Case Report

Follicular bronchiolitis in an adult patient with common variable immunodeficiency

3-year follow-up

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Key words
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- Common variable immunodeficiency
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SUMMARY. Pulmonary manifestations of common variable immunodeficiency, apart from lung infections, include interstitial lung disease such as bronchiolitis. Follicular bronchiolitis as a result of immunodeficiency is mostly described in children. The interesting case of a 35 year old female patient is presented. The patient was admitted to our Department for the investigation of fever up to 38.5 oC for a period of 3 months. The patient had been diagnosed with follicular bronchiolitis 2 years ago. Upon admission the patient was febrile and presented mild cough. Blood tests revealed anemia and leucopenia. Chest-X ray was normal, but the high-resolution CT scan showed subcarinal lymph nodes, ground glass opacities and nodules. Bronchoscopy revealed no specific findings. Bronchoalveolar lavage showed a high percentage of lymphocytes. The results of pulmonary function tests revealed a restrictive disorder. Due to raised suspicion for a lymphoproliferative disease, the patient underwent bone marrow biopsy that was normal. A significant decrease of IgA, IgM and IgG was afterwards detected and the patient was diagnosed with common variable immunodeficiency. Subsequently she started treatment with intravenous immunoglobulin. The patient's follow-up 3 years after the immunodeficiency diagnosis as well as response to treatment are presented. ***Pneumon 2014, 27(2):163-168.***

INTRODUCTION

Apart from infectious complications, patients with common variable immunodeficiency (CVID) may develop interstitial pneumonia[1]. This disease is called granulomatous lymphocytic interstitial lung disease (GLILD)[2] and is histologically diagnosed[3]. GLILD is characterized by the combination of granulomatous and lymphoproliferative histologic patterns, such as lymphocytic interstitial pneumonia, lymphoid hyperplasia and follicular bronchiolitis (FB)[2].

LB is a benign lymphoproliferative disease of the respiratory system[4].

It may be idiopathic or secondary to collagen vascular disease, immunodeficiency or hypersensitivity[5-7]. The term bronchiolitis defines an inflammatory and potentially fibrosing condition affecting mainly the intralobular conducting and transitional small airways[8]. Extended clinical, radiological examinations as well as pathological confirmation are required for the diagnosis[9].

Only a small number of cases of FB proven by lung biopsy in children and adults are reported and in the literature most of them are associated with Sjogren's syndrome and rheumatoid arthritis[10-12]. We present the interesting case of a 35-year-old woman that was diagnosed with CVID-associated FB. The patient's 3-year follow-up and response to treatment are also presented.

CASE REPORT

A 35 year old female patient was admitted to our Department presenting febrile episodes fluctuating up to 38°C which had persisted for 3 months, under the diagnosis of FB. These episodes had been attributed to recurrent bronchitis.

The patient had been diagnosed with FB 2 years ago, when she was admitted to a Pulmonary Department for the investigation of recurrent episodes of fever without any other accompanying symptoms. At that time chest CT scan showed radiological findings of interstitial lung disease with nodular pattern. A lung biopsy performed by video-assisted thoracoscopic surgery (VATS) revealed follicular bronchiolitis. More specifically lymphatic tissue with germinal centers was detected (Figure 1A). The presence of both B and T lymphocyte population minimized the possibility of malignancy (Figures 1B and 1C). The diagnosis was based on immunochemistry where the germinal centers were negative to the bcl2 stain (Figure 1D). Both bone marrow aspiration and biopsy were negative for malignancy. At that time the aim of the investigation was exclusion of malignancy and no further tests were performed. The patient had been treated with corticosteroids (32mg of methylprednisolone with gradual tapering) for about 8 months. During treatment she presented with lower respiratory tract infections and no response in HRCT findings was observed.

