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AUTOANTIBODIES DIRECTED AGAINST INSULIN RECEPTOR DURING THE COURSE OF CASTLEMAN DISEASE: A NEW CASE REAFFIRMING AUTOIMMUNE HYPOGLYCEMIA AS A RELAPSE WARNING SIGNAL

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ABSTRACT

This case study presents the case of a 54-year-old human immunodeficiency virus (HIV)-positive male who developed type B insulin resistance syndrome (TBIRS) in conjunction with a relapse of human herpesvirus 8 (HHV8)-positive multicentric Castleman disease (MCD). This case is only the sixth reported instance of TBIRS associated with HHV8-associated MCD. The diagnosis was confirmed by the presence of anti-insulin receptor autoantibodies, and the patient was treated effectively with rituximab, with no relapse in follow-up.

The cases described are discussed, along with the differences between them and our own case. Additionally, the potential for an autoimmune complication of MCD, even when HIV is well controlled, is addressed, as well as the available therapeutic approaches.

KEYWORDS

Multicentric Castleman disease, hypoglycemia, autoimmune disease, type B insulin resistance syndrome

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LEARNING POINTS

- Unexplained hypoglycemia can reveal autoimmunity against insulin receptors associated with lymphoproliferative disorders, including multicentric Castleman disease.
- Autoimmune hypoglycemia can occur independently of inflammatory signs or uncontrolled human immunodeficiency virus infection in patients with multicentric Castleman disease.

INTRODUCTION

Autoimmune hypoglycemia due to autoantibodies directed against insulin receptors is a rare condition that may be associated with hematological diseases. In this report, we describe anti-insulin receptor antibody-linked hypoglycemia as the first sign of relapse in a patient with human herpesvirus 8 (HHV8) positive multicentric Castleman disease (MCD).

CASE DESCRIPTION

A 54-year-old man was referred to the Endocrinology Department (Hôpitaux Civils de Colmar, Colmar) for a 2-month history of night sweats, tremors, headaches, and paroxysmal malaise. The patient's medical history included human immunodeficiency virus (HIV) infection, complicated by HHV8 positive MCD revealed by autoimmune thrombotic thrombocytopenic purpura 2 years before. He did not have any history of diabetes, and his only medication consisted of HIV antiretrovirals (bictegravir-emtricitabine-tenofovir alafenamide).

Parameter	Result
Age (years)	54
Sex	Male
Years since MCD diagnosis and hypoglycaemia	1
Clinical findings	Lymphadenopathy, Splenomegaly
Serum C-reactive protein (mg/l)	16
Serum gamma globulins (g/l)	21.8
HHV8 RT-PCR (log)	3.9
Serum CD4+ T cells (/mm^3)	558
HIV viral load	Undetectable
Fasting Glycemia (mmol/l, reference: 3.5-6.1 mmol/l)	2.64
Serum insulin (mIU/l, reference: 2-17 mIU/l)	3.54
Proinsulin (pmol/l , reference: 1.13-4.21 pmol/l)	0.950
C-peptide (nmol/l , reference: 0.26-1 nmol/l)	0.0695
Anti-insulin receptor antibody	Positive
Anti-insulin antibody	Negative

Abbreviations: MCD, multicentric Castleman disease; HHV8, Human herpesvirus 8; RT-PCR, real-time polymerase chain reaction; HIV, human immunodeficiency virus.

Table 1. Clinical and biological characteristics of the patient at hypoglycaemia onset.

Physical examination was remarkable for supracentimetric lymphadenopathies in the right axilla, cervical, and supraclavicular regions. No fever, no B symptoms, no hepatosplenomegaly, no cutaneous signs were noted. The patient had a body mass index of 27.7 kg/m^2 with a gain of 8 kg associated with the consumption of snacks to restore normal glycemia values (weight 81 kg, height 171 cm).

