Aims and objectives

PPFE (pleuroparenchimal fibroelastosis) is a rare interstitial pneumonia, recently included in the updated classification of IIPs (idiopathic interstitial pneumonias) [1], first described by Amitani et al. as a fibrosis of the upper lobes [2] and then recognized as a novel clinicopathological entity by Frankel et al. who coined the term "PPFE" [3].

It is typically distributed in the upper zones, bilaterally; HRCT shows pleuroparenchimal thickening associated with fibrosis (traction bronchiectasis, moderate reticular abnormalities, superior hilar retraction) and platythorax; consolidations might be present, mainly in the upper zones, while fibrosis can occur in the middle or lower zones, as UIP or possible UIP [3-5].

Extrathoracic involvement is typically absent in PPFE.

Idiopathic forms of PPFE generally involve patients in the 5th/6th decade, without any significant difference in percentage between males and females; the majority have never smoked and there is often a history of recurrent infections and/or of autoimmune disease [6]. Secondary forms mostly occur as a late complication of lung [6-8] or hematopoietic stem cell transplantation (HSCT) [6, 7]; moreover, rare familiar cases have been observed [3,9]; recently a relationship with exposure to some chemotherapeutic agents has been described [10].

Clinically the main features include cough, dyspnea, spontaneous pneumothorax, weight loss, flattening of the thoracic cage [11] and restrictive pulmonary function decline [3-7, 12-17].

The pathological features of PPFE are intense, elastic fibrosis of visceral pleura and subpleural lung with intra alveolar involvement and characteristically sharply demarcated from the adjacent normal lung [3, 4, 6, 7, 13, 14, 18, 19].

If the disease is strongly suspected on clinical and radiological grounds, a label of "consistent with PPFE" has been proposed [6, 13]. In these cases the biopsy is not advised, due to the high risk of pneumothorax in these patients [10, 13]. However, the acronym PPFE is reserved only for pathologically documented cases [13].

The clinical course is progressive: although some cases take years to develop, others rapidly progress to respiratory failure [2, 6, 10, 12, 13, 18]. Once PPFE becomes symptomatic, outcome is poor despite ventilatory support [12] with a 40%-66% mortality rate in few years [6, 7, 10, 13, 15, 20].

Our study had two main purposes: the first was to evaluate the prevalence of PPFE amongst lung and allogeneic hematopoietic stem cell transplantation recipients (HSCT);
the second was to evaluate the prevalence of idiopathic PPFE amongst the general population.

**Methods and materials**

An expert thorax radiologist (M. Zompatori) retrospectively reviewed HRCT exams from the database of our Department (Pneumonefro-Radiology Department, Policlinico S. Orsola, Bologna, Italy) dating back to 2007, in order to select cases that radiologically fulfilled PPFE criteria. Secondary forms were researched reviewing HRCT exams from 53 lung transplant recipients and 700 allogeneic HSCT recipients.

Idiopathic cases were examined analyzing all HRCT exams of which the reports contained such terms as "pneumothorax", "apical fibrosis", "apical thickening", "apical scarring".

For each case selected, consistent with PPFE, the following details were retrieved: clinical characteristics, laboratory and functional data, pathological findings (available only for 1 patient) and metabolic data (PET-FDG available for 3 patients).

During the process of selecting our cases, we excluded those with apical fibrosis and pleuroparenchimal thickening due to tubercosis, tubercosis pneumothorax treatment, aspergillosis, radiation therapy, exposure to asbestos, heamothorax, connective tissue disease or sarcoidosis.

**Results**

We identified 8 cases clinically and radiologically consistent with PPFE: 1 case amongst allogeneic HSCT recipients, 4 cases amongst lung transplanted patients and 3 idiopathic cases amongst the general population.

These results show that PPFE has a prevalence of 7.5% amongst lung recipients, 0.1% amongst HSCT recipients and 0.06% amongst the general population.

Complete clinical, laboratory and radiological details are summarized in **Table 1** on page 7, **Table 2** on page 7 and **Table 3** on page 8.

Amongst the 8 selected cases, none of them had ever smoked, 7 were male and 1 was female (age range 33-72yrs, median 54yrs).
7 patients presented symptoms such as dyspnea and dry cough; 1 patient with low extensive fibrosis was asymptomatic. Spontaneous pneumothorax was observed in a single idiopathic case (Fig. 1 on page 7). (Table 1 on page 7)

Recurrent lower respiratory infections had been reported in all lung recipients and for 3 patients infections were supported from Cytomegalovirus (Table 1 on page 7, Table 2 on page 7).

Regarding the exposure to chemotherapeutic drugs (Table 1 on page 7), all lung recipients underwent triple immunosuppressive therapy including corticosteroid, mycophenolate or azathioprine, cyclosporine or tracrolimus; the HSCT recipient was treated with cyclophosphamide during the conditioning regime.

3 patients were found to have autoantibodies in their serum (Table 2 on page 7): anti HLA versus the transplanted lung (1 lung recipient), ANA and rheumatoid factor (2 patients with idiopathic PPFE).

The pulmonary physiology (Table 2 on page 7) demonstrated a progressive loss of allograft function amongst all lung transplanted patients: one showed a restrictive pattern and the others a mixed pattern because fibrosis established itself alongside an airway disease (tracheomalacia, bronchial anastomotic stenosis). The HSCT recipient demonstrated a progressive lung decline after the transplantation, presenting firstly as a mixed defect (due to concomitant COPD), then a predominant restrictive pattern. All the idiopathic cases showed a restrictive pattern.

