PARTICULAR EVOLUTION OF TYPE 1 DIABETES MELLITUS ASSOCIATED WITH OTHER AUTOIMMUNE DISEASES – A CASE REPORT

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Abstract

Type 1 diabetes mellitus with autoimmune pathogenesis can be associated with other autoimmune disorders. The most frequent association is with endocrine diseases but many others organs and systems can be affected. This cluster of autoimmune diseases, called polyglandular autoimmune syndrome-PAS, seems to be more probable among patients with older age at the onset of diabetes and female gender. These disorders must be detected and treated in order to provide good metabolic control for these patients, prevent complications, and to increase quality of life. We intended to present the case of a type 1 diabetic female patient, who associated successively, in 3 years autoimmune thyroiditis, pernicious anemia and autoimmune hepatitis. Each time metabolic control was affected and glycated hemoglobin increased. This kind of patients need special care from a multidisciplinary team. The treatment of associated conditions was followed by an improvement in glycemic control expressed by glycated hemoglobin and an increased in the quality of life.

key words*: type 1 diabetes mellitus, autoimmune disease, autoimmune thyroiditis, pernicious anemia, autoimmune hepatitis, polyglandular autoimmune syndrome-PAS.*

Introduction

Current classification of diabetes recognizes 4 classes, first being type 1 diabetes mellitus due to beta cell destruction by autoimmune mechanisms (type 1A more frequent) and idiopathic (type 1B) [1,2]. Clinical practice shows that type 1A diabetes mellitus (Type 1DM) is frequently associated with other endocrine autoimmune disorders especially autoimmune thyroiditis [3,4,5]. The clinical and subclinical autoimmune involvement of different endocrine organs in the same subject led to the concept of autoimmune polyendocrine syndrome [5,6].

Polyglandular autoimmune syndromes (PAS) are rare polyendocrinopathies characterized by the failure of at least two

endocrine glands as well as various nonendocrine organs disorders, caused by an immune-mediated destruction of tissues. It has been described two major subtypes of PAS: type I and type II according to age of presentation, characteristic patterns of disease combinations and different modes of inheritance. Type I or juvenile form usually appears in childhood or adolescence, it is defined by a chronic mucocutaneous candidiasis, hypoparathyroidism, adrenal failure and genetic studies have shown an autosomal recessive inheritance in a single gene. PAS II occurs in adulthood, it is characterized by primary adrenal failure (40-50%), autoimmune thyroid disease (70-75%), type 1 diabetes mellitus (50-60%) and other disorders: pernicious anemia, alopecia areata, rarely vitiligo and gonadal failure. PAS II affects more frequently women than men. PAS II is a polygenic disorder and genetic studies have shown an autosomal dominant inheritance [7].

The prevalence among all age type 1 DM patients of organ–specific autoantibodies is 29% for thyroid, 10.1% for celiac disease and 1.6% for adrenal gland [3,6,8]. In a clinical research on 151 adult patients with type 1 DM from our clinic we found a 27.1% prevalence of other autoimmune diseases [9].

Pernicious anemia is a chronic illness caused by impaired absorption of vitamin B-12 because of the lack of intrinsic factor in gastric secretions [10,11,12]. The disease is called pernicious anemia because it was fatal prior to the discovery of its pathogenesis and treatment [10,11,12]. Patients on appropriate treatment have now a normal lifespan [12]. Antiparietal cell antibodies occur in 90% of patients with pernicious anemia [10, 12]. A greater association than anticipated exists between pernicious anemia and other autoimmune diseases, which include thyroid disorders, type 1 diabetes mellitus, ulcerative colitis, Addison disease, infertility, and acquired agammaglobulinemia [12]. The prevalence of parietal gastric cell antibodies among patient with autoimmune diabetes (type 1 DM and latent autoimmune diabetes in adults LADA) was reported to be ~ 17.2% [13].

Autoimmune hepatitis is a chronic disease of unknown cause, characterized by continuous hepatocellular inflammation and necrosis, which tends to progress to cirrhosis [14,15]. Immune serum markers frequently are present, and the disease often is associated with other autoimmune diseases [14,15,16]. There are 3 types of autoimmune hepatitis. Autoimmune hepatitis type 1 is characterized by positive test results for anti–smooth muscle antibody (ASMA) and antinuclear antibody (ANA). Type 2 disease is marked by a positive test result for anti–liver-kidney microsomal antibody (anti–LKM-1 antibody). Type 3 is marked by a positive test result for anti-SLA (soluble liver antigen) antibody [14,15,16]. Type 2 autoimmune hepatitis is frequently associated with other autoimmune diseases (pernicious anemia, type 1 diabetes mellitus) [14,15,17].