Episodes of fasting hypoglycemia were documented with plasma glucose at 2.6 mmol/l, associated with low but non-suppressed insulin levels (3.5 mU/l), while proinsulin and C peptide levels were decreased (0.95 pmol/l - normal range: 1.13-4.21 pmol/l, and 0.0695 nmol/l - normal range: 0.26-1 nmol/l, respectively) and insulin autoantibodies were negative *(Table 1)*. The thoraco-abdomino-pelvic (TAP) scan showed supracentimetric lymphadenopathies and splenomegaly. The patient was then referred to the Clinical Immunology Department for further investigation. Upon admission, the patient had a HHV8 viral load of 8,000 copies/ml (3.9 log), with an undetectable HIV viral load and a CD4 lymphocyte count of 558/mm^3. He presented with a polyclonal hyperglobulinemia (21.8 g/l) and the serum levels of C-reactive protein was increased (16 mg/l). A positron emission tomography (PET)-CT scan conducted 2 months prior as part of the follow-up for Castleman's disease revealed spleen and lymph node (axillary and occipital-cervical region) hyperfixation.

The combination of hyperfixation on the PET scan, HHV8 copy number, and hormonal profile led us to hypothesize that hypoglycemia could result from anti-insulin receptor autoantibodies produced during a relapse of Castleman's disease *(Table 1)* despite the patient not fulfilling all criteria for MCD flare as defined by Gérard et al.[1]. A sample of patient serum was collected for anti-insulin receptor autoantibody screening, then we started rituximab infusions (375 mg/m^2/week), in addition to continuous intravenous glucose. After 15 days and three infusions of rituximab, glucose administration was stopped *(Fig. 1A)*.

At the 1-month assessment, there was no recurrence of hypoglycaemia, HHV8 viral load was undetectable, and the presence of anti-insulin receptor autoantibodies was confirmed by showing the ability of the patient's serum to

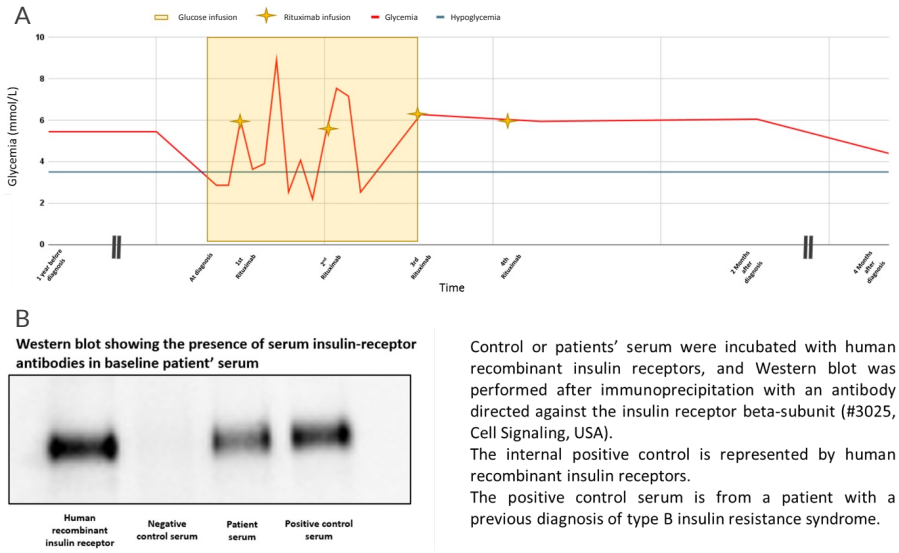


Figure 1. A) Graphic representation of random blood glucose levels over time with response to rituximab infusion; B) Anti-insulin receptor beta antibodies screening by Western blot. Control or patients' serums were incubated with human recombinant insulin receptors.

immunoprecipitate recombinant human insulin receptors *(Fig. 1B)*. After 6 months follow-up, the patient was still in MCD remission and without relapse of hypoglycemia.

