Finally, LENT is a valuable tool in this setting but needs to be used with caution in MPE patients with LA carrying EGFR mutations, as it seems to underestimate their survival, even though these patients seem to have worse outcomes under tirosine kinase inhibitor therapy compared with patients with the same diagnosis but without MPE.[13,14] Nevertheless, it seems clear they still have a better prognosis than LA patients with MPE with wild-type EGFR.

Although EGFR mutations appear only in a small subset of LA, this is frequently the most common malignancy causing MPE and, furthermore, there is data suggesting that the rate of EGFR mutation is higher in LA patients with MPE.[15] These data highlight the importance of seeking tools to accurately predict survival in these patients.

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https://doi.org/10.1016/j.arbres.2020.01.004

Rhinoconjunctivitis and Occupational Asthma due to Buckwheat Flour Allergy☆

Rinoconjuntivitis y asma ocupacional por alergia a harina de trigo sarraceno

To the Editor,

Buckwheat or saracen (*Fagopyrum esculentum)* is a herbaceous plant of the *Polygonaceae* family, native to Central Asia. It has a high nutritional value, with a higher protein and fatty acid content than cereals.[1,2] Cases of IgE-mediated buckwheat allergy have been reported, caused by both inhalation of flour and ingestion. It presents with rhinoconjunctival, bronchial, gastrointestinal, and cutaneous symptoms, and even anaphylaxis.[3–5] We report a case of rhinoconjunctivitis and occupational asthma due to buckwheat flour allergy in a baker.

Our patient was a 45-year-old man with a history of allergic rhinitis due to dust mite sensitization who had been a baker for 26 years. He consulted due to an 8-month history of episodes of cough, dyspnea, sneezing, watery rhinorrhea, nasal congestion, and ocular pruritus, occurring exclusively in the workplace on the days that his colleague was kneading dough with buckwheat flour. His symptoms remitted at home.

On physical examination, the patient had bilateral nasal obstruction and was in good general condition, afebrile and eupneic, with normal cardiopulmonary auscultation. The allergy work-up began with skin tests (prick test) with battery of airborne allergens and foods (commercial extracts) including wheat flour, barley, rye, oats, maize, rice, gliadin, nuts, milk, egg and lipid-carrying proteins. Results were positive for dust mites and 5% P/V buckwheat flour extract (9 mm×7 mm). In addition, prick-to-prick tests were performed with an extract of buckwheat prepared by us from flour provided by the patient, which gave a positive result (18 mm×11 mm) (Fig. 1). The study was then extended by determining IgE using the ImmunoCAP method™ (purified extract) with the following results: total IgE 187 KU/l, specific IgE for buckwheat 15.4 KU/l, wheat and rye <0.1 KU/l, *Dermatophagoides pteronyssinus* 10.1 KU/l, and *Lepidoglyphus destructor* 1.98 KU/l.

Chest X-ray showed no pathological changes. Spirometry was normal: forced vital capacity (FVC) 6060 ml (115%), forced expiratory volume in 1 s (FEV_1) 4820 ml (113.5%), FEV1/FVC (80.63%), with a negative bronchodilator test, and FeNO of 115 parts per billion. The nonspecific bronchial challenge test with methacholine performed while the patient was still working was positive (0.022 mg).

In view of the findings described, we decided to perform a specific bronchial challenge test (SBCT) while he was on sick leave. Initially there was no variability after exposure to placebo. Four

☆ Please cite this article as: Pascual Erquicia S, Bernaola Abraira M, Dorado Arenas S, Urrutia Landa I, Arrizubieta Basterrechea I, Bronte Moreno O, et al. Rinoconjuntivitis y asma ocupacional por alergia a harina de trigo sarraceno. Arch Bronconeumol. 2020;56:466–468.

