung transplantation was proposed and successfully performed.

Fig. 1. (A) Chest x-ray showing reticulonodular densities. (B) HRCT scan showing diffuse interstitial thickening of the intra-interlobular septa, diffuse reticulonodular densities, and a predominance of ground glass opacities at the lung bases.



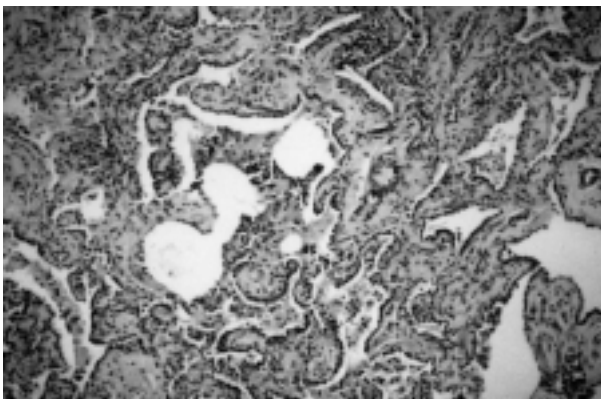
At present, 4 years after the procedure the patient appears clinically stable. The spirometry is within normal values; the patient has returned to a fully active life.

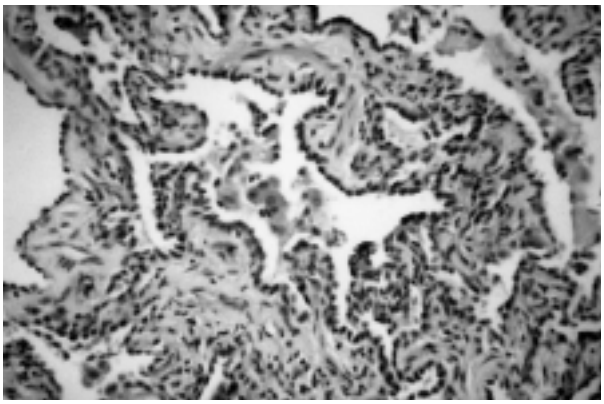
Discussion

We report on a patient with idiopathic ILD unresponsive to corticosteroid treatment in whom progressive pulmonary deterioration, complicated by severe failure to thrive and recurrent respiratory infections contraindicating more aggressive immunosuppressive drugs, led to the decision of lung transplantation.

Currently, pediatric ILD are being reported more frequently than in the past [1]. For most patients, respiratory pathogens, mainly viruses, are the primary causative agents and the episodes are self limited. However, a limited number of cases may present with progressive si-

Fig. 2. (A) Low magnification micrograph of the thoracoscopic lung biopsy specimen showing uniform thickening of the alveolar wall with large numbers of proliferating fibroblasts and dense deposits of collagen and elastin fibers. Alveolar contents show a large number of macrophages. Hematoxylin and eosin; original magnification: x 125. (B) High magnification micrograph of the same specimen showing fibrosis of alveolar septa with large numbers of proliferating fibroblasts. Note the type 2 alveolar cells hyperplasia and the macrophages into the alveolar space. Hematoxylin and eosin; original magnification: x 250.





gns and symptoms and do not respond to oral steroids [3]. More aggressive immunosuppressive agents may be administered, but conflicting results have been obtained in both children and adults [2]. A recent preliminary study of adults treated with interferon gamma plus prednisolone has demonstrated substantial improvement in the patients who had had no response to steroids alone [4]. Lung transplantation may thus represent an alternative and successful option.

According to the Katzenstein classification, most idiopathic ILD are rarely seen in children, with the only exception of non specific pneumonitis (NSIP). NSIP is defined as a chronic form of ILD lacking both the heterogeneity and the variegated pattern of usual pneumonitis (UIP), as well as the extensive accumulation of pigmented alveolar macrophages that characterizes the desquamative pneumonia (DIP) [5]. The pathologic criteria of NSIP include interstitial inflammation and/or fibrosis, the proportion of which could vary over a spectrum ranging from pure chronic inflammatory cell infiltration to fibrosis without any interstitial component [5]. The clinical features mainly include a subacute onset, the relative lack of clubbing, a rather low mortality rate, good response to steroids and frequent clinical recovery [6]. Nevertheless some cases may exhibit clinical and hystological features resembling idiopathic interstitial fibrosis, and these patients seem to be at greater risk of dying than those with cellular, non fibrotic lesions.

Whether our patient would fit the Katzenstein model of the histological and clinical course of ILD is still open to question. Presenting symptoms, chest examination, lung imaging findings showing interstitial reticulonodular pattern prominent at the lung bases with ground-glass opacities, and finally the poor response to steroids with progressive clinical deterioration make it difficult to distinguish this case from UIP. The lung biopsy indicated a fibrotic lung disease with type II cells hyperplasia and fibroblast proliferation, which is very uniform; this would be very atypical for UIP, in which the distribution of these changes is rather patchy. The histological pattern looks more like what was described by Katzenstein as NSIP type III, which is characterized by minimal inflammation but extensive fibrosis [5]. BAL findings in this case were also somewhat atypical, in that there was an extremely high eosinophil count. While eosinophilia in ILD indicates poor prognosis [7], it usually does not reach this level, but this still remains a possibility.

A recent multicentre survey on pediatric ILD pointed out the difficulties in applying the classification of adults ILD to children [8]. In this study, in 61% of the cases in whom the pathologists were unable to classify the histological pattern, the term of «non classified fibrosis» was used; in the remaining 35% a clear histological definition of the disease as DIP or UIP or NSIP or LIP was made.

Registry data from the International Society for Heart and Lung Transplantation demonstrates that ILD is the second most common indication for lung transplantation [9]. The successful outcome achieved in our patients after the lung transplant confirms that with increasing technical refinements and experience lung and/or heart-lung transplantation can be hopefully successful even in pediatric patients with ILD.

In conclusions, our knowledge about ILD in children has been limited in the past by the perception that it is uncommon at this age. The availability and applicability of diagnostic procedures in children has resulted in an increased number of pediatric diagnoses [8]. Finally, we confirm that even in children unresponsive to oral glucocorticoids, progressive ILD represents an indication for lung transplantation.

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