

# Usual interstitial pneumonia in a patient with celiac disease and polyglandular syndrome IIIA

**Likurgos Kolilekas<sup>1</sup>**  
**Effrosyni D. Manali<sup>2</sup>,**  
**Melpomeni Peppas<sup>3</sup>,**  
**Themistocles Chamogeorgakis<sup>4</sup>,**  
**Amalia Papadopoulou<sup>2</sup>,**  
**Christina Triantafillidou<sup>5</sup>,**  
**Konstantinos Kagouridis<sup>2</sup>,**  
**Dimitra Rontogianni<sup>6</sup>,**  
**Anna Karakatsani<sup>2</sup>,**  
**Spyros A. Papiris<sup>2</sup>**

<sup>1</sup>7<sup>th</sup> Pulmonary Department, Athens Chest Hospital, Greece

<sup>2</sup>2<sup>nd</sup> Pulmonary Department, "Attikon" University Hospital, Athens Medical School, National and Kapodistrian University of Athens, Greece

<sup>3</sup>2<sup>nd</sup> Department of Internal Medicine, "Attikon" University Hospital, Athens Medical School, National and Kapodistrian University of Athens, Greece

<sup>4</sup>Department of Cardiothoracic Surgery, "Attikon" University Hospital, Athens Medical School, National and Kapodistrian University of Athens, Greece

<sup>5</sup>6<sup>th</sup> Pulmonary Department, Athens Chest Hospital, Greece

<sup>6</sup>Department of Pathology, "Evangelismos" General Hospital, Athens, Greece

### Key words

- Usual interstitial pneumonia
- Pulmonary fibrosis
- Celiac disease
- Polyglandular syndrome IIIA

### Correspondence to:

Likurgos Kolilekas,  
Consultant, 7th Pulmonary Department, Athens Chest Hospital "Sotiria",  
152 Mesogion Ave, 11527, Athens, Greece  
Tel.: +30 210 7763306, Fax: +30 210 77681911,  
e-mail address: lykol@yahoo.gr

**ABSTRACT.** We present for the first time a patient, who from his first months of life developed several autoimmune endocrine and non disorders such as type 1 diabetes, autoimmune thyroiditis, and vitiligo [the constellation of polyglandular autoimmune syndrome IIIA (PG IIIA) manifestations], severe osteoporosis, as well as celiac disease (CD) diagnosed at the age of 9 years-old. Corticosteroids were administered in addition to gluten-free diet, because of partial response, for two decades. During the last 3 years he developed finger clubbing and progressive dyspnea on exertion and was hospitalized repeatedly because of lower respiratory tract infections. The persisting and aggravating chronic dyspnea and diffuse interstitial pattern on chest imaging, led to extensive investigation in order to further characterize his lung disease, disclosing usual interstitial pneumonia (UIP) histologic type lung involvement. On his last admission in our department because of fever and severe deterioration of respiratory status, the patient developed acute lung injury (ALI)/acute respiratory distress syndrome (ARDS), the so called UIP "acute exacerbation", ending to death. *Pneumon* 2014, 27(4):345-349.

## INTRODUCTION

Celiac disease (CD) is a chronic inflammatory disorder of the small bowel that is triggered by the ingestion of wheat gluten and related proteins of rye and barley in genetically susceptible individuals<sup>1</sup>. Celiac disease is frequently associated with autoimmune disorders, including several autoimmune endocrinopathies, and patients affected present increased susceptibility for the development of T-cell lymphoma. Polyglandular autoimmune syndrome type IIIA (PAS IIIA) which encompasses autoimmune thyroiditis and type 1 diabetes mellitus, and occasionally other autoimmune manifestations is seldom reported associated to celiac disease.<sup>2,3</sup> Usual interstitial pneumonia (UIP) is the histologic pattern of a dreadful, chronic and irreversibly progressive lung disease called pulmonary fibrosis, which may be seen alone [idiopathic pulmonary fibrosis, (IPF)] or associated to

several conditions among them autoimmune rheumatic disorders, drugs, environmental factors<sup>4,6</sup>. In celiac disease, respiratory involvement is rarely reported and to the best of our knowledge never in the form of pulmonary fibrosis and its related complications. Exacerbations in pulmonary fibrosis represent acute, clinically significant deteriorations of “unidentifiable” cause that transform the slow and more or less steady disease decline to the unexpected appearance of acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) ending to death<sup>7</sup>. We present for the first time, the case of a 29-year-old male patient with CD presenting the constellation of PAS IIIA manifestations, and pulmonary fibrosis, developing a devastating “acute exacerbation”.

