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Diabetic Ketoacidosis Revealing Adult Cystic Fibrosis Associated with Graves' Disease: About One Case

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

Cystic fibrosis is most often diagnosed in the first years of life due to pancreatic insufficiency and respiratory damage with chronic bronchial suppuration. However, moderate or monosymptomatic forms may only appear in adulthood. As for Graves' disease, it is an autoimmune pathology causing hyperthyroidism, its most characterising manifestation being a homogeneous goiter. It preferentially affects relatively young women, but can occur at any age. The association of cystic fibrosis and Graves' disease is a possibility described in the medical literature and that our case illustrates, this association can be fatal when cystic fibrosis is responsible for diabetes at the insulin deficiency stage and the latter is associated to hyperthyroidism canceling out any effect of insulin treatment, thus endangering its vital prognosis.

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1. INTRODUCTION

Cystic fibrosis is the most common serious genetic disease in the caucasian population, with autosomal recessive transmission, the recessive nature implies that only patients who have inherited 2 mutated genes will be affected by the disease. The cystic fibrosis gene (CF gene), located on the long arm of chromosome 7, was discovered in 1989. The protein encoded by this gene is called CFTR or cystic fibrosis transmembrane conductance regulator, it has the characteristics of an ion channel transmembrane [1]. The incidence of Cystic fibrosis is 1/2500 births. One in 25 people is a healthy carrier or heterozygous. The median survival, which was 5 years in 1963, has increased considerably and exceeds 30 years. From now on, cystic fibrosis is no longer an exclusively pediatric disease, since the third of patients suffering from it are adults. This late discovery has broadened the spectrum of possible manifestations and complications, justifying specific treatment. [2]

Graves' disease is an autoimmune pathology causing hyperthyroidism, its most characteristic manifestation being a homogeneous goiter. It preferentially affects relatively young women, but can occur at any age. Our work reports the case of a patient admitted to intensive care for a state of diabetic ketoacidosis which revealed cystic fibrosis associated with Graves' disease. [3]

2. CASE PRESENTATIONS

The case is about a female patient 36-years-old, treated since 4 years for Diabetes having been discovered at the age of 32 by the occurence of a ketoacidosis at that time, initially after treating the ketoacidosis the patient was put on oral antidiabetics (metformin 2g/day and gliclazide 60mg/day) with a good observance of the treatment but without improvement, the patient presented 3 other episodes of diabetic ketoacidosis while taking correctly her medication, the last one dates back to 3 months before her current admission to intensive care and for which she stayed in the endocrinology department of the Ibn Rochd University Hospital where type I diabetes and Graves' disease were identified and placed on intermediate insulin 30 IU in the morning and 20 IU in the evening and on carbimazole 40 mg. The patient also stayed in the dermatology department for significant hair loss; the diagnosis of alopecia areata was made, for which she was placed on local corticosteroids without improvement. The patient is also followed in the Psychiatry department of the Ibn Rochd University Hospital for depressive syndrome treated by anxiolytics and SSRI type antidepressants.

The patient's recent episode dates back to 2 days before her admission and that started with an intense thirst with polydipsia and kussmaul dyspnea, vomiting and abdominal pain complicated by alterated consciousness and confusion having motivated the hospitalization of the patient in the polyvalent intensive care unit of the hospital 20 Aout University Hospital: the examination on admission found a confused and slightly agitated patient with a glascow score of 12/15th, low blood pressure at 95/57mmHg, tachycardia at 120Bpm, polypnea at 27Cpm and ambient air saturation at 90%, the patient was dehydrated, capillary blood glucose was at 5g with presence of a ketonuria of 4-cross on urine strips. The blood pH was at 6.7 and HCOO3 concentration was at 2.7mmols. After stabilization of the patient: put on insulin infusion with rehydration and oxygen therapy by high concentration mask. Facing 03 organ-specific autoimmune diseases, the opinion of an internist was sought.