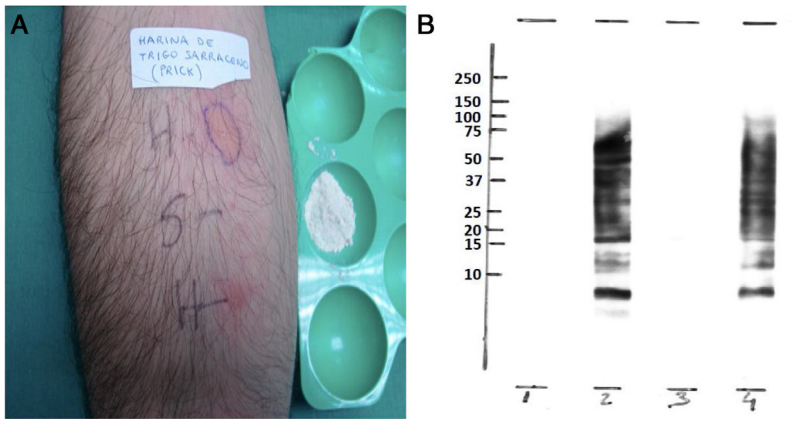

Fig. 1. (A) Prick-to-prick with buckwheat flour. (B) IgE-immunodetection of buckwheat flour extracts. 1: buckwheat (non-reducing conditions) + negative control. 2: buckwheat (non-reducing conditions) + patient serum. 3: buckwheat (reducing conditions) + negative control. Buckwheat (non-reducing conditions) + patient. On the left, position of the molecular weight markers (10, 15, 20, 25, 37, 50, 75, 100, 150, 250 kDa).

minutes after the first exposure to the allergen in the cabin using a mixture of lactose and buckwheat flour, acquired externally, at low concentration, using the method described by Pepys, the patient presented severe bronchospasm with a 35% fall in FEV_1 from baseline.

Finally, in order to identify the specific proteins of the buckwheat that induced IgE antibody synthesis in this patient, immunoblotting was performed, using the same extract made from the flour provided by the patient. Several IgE binding bands against different extract proteins were detected in reducing and non-reducing conditions (from <9 to 75 kDa) (Fig. 1).

Although we could not rule out the presence of mites in the extract used for skin tests, immunoblotting and SBCT, the determination of specific IgE by ImmunoCAP™ confirmed sensitization to buckwheat flour.

The patient was diagnosed with IgE-mediated occupational rhinoconjunctivitis and asthma due to buckwheat flour allergy. He was advised to avoid exposure to this flour and to start treatment with long-acting bronchodilators and inhaled corticosteroids to avoid progression and chronification of symptoms.

Buckwheat, despite its name, has no taxonomic relationship with wheat. Due to its high nutritional value, and the absence of gluten, this flour is ideal for the preparation of celiac products, and its use as an ingredient of foods considered "ecological" is currently increasing.

Several cases of hypersensitivity reactions to buckwheat have been described, mainly in Japan where, due to high local consumption, it causes up to 3% of cases of anaphylaxis in this population.[4]

The prevalence of respiratory symptoms in an occupational setting among bakers is high: 5%–10% for asthma and 15%–20% for rhinitis.[6,7] Sensitization is 4.2% per person per year in exposures of less than 4 years[8] (1.0% in longer exposures),[9] and this rate increases at higher doses of allergen, especially in atopic patients.[6] In bakers, the causative allergens are mostly high molecular weight flour proteins, but other agents present at all stages, from cereal production to bread making (pesticides, contaminants such as mites, fungi, enzymes, etc.), must be taken into account. Buckwheat is a pseudocereal that contains several high molecular weight proteins and, like other allergenic sources, requires a period of exposure to induce sensitization that produces an IgE-mediated hypersensitivity reaction.

Diagnosis requires demonstrating sensitization by skin and/or immunological tests and relating exposure to symptoms. SBCT is the gold standard for diagnosing occupational asthma, as it is the only test that establishes an etiological diagnosis through controlled exposure to increasing doses of the suspected agent while monitoring FEV_1.

The most effective preventive method is to control the level of allergenic exposure in order to reduce the number of sensitized workers. Reducing exposure and using protection may reduce symptoms, but the only measure that improves lung function is to avoid exposure.[10,11]

The importance of this case lies in the scarce availability of literature on occupational asthma due to buckwheat sensitization.[12–15] According to hospital records, it can induce serious reactions, although these are rare.[3–5] The absence of studies and underdiagnosis due to lack of suspicion make it difficult to estimate the prevalence of this allergy.

Buckwheat is also becoming more prominent in the food sector in Europe because of increased consumption of gluten-free foods. The need for it to be declared as a food allergen should be considered to avoid accidental exposures with significant risks.

Acknowledgement

In memory of Dr. Eulalia Camino (our beloved *Lali*).

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https://doi.org/10.1016/j.arbr.2020.02.004

Pulmonary Manifestation of a Primarily Mucocutaneous Hereditary Disease☆

Manifestación pulmonar de una enfermedad hereditaria de expresión fundamentalmente mucocutánea

Dear Editor,

Dyskeratosis congenita or Zinsser-Cole-Engman syndrome is a rare hereditary disease with multisystemic involvement. At least 12 genes related to telomere maintenance have been implicated in the pathogenesis of the disease.

