Diabeticketoacidosisrevealingadultcysticfibrosisassociatedwith Graves' disease: about one case

Abstract :

Cysticfibrosisismostoftendiagnosed in the first years of life due to pancreaticinsufficiency and respiratory damage withchronic bronchial suppuration. However, moderate or monosymptomaticformsmayonlyappear in adulthood. As for Graves' disease, itis an autoimmunepathologycausinghyperthyroidism, itsmostcharacterising manifestation being a homogeneousgoiter. It preferentially affects relativelyyoungwomen, but can occur at anyage. The association of cysticfibrosis and Graves' diseaseis a possibilitydescribed in the medicalliterature and thatour case illustrates, this association can be fatal whencysticfibrosisisresponsible for diabetes at the insulindeficiency stage and the latter isassociated to hyperthyroidismcanceling out anyeffect of insulintreatment, thusendangeringits vital prognosis.

Introduction :

Cysticfibrosisis the mostcommonseriousgeneticdisease in the caucasian population, with autosomal recessive transmission, the recessive nature impliesthatonly patients who have inherited 2 mutatedgeneswillbeaffected by the disease. The cysticfibrosisgene (CF gene), located on the long arm of chromosome 7, wasdiscoveredin 1989. The proteinencoded by thisgeneiscalled CFTR or cysticfibrosistransmembrane conductance regulator, it has the characteristics of an ion channeltransmembrane. The incidence of Cysticfibrosisis 1/2500 births. One in 25 peopleis a healthy carrier or heterozygous. The mediansurvival, whichwas 5 yearsin 1963, has increasedconsiderably and exceeds 30 years. Fromnow on, cysticfibrosisis no longer an exclusivelypediatricdisease, since a third of patients are adults. This latediscovery has broadened the spectrum of possible manifestations and complications, justifyingspecifictreatment. [1]

Graves' diseaseis an autoimmunepathologycausinghyperthyroidism, itsmostcharacteristic manifestation being a homogeneousgoiter. It preferentially affects relativelyyoungwomen, but can occur at anyage. Our work reports the case of a patient admitted to intensive care for a state of diabeticketoacidosiswhichrevealedcysticfibrosisassociatedwith Graves' disease.

Case présentations :

This is a 36-year-old patient, originallyfrom and resident in Casablanca, divorced and mother of 3 children, without profession. Followed for 4 years for Diabeteshaving been discoveredduringketoacidosis, initiallyplaced on oral antidiabetics (metformin 2g/day and gliclazide 60mg/day) with good compliance withtreatment but withoutimprovement, the patient presented 3 otherepisodes of diabeticketoacidosisundertreatment, the last of which dates back 3 monthsbeforehercurrent admission to intensive care and for whichshestayed in the endocrinologydepartment of the Ibn Rochd University Hospital where type I diabetes and Graves' diseasewereidentified and placedundertreatment. intermediateinsulin 30 IU in the morning and 20 IU in the evening and undercarbimazole 40 mg. The patient alsostayed in the dermatologydepartment for significanthairloss; the diagnosis of alopeciaareatawas made, for whichshewasplaced on local corticosteroidswithoutimprovement. The patient isalsofollowed in the

Psychiatrydepartment of the Ibn Rochd University Hospital for depressive syndrome underanxiolytics and SSRI type antidepressants.

The patient'srecenthistory dates back to 2 daysbeforeher admission with the onset of intense thirstwithpolydipsia and kussmauldyspnea, vomiting and abdominal pain complicated by impairedconsciousness made by confusion havingmotivated the hospitalization of the patient in the multipurpose intensive care unit of the August 20 hospital of the Ibn Rochd University Hospital: the examination on admission found a confused and slightlyagitated patient with a glascow of 12/15th, hypotensive at 95/57mmHg, tachycardic at 120Bpm, polypneic at 27Cpm and ambient air saturation at 90% and dehydrated, capillaryblood glucose was at 5g withpresence of ketonuria on 4-cross urine strips. Afterstabilization of the patient: put on insulin infusion withrehydration and oxygentherapy by high concentration mask. Facedwith the notion of 03 organ-specificautoimmunediseases, the opinion of an internistwassought. The interview with the familyrevealed the followingelements:

