Eur Ann Allergy Clin Immunol Vol 47, N 3, 95-98, 2015

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Severe bronchiectasis in a patient with common variable immunodeficiency

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Key words
CVID; bronchiectasis; Pseudomonas

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Summary
Background. *Bronchiectasis are common in Common Variable Immunodeficiency. These patients are prone to infection, leading to progressive lung destruction and accelerated FEV1 decline.* ***Clinical case.*** *40 year-old man, with recurrent respiratory infections, autoimmunity and diarrhea since age 7. At 17 CVID was diagnosed and IVIgG was started. During the following years, respiratory symptoms progressively worsened and bronchiectasis was found on thoracic computed tomography. Bronchoscopy revealed Pseudomonas aeruginosa in bronchoalveolar lavage and bronchial secretions cultures. Eradication therapy led to clinical improvement.* ***Discussion.*** *This case report stresses the importance of regular microbiological screening and appropriate antibiotherapy. Early/aggressive treatment may significantly impact on patients' evolution.*

Introduction

Common variable immunodeficiency (CVID) is the most common primary immunodeficiency in adults, with a prevalence of 1/50 000 in Western Countries (1-4). Patients are diverse in regard to clinical presentation, that includes increased susceptibility to infection, autoimmunity, granulomatous disease and unexplained polyclonal lymphoproliferation (2).
Bronchiectasis are a common finding in CVID, reported in up to 29% patients (1,5,6). In contrast, *Pseudomonas aeruginosa* infection is seldom reported (4,7,8). The authors report a case of CVID and *Pseudomonas aeruginosa* infected bronchiectasis, illustrating the severity of this combination in CVID.

Case report

A 40 year-old man was referred to Immunoallergology Department due to recurrent respiratory infections. Since 7 year-old until adolescence, he had several hospital admissions due to hemolytic anemia, thrombocytopenia and pneumonia, occasionally complicated with pleural effusions. By age 15, the patient developed intermittent diarrhea and was diagnosed with terminal ileitis, requiring systemic corticosteroids for a short period, although total duration and doses were not possible to determinate. One year later, abnormal chest X-ray findings led to pulmonary surgical biopsy, which revealed lymphocytic interstitial pneumonitis.
By age 17, he was admitted due to meningitis and sepsis. Blood analysis revealed hypogammaglobulinemia (IgG 250 mg/dl [RV: 751-1560 mg/dl], IgA 45 mg/dl [RV: 82- 453 mg/dl], and IgM 77 mg/dl [RV: 46-304 mg/dl]). Secondary causes for hypogammaglobulinemia were excluded, and CVID was diagnosed. He started replacement therapy with IVIgG (0.5 g/Kg/month).
From age 22, diarrhea became persistent, with a mean of 2-3 daily liquid stools. *Giardia lamblia* was identified in different occasions and treated with metronidazole.

By age 38, despite regular IVIgG treatment and maintaining pre-infusion IgG serum levels around 600 mg/dl, he reported persistent cough and bronchorrhea requiring frequent antibiotic courses (> 6/year) and hospital admissions.

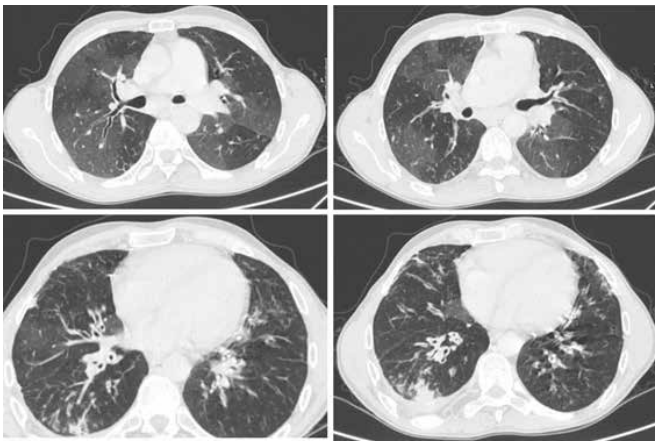
In his first physical examination in Primary Immunodeficiency clinic he presented low body mass index (BMI 17.9), tachypnea, diminished breath sounds, bronchospasm and rales in the inferior 2/3 of both hemithoraces. He also presented hepatomegaly and marked splenomegaly (palpable splenic notch by the medial line). Laboratory evaluation revealed serum IgG 1050 mg/dL (under IVIgG replacement), decreased IgA (4 mg/dl) and IgM (9 mg/dl); and zinc, iron and B12 vitamin deficits, as well as increased alkaline phosphatase, β2-microglobulin and angiotensin conversing enzyme serum levels. Fecal fat test and serum albumin were normal, and sweat test was negative. Bacterial and parasitological exams of stools were negative, and HIV1 and 2 antigens were not detected in serum. Lung function tests showed severe large and small airway obstruction and low carbon monoxide diffusion (**table I**). Thoracic CT-scan showed bronchiectasis and bronchiolectasis, more evident in the medium and lower lobes, bilateral mosaic pattern and multiple infra-centimetric ganglia in various chains (**figure 1**). Upper gastrointestinal tract endoscopy showed chronic pangastritis and atrophic duodenitis.

