

final diagnosis.⁶ Differential diagnosis between an anaplastic thyroid carcinoma and a secondary tumor is often difficult. The presence of cervical adenopathies, advanced patient age, and neoplastic history may suggest a metastatic tumor, but a positive thyroglobulin test will provide definite diagnosis of an anaplastic carcinoma.⁷ In the case reported, the patient's age, the rapid growth of previously known goiter, and stone-hard consistency suggested anaplastic carcinoma rather than metastasis. Thyroid metastases are usually diagnosed in advanced disease stages and are associated with a life expectancy of only a few months.⁵ Although treatment is palliative in nature, thyroid surgery may improve symptoms and the quality of life in these patients.

In conclusion, when faced with a patient with a history of tumor and a thyroid nodule, a cytological evaluation should be performed on a sample taken by fine needle aspiration to rule out a potential metastatic origin.⁷

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Patient with diabetes and impaired hearing[☆]

Paciente con diabetes e hipoacusia

We report the case of a 34-year-old female patient referred for assessment of diabetes mellitus (DM). Her personal history included bilateral hypoacusis, chronic left otitis media, asymptomatic anteroseptal preexcitation with normal coronary arteries, and DM diagnosed at 24 years of age for mild hyperglycemia. Her family history included a maternal grandmother with DM and epilepsy, a mother with DM since 21 years of age and hypoacusis, a maternal uncle with DM and hypoacusis, and a diabetic brother diagnosed at 30 years of age, also with hypoacusis. The patient's mother had died from an episode of hypoglycemia, and her grandmother at 36 years of age during a seizure (Fig. 1).

The patient was initially treated with oral hypoglycemic drugs (metformin and sulfonylureas), and during the previous four years with insulin, with poor glycemic control in all cases. No acute or chronic metabolic complications were reported. Physical examination was normal, with a body mass index of 23 kg/m². The results of supplemental tests were as follows: glycosylated hemoglobin, 7.9%; C-peptide, 0.22 ng/mL (reference range, 1.00–4.00); and

negative anti-glutamic acid decarboxylase (GAD65), anti-pancreatic cell cytoplasm (ICA), anti-tyrosine phosphatase (IA-2), and anti-insulin antibodies. Because of her family history and DM data, a genetic study was performed of mitochondrial DNA (mtDNA) in blood (white blood cells). Using the direct sequencing method of the tRNA^{Leu} gene (transfer ribonucleic acid), the 3243A>G mutation was detected in mtDNA with heteroplasmy levels of approximately 31%. Using a PCR-RFLP method (polymerase chain reaction and restriction fragment length polymorphisms using microfluid detection in a 2100 Bioanalyzer [Los Angeles, USA]), heteroplasmy was 30%. The patient was diagnosed with maternally inherited diabetes and deafness (MIDD), treatment was started with Q10 coenzyme 150 mg/day, and insulin therapy was optimized. No muscle biopsy was performed to study the respiratory chain or for the detection of ragged red fibers because this is an invasive test that would not have provided additional data for diagnosis and treatment. Conductive hypoacusis with a mean threshold at 65 decibels (dB) in the right ear and mixed hypoacusis with a mean perception threshold at 65 dB in the left ear were confirmed as syndrome co-morbidities. She had an estimated 63% hearing impairment in her right ear, an estimated 95% hearing impairment in her left ear, and an estimated 65% impairment in binaural hearing. Eye fundus examination and echocardiogram were normal, as well as microalbuminuria.