Upon admission to our Department, the patient was febrile up to 38,5°C and presented with mild cough and whitish expectoration, without evidence of a collagen tissue disease. Clinical examination was not remarkable for specific findings. The blood tests showed leucopenia with WBC 2,660κ/μl (57% neutrophils, 37% lymphocytes), anemia with hemoglobin 10.4g/ml, Hct 34% and platelets 114000 κ/μl. The serum biochemical profile was within normal limits as well as the inflammation markers (erythrocyte sedimentation rate, procalcitonin and CRP). The patient's chest X-ray was normal (Figure 2). However, the HRCT scan revealed enlarged subcarinal lymph nodes, ground glass opacities alternating with areas of nodular lesions, situated at the lower lobes bilaterally, middle lobe and lingula. Moreover bronchiolectasis and thickening of interlobular septa were detected (Figure 3). Pulmonary function tests revealed a restrictive pattern, with FEV1 2.64 L (80.4%), FVC 2.67L (70.6%), FEV1/FVC 94.18%, DLCOco 56.2 %. In the 6-minute walk test (6MWT), the patient walked 285 meters without displaying any desaturation. Given her DLCOco and her performance in 6MWT and the patient underwent echocardiogram and CT angiography that were normal. Her performance was finally attributed to deconditioning. Bronchoscopy did not reveal any intrabronchial abnormalities. The BAL was of moderate cellularity, with a high percentage of lymphocytes 43%. In the analysis of T-cells, CD4 and CD8 showed a percentage of 45% and 53% respectively with a ratio of 0.89 (higher than the one in blood - 0.49). The percentages of neutrophils and eosinophils were slightly increased (10% and 1% respectively). The BAL cytological examination was negative for malignancy. *S. pneumoniae* was isolated and treatment was initiated. The tests for serum rheumatoid factor, c-ANCA, p-ANCA, anti-CCP, anti-Ro, anti-La and anti-DNA were negative. Because of the recurrent episodes of infection, suspicion was raised upon immunodeficiency and serum immunoglobulins were measured and found significantly decreased: IgM: 4,2 mg/dl (normal values 46-403 mg/dl), IgA: 6.7 mg/dl (normal values 82-453 mg/dl) and IgG: 33.3 mg/dl (normal values 751-1560 mg/dl). Electrophoresis of serum proteins revealed a very low ratio of gamma globulins (Table 1).

In addition, due to the low white blood cell count and anemia, the patient underwent bone marrow aspiration and biopsy, in the context of investigation for malignancy. The immunophenotype of mononuclear cells showed a significant decrease in the B-lymphocyte population whereas the bone marrow biopsy was normal without any evidence of malignancy.

Based on the patient's medical history and the laboratory results the diagnosis of CVID was made and the patient was treated with intravenous immunoglobulin. Ten days post treatment IgG levels increased from 33mg/dl to 218 mg/dl. The patient was then transferred to an Internal Medicine Department for further hospitalization