There is a general genetic susceptibility for autoimmune disorders, all these diseases being associated with HLA (human leukocyte antigen) DR3, DR4. [4,5,12,17]

Case presentation:

A 65 years old women presented to our clinic for polyuria, polydipsia, weight loss 10 kg in 3 weeks. She had been diagnosed with

diabetes mellitus 3 months before and she was receiving a treatment with the oral antidiabetic drug Gliclazidum 60 mg daily. From personal history we found out that she had high blood pressure treated with Enalaprilum 20 mg daily. Nobody in her family had diabetes.

Physical examination revealed: Height 163 cm, weight 60 kg, BMI=22.5 kg/m2, moderate dehydration, systolic blood pressure SBP=120 mmHg, diastolic blood pressure DBP=70mmHg, heart rate 88/min; clinical examination of thyroid gland was normal.

Laboratory data: fasting plasma glucose 354 mg/dl, glycosuria, ketone body present in urinalysis, glycated hemoglobin 10.7%, GAD antibody positive (ELISA method), ICA antibody positive (ELISA method), total cholesterol 230 mg/dl, LDL cholesterol 151 mg/dl, TSH=10.77 microUI/ml (MEIA method; normal value 0.45-4.67), ATPO>1000 IU/ml (MEIA method; normal values 0-12), free T4=0.97 ng/dl. (See also table no 1). Serum sodium and potassium concentrations were normal. Abdominal ecography was normal, also the ECG was normal. We performed thyroid ecography which revealed mild increased in thyroid volume, hypodense structure suggestive for autoimmune thyroiditis (fig1).

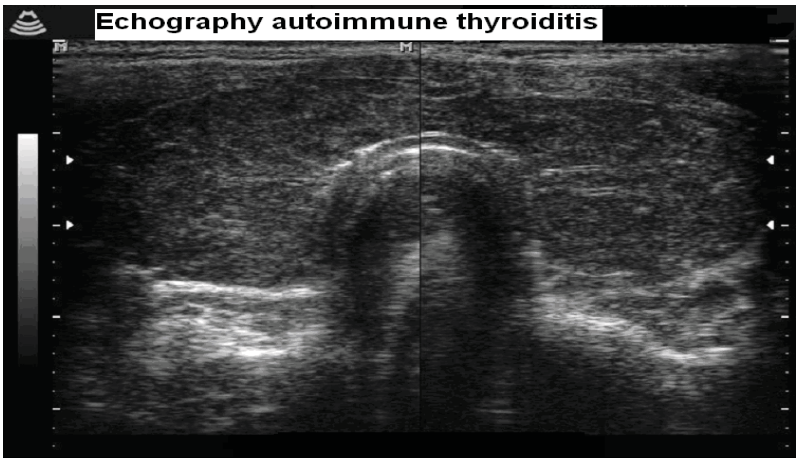

Fig. 1: Thyroid ecography

We established the following diagnosis: Type 1 diabetes mellitus, autoimmune thyroiditis with subclinical hypothyroidism, systemic hypertension, dyslipidemia (hypercholesterolemia probably in hypothyroid context). Adrenal insufficiency was not considered due to high blood pressure, normal skin pigmentation and normal serum sodium and potassium levels. We started insulin treatment and obtained an acceptable glycemic control with 2 injections of premixed insulin, total dose 30 units daily (0.5 unit/kg). Also she started treatment for hypothyroidia with Euthyrox initially 25 microg daily for 7 days followed by 50 microg daily.

The patient came back to our clinic five months later (second visit) in good condition for a routine check. We noticed a weight gain of 5 kilos but BMI was in normal ranges 24.4 kg/m2. Laboratory data revealed: glycated hemoglobin 7%, TSH=4.87 microUI/ml (above upper limit) and normal lipid profile. We increased the dose of Euthyrox at 75 microg daily.

After two and half years from the first visit, she was again admitted to our clinic with

fatigue, increased glycemic values on personal glucometer, poliuria, polidipsia, lower limbs paraesthesia. Physical examination revealed paleness, asthenia, smooth tongue with loss of papillae, weight 62 kilos, SBP=120 mmHg, DBP=70 mmHg.

Laboratory data revealed: hemoglobin=10.5 g/dl, mean cell volum MCV=128 fL, mean cell hemoglobin MCH= 39 pg, glycated hemoglobin HbA1c = 10.84 %, fasting blood glucose 278 mg/dl, urinalysis: glucose present, ALT=104 U/l, AST=113 U/l, LDH 1236 U/L (normal range 313- 618 U/L), gamma globulin increased, B12 vitamin 65 pmol/L (Immunochemical assay with electrochemiluminiscent detection (ECLIA) normal ranges 191-663 pmol/L), antiparietal cell antibodies present (ELISA method), antinuclear antibody (ANA) present (ELISA method), anti–smooth muscle antibody (ASMA) present (ELISA), Anti–liver-kidney microsomal antibody (anti–LKM-1) negative (ELISA). Viral markers for C and B hepatitis were negative.

