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A case of severe allergic eosinophilic asthma with nasal polyposis in a patient affected by Birt-Hogg-Dubé syndrome successfully treated with benralizumab

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Key words

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

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Summary

Birt-Hogg-Dubé (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 which 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 he was treated as a severe asthmatic patient for several years with ICS + LABA and with high doses of OCS. When we tried to reduce OCS, the patient's symptoms worsened, so we requested a HRTC scan that showed the 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 an high percentage of eosinophils. For this reason, we opted for the administration of benralizumab (4, 5) which resulted in an excellent asthma control and in an increased quality of life.

Impact statement

Other comorbidities can often be hidden in patients with severe asthma as in our case, which is why patients need to be studied to further improve their clinical condition and quality of life.

Introduction

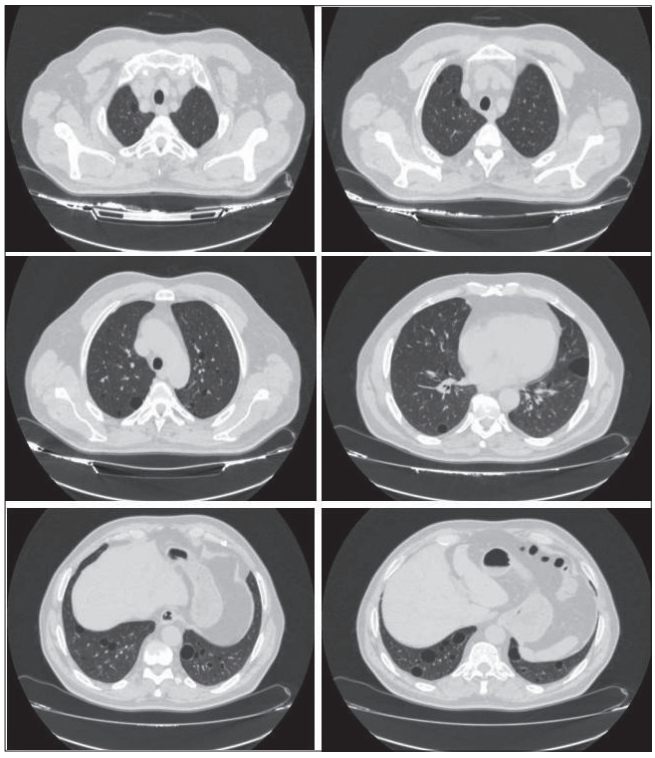
Birt-Hogg-Dubé (BHD) syndrome is an autosomal dominant genetic disorder caused by a mutation in the FLCN gene, which codes for the protein folliculin. The function of the protein is not really clear, but it seems to be a tumor suppressor, with a role in the restriction of the cell growth. It is expressed 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 have kidney tumours and spontaneous pneumothorax. Asthma is a chronic respiratory disease characterized by chronic airways inflammation. In the management of the asthmatic patient the goal is to reach disease control assessed by 1) questionnaires (Asthma Control Test (ACT) or Asthma Control Questionnaire (ACQ)) and 2) 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 inadequately controlled severe eosinophilic asthma despite the high-doses inhaled corticosteroids plus the long-acting β-agonists (5).

Case report

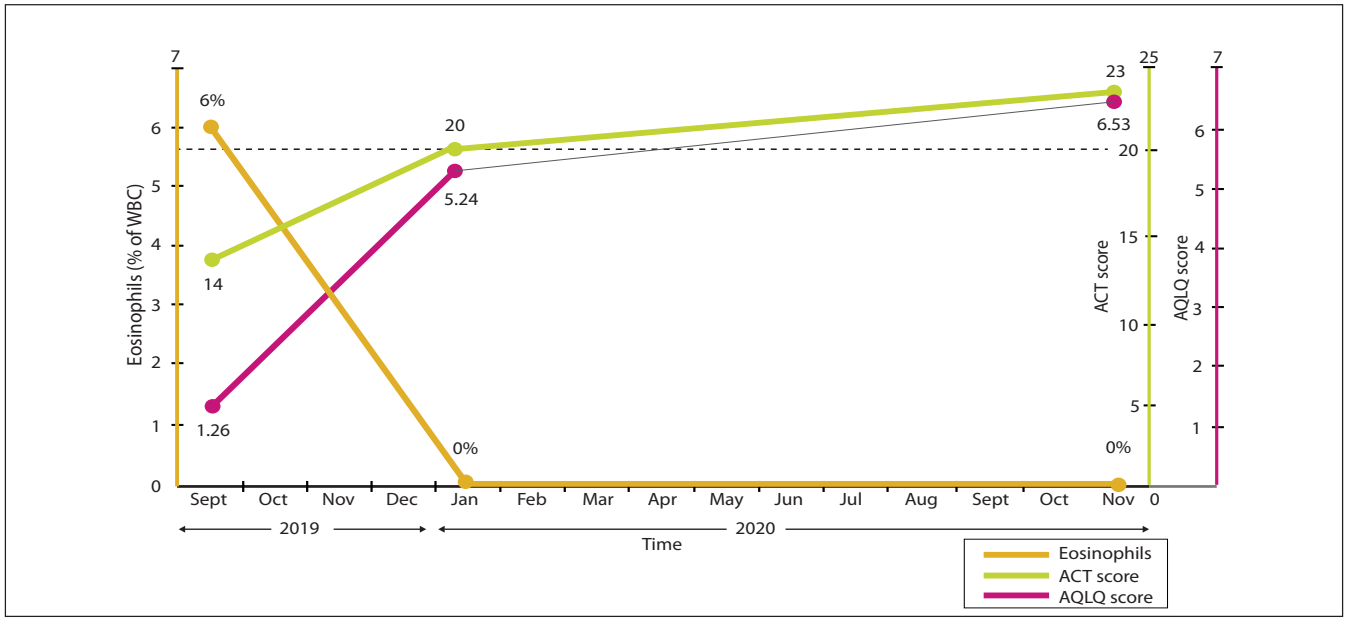
In 2017 came to our attention a 68-year-old never smoker male patient. In anamnesis he had only hypertension in pharmacological treatment, non-controlled atopic asthma and nasal polyposis treated surgically. He referred to our clinic with frequent prolonged respiratory tract infections (including recurrent wheezing attacks) and progressive decline in lung function with shortness of breath and cough. He reported he was treated with ICS + LABA and high doses of oral corticosteroid (OCS) with partial improvement but when he tried to stop or reduce OCS administration, his asthma became 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 (**figure 1**) (7, 8).

Figure 1 *- HRTC scan showed 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 a dosage of alpha1-antitrypsin that resulted in normal range (150 mg/dl - v.n. 95/175 mg/dl) and a 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, missing in our patient. 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 a patient affected by BHD syndrome in the literature (3) − with an effect nonsense R477X. Then, we concluded for BHD syndrome, but the patient still 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, a high percentage of eosinophils in the peripheral blood (6% - 723 cell) was evident. 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, we opted for benralizumab, anti-IL-5 antibody, which is indicated as an add-on maintenance treatment in adult patients with severe inadequately controlled eosinophilic asthma, despite the 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 an 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 beginning of the 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 (**figure 2**).

Figure 2 *- Progress from beginning of benralizumab to November 2020.*



Discussion and conclusions

This case report has two purposes:

1. 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;
2. 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 know the indications for the biological therapy. After the therapy with benralizumab, our patient finally controlled its symptoms with an increase of quality of life.

Fundings

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

Conflict of interests

The authors declare that they have no conflict of interests.

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