### CASE PRESENTATION

A 31 year-old non-smoker male, underweight (BMI 14), presented to the emergency department because of progressive dyspnea on exertion lasting a week, dry cough, fever and tachypnea.

His medical history was rich and long-lasting. Type 1 diabetes mellitus was diagnosed first at the age of 7 months. Celiac disease was diagnosed at 9 years of age on the basis of malabsorption, villus atrophy on small bowel biopsy and high anti-endomysial, anti-gliadin and anti-transglutaminase antibodies titers. Corticosteroids were administered in addition to gluten-free diet, because of partial response, for all these years (10 mg/die prednisolone). Autoimmune thyroiditis was diagnosed at the age of 16 years. Vitiligo appeared soon after and osteoporosis was documented as well. The patient also reported progressive dyspnea on exertion and cough for the last 3 years, and the development of finger clubbing was documented since then. Six months ago, he was admitted in another hospital because of “pneumonia” due to *Pneumocystis Jirovecii* that was successfully treated. On that occasion, the chest roentgenogram and CT disclosed again the same diffuse interstitial pattern attributed to the infection in course. Physical examination revealed bilateral crackles (Velcro like) on lung auscultation, a respiratory rate of 30 breaths per minute and hypoxemia. Chest X-ray on admission showed a diffuse interstitial pattern (Figure 1). High resolution computerized tomography (HRCT) of the chest revealed ground glass opacities, extensive reticular pattern and traction bronchiectasis, indicating thus a possible interstitial lung disease (Figure 2 a, b). Bronchoalveolar lavage was performed and quan-

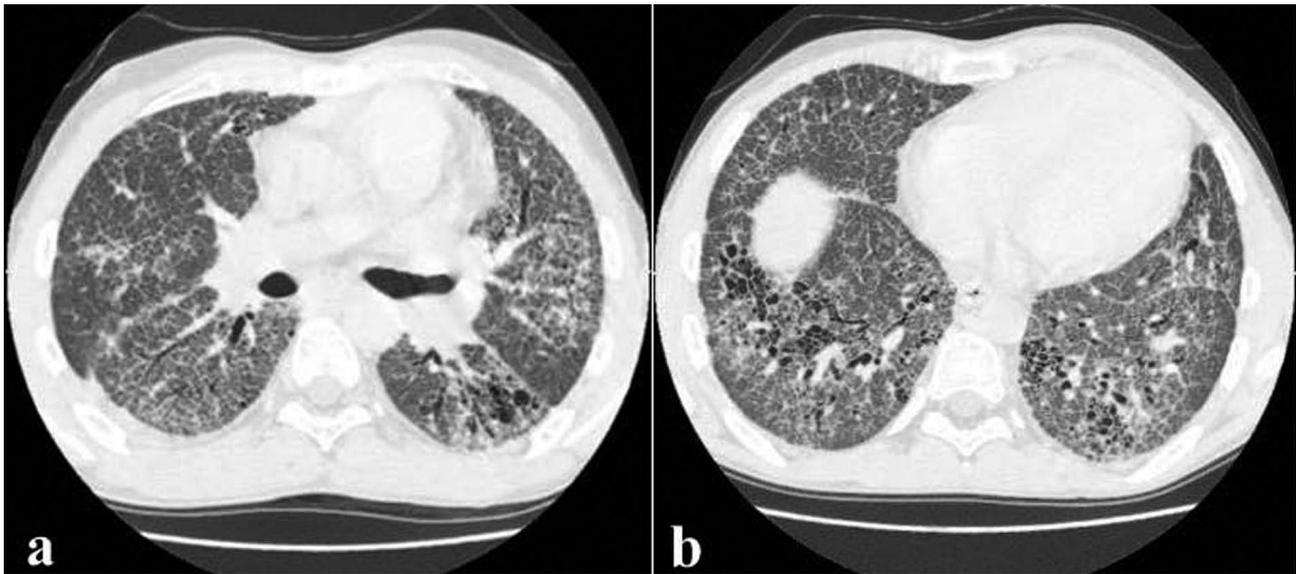


**FIGURE 1.** Chest X-ray depicting a hazy opacification especially in both middle and lower lung fields upon an extensive reticulation.