- The patient comesfrom a first-degreeconsanguineousmarriage
- The notion of a brother and twosistersdying at a youngagefromrespiratoryailmentsfollowingrepeatedrespiratory infections
- The notion of repeatedrespiratory infections sincechildhoodwith the notion of chronic constipation withrepeatedbacterial digestive infections withbronchodilator use

The clinicalexaminationfound a conscious patient, confusedwith a Glascow of 14/15th, hypotensive at 101/62mmHg and tachycard at 126Bpm, polypneic at 24 cpmwith saturation at 97% undertelescopewith a flow rate of 5L. The patient presentedwithbilateralexophthalmos more significant on the right, a mobile goiterwhenswallowing, firm and painless, significantalopecia, a state of weightloss and malnutrition, a bladder globe with a predominantlumbar contact on the right. The remainder of the examinationwasunremarkable.

Fig 1 : Image of the alopeciafromwhich the patient suffered

Facedwith the elements of the interrogation, cysticfibrosiswasmentioned, a sweat test wascarried out which came back positive with a chlorinelevel of 97mEq/l, the search for the mutation of the

CFTR proteinwasrequested but not carried out due to lack of means. For hisdiabetes, a check-up looking for anti-IA2, anti-GAD, anti-insulin and anti-islet of Langerhans antibodieswascarried out and which came back negative, whichexcludesdiabetes 1 and thereforeitwouldbe a classic complication of cysticfibrosis, an infectiousassessmentwascarried out in search of a cause of decompensation of the patient'sdiabetes made of ECBC salivary return, the chest x-ray found an appearance suggestive of dilation of the bronchi.

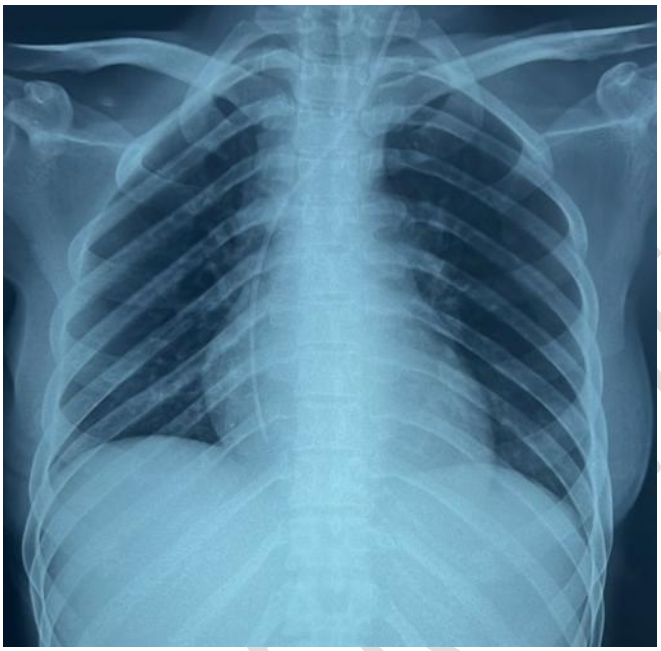
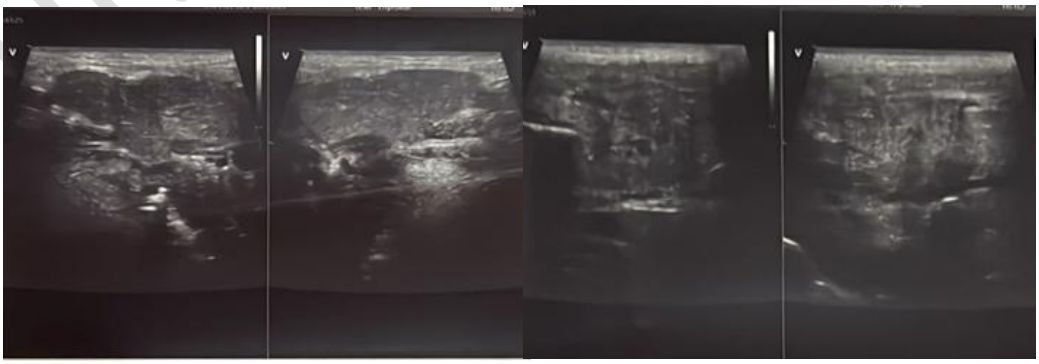
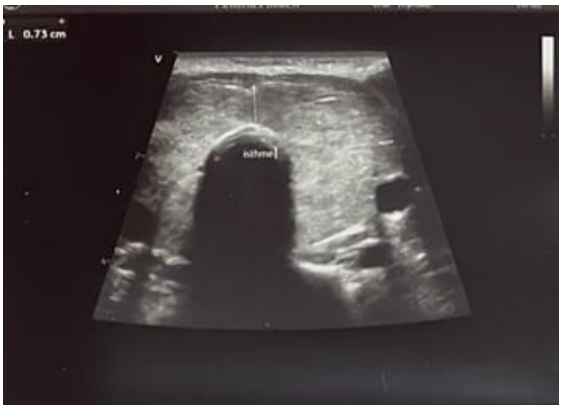