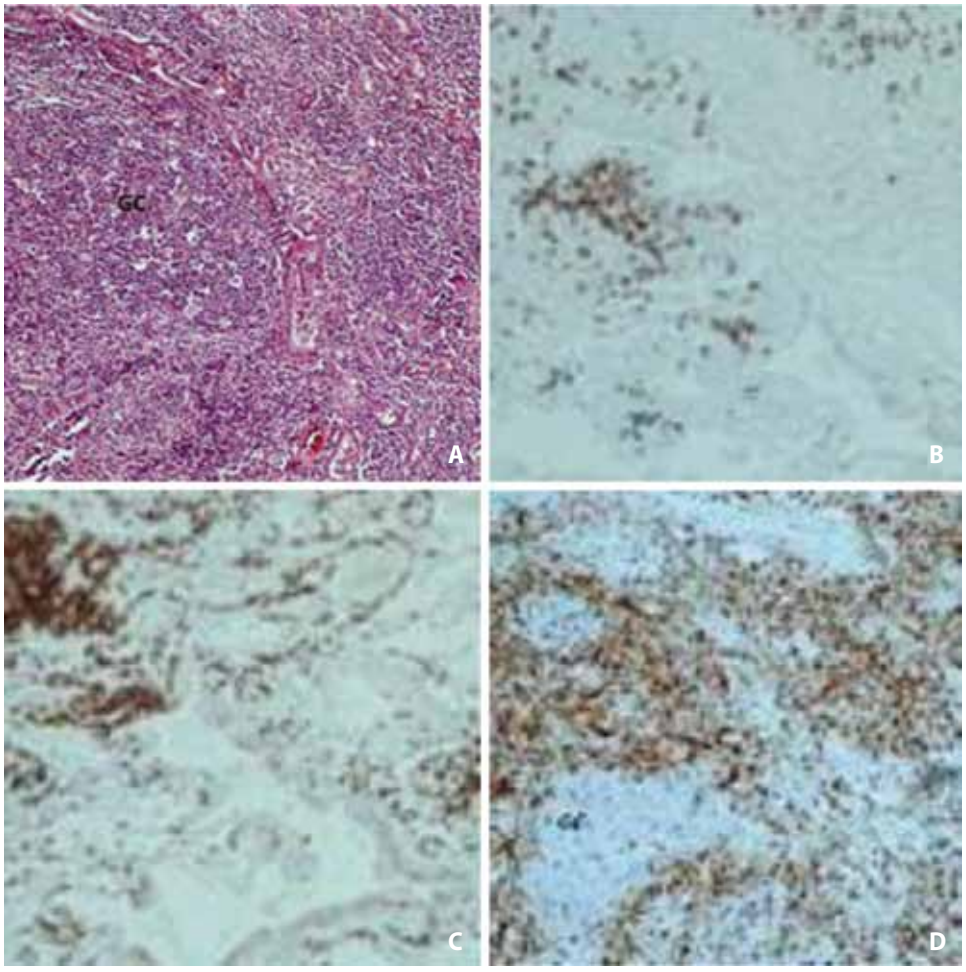

FIGURE 1. Lung biopsy. A: lymph tissue that surrounds partially or wholly the bronchioles, with the presence of germinal centers (GC) (H+E X 100). B: mixed population of B and T lymphocytes. On figure B there are CD20 positive lymphocytes and on figure C CD3 positive lymphocytes (immunochemistry stain). D: Lung biopsy: Germinal centers that are negative to the bcl2 stain (immunochemistry stain).

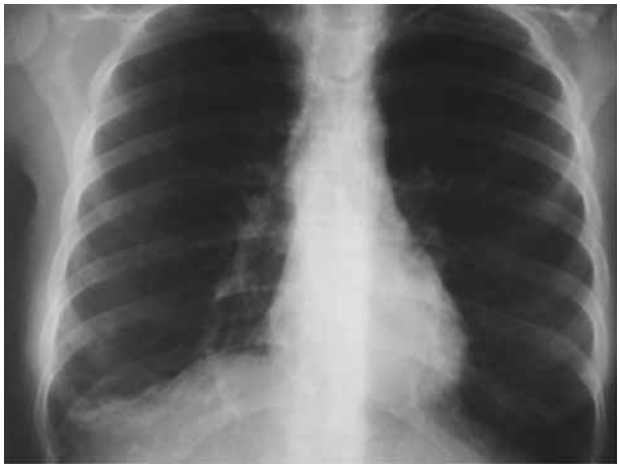

FIGURE 2. Chest X-ray upon admission to the Department, without significant findings.

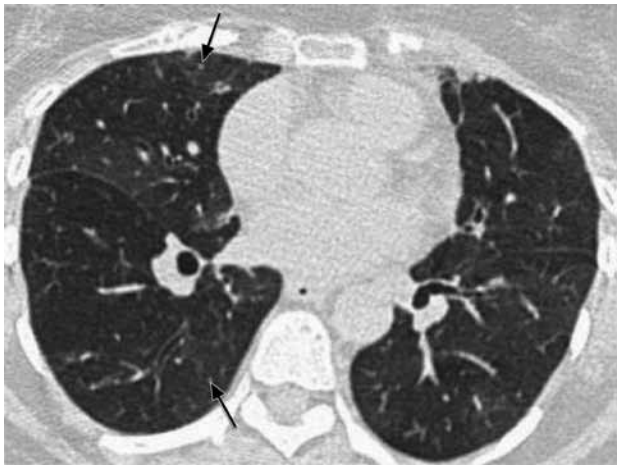

FIGURE 3. High resolution CT of the chest, where ground glass opacities and nodular lesions.

TABLE 1. Electrophoresis of serum proteins

Fraction	%	Normal values
Albumin	70.4	55.8 - 66.1
Alpha 1	7.0	2.9 - 4.9
Alpha 2	5.3	7.1 - 11.8
Beta 1	8.1	4.7 - 7.2
Beta 2	5.7	3.2 - 6.5
Gamma	3.5	11.1 - 18.8

