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SCIENTIFIC LETTERS

Fulminant type 1 diabetes mellitus associated with pembrolizumab☆

Diabetes fulminante secundaria a tratamiento con pembrolizumab

Fulminant diabetes is a subtype of type 1 diabetes (type 1B) characterized by the rapid destruction of the pancreatic beta-cells, resulting in a total insulin deficiency within a few days.[1]

We report the case of a 58-year-old male patient diagnosed with stage IV metastatic melanoma in 2010. Treatment was initially provided in the form of a BRAF/MEK inhibitor, with a poor response. Pembrolizumab 2 mg/kg every three weeks was therefore started as second line therapy. Three months after starting this drug, the patient reported to the emergency room due to polydipsia, polyuria, anorexia and asthenia over the previous four days, with a weight loss of 5 kg. The plasma glucose level was 602 mg/dl, with ketonuria, pH 7.08, and bicarbonate 10.1 nmol/l. Peptide C was almost undetectable (0.007 nmol/l), with HbA1c 7.4%. Pancreatic autoimmune tests (GAD and IA2 antibodies) were negative. The patient was therefore diagnosed with fulminant diabetes secondary to pembrolizumab.

This new diabetes subtype was described in Japan in 2000, and is characterized by a sudden onset, the absence of diabetes-related antibodies, and pancreatic enzyme elevation. Three criteria for establishing the diagnosis have been proposed: the presence of ketosis or ketoacidosis in the first 7 days from the onset of symptoms of hyperglycemia, blood glucose >288 mg/dl (16 mmol/l) with HbA1c < 8.7% (NGSP units) and peptide C < 0.10 nmol/l (basal) or <0.17 nmol/l (stimulated).[2,3]

This type of diabetes affects both sexes equally, and the mean patient age at onset ranges from 35 to 45 years. The exact etiopathogenesis of fulminant diabetes is unknown, but environmental and immune factors are believed to play a significant role. From the histopathological prospective, the disease is characterized by a mononuclear cell infiltrate affecting both the endocrine and exocrine pancreas. The epidemiological association with certain viruses as potential triggering agents is more constant than in type 1A diabetes. An association with the HLA DR4-DQ4 haplotype (DRB1*0405-DQA1*0302-DQB1*401) has been found. This haplotype is more common in the Japanese population, and is not associated with type 1A diabetes in this population. It also differs from the HLA DR4 haplotype associated with type 1A diabetes found in the Caucasian population (DR4-DQ3). This latter haplotype and the DR3 haplotype are infrequent in the Japanese population. These data may explain the high prevalence of fulminant diabetes within the context of type 1 disease in Japan, where it is estimated to account for 20% of all diagnoses of type 1 diabetes.[4]

In addition to HLA, immune response regulatory pathways have also been implicated. These are pathways which down-regulate T-cell activation, and include CTLA-4 and PD-1 membrane receptors. A decrease in the expression of these molecules has been observed in fulminant diabetes, possibly related to the immune response hyperactivation seen in these patients.[5]

There have been a number of very important advances in immunomodulating therapy for cancer in recent years. Such therapies involve the use of monoclonal antibodies that inhibit immune checkpoints, and include pembrolizumab and nivolumab (which inhibit PD-1), and ipilimumab (which inhibits CTLA-4). By blocking these control points, the drugs favor an immune response against cancer cells, but also have significant adverse effects.[6]

A PubMed search using the key word ''diabetes'' and the names of the three monoclonal antibodies identified 17 cases of diabetes secondary to these drugs. Ten cases (4 of fulminant diabetes) were secondary to nivolumab and 7 (one of fulminant diabetes) to pembrolizumab. No cases secondary to ipilimumab have been reported.[7–9] These differences may be due to the different mechanisms whereby PD-1 and CTL-4 inhibit the immune response.

In conclusion, fulminant diabetes mellitus is a clinically important but uncommon condition. Its incidence may be expected to grow with the increasingly widespread use of immunotherapy in cancer patients. The oncological team, the patients subjected to such treatments, and endocrinologists should be familiarized with the warning symptoms in order to secure early diagnosis and treatment.

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Metabolic syndrome: First prevalence study in primary care, Honduras☆

Síndrome metabólico: primer estudio de prevalencia en atención primaria, Honduras

Metabolic syndrome (MS) is becoming one of the main public health problems of the 21st century.[1] Its pathogenesis is complex, with many uncertainties remaining.

MS is defined as a series of risk factors for type 2 diabetes mellitus (T2DM), cardiovascular disease, non-alcoholic fatty liver disease, and obstructive sleep apnea, characterized by insulin resistance and compensating hyperinsulinism associated with carbohydrate and lipid metabolic disorders, high blood pressure (HBP) and obesity.[2,3]

A cross-sectional, observational, analytical study with probabilistic, stratified, and randomized sampling is reported here. Confidence level: 95% and error: 5%. The study objective was to assess the prevalence of MS in the population over 18 years of age (n = 4836) in the municipality of San Ignacio, Francisco Morazán, Honduras, within the context of a primary care public health strategy initiative involving 16 of its communities, from September to December 2015, with a global population of 8831 inhabitants. The study protocol was evaluated and approved by the bioethics committee of the scientific research unit (registry no. 00003070).

The inclusion criteria were: permanent residents in the municipality over 18 years of age who gave their informed consent to participate in the study. Pregnant women, patients with disabling diseases or cognitive impairment, temporary residents who would therefore be unavailable for assessment and follow-up, and subjects who did not give their written informed consent were excluded from the study.

The study was divided into two phases. A first phase was designed to identify the risk factors using a screening protocol validated by the School of Medical Sciences of the Universidad Nacional Autónoma de Honduras, which evaluated the sociodemographic variables collected in a personal interview: age, sex, race, educational level, occupation, community of residence, and socioeconomic level. The clinical data recorded included prior diagnosis and/or any family history of T2DM and HBP, alcohol and/or tobacco consumption, and the measurement of the abdominal circumference (AC) as an anthropometric variable. A total of 2525 inhabitants meeting the inclusion criteria were interviewed (males: 791, females: 1734). Of these, 1380 (males: 377, females: 1003) met the defined risk criteria (score $\geq$ 5) and were subsequently evaluated in the second phase of the study, consisting of a clinical/anthropometric evaluation:

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