Fig 2 : X-ray of the patient revealing an aspect of dilation of the bronchi

The rest of the bloodrevealed anegative HIV1+2 serology, CMV IgM negative IgG positive at 22IU, EBV IgM negative IgG positive at 47IU, hepatitisserologies (HVC and HVB) negative, ECBU havingfoundleukocyturiawithhematuria and isolated a multiresistant Klebsiella Pneumonia, in front of the lumbar contact and the bladder globe the patient wascatheterizedbringing back 2L of cloudy urine thenbenefitedfrom a renovesicalultrasoundwhichrevealedmoderatebilateraluretero-hydronephrosiswithbladderresiduewhichcould correspond to a urinary infection, a complement by URO scan wasindicated but not carried out, for histhyroiditis a TRAK assaywascarried out which came back positive, the TSH levelhadcollapsed to 0.01mIU/L with a T3L level at 12pmol/L and T4L at 35pmol/L and the cervical ultrasoundrevealed a leftlobargoiterwithheterogeneous pseudo-nodular gland consistent with Graves' disease.



3(a)



3(b)

Fig3 a,b : Cervical ultrasound of the patient: Leftlobargoiterwithheterogeneous pseudo-nodular gland consistent with Graves' disease

The patient unfortunatelydiedfollowingsepticshockwith a urinarystarting point caused by multidrug-resistant Klebsiella pneumoniae.

WhatisCysticFibrosis: [1]

Cysticfibrosisis the mostcommonseriousgeneticdisease in the white population, with autosomal recessiveinheritance. The mediansurvival, whichwas 5 yearsin 1963, has increasedconsiderably and exceeds 30 years.

- **Genetics:**

The cysticfibrosisgene (CF gene), located on the long arm of chromosome 7, wasdiscoveredin 1989. The proteinencoded by thisgeneiscalled CFTR or cysticfibrosistransmembrane conductance regulator;it has the characteristics of a transmembrane ion channel. The mostfrequent mutation (70%) is a deletion of threenucleotidesresulting in the absence of an aminoacid:phenylalanine, normallylocated at position 508 on the CFTR protein (hence the symbolicdesignation DF508). More than 1000 CF gene mutations have now been characterized. Mutations of the CFTR gene are classifiedaccording to the mechanism by whichthey can cause a total or partial loss of CFTR function: class I includes mutations affecting the synthesis of the CFTR protein, class II thosewhich alter maturation processes. and/or intracellulartraffickingsuch as the DF508 mutation, class III thosewhich alter the regulation of the chloridechannel, 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.