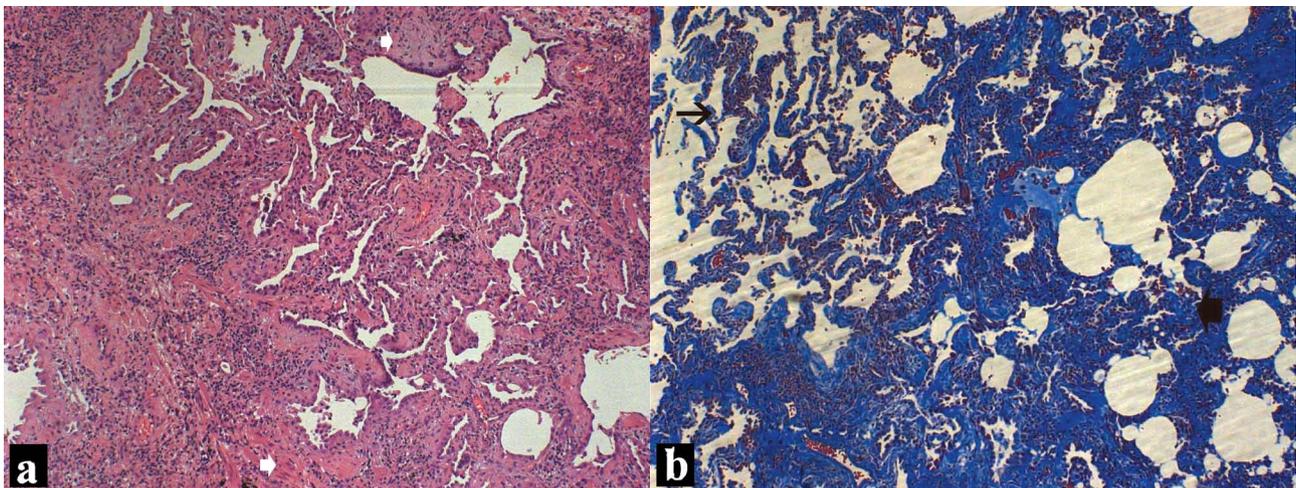
titative cultures grew positive for *Klebsiella Pneumoniae* species successfully treated with antimicrobials. During his hospital stay, gastroenteroscopy, capsule endoscopy and histologic examination of small-intestinal biopsy samples revealed alterations suggestive of CD without further complications.

On the follow-up, the patient reported further deterioration of dyspnea. Since new chest imaging showed no changes after remission of infection, further investigation was performed with lung function tests, showing a severe restrictive pattern (FEV<sub>1</sub>=24% predicted, FVC=22% predicted, and FEV<sub>1</sub>/FVC=91,6%). Measurements of static volumes and diffusing capacity were not obtained because of inability of the patient to perform the manoeuvres. The 6-minute walking test was interrupted at 2 minutes due to significant oxygen desaturation. Considering the clinical, functional and chest imaging findings suggestive of a not determined interstitial lung disease, a lung biopsy through video-assisted thoracoscopic surgery was considered mandatory and disclosed findings consistent with UIP histologic type lung involvement (Figure 3 a, b). The patient presented no family history significant for autoimmune rheumatic diseases and both the clinical and laboratory examination did not reveal any findings compatible with such a disease.

Low dose mycophenolate mofetil (1 gr/die) was added to his treatment by the gastroenterologist, mostly because of his primary disease considered not adequately controlled and, regarding the established pulmonary fibrosis,



**FIGURE 2 a, b.** HRCT of the chest at two different levels depicting ground glass upon a reticular pattern (thickening of the interlobular septa) and cylindrical traction bronchiectasis.



**FIGURE 3. a.** Remodeling of the normal lung architecture with epithelial metaplasia and thickening of the interstitium by varying degrees of mononuclear cell infiltration and collagen deposition. Mucus as well as desquamative pneumocytes are present in several of the airspaces. Marked fibrosis with dense collagenous scarring with irregularly shaped cystic spaces (honeycombing) is noted. Temporal heterogeneity is manifested by the presence of dense acellular collagen and scattered fibroblastic foci (arrowheads). H&E stain (x 200). **b.** Similar lesions as described in 3a in Trichrome Blue (Masson's) Stain (connective tissue is stained blue). Note the patchy character of the lesions of the lung characterized by the interchange of normal alveolar tissue (arrow) with advanced UIP lesions (arrowhead).

the patient was referred to the National Transplantation Center for pre-transplantation evaluation<sup>68</sup>.

Eighteen months after his first admission in our department he was readmitted because of fever, purulent sputum and severe respiratory failure. *Klebsiella Pneumoniae* spe-

cies grew again from sputum cultures and immediately treated with the appropriate antimicrobials. However, the clinical course of the patient further deteriorated and ALI/ARDS developed (Figure 4) requiring ICU translocation for ventilatory support.



**FIGURE 4.** HRCT of the chest. Extensive ground glass opacification superimposed on the previously described reticular pattern compatible with the clinical development of acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) upon usual interstitial pneumonia (UIP).