The interview by the internist with the family revealed the following elements :

- The patient comes from a first-degree consanguineous marriage
- The notion of a brother and two sisters dying at a young age from respiratory failure secondary to repeated respiratory infections
- The notion of repeated respiratory infections since childhood with the notion of chronic constipation with repeated bacterial digestive infections
- The notion of bronchodilator use without any asthma
- The notion of dilatation of bronchi

The clinical examination found a conscious patient, confused with a Glascow of 14/15th, with a blooed pressure at 101/62mmHg and tachycardia at 126Bpm, polypneia at 24 cpm with saturation at 97% under nasal canula with an oxygen flow rate of 5L. The patient presented a bilateral exophthalmos more significant on the right, a mobile goiter when

swallowing, firm and painless, significant alopecia, a state of weight loss and malnutrition, a bladder globe with a predominant lumbar contact on the right. The rest of the examination hasn't found any other abnormalities.

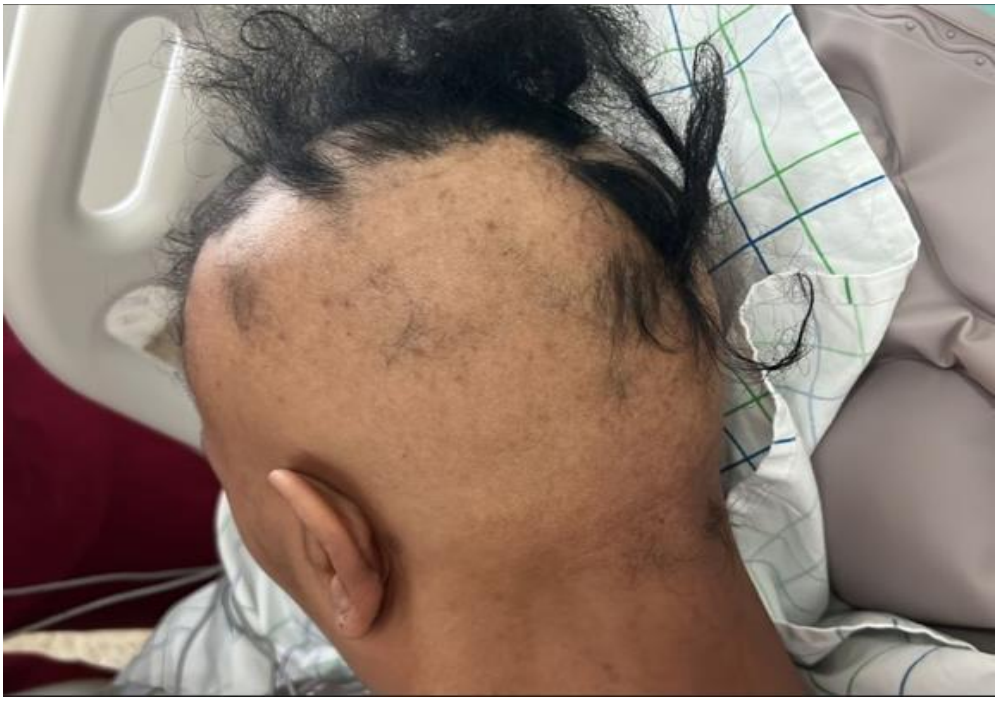

Fig. 1. Image of the alopecia from which the patient suffered

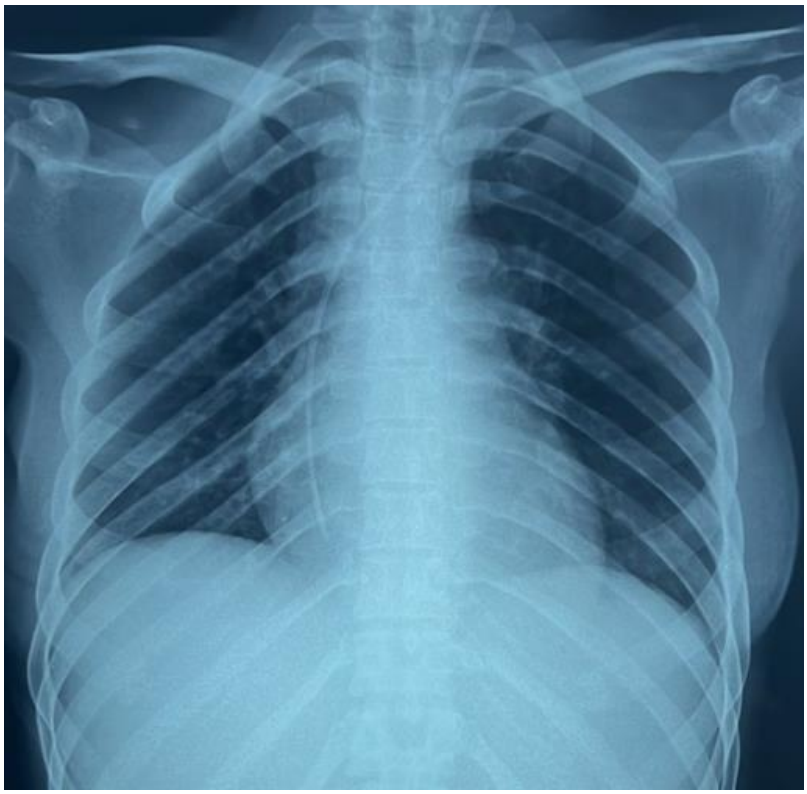

Fig. 2. X-ray of the patient revealing an aspect of a dilation of the bronchi

Faced with the elements of the interrogation, cystic fibrosis was mentioned, a sweat test was carried out which came back positive with a chlorine level of 97mEq/l, the search for the mutation of the CFTR protein was requested but not carried out due to lack of means. To identify which type of diabetes the patient had tests looking for