- **Pathophysiology:**

Ion transferabnormalities (inhibition of chlorinesecretion and increased sodium absorption at the apical pole of epithelialcells) are responsible for the thickening of secretions in the bronchi, pancreaticducts, intestine, and respiratory tracts. bileducts and vas deferens in humans.

- **Clinicalmanifestations:**

The clinicalpicture combines, in the classicform, dilatation of the bronchi and exocrine pancreaticinsufficiency.

1. **Respiratorymanifestations:**

Respiratory manifestations dominate the clinicalpicture in most cases and determine the vital prognosis. Theyoftenappear in childhood, in more than 80% of cases during the first year of life. Clinicalsigns The symptomatologyis non-specific, dominated by a chroniccough, accompanied by purulent and viscous expectoration. In infants, itisfrequently a case of persistent, recurringbronchitis. Sibilants are possible. Low-volume hemoptysisiscommon in adults. On clinicalexamination, clubbingisusual and thoracicdystrophydevelopsCysticfibrosis 35 in parallelwith the onset of respiratoryfailure. Cyanosis of the extremities, whenitexists, testifies to the progression of respiratory damage. On auscultation, cracklingrales and bronchial rales can beheard, but the auscultation signs are oftendiscreet, in contradiction with the richness of the radiologicalsigns. Evolution The progression occurs in flarescharacterized by a worsening of functionalrespiratorysymptoms, but also by a deterioration in general condition with major asthenia, anorexia and weightloss. The fever, sometimes high, isinconsistent. This developmentispunctuated by complications which can be life-threatening: pneumothorax thatoftenrecurs and is more common in adults, sometimes massive hemoptysis. Deathgenerallyoccursfollowing an exacerbation of respiratorysigns.

2. **Digestive manifestations:**
   a. **Pancreaticdamage:**

Exocrine pancreaticinsufficiencyexistsin 85% of patients. Untreated, itmanifestsitself as abdominal pain and steatorrhea. The dosage of fecalpancreaticelastaseiswellcorrelatedwithpancreatic damage, falling in the event of externalpancreaticinsufficiency. The study of the fecal flow of fats and their absorption coefficient quantifies the importance of lipidmaldigestion. Flares of acute pancreatitis are possible, mainly in patients withpancreaticsufficiency.

Diabetes can appearduring the progression of the disease, whenpancreaticfibrosisextends to the islets of Langerhans, and itsfrequencyincreaseswithage. Orallyinducedhyperglycemiaisindicated once a yearafter the age of 10 for the purpose of screening for diabetes.

   b. **Intestinal damage:**

Meconiumileusreveals the diseasein 15% of cases of cysticfibrosis. Subsequently, subocclusive or occlusive episodesmayoccur, with abdominal pain and sometimes a mobile mass upon palpation of the right iliacfossa. The treatmentremainsmedical.

   c. **Hepatobiliarydamage:**

Hepatomegaly and biologicalcholestasis are common, but biliarycirrhosisdevelops in only 5 to 10% of patients. It can thenbecomplicated by portal hypertension and hepatocellularinsufficiencywithrisk of digestive bleeding and edematoasciticdecompensation. The gallbladderisfrequentlyatrophic. Furthermore, gallbladderlithiasisis more oftenobservedwithprolongedsurvival.

   d. **Gastroesophageal reflux :**

It iscommon, mainlysecondary to chronicbronchopneumopathy.

   e. **Nutritionaldisorders:**

Nutritionaldeficiencies are the consequence of fat malabsorption and chronicrespiratoryinsufficiency, but also of a restingmetabolismgreaterthan 25% of normal. Hypolipidemiawith a reduction in triglycerides and cholesteroliscommon, as is malabsorption of fat-soluble vitamins (E, A, D and K).

f. ENT damage:

It isalmost constant, resulting in a chronicrhinosinus infection. In adults, thereisradiologicalpansinusitis, whichis not alwayssymptomatic. Nasosinusalpolyposisexists in a quarter of patients.

g. Allergicmanifestations:

They are common, whichis not withoutproblems in the event of an allergy to antibiotics.

h. Osteoarticularmanifestations:

Arthralgia, sometimes part of a picture of arthritislinked to immunologicalconflicts, is more frequent in adulthood and can befoundin 5 to 10% of adultseries. Osteoporosisalso poses problemswithincreasinglifespan.

i. Genitalmanifestations:

Pubertyisdelayed in both sexes. Men are sterile in more than 95% of cases, due to obstructive azoospermiacaused by bilateralatresia of the vas deferens. However, the testes are normal and spermatogenesisremains active. Infertilitytreatment by intracytoplasmicsperm injection (ICSI) can nowbeoffered to them. In women, thereis no morphologicalabnormality of the genital tract, but fertilityisreduced due to thickening of cervical mucus. Pregnancyis possible, but the indications depend on the respiratory and nutritional state. Contraception using a mini-pilliswelltolerated. Genetic counseling, withgeneticanalysis of the spouse, isindicatedbeforeanypregnancy.

- **Diagnosis :**

The diagnosis of cysticfibrosisisconsideredbased on respiratory and/or digestive clinicalsigns. It isconfirmed by the sweat test and/or the identification of two CF gene mutations.

1. Sweat test:

It is positive when the chlorine concentration isgreaterthan 60 mmol/l by the pilocarpine iontophoresismethod and twomeasurements are necessarybeforeconfirming the diagnosis. It must becarried out in an experiencedlaboratory.

2. Geneticanalysis:

It must becarried out if thereisany suspicion of cysticfibrosis. The identification of two mutations on the CFTR genemakesit possible to confirm the diagnosis in the rare cases of a negative or doubtful sweat test.

Whatis Graves' disease: [2]

Graves' diseaseis an autoimmunepathologycausinghyperthyroidism, itsmostcharacteristic manifestation being a homogeneousgoiter. It preferentially affects relativelyyoungwomen, but can occur at anyage.

- **Clinicalmanifestations:**
  1. **General manifestations:**rapid and significantweightloss
  2. **Skin manifestations:**sweating, warm and smooth skin, localizedmyxedema (characteristic tibial myxedema)

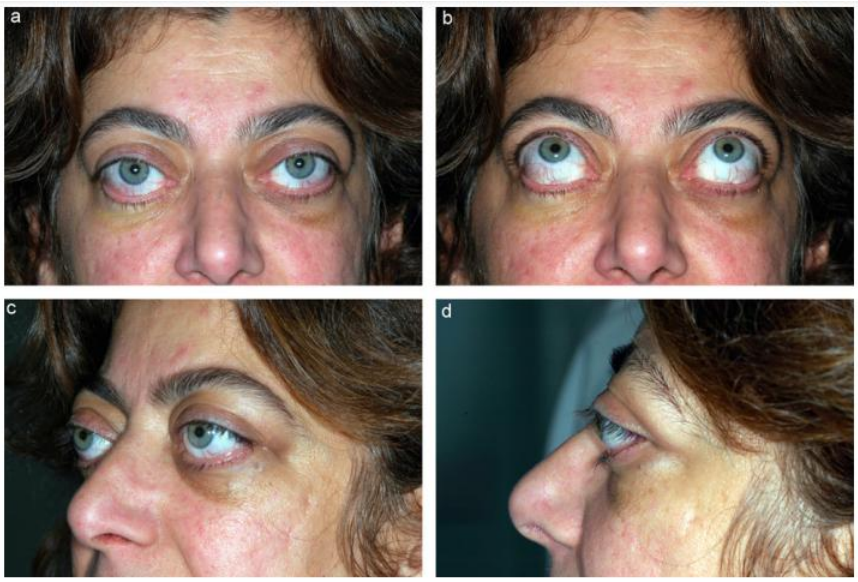


Fig 4 : Image illustratingexophthalmos in Graves' disease [4]