## DISCUSSION

Previous reports have shown an association of CD with several autoimmune endocrine and non disorders as well as a short list of known and of unknown etiology pulmonary disorders, but to the best of our knowledge, this is the first ever reported association with PAS IIIA and UIP<sup>7,9</sup>. During his clinical course the patient developed the most devastating complication of pulmonary fibrosis, the so called “acute exacerbation”, requiring intensive care unit (ICU) management.<sup>7,9</sup>

Celiac disease usually presents between the ages of 4 and 24 months, though its diagnosis is increasingly being made in adults. Most patients improve after starting a gluten-free diet. Refractory disease may require additional treatment with corticosteroids or other immunosuppressants as in our patient.<sup>1</sup> Persistent symptoms in CD may also be caused by associated disorders, disease complications, or noncompliance to the diet. Associated autoimmune disorders increase substantially with increasing age at diagnosis probably related to the long-lasting exposure and absorption of gluten antigens as in our patient. Autoimmune polyendocrinopathy such as PAS IIIA is seldom reported associated to CD.<sup>10</sup> On the other hand, associated with CD lung disorders are occasionally reported and include idiopathic pulmonary haemorrhage<sup>11</sup>, sarcoidosis<sup>12</sup>, extrinsic allergic alveolitis<sup>13</sup>, Langerhan’s cell histiocytosis<sup>14</sup>, lymphocytic bronchoalveolitis<sup>15</sup>, bronchiectasis<sup>16</sup>, and bronchial asthma<sup>17</sup>.

The reason for the development of several autoimmune as well as lung disorders with CD remains to be defined<sup>18</sup>. In CD, gluten peptides, after crossing the enteric epithelium, are deamidated by tissue transglutaminase and then presented by DQ2+ or DQ8+ antigen-presenting cells to pathogenic CD4+ T cells. Once activated, the CD4+ T cells drive a T-helper-cell type 1 (TH1) response leading to tissue damage.<sup>1</sup> Transglutaminase is a ubiquitous enzyme controlling apoptosis and one of the targets of autoantibodies in CD. Apoptosis is considered among the mechanisms involved in the development of associated autoimmune polyendocrinopathies.<sup>3</sup> On the other side, UIP is the histologic counterpart of pulmonary fibrosis, a chronic, irreversibly progressive lung disease that is considered multifactorial<sup>19,20</sup>. Studies regarding the possible role of major histocompatibility complex (MHC) suggest that some MHC polymorphisms confer susceptibility to IPF, by the induction of alveolar epithelial cell apoptosis, a critical process in the development of uncontrolled lung fibrosis<sup>21</sup>. The concurrence of several favourable conditions, genetic, immunologic as well as environmental might relate for the emergence of this rare combination of disease entities in our patient. Furthermore, in UIP T lymphocytes may modulate the inflammatory and healing responses in the lungs in a profibrotic or antifibrotic manner, depending on their phenotype<sup>22</sup>. Phenotypic reshaping of T lymphocytes towards TH1 response may be influenced by the immunological response occurring in CD probably in a protective manner and this might explain the rare association of CD with fibrotic lung disorders.<sup>22</sup>

The patient of the present report has a histopathological confirmed diagnosis of UIP and developed the most devastating complication of this disease the so called “acute exacerbation”<sup>9</sup>. Several reports employing surgical biopsy or autopsies have shown in such cases the histological picture of diffuse alveolar damage (DAD), the tissue counterpart of ALI/ARDS, upon UIP. The development of DAD upon UIP may relate to a clinically occult infection, aspiration or a distinct pathobiological process.<sup>9</sup> By definition UIP “exacerbations” should be considered in UIP patients that develop ALI/ARDS, only “after excluding identifiable causes of lung injury”. However, even after the exclusion of any identifiable and treatable factor(s) inducing exacerbations, the most important etiologic hypothesis remains that of a clinically occult infection which precipitates an already UIP scarred lung into DAD.<sup>9</sup> Viruses and bacteria on traction bronchiectasis are the best etiological candidates. In our patient the development of pulmonary fibrosis exacerbation might probably

relate to immunosuppression favoring the development of persistent colonizers of the bronchial tree to overt infectious pathogens.

Early identification of CD patients is important since it may result in the treatment of subclinical CD and in the avoidance of development of associated disorders including those from the lung that may reveal fatal.

In the present case report, it became obvious that the use of immunosuppressive treatment for two decades for CD did not prevent the development and progression of pulmonary fibrosis and encouraged instead recurrent infections to occur that proved to be fatal, showing that way the inefficacy of such treatment options in pulmonary fibrosis<sup>9</sup>. Furthermore despite immediate and timely pre- transplant evaluation the patient was not finally transplanted due among other reasons most probably to the lack of a well-organized national lung transplantation program.

## COMPETING INTERESTS

All the authors declare that they do not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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