In terms of clinical symptoms, nail dystrophy, reticular pigmentation, and oral leukoplakia are the most common manifestations in this disease. Pulmonary fibrosis, although it affects only 20% of patients, causes the greatest morbidity and mortality.[1]

We report the case of a 49-year-old man, referred to a pulmonology outpatient clinic due to a 6-month history of dry cough. He had seasonal rhinoconjunctivitis and dust allergy and worked in a transport company in frequent contact with truck exhaust fumes. In 2000, he was diagnosed with X-linked congenital dyskeratosis by the dermatology department, with symptoms of nail dystrophy, reticular pigmentation, and oral leukoplakia (Fig. 1A). He was also being monitored by the hematology department for aplastic anemia. Karyotype analysis in peripheral blood and bone marrow was normal. Regarding family history, only one cousin on his mother's side had been diagnosed with congenital dyskeratosis. His parents were dead and his brothers had also died when they were young, cause unknown.

Lung auscultation revealed bibasal velcro crackles and resting oxygen saturation by pulse oximetry was 98%. Chest X-ray showed predominantly reticular involvement in both upper lobes and blood test results, including the autoimmunity study, were normal.

The patient showed evidence of moderate restriction and decreased carbon monoxide diffusion capacity (DLCO) in respiratory function tests (FEV_1 71%; FVC 71%; FEV_1/FVC 60%; TLC 66%; DLCO 62%). He also had significant desaturation during the 6-minute walk test, and covered less distance than predicted, showing moderate dyspnea at the end of the test.

The study was extended with high-resolution computed tomography (HRCT) which showed diffuse parenchymal involvement, with increased volume reduction in the left hemitorax and reticular opacities with bronchiectasis and traction bronchiolectasis in both upper lobes and the lingula, consistent with fibrosing disease Fig. 1).

Bronchoscopy was also performed with aspiration and bronchoalveolar lavage: cytology and microbiological results were negative. Given these findings, antifibrotic treatment was started with nintedanib, which was well tolerated.

Telomeres were analyzed in the Telomeropathy Detection Department of the CSIC Institute of Biomedical Research. The study showed that the patient's telomere length was below the 10th percentile compared to the healthy population of the same age. Exon sequencing of the *DKC1* gene, associated with X-DC, showed the pathogenic variant (NM_001363.4) c.203rd>G; p.H68R in exon 4 of the *DKC1* gene in homocygosis. A family genetic study was not possible, as the patient's brothers and parents had died.

A diagnosis of mild-moderate fibrosing disease (GAP 3, stage I), associated with congenital dyskeratosis with hematological and cutaneous involvement and telomere shortening, was given.

In the last 3 months, the patient presented functional progression (57% FVC and 26% DLCO) and radiological progression on HRCT, with signs of honeycombing, with multiple cysts predominantly in the upper lobes and in the left lung, and an increased pulmonary artery caliber indicating pulmonary hypertension.

Given this rapid decline, with poor response to treatment, he was referred to 3 reference centers to be evaluated for lung transplantation. All centers rejected the procedure due to the high risk, given their limited experience in this type of patients, and the poor prognosis and likelihood of post-transplantation morbidity. Palliative care was intensified, particularly for the patient's disabling dyspnea. In June 2019, he died of respiratory failure.

The true prevalence of dyskeratosis congenita is unknown. It has been estimated to affect approximately 1 in 1 million of the population. Genetic variants with different degrees of penetrance and severity and 3 types of genetic inheritance have been identified: autosomal recessive, X-linked, and autosomal dominant.[2]

Genes associated with congenital dyskeratosis and telomere shortening to date include *CTC1, ACD, NHP2, DKC1, PARN, NOP10, TERC, RTEL1, TINF2, TERT*, and *WRAP53*. The dyskerin pseudouridine synthetase 1 (*DKC1*) gene is the most common (30%) and inheri-

☆ Please cite this article as: Guevara Velázquez V, González JM, García Arias-Salgado E, Cordovilla Pérez R, Iglesias Heras M, Hernández Mezquita MÁ, et al. Manifestación pulmonar de una enfermedad hereditaria de expresión fundamentalmente mucocutánea. Arch Bronconeumol. 2020;56:468–469.