and monthly administration of the treatment. The patient is currently followed-up by the Interstitial Lung Disease out-patient clinic of our Department. On her next follow up about six months later she underwent pulmonary function testing which showed deterioration regarding FEV1 attributed to an episode of bronchitis. FEV1 was 2.16 L (65.9%), FVC 2.53 L (66.9%), FEV1/FVC 85.08, DLCOco 61.6%. The chest HRCT was stable but splenomegaly was found. The patient was referred to the hematology department and splenectomy was decided due to refractory cytopenia (WBC 1750 κ/μl (54% neutrophils, 32% lymphocytes), hemoglobin 8.2g/ml, Hct 27.1 and platelets 150.000 κ/μl). Spleen biopsy revealed enlargement of the red pulp and haemosiderin deposition, findings compatible with hypersplenism. The post splenectomy blood cell values were significantly improved (WBC 9670κ/μl (78% neutrophils, 13% lymphocytes), hemoglobin 10.7g/ml, Hct 34% and platelets 108.000 κ/μl). The patient did not report any infections and she was under treatment with amoxicillin for a total of 2 years while the monthly administration of immunoglobulin was continued. In the last visit, 3 years after CVID diagnosis, her blood tests are normal (WBC 11.100κ/μl (41% neutrophils, 48% lymphocytes), hemoglobin 14.2g/ml, Hct 43.2% and platelets 313.000 κ/μl). The chest HRCT scan showed an increase in the number of nodules and bronchiolectasis, as well as evidence of fibrosis with concomitant elimination of the ground glass infiltrations (Figure 4). Her performance during the 6MWT was deteriorated as she developed dyspnoea and desaturation to 85% after 4 minutes of walking. On the contrary, the patient's spirometry was improved by FEV1 2.85 L (87.7%), FVC 3.01 L (80.1%) and DLCOco 68%. A new echocardiogram revealed a PASP of 40mmHg, but unfortunately the patient refused further evaluation of pulmonary hypertension with right heart catheterization.

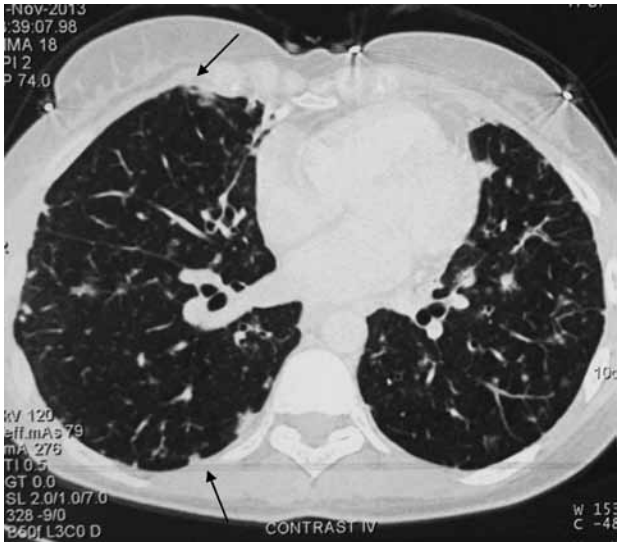

FIGURE 4. High resolution CT of the chest 3 years after the diagnosis, which showed an increase in the number of nodules and bronchiolectasis, findings of fibrosis and elimination of the ground glass infiltrations.

DISCUSSION

Bronchiolitis is an inflammatory and potentially fibrosing condition affecting mainly the intralobular conducting and transitional small airways[8]. Bronchiolitis may be primary or idiopathic which is are or secondary to several factors such as infections, smoking or hypersensitivity[8]. FB is described as lymphoid hyperplasia of bronchial associated lymphoid tissue (BALT) and is histologically characterized by the presence of proliferative lymphoid follicles along the bronchioles[5] of diameter 1-2mm[6]. The hyperplastic lymphoid tissue constitutes a BALT response to a continuous antigenic stimulation[7] and can be developed in such a way among the bronchioles that can even cause airway obstruction[13]. Major features for the pathologic diagnosis are the allocation of the lymphoid follicles and the proliferative lymphoid tissue and the positive stain of B cells for CD20 and CD79 markers[14]. Those features assist the differential diagnosis from nodular lymphoid hyperplasia, lymphoid interstitial pneumonia (LIP) and BALT lymphoma[14]. FB is found at lung biopsies of patients with interstitial pneumonia due to various causative factors and is mostly attributed to connective tissue diseases, immunodeficiency, hypersensitivity reaction, but it can also be idiopathic[5,6]. Rheumatoid arthritis and Sjogren's syndrome are the main connective tissue diseases associated with FB. Patients included in the

above diseases are usually adults with an average age of 44 years[15], while in the cases of immunodeficiency, the average age is 16 years[15]. The interesting feature of the case report is that the age of diagnosis was 35 years even though the underlying cause of FB was CVID.