anti-IA2, anti-GAD, anti-insulin and anti-islet of Langerhans antibodies wer carried out and which came back negative, which excludes type I diabetes and therefore it would be a classic complication of cystic fibrosis, an infectious assessment was carried out in search of the causes of decompensation of the patient's diabetes made of cytobacteriological examination of sputum which returned polymorphic and salivary, the chest x-ray found an appearance suggestive of dilation of the bronchi.

The rest of the blood revealed a negative type 1 and 2 HIV serology, the Cytomegalovirus serology was IgM negative IgG positive at 22 IU, the Epstein-Batt Virus was IgM negative IgG positive at 47 IU, hepatitis serologies (B-type and C-type) negative, the cytobacteriological examination of urines having found leukocyturia with hematuria and isolated a multiresistant Klebsiella Pneumonia, in front of the lumbar contact and the bladder globe the patient was catheterized bringing back 2L of cloudy urine then benefited from a renovesical ultrasound which revealed moderate bilateral uretero-hydronephrosis with bladder residue which could correspond to a urinary infection, a complement by URO6scan was indicated but not carried out, for her thyroiditis a TRAK assay was carried out which came back positive, the TSH level had collapsed to 0.01mIU/L with a T3L level at 12pmol/L and T4L at 35pmol/L and the cervical ultrasound revealed a left lobar goiter with heterogeneous pseudo-nodular gland correpsonding to a Graves' disease.

The patient unfortunately died following septic shock with a urinary starting point caused by multi-resistant Klebsiella pneumoniae.