3. **Cardiovascularmanifestations:**rapid and jumping pulse, hypertension, dyspnea, rhythmdisturbancessuch as atrial fibrillation
4. **Muscle manifestations:**tremors, muscle weakness, muscle atrophy
5. **Psychiatricmanifestation:**nervousness, excitability, insomnia, agitation
6. **Digestive manifestations:**occasionaldiarrhea, increasedappetite
7. **Goiter:** diffuse, homogeneous, blowing and vascular, is a verycharacteristicsign of the disease.
8. **Orbitopathy:** or Gravesianophthalmopathyisalsospecific, but not systematicallyfound (50% of cases). It isenough to make the diagnosis

- **Positive diagnosis:**

The diagnosisisbased on the presence of specificclinicalelements. Whenthey are not found, certain examinations can becarriedout:

1. **Cervical ultrasound:**whichshouldreveal a veryvascularized, homogeneous and diffuse hypoechoic gland
2. **Scintigraphy:**which must show diffuse and homogeneous hyperfixation of the isotope

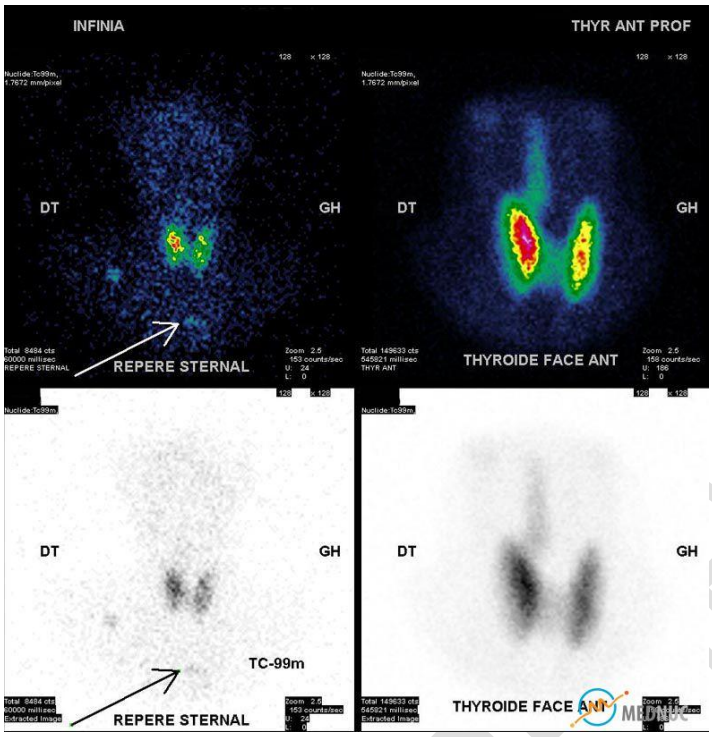


Fig 5 : Thyroidscintigraph image suggests Graves' disease [5]

3. **The dosage of anti-TSH receptorantibodies (TRAK)** of whichonly the presence or absence is of diagnostic interest, but the concentration of whichis not a prognosticelement and is not involved in the monitoring of the patient.

Discussion :

Cysticfibrosisis a condition of the Caucasian population thatappearsearly and ismostoften fatal at a youngage and itisonlyrecentlythat the discovery of thisdiseaseisbecoming more and more common. Our case illustrates all the complexity of the diagnostic process requiringmultidisciplinary collaboration and the necessary intervention of an internist, the interrogation is an important phase, in the case thatwe report itbrought out the notion of first degreeconsanguinity of the parents of the patient, the familyhistory of the deaths of 03 childrenincluding 1 boy and 2 girls at a youngagefollowingrepeatedrespiratory infections complicated by severerespiratorydistress, the notion of repeatedrespiratory infections in the childhood of the patient patience with the use of bronchodilators, a history of chronic constipation all suggestive signs of possible cysticfibrosis. Diabetesdiagnosed at the age of 32 wouldalsoraise a good number of questions, diabetes in youngsubjects must always and necessarilybeexplored on the etiologicallevel, autoimmunediabetesimplies the necessarysearch for autoantibodies and not retainedonly on agewhich can point towards a secondaryorigin, or even of the MODY or mitochondrial type, moreoveranynon-response to treatmentunder cover of good compliance shouldraise the question of the diagnosisretained and the choice of treatment, the association with Graves' diseasewasreported by an Italian team reporting in December 2022 a case associatingjuvenileidiopathicarthritis, Graves' disease and cysticfibrosis [3], this association in adults has a poorprognosiswhencysticfibrosis has already been complicated by diabetesbecausethyroid hormones block the expression of receptorsinsulinwhichmakestreatment of diabetesuseless and can lead to decompensation of diabetes and thereforeitis a surgical emergency especiallysince the patient was in ketoacidosis. Unfortunately the patient wasurgentlyadmittedwith a urinarycatheterplaced in the emergency room, whichexplains the multi-resistant nature of Klebsiella Pneumoniae, directing us towards the

