Abstract

Birt-Hogg-Dubè (BHD) syndrome is a rare genetic pathology characterized by cutaneous fibrofolliculomas, pulmonary cysts and kidney tumours.[1] Severe asthma is the most serious form of asthma that does not respond to standard treatments.[2] We present the case of a 68 years old male patient who had frequent respiratory tract infections, shortness of breath and decline in lung function, nasal polyposis and hypertrophy of the nasal turbinates, for this reason was treated as a severe asthmatic patient for several years with ICS+LABA and high doses of OCS. When we tried to reduce OCS the patient had worsening of the symptoms, we requested a HRTC scan that showed presence of several cysts spread ubiquitously. The patient had a family history of pneumothorax, for this reason we requested a genetic test that resulted in a heterozygous point mutation on exon 12 (c.1429 C>T) of FLCN gene.[3] Despite the diagnosis of BHD syndrome the patient's clinical condition kept on suggesting an underlying severe asthma and the blood tests we requested pointed out a high percentage of eosinophils, for this reason we opted for the administration of benralizumab[4,5] that resulted in an excellent asthma control and increased quality of life.

Keywords
Birt-Hogg-Dubé; severe asthma; pneumothorax; benralizumab; eosinophilic asthma;

Introduction

Birt-Hogg-Dubé (BHD) syndrome is an autosomal dominant genetic disorder caused by a mutation in the FLCN gene, which codes for the protein folliculin. The function of this protein is not really clear but it seems to be a tumor suppressor, with a role in the restriction of the cell growth, and it is expressed in the skin, distal nephrons and type I pneumocytes. Patients with BHD syndrome usually have fibrofolliculomas and pulmonary cysts, in a minor percentage of the cases kidney tumours and spontaneous pneumothorax. Asthma is a chronic respiratory disease characterized by chronic airways inflammation. The goal in the management of the asthmatic patient is to reach disease control, assessed by questionnaires (Asthma Control Test (ACT) or Asthma Control Questionnaire (ACQ)) and a recent anamnesis of re-exacerbations. Severe asthma does not respond well to standard treatments, one of the most effective treatments for this life-threatening form of asthma is the biological therapy with humanized anti-immunoglobulin (Ig).[6] Benralizumab is a humanized IgG1k monoclonal antibody that interacts with an extracellular IL-5Rα epitope, it is indicated as an add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting β-agonists.[5]

Case report

In 2017 came to our attention a 68 year old never smoker male patient. In anamnesis he had only hypertension in pharmacological treatment, non controlled atopic asthma and nasal polyposis treated surgically. He referred to our clinic with frequent prolonged respiratory tract infections (including recurrent wheezing attacks) and progressive decline in lung function with shortness of breath and cough. He reported that was treated with ICS+LABA and high doses

of oral corticosteroid (OCS) with partial advantage but when he tried to stop or reduce OCS administration, his asthma was poorly controlled because of repeated exacerbation and relapse. The symptoms were suggestive of severe refractory asthma. The spirometric examination resulted in a mild obstruction (FEV1 2.62 - 93% ; FVC 3.81 - 103% ; FEV1/FVC 69). We requested a HRTC scan that showed us the presence of several cysts, spread ubiquitously but more frequent at the lung bases (**Fig.1**). [78]

(**Fig.1**).
HRTC scan showing the presence of thin-walled, round and ovoid pulmonary cysts predominating in the lower-medial zones of both lungs.

We performed a bronchoscopy with BAL that was essentially normal with a value of CD1+<5%. We also performed dosage of alpha1 –antitrypsin that resulted in normal range (150 mg/dl - v.n.95/175 mg/dl) and dosage of autoantibodies that didn't show anything significant. Delving into the family history, we discovered that the patient has one brother and two sisters with a history of spontaneous pneumothorax and lung cysts although our patient hadn't a story of spontaneous pneumothorax. Furthermore, visiting one of the two sisters, we found the presence of fibrofolliculomas on her face that our patient did not have. To confirm the diagnosis of BHD syndrome, we performed a molecular analysis on DNA by direct sequencing of the gene FLCN. The genetic tests, performed on the patient and his sister, showed a heterozygous point mutation on exon 12 (c.1429 C>T) of FLCN gene, already described in literature in a patient affected by BHD syndrome [3], with an effect nonsense R477X. Then we concluded for BHD syndrome but still the patient kept suffering from shortness of breath, cough and progressive decline in lung function. The patient was also affected by nasal polyposis and hypertrophy of the nasal turbinates in therapy with intranasal steroid and experiencing nasal discharge and nasal obstruction. In the blood test we requested there was evidence of a high percentage of eosinophils in the peripheral blood (6% - 723 cell). Since comorbidities and non-compliance with treatment were excluded and the inhalation technique was checked, all the criteria for the initiation of biological therapy were fulfilled. Based on the clinical and laboratory data available to us, we opted for benralizumab, anti-IL-5 antibody, that is indicated as an add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting β-agonists as suggested by Bleecker et al. (9). After signing an informed consent, we initiated the benralizumab treatment. Consequently, benralizumab has been administered to our patient by subcutaneous injection of 30 mg every 4 week for the first 3 doses and then every 8 weeks thereafter, in addition to the standard therapy. This therapeutic approach resulted in excellent asthma control (ACT pre-benralizumab 12; ACT post-benralizumab 23; $p<0.05$), decreased number of respiratory tract infections, suppression of the chronic use of OCS, and increased quality of the patient's life (AQLQ pre-benralizumab 1.26; AQLQ post-benralizumab 6.53; $p<0.05$). The benefit of this therapy was evaluated every 6 months. After 12 months, the treatment was well-tolerated, and we assessed the effectiveness of this therapeutic modality and it has been shown to be efficient. We also observed a clear reduction of blood eosinophil counts, which at one year from the start of treatment were 0%. Since no adverse effects have been observed, we decided to continue the treatment with benralizumab

up till now. Nowadays, our patient has been on treatment with benralizumab for 14 months, he has no clinical symptoms, with improved spirometry parameters (FEV1 after 6 months 2.75 - 96% and FEV1 after 12 months 2.87 - 99%) and no more exacerbations. **(Fig.2)**

Fig.2 Progress from beginning of benralizumab to November 2020.

Discussion

This case report has two purposes, to focus the attention on a rare disease that should be known by clinicians, especially pulmonologists, and thoracic surgeons in order to avoid diagnostic delays and inappropriate therapies and to centre the attention on the therapy with Benralizumab in patients with non-controlled severe asthma that does not respond to high doses of corticosteroids. Patients with BHD come to our attention for incidental finding to HRTC of cystic lesions or for spontaneous pneumothorax, this is why it's important to know the pathology for the differential diagnosis, while clinicians have to check if patients with non controlled severe asthma have the indications for the biological therapy. After the therapy with Benralizumab our patient finally controlled its symptoms with an increase in quality of life.

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Neither financial support nor a grant was received for this study.

Conflict of interests

The authors declare they have no conflict of interests.

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