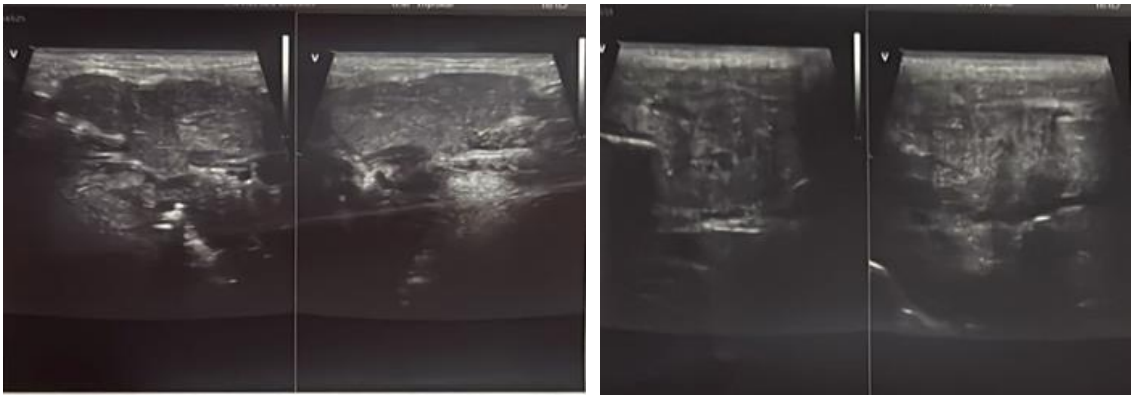

Fig. 3a.

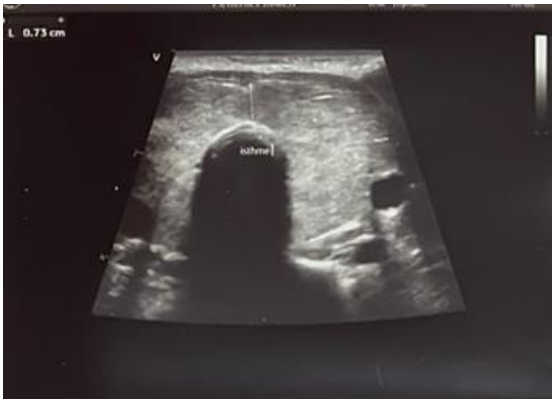

Fig. 3b.

Fig. 3 a et b. Cervical ultrasound of the patient: Left lobar goiter with heterogeneous pseudo-nodular gland consistent with Graves' disease

3. DISCUSSION

Cystic fibrosis is the most common serious genetic disease in the white population, with autosomal recessive inheritance. The median survival, which was 5 years in 1963, has increased considerably and exceeds 30 years. The cystic fibrosis gene (CF gene), located on the long arm of chromosome 7, was discovered in 1989. The protein encoded by this gene is called CFTR or cystic fibrosis transmembrane conductance regulator has the characteristics of a transmembrane ion channel. The most frequent mutation (70%) is a deletion of three nucleotides resulting in the absence of an amino acid: phenylalanine, normally located at position 508 on the CFTR protein (hence the symbolic designation DF508). More than 1000 CF gene mutations have now been characterized. Mutations of the CFTR gene are classified according to the mechanism by which they can cause a total or partial loss of CFTR function: class I includes mutations affecting the synthesis of the CFTR protein, class II those which alter maturation processes. and/or intracellular trafficking such as the DF508 mutation, class III those which alter the regulation of the chloride channel, class IV mutations alter the conductance of the CFTR channel and those of class V reduce the quantity of functional CFTR channels at the membrane. Class I to III mutations are called “severe” while class IV and V mutations are “moderate”, the presence of at least one moderate mutation determining a “moderate” genotype. These mutations are responsible of ion transfer abnormalities (inhibition of chlorine secretion and increased sodium absorption at the apical pole of epithelial cells) which are responsible of the thickening of secretions in the bronchi, pancreatic ducts, intestine, and respiratory tracts and bile ducts [1]. Clinically cystic fibrosis combines, in the classic form, dilatation of the bronchi and exocrine pancreatic insufficiency. Diabetes can appear during the progression of the disease, when pancreatic fibrosis extends to the islets of Langerhans, and its frequency increases with age. The diagnosis of cystic fibrosis is considered based on respiratory and/or digestive clinical signs. It is confirmed by the sweat test whith a high level of chlorine and/or the identification of two CF gene mutations [1,3,4].