nosocomial origin of the germisolated at the ECBU, in an immunocompromised area of diabeticketoacidosis and thyrotoxicosis. Unfortunately the patient presentedsepticshockwhichwas fatal.

Conclusion :

Cysticfibrosisismostoftendiagnosed in the first years of life due to pancreaticinsufficiency and respiratory damage withchronic bronchial suppuration. However, moderate or monosymptomaticformsmayonlyappear in adulthood. Cysticfibrosisremains a seriousdisease for whichthereiscurrently no curative treatment, but life expectancyisgraduallyimproving due to better care by specializedmultidisciplinary teams, optimization of respiratoryphysiotherapy, antibiotictherapy and nutritional care.

Graves' diseaseis an autoimmunediseaseconstituting a fairlycommonetiology of hyperthyroidism. Itsdiagnosisisofteneasy, its management stillremainsdifficult.

The association of cysticfibrosis and Graves' diseaseis a possibilitydescribed in the medicalliterature and thatour case illustrates, this association can be fatal whencysticfibrosisisresponsible for diabetes at the insulindeficiency stage and the latter isassociated to hyperthyroidismcanceling out anyeffect of insulintreatment, thusendangeringits vital prognosis.

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[2] Graves' disease:epidemiological, clinical and therapeuticstudy: about 40 cases Dr S. Ali ∗, Dr W. Elajmi, Pr H. Hammami Tunis Military Hospital, Tunis, Tunisia SFE Marseille 2020 / Annales d'Endocrinologie 81 (2020) 315–350

[3] Journal of ClinicalMedicine Case Report Concomitant Use of Elexacaftor/Tezacaftor/Ivacaftor and Etanercept in a CysticFibrosis Patient withJuvenileIdiopathicArthritis Sara Immacolata Orsini 1,†, EdoardoMarrani 2,* ,† , IlariaPagnini 2, Giovanni Taccetti 3 , Vito Terlizzi 3 and Gabriele Simonini 2 1 Department of Woman, Child and of General and SpecializedSurgery, UniversitàdegliStudidellaCampania “Luigi Vanvitelli”, 80138 Naples, Italy 2 PediatricRheumatology Unit, Meyer Children's Hospital IRCCS, 50139 Florence, Italy 3 Department of PediatricMedicine, Meyer Children's Hospital IRCCS, CysticFibrosisRegional Reference Center, 50139 Florence, Italy

[4] SFO CONFERENCE-DEBATE / Exophthalmos and enophthalmosBasedowianexophthalmos Basedow exophthalmos S. Moraxa,∗, I. Badelonb a Fondation A. de Rothschild, Department of Orbito-palpebral Reconstructive Plastic Surgery-Neuro-ophthalmology, Paris, France b Ophthalmology service

[5] Diffuse and homogeneous hyperfixation withvisualization of the pyramidal lobe (or Lalouettepyramid). Lalouettepyramid (Pierre Lalouette 1711-1792):median and inconstant thyroid lobe of pyramidal shape. TRACER: 99mTc (pertechnetate) CENTER / CAMERA: Perpignan University Hospital.