It was inferred that her brother, mother, uncle, and grandmother carried the 3243A>G mutation. Her mother and grandmother had died from complications associated

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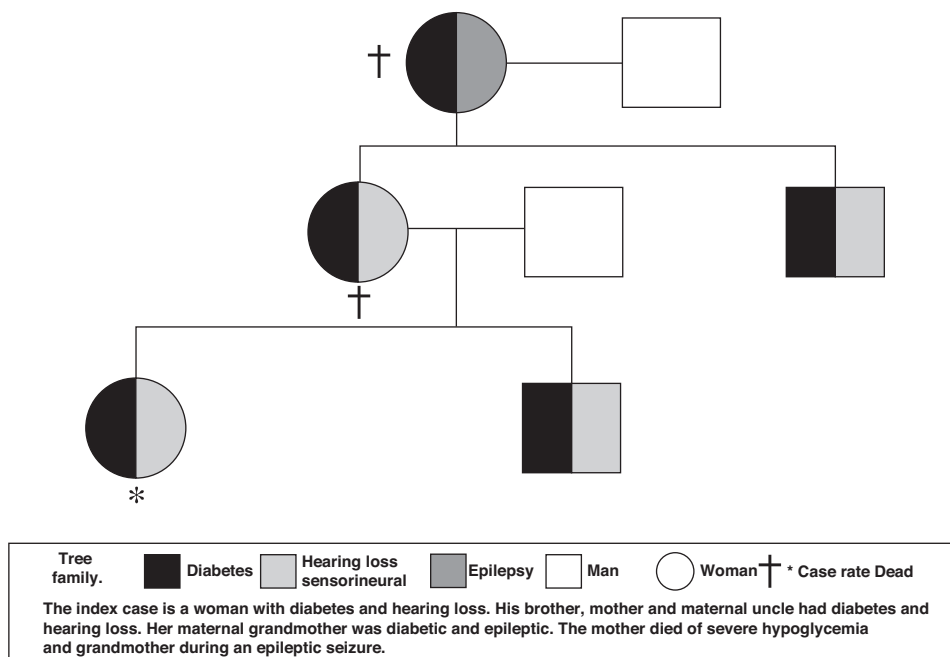


Figure 1 Family tree of the reported case.

with this mutation. Genetic counseling was provided to the patient, and genetic study of her brother and uncle was recommended.

Mitochondrial diabetes¹ accounts for 0.2–2% of all form of diabetes. It is maternally inherited. The most common causative mutation is the 3243A>G mutation (substitution of adenine for guanine at position 3243) in the tRNA^{Leu} gene of mtDNA. There are 2–10 copies of mtDNA by cell (polyplasm). In this syndrome, copies of mutated and non-mutated mtDNA coexist in the same cell (heteroplasmy). The proportion of mutated mtDNA and the tissue where it is located condition the phenotype. If low levels of heteroplasmy exist, only MIDD will occur. If heteroplasmy levels are higher, MELAS syndrome (mitochondrial myopathy, encephalopathy, epilepsy, lactic acidosis, and stroke-like episodes) will additionally occur.

Cells with high replication rates tend to select healthy mitochondria (e.g. peripheral blood white blood cells), while cells with low replication rates (e.g. muscle, oral mucosa, and urinary epithelium cells) tend to accumulate abnormal mitochondria. It is therefore convenient to perform a mutation study in the latter.

Mitochondrial diabetes has a 100% penetrance. Mean age at onset is 38 years. Higher heteroplasmy levels cause an earlier start. The condition is due to a decrease in insulin secretion stimulated by glucose not mediated by an autoimmune mechanism.² The sequence of events³ is as follows: (1) the substitution of adenine for guanine at position 3243 of mtDNA causes the dimerization of tRNA leading to impaired aminoacylation; (2) an increase in the mitochondrial degradation of proteins encoded by mtDNA; (3) a decrease in the activity of enzyme complexes of the respiratory chain; (4) a reduction in adenosine triphosphate (ATP) synthesis; (5) a decrease in the adenosine triphosphate/adenosine diphosphate ratio (ATP/ADP); and (6) a reduction in insulin secretion (through ATP-dependent

potassium channels) and, hypothetically, β -cell apoptosis. Mitochondrial diabetes may be confused with both type 1 and type 2 DM. Patients will always require insulin, usually after a mean of 3.9 years. Microvascular complications⁴ (retinopathy 8%, nephropathy 28%) and macrovascular complications⁴ (ischemic heart disease 7%, peripheral vascular disease 3%) usually occur. Treatment consists of insulin secretagogues and eventually insulin. Metformin should be avoided because of the high risk of lactic acidosis in these patients. Adequate carbohydrate consumption is required because hypoglycemia triggers stroke-like episodes.