The radiological analysis (Table 3 on page 8) allowed us to identify four grades of PPFE severity, based on extension and pleuroparenchimal findings; 5 patients (3 of which were lung transplanted and 2 idiopathic PPFE) showed a moderate fibrosis (grade 2-3); 2 cases (1 idiopathic and 1 HSCT recipient), presented an asymmetric distribution with severe fibrosis in one lung (grade 4) and moderate fibrosis in the other (grade 2) (Fig. 2 on page 5). Only one case (lung transplanted) demonstrated mild alterations (grade 1).

Fibrosis of the lower lobes coexisted with PPFE in 5 patients: 3 cases presented a form of diffuse PPFE and 2 cases presented lower fibrosis that radiologically fulfilled the NSIP (a patient underwent a double lung transplantation) and UIP (a patient with idiopathic PPFE, Fig. 3 on page 8) criteria.

We were not able to evaluate the progressive chest flattening because no chest radiograph was available before the diagnosis of fibrosis.

PET-FDG imaging (Table 3 on page 8), available for 3 patients, showed hypermetabolic areas corresponding to the pleuroparenchimal thickenings.

Regarding the clinical and radiological progression, it was slow for 5 patients and rapid for one of them (Fig. 4 on page 9); the evolution was not evaluated for the other patients in the absence of sufficient data.
**Fig. 2**: Case 5: M, 33 yrs. HSCT. Asymmetric PPFE distribution: right lung severe fibrosis (grade 4); left lung moderate fibrosis (grade 2)

**Table 1**: Clinical characteristics. L: left lung; R: right lung; yrs: years; CMV: cytomegalovirus; HSCT: hematopoietic stem cell transplantation; a/c GVHD: acute/chronic graft versus host disease; PPFE: pleuroparenchymal fibroelastosis; ILD: interstitial lung disease; CLAD: chronic lung allograft dysfunction; RAS: Restrictive allograft syndrome; Hx: history. Occ/env: occupational/environmental allergen exposure; -: No data.

**Fig. 1**: Case 7. F, 68. Idiopathic PPFE. Recurrent left pneumothorax.
Table 2: Laboratory data. Neg: negative. HSTC: hematopoietic stem cell transplantation; BAL: bronchoalveolar lavage; L: left lung; R: right lung; CMV: Cytomegalovirus; PPFE: pleuroparenchimal fibroelastosis; ANA: anti-nuclear antibody; HLA: human leukocyte antigen; IL-6/8: interleukin 6/8; TLCO: transfer factor of the lung for carbon monoxide; -: No data.

<table>
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<th>Case</th>
<th>Antigens</th>
<th>BAL</th>
<th>Aspergillus</th>
<th>CMV</th>
<th>TB</th>
<th>Pulmonary physiology pattern</th>
<th>TLCO</th>
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<tr>
<td>1</td>
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<td>neg</td>
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<td>neg</td>
<td>Mixed pattern</td>
<td>-</td>
<td>-</td>
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<tr>
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<td>anti-KA vs the transplanted lung</td>
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<td>positive</td>
<td>neg</td>
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<td>-</td>
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</tr>
<tr>
<td>4</td>
<td>neg</td>
<td>-</td>
<td>Aspergillus and S. S. neg</td>
<td>neg</td>
<td>neg</td>
<td>Mixed pattern; initially restrictive then also restrictive</td>
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<tr>
<td>5</td>
<td>neg</td>
<td>-</td>
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<td>Restrictive</td>
<td>decreased</td>
<td>PPFE</td>
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<tr>
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<td>-</td>
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<tr>
<td>7</td>
<td>ANA</td>
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<td>Restrictive</td>
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<td>-</td>
</tr>
<tr>
<td>8</td>
<td>ANA</td>
<td>-</td>
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<td>neg</td>
<td>-</td>
<td>Restrictive</td>
<td>decreased</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 3: Imaging findings. HSCT: hematopoietic stem cell transplantation; L: left lung; R: right lung; PPFE: pleuroparenchimal fibroelastosis; NSIP: nonspecific interstitial pneumonia; UIP: usual interstitial pneumonia; exp: expiratory CT scan; PET: positron emission tomography; PAH: pulmonary arterial hypertension; RPA: right pulmonary artery; LPA: left pulmonary artery; -: No data.
Fig. 3: Case 8. M, 71. Idiopathic PPFE. Apical PPFE coexisting with UIP at the lower lobes.
Fig. 4: Case 3. M, 52 yrs. Double lung transplantation. Rapid PPFE progression with a new pleuroparenchimal consolidation in the anterior segment of the right upper lobe.
Conclusion

We have described 8 cases, clinically and radiologically consistent with PPFE, showing a prevalence of 7.5% amongst lung recipients, 0.1% amongst HSCT recipients and 0.06% amongst the general population as idiopathic PPFE.

The high prevalence amongst lung transplanted patients was previously unknown and could suggest that recurrent infections or autoimmune damage may have a role in the pathogenesis of the disease.

25% of patients with PPFE presented also a different, associated pattern of ILD at the lower lobes, suggesting that some patients are genetically predisposed to develop different kinds of lung fibrosis.

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References