Graves' disease is an autoimmune pathology causing hyperthyroidism, its most characteristic manifestation being a homogeneous goiter. It preferentially affects relatively young women, but can occur at any age. Clinicaly it is responsible of rapid and significant weight loss, sweating, warm and smooth skin, localized myxedema (characteristic tibial myxedema), rapid and jumping pulse, hypertension, dyspnea, rhythm disturbances such as atrial fibrillation, muscle weakness, muscle atrophy, nervousness, excitability, insomnia, agitation, occasional diarrhea, increased appetite, goiter and exophtalmia (Gravesian ophthalmopathy). The diagnosis is based on the presence of specific clinical elements [5]. When they are not found, certain examinations can be carried out: Cervical ultrasound: which should reveal a very vascularized, homogeneous and diffuse hypoechoic gland, scintigraphy: which must show diffuse and homogeneous hyperfixation of the isotope and biologicaly by dosing the TRAK antibodies. Our case illustrates all the complexity of the diagnosis process requiring multidisciplinary collaboration and the necessary intervention of an internist, the interrogation is an important phase, in the case that we report it brought out the notion of first degree consanguinity of the parents of the patient, the family history of the deaths of 03 children including 1 boy and 2 girls at a young age following repeated respiratory infections complicated by severe respiratory distress, the notion of repeated respiratory infections in the childhood of the patient patience with the use of bronchodilators, a history of chronic constipation all suggestive signs of possible cystic fibrosis. Diabetes diagnosed at the age of 32 would also raise a good number of questions, diabetes in young subjects must always and necessarily be explored on the etiological level, autoimmune diabetes implies the necessary search for autoantibodies and not retained only on age which can point towards a secondary origin, or even of the MODY or mitochondrial type, moreover any non-response to treatment under cover of good compliance should raise the question of the diagnosis retained and the choice of treatment, the association with Graves' disease was reported by an Italian team reporting in December 2022 a case associating juvenile idiopathic arthritis, Graves' disease and cystic fibrosis [6], this association in adults has a poor prognosis when cystic fibrosis has already been complicated by diabetes because thyroid hormones block the expression of receptors insulin which makes classic treatments of diabetes alone useless and can lead to decompensation of diabetes and therefore it is important to treat simultaneously the Graves’ desease but still it’s a surgical emergency just

after stabilizing ketoacidosis of the patient [7]. Unfortunately the patient was urgently admitted with a urinary catheter placed in the emergency room, which explains the multi-resistant nature of Klebsiella Pneumoniae, directing us towards the nosocomial origin of the germ isolated at the ECBU, in an immunocompromised area of diabetic ketoacidosis and thyrotoxicosis. Unfortunately the patient presented septic shock which was fatal.

4. CONCLUSION

Cystic fibrosis is most often diagnosed in the first years of life due to pancreatic insufficiency and respiratory damage with chronic bronchial suppuration. However, moderate or monosymptomatic forms may only appear in adulthood. Cystic fibrosis remains a serious disease for which there is currently no curative treatment, but life expectancy is gradually improving due to better care by specialized multidisciplinary teams, optimization of respiratory physiotherapy, antibiotic therapy and nutritional care.

Graves' disease is an autoimmune disease constituting a fairly common etiology of hyperthyroidism. Its diagnosis is often easy, its management still remains difficult.

The association of cystic fibrosis and Graves' disease is a possibility described in the medical literature and that our case illustrates, this association can be fatal when cystic fibrosis is responsible for diabetes at the insulin deficiency stage and the latter is associated to hyperthyroidism canceling out any effect of insulin treatment, thus endangering its vital prognosis.

CONSENT

As per international standards or university standards, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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