Radiological findings of FB show a remarkable variability. Chest X-ray can be within normal limits or present bilateral small nodular or reticulonodular infiltrates[16]. The main finding on chest HRCT is a mixed model with small centrilobular nodules 1-12mm in diameter[6] and patchy ground glass infiltrates[6]. Concerning the pulmonary function tests, a normal, restrictive, obstructive or mixed pattern may be exhibited[7]. The prognosis and treatment of FB depend on the causative agent and the treatment options[6].

As mentioned before, FB may occur in the setting of immunodeficiency. Primary immunodeficiency syndromes are relatively rare compared to secondary immunodeficiency syndromes, that are mainly caused by malignant diseases, bone marrow transplantation or administration of drugs for the treatment of connective tissue diseases[17]. The most common primary immunodeficiency syndrome is CVID and it comprises a heterogeneous group of disorders, in which the failure of immunoglobulin and antibody production leads predominantly to recurrent infections[18].

The incidence of the disease varies from 1:10,000 to 1:50,000 in Europe and North America[19]. Although 4 genes related to the phenotype of CVID have been identified, 90% of patients show no mutations to them[19]. The main stepping stone for the diagnosis is the exclusion of other causes of immunodeficiency[18]. The patients' age should be over 4 years[18,20]. The disease can occur at any age but mainly affects patients on their first or third decade of life[19,20]. The levels of serum IgG should be less than 450mg /dl and the levels of IgA and IgM below the lower normal limit (the value of IgM may be normal or even increased in some cases)[18]. Opportunistic or recurrent infections occurs in the majority of patients, while 10% may be free of infections despite the low antibody levels. An important prerequisite for diagnosis is the lack of antibody production after vaccination or exposure to antigens[18]. In order to set the diagnosis, a period of 2 years should go by without manifestation of lymphoid tissue malignancy[18]. This criterion was met in our case, since bone marrow biopsies were repeatedly negative for malignancy in a 2-year period.

Pulmonary manifestations of CVID are recurrent infections and more rarely development of interstitial lung disease[17,18,20,21]. Bronchiectasis are a common finding, and their presence is an indicator of poor prognosis potentially reversible, if an effective treatment is administered for acute infections[19]. The co-administration of immunoglobulin intramuscularly or intravenously and appropriate antibiotics is crucial for the treatment of the infections[17,20,21,22]. Replacement therapy appears to be associated with reduction in the frequency and severity of infections, reduction of antibiotic use and prevention of irreversible damage[22,23].

The interstitial lung disease associated with CVID is the granulomatous - lymphocytic interstitial lung disease (GLILD)[2,24,25] which is characterized by the combination of granulomatous and lymphoproliferative histologic patterns, such as lymphocytic interstitial pneumonia, lymphoid hyperplasia and follicular bronchiolitis (FB)[2]. The infection by human herpes virus type 8 (HHV8) appears to be involved in the pathogenesis of the disease[2,26,27].

GLILD is often accompanied by splenomegaly, adenopathy and liver disease[3]. Splenectomy has been used in CVID patients despite understandable concerns regarding risk of infectious diseases. Most common reason for splenectomy are autoimmune cytopenia, thrombopenic purpura, autoimmune haemolytic anemia and lymphoproliferative disorder[28].

The prognosis of patients with CVID depends not only on respiratory symptoms but on other systems as well[20]. The histological finding of FB is linked to favorable prognosis for the patient[29]. Survival for the patients developing GLILD is reduced compared to those who develop the infectious manifestations, whose survival has improved[30,31]. The increase in survival is due to the development of more effective antibiotics and the administration of substitute IgG immunoglobulin[30]. It is unclear if immunoglobulin replacement therapy contributes to the prevention of pulmonary damage to patients with interstitial lung disease[32]. Several studies with series of patients showed that pulmonary function deteriorates even though replacement therapy is administered[33], as it was observed in our patient. Early diagnosis and treatment play a very important role for the prognosis of the disease[1]. Our patient's clinical course might have been different, if the immunodeficiency had been diagnosed earlier. Furthermore, the administration of corticosteroids without previous investigation for possible immunodeficiency, added to the patient one more factor of immunosuppression.

FB as a result of CVID is not a common combination. We presented the interesting case of patient diagnosed with CVID associated-FB at a relatively old age who re-

ported no symptoms during childhood. The delay from pathological diagnosis of bronchiolitis to the definition of the causative agent was significant since CVID was not included in the initial differential diagnosis. Immunodeficiency should be considered in every patient with recurrent episodes of infections, regardless of age. Due to the poor prognosis of the disease, the need for an effective treatment is crucial.

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