Sensorineural hypoacusis^{4,5} occurs at a mean age of 33.2 years before, concomitant with, or after diabetes. The most affected ear structures are the stria vascularis and ciliated cells. A progressive and almost universal hearing loss results. Its progression is more marked in males and in patients with higher heteroplasmy levels. Treatment consists of a cochlear implant.

Myopathy occurs as pain and weakness in the lower limbs, and ragged red fibres in skeletal muscle biopsy.

Epilepsy is due to hyperexcitability caused by decreased energy. Drugs that decrease L-carnitine levels (benzodiazepines, valproic acid, phenytoin, phenobarbital) should not be used to treat epilepsy, and propofol should be used instead, if necessary. Stroke-like episodes, also called 'metabolic strokes', may occur due to increased lactic acid levels in the area causing a decrease in pH and an increased blood flow. Arteriography shows no occlusion of major brain vessels and no specific territorial limit. Stroke-like episodes may be triggered by hypoglycemia, fever, or intercurrent disease.

Proteinuria⁶, which is usually confused with diabetic nephropathy, may occur. Histological findings include focal and segmental glomerulosclerosis, with hyalinized glomeruli and necrosis of myocytes of arterioles and small arteries.

Other potential changes in this syndrome include pre-excitation syndrome, left ventricular hypertrophy, dilated cardiomyopathy⁷, retinal macular dystrophy, intestinal pseudo-occlusion, neuropsychiatric changes, lactic acidosis, and complications during pregnancy (prematurity, placenta accreta).⁸

Diagnosis is based on molecular studies which look for the mtDNA mutation. Two techniques may be used, sequencing and PCR-RFLP.

Treatment consists of the administration of coenzyme Q10, an electron transporter of the respiratory chain which acts as an antioxidant, protecting cell membrane phospholipids and low density lipoprotein cholesterol from the oxidative damage caused by free radicals. Administration of Q10 at a dosage of 150 mg/day for three years delays the occurrence of insulinopenia and hearing loss and decreases post-exercise lactate levels.⁹ However, other authors have not supported these findings.¹⁰ Statins should be used with care because they decrease coenzyme Q10 levels. Other treatments used in other mitochondrial syndromes include arginine, L-carnitine, and multivitamin complexes.

In conclusion, although the prevalence of mitochondrial diabetes in the diabetic population is low, its diagnosis is important because it has a different prognosis and treatment. It should be suspected in the presence of a personal and/or family history of diabetes and deafness or microvascular complications that do not correlate with diabetes duration, and in slim diabetic patients with negative pancreatic autoimmunity.

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Lupus, graves' disease, and vasculitis. A case report[☆]

Lupus, enfermedad de graves y vasculitis. A propósito de un caso

Autoimmune thyroid disease (AITD), characterized by the presence of antibodies against thyroid antigens, is associated with a number of non-organ-specific rheumatological disorders such as systemic lupus erythematosus (SLE), rheumatoid arthritis, and Sjögren's syndrome.^{1,2} For example, while the prevalence of subclinical hypothyroidism

(SCH, normal T4 with elevated TSH) is 4.3% in the general population,³ it is increased to 11–13% in patients with SLE.^{4,5} Similarly, the prevalence of anti-thyroid peroxidase antibodies (anti-TPO) is 10–12% in the general population,^{3,6} but 17–23% in SLE patients.^{4,5} Clinical or subclinical hypothyroidism is usually common in patients with SLE and accounts for more than 87.5% of thyroid function changes in these patients.^{5,7} As regards Graves' disease (GD), it is less common in both the general population (0.5%)³ and patients with SLE (1.7%).¹

Antithyroid drugs are associated with adverse events, and most of them are mild and uncommon (less than 5%), but, in some cases, they may cause severe autoimmune disorders such as vasculitis, polyarthritis, or drug-induced lupus.⁸ Vasculitis associated with antithyroid drugs usually consists of a combination of polyarthralgia and skin lesions. However, it may affect other organs such as kidney, lung,

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