Abdominal ultrasound revealed liver with hyperechogen structure (steatosis aspect) and upper gastrointestinal endoscopy showed gastric mucosa atrophy. Liver biopsy showed chronic inflammatory cell infiltrate with plasma cells, interface hepatitis (piecemeal necrosis), and no fibrosis.

Peripheral smear of blood: macrocytes are observed, and the red blood cells show ovalocytosis, polymorphonuclear leucocyte with hyper segmentation (fig. 2).

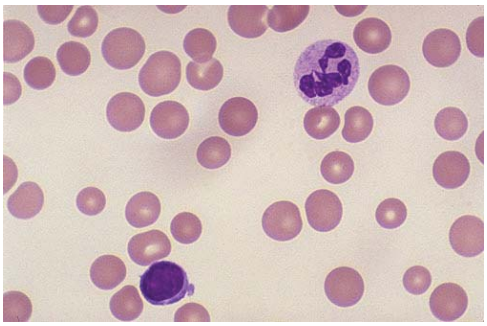

Fig. 2: Peripheral smear of blood.

Table 1. Laboratory parameters according to visits.

Parameters	First visit	Second visit (after 5 months)	Third visit (after 2.5 years)	4th visit (after 3 months from third visit)
Hb (g/dl)	15	14.1	10.5	14.7
Ht (%)	47	46	34	44.7
MCV fl	90	91	128	93
MCH pg	30.9	32	39	34
HbA1c (%)	10.7	7	10.84	7.1
AST U/l (N :9-48)	42	40	104	56
ALT U/l (N:5-49)	43	39	113	72
LDH U/l (N:313-618)	564	513	1236	558
TSH µIU/ml (N: 0.45-4.67)	10.77	4.87	3.92	4.1
Insulin dose (unit/kg)	0.5	0.6	0.83	0.67

We established following diagnosis: pernicious anemia and type 1 autoimmune hepatitis.

We intensified insulin treatment for type 1 diabetes mellitus to 3 injections daily (premixed analog in the morning, rapid analog at noon and premixed analog in the evening), total dose 52 units/day, 0.83 units/kg with a satisfying glycemic profile. Following hematological examination we started treatment for pernicious anemia with B12-vitamin 1000 microg (Milgamma N®

ampoule 2ml) daily for 10 days, 1000 microg three times a week for 2 weeks, afterwards 1000 microg twice a week for 2 weeks and 1000 microg once a week for 4 weeks. She received hepatoprotective drugs and the treatment with prednisone was temporized due to lack of absolute indication criteria and to coexisting comorbidities [14,15].

She came back to our clinic 3 months later to clinical control. She had no symptoms, physical examination improved significantly and laboratory data revealed hemoglobin 14.7g/dl, hematocrit 44.7%, MCV 93fl, MCH 34 pg, glycated hemoglobin 7.1%, ALT=72 U/l; AST=56 U/l.

Discussions and conclusions

In our case a female patient with adult onset type 1 diabetes mellitus developed successively three other autoimmune diseases: autoimmune thyroiditis with hypothyroidism, pernicious anemia and autoimmune hepatitis. We can consider the diagnosis of polyglandular autoimmune syndrome PAS associated with other autoimmune disorders.[7] The most probable form is PAS II (adult age, female gender, characteristic patterns of disease combinations) without adrenal failure [7,8,9]. Each time metabolic control expressed by glycated hemoglobin was affected and we had to intensify the insulin treatment in order to control plasma glucose. Higher doses were needed when patient was admitted with pernicious anemia. Endocrine autoimmune diseases, especially thyroiditis, are frequently associated with type 1 diabetes mellitus [3,4,5,6,8,9]. Due to frequent association of thyroid dysfunction with diabetes mellitus, ADA (American Diabetes Association) recommends to perform TSH in all patients with type 1 diabetes mellitus at the onset and yearly afterwards [2]. Pernicious anemia seems to be more frequent than anticipated in patients with autoimmune diabetes. It is a serious condition which should be treated as soon as possible and for the rest of the life [12,13].

There are few data regarding the prevalence of autoimmune hepatitis in type 1 diabetes mellitus and this association seems to be underestimated [15,17]. The frequent increase in the transaminases are attributed to steatohepatitis and/or to poor metabolic control. Any hepatitis in patients with autoimmune diseases, especially women, should be further investigated for a possible diagnosis of autoimmune hepatitis [15,17].

For all patients with type 1 diabetes mellitus we have to search the presence of other autoimmune diseases, especially in cases with the onset in adulthood and female gender [2,5,6,8,17]. These associated autoimmune diseases should be treated and the insulin regimen, should be intensified in order to provide better metabolic control and avoid complications.

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