Immunophenotyping of peripheral blood lymphocytes revealed normal B cell counts with decreased frequency of switched-memory B cells and expansion of B cells expressing low levels of CD21 (CD21lo subpopulation), as well as CD4+ naive T-cells depletion and increased frequency of CD4+ and CD8+ T lymphocytes expressing memory and activation markers.

IVIgG replacement dose was increased (1.2 g/Kg/month) in order to achieve pre-infusion serum IgG levels around 1000 mg/dl. Respiratory care was optimized, based on inhaled therapy (salmeterol and fluticasone association 50/500 mcg *bid* and tiotropium 18 mcg *tid*), oral n-acetilcysteine 600 mg opd (once per day) and regular respiratory physiotherapy. He also started oral omeprazole and replacement therapy with zinc, iron, vitamins D and B12.

We observed noticeable improvement of gastro-intestinal complaints, although bacteriological and parasitological exams of stools were negative in different occasions. Due to progressive worsening of bronchial obstruction (**table 1**) and suppuration requiring frequent courses of antibiotics, bronchofibroscopy was performed and revealed abundant purulent secretions, and *Pseudomonas aeruginosa* was isolated in both bronchoalveolar lavage and bronchial secretions cultures. The patient was admitted for eradication therapy with ceftazidime 2 g *tid*, amikacin 1g opd and ciprofloxacin 750 mg *bid* for 2 weeks, in accordance with antibiogram, and discharged on inhaled tobramycin 300 mg bid in alternate 28-day courses during one year and daily respiratory physiotherapy, in addition to the previous therapy. During the first year on tobramycin he had 3 exacerbations of bronchorrhea requiring oral antibiotic. Bacteriological exam of bronchial secretions was negative in different occasions. One year later, prophylaxis with azithromycin 500 mg 3 days/week was started due to return of fatigue, cough and bronchorrhea. This regimen was held for a period of one year with global clinical improvement, increased exertion capacity, decreased cough and sputum and weight gain (BMI 20).

Figure 1 *- Toracic CT scan (38 years old): Bronchiectasis and bronchiolectasis (upper left), mosaic pattern (upper right), tree-in-bud (lower left).*



Discussion

According to the European Immunodeficiency Society (ESID), clinical diagnosis of CVID requires the presence of at least one of the following: increased susceptibility to infection, autoimmune manifestations, granulomatous disease, unexplained polyclonal lymphoproliferation or an affected family member with antibody deficiency (9). In addition, there must be a marked decrease in serum IgG (< 2SD of the normal levels for age) and IgA, with or without low IgM in at least 2 measurements, and at least one of the following criteria must be met: poor antibody response to vaccines, exclusion of other secondary causes of hypogammaglobulinemia, diagnosis after 4 years old, and no evidence of profound T cell deficiency (9). In a recent European multicentric CVID cohort including 2212 patients, the total frequency of clinical features was evaluated in 902. The most common complications reported were pneumonia (32%), autoimmunity (29%), splenomegaly (28%), bronchiectasis (23%), granuloma (9%) and enteropathy (9%) (1). Heterogenous immunological phenotypes may underlie the clinical variability in CVID. The EUROclass classification arised from a multicentric study which evaluated 303 CVID

Table 1 *- Summary of the patient's lung function tests.*

Date	FEV_1/FVC (%)	FEV_1 (%)	FVC (%)	FEF 50/75 (%)	RV/ TLC (%)	Raw (kPa*s/L)	DL_{CO}/ DL_{CO}/ VA (%)	pO_2/pCO_2
Before referral to PID clinic	69	34	40	22/27	177/75	0,44	54.7/118.4	69/38
PA bronchiectasis' infection	47	24	42	8/6	213/88	1,00	55.6/125.7	73.1/39.4
9 months after tobramycin	57	24	34	10/9	235/89	1.20	44.0/98.8	
Beguining of azythromycin	47	26	46	10/13	196/87	0.98	58.6/120.1	74.9/43.0
7 months after azitromycin	52	44	44	11/5	189/83	0.78	42.7/95.9	

Legend
DLco: carbon monoxide diffusion; FEF: forced expiratory flow; FEV1: forced expiratory volume in the 1st second; FVC: forced vital capacity; PA: *Pseudomonas aeruginosa*; Raw: airway resistance; RV: residual volume; TLC: total lung capacity.

patients in order to improve and unify previous smaller-based classification schemes (10). According to this classification, a significant decrease in switched memory B cells (smB-) was associated with splenomegaly and granulomatous disease (10). Also, lymphoproliferation was associated with transitional B cell (smB-Trhi) expansion (lymphadenopathy) and CD21low B cells expansion (splenomegaly) (10).

The patient we present was classified according to EUROclass (10) as B+; SmB-; Trnorm; 21lo. He presented normal B cell count (B+), as described for most CVID patients (6); low frequency of switched-memory B cells (SmB-), which has been associated with chronic pulmonary disease (11,12), granulomatous disease and lymphoid proliferation (splenomegaly) (13,14); and abnormal expansion of B cells with decreased expression of CD21 expression (21lo), that has been associated with splenomegaly (10), autoimmunity (14), higher number of respiratory tract infections (14) and chronic respiratory disease (14), all features that our patient displayed.

Bronchiectasis in CVID has been related to severe/recurrent respiratory tract infections, unregulated inflammation, low numbers of memory B cells and CD4+ T-cell count below 700/µl (15,16). Several reports have suggested that maintaining high serum IgG levels is associated with a cutback in the progression of lung deterioration and decrease in frequency of severe bacterial infections (1).

In a cohort of 89 adults with non-CF bronchiectasis and followed for 5.7 ± 3.6 years, *Pseudomonas aeruginosa* was found in 12% to 33% patients (17). In this same cohort, a significant number of idiopathic causes was reported (77%) and thus assigning a minimal percentage of bronchiectasis to hypogammaglobulinemia (1%) (17). *Pseudomonas aeruginosa* infection in patients with non-CF bronchiectasis has been associated with more severe and rapid radiologic and lung function decline, as well as with an increase in mortality (18).

The combination of antibiotics administered to our patient upon *Pseudomonas aeruginosa* isolation, has been recommended for treatment of severe exacerbations in patients with non-CF bronchiectasis (19). During the subsequent year, chronic suppression with tobramycin aimed to reduce the bacterial load and associated inflammation. Anti-inflammatory and immunomodulatory properties have been claimed to macrolides (19,20). In the case we present, treatment with azithromycin was associated with clinical improvement and important increase on FEV1 in sequential lung function tests (**table 1**). Both decrease in exacerbations, after *Pseudomonas*' eradication, and anti-inflammatory properties of azithromycin have possibly contributed to this favorable evolution. In a recent meta-analysis of randomized and controlled trials, Zhuo *et al*. analyzed the efficacy and safety of macrolide therapy in adults with non-CF bronchiectasis (21). The authors found that there was a significant reduction in pulmonary exacerbations in patients undergoing macrolide treatment in association with improvement in lung function (21) and quality of life as compared to placebo group (22).

Prophylaxis in non-CF-bronchiectasis is not consensual (2,19), since limited results have been reported on it, and even less on CVID. The potential development of resistance is another area of concern, particularly in patients with bronchiectasis who might be infected with *Mycobacterium* species. Therefore, when considering this therapy, careful exclusion of Mycobacteria infection should be undertaken (23).

In our patient, the therapeutic regime used led to eradication of *Pseudomonas*, since subsequent regular microbiological sputum analyses were consistently negative for *Pseudomonas* infection, two years after completing the antibiotic treatment.

Because of the severity of pulmonary structural changes and functional deterioration, we have considered the adequacy of pulmonary transplant in this case which is reported in very few cases in the literature, with an average survival of only 2 years (24,25-27). In conclusion, prompt diagnosis and IVIgG therapy might decrease the frequency of complications (6). Bronchiectasis is frequent in patients with CVID. Infection contributes to pulmonary destruction and accelerated lung function

decline. Timely and adequate treatment may prevent chronic colonization, as well as delay lung function deterioration.

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