DISCUSSION

Type B insulin resistance syndrome (TBIRS) is a rare autoimmune disease due to the presence of serum anti-insulin receptor antibodies[2]. Only 115 cases of TBIRS had been described up to 2019. Patients typically present with signs of insulin resistance, including acanthosis nigricans and uncontrollable hyperglycaemia despite extremely high-dose insulin therapy. A minority of patients may experience isolated hypoglycaemia, as was the case with our patient[3,4]. Hyper or hypoglycemia results from different effects of insulin receptor autoantibodies that interfere with insulin binding to its receptor, insulin signaling, and/or receptor-mediated degradation of insulin. Episodes of hypoglycemia and hyperglycemia may occur in the same patient[2]. Although novel *in vitro* assays dedicated to serum insulin receptor autoantibodies were recently developed[5], commercial detection tests for insulin receptor antibodies are not yet commercially available and diagnosis of TBIRS mainly relies on insulin binding or immunoprecipitation-based techniques performed in a small number of research laboratories worldwide[6,7]. TBIRS is primarily associated with autoimmune and/or connective tissue diseases. It is also associated with lymphoproliferative disorders, including Hodgkin's lymphoma, myeloma, and HHV8+ MCD[2,4,8].

HHV8-positive MCD is a multicentric lymph node pathology driven by uncontrolled HHV8 infection. The disease usually occurs in immunocompromised individuals in whom it can be associated with Kaposi sarcoma, lymphadenopathy, organomegaly, deterioration of the general condition, cytopenia, and systemic symptoms during flares[9].

Arnautou et al.[4] reported 5 male patients with HHV8+ MCD and recurrent hypoglycemia due to insulin receptor autoantibodies, which represented 1.9% of the French MCD cohort. Two patients were HIV-positive and only one had Kaposi sarcoma. Autoantibodies directed against insulin receptors led to hypoglycemia in all patients, associated with hyperglycemic episodes in one patient after etoposide therapy. Each case occurred during a relapse of MCD. All 5 patients were effectively treated with weekly rituximab regimens. Codish et al.[10] described a sixth case of recurrent hypoglycaemia in a patient with HHV8+ MCD but TBIRS could not be diagnosed as insulin receptor antibodies were not tested.

We describe here the sixth confirmed case of TBIRS in a patient with HHV8+ MCD. Non-suppressed insulin levels with very low C-peptide associated with hypoglycemia, which initially led us to consider the possibility of factitious hypoglycaemia, are also compatible with the diagnosis of TBIRS due to the decreased insulin receptor-mediated insulin clearance in the presence of anti-insulin receptor autoantibodies[2-4]. The diagnosis was confirmed by the detection of anti-insulin receptor antibodies by immunoprecipitation followed by Western Blot analysis *(Fig. 1B)*. The patient exhibited favorable immuno-virological control, with an undetectable HIV viral load and a CD4 count exceeding 500/mm^3. Patient 4 in the Arnautou et al.[4] series also demonstrated a HIV virological control status, with a viral load below 50 copies, but the CD4 count was 432/mm^3. Patient 3 in the London et al.[11] series, which focused on thrombotic thrombocytopenic purpura associated with HHV8-positive MCD, exhibited a nearly virologically controlled state. The 2 other patients with HIV infection in the same series also had low viral loads (less than 500 copies/ml). This leads to the conclusion that autoimmune complication of MCD can occur even when HIV is well controlled.

Therapeutic management followed a biphasic approach. For glycemic control, the first strategy was based on an adapted diet, with therapeutic education and continuous glucose monitoring. However, due to persistent hypoglycemia at night, continuous intravenous administration of glucose was needed. Concomitantly, we used an immunomodulating treatment, which was proved to be efficient in TBIRS[3,4,8]. Corticosteroid therapy, which has been used in several

reports, was not considered here due to the patient's history of HHV8+, HIV+ MCD and the risk of inducing Kaposi's sarcoma. Due to the high probability of TBIRS associated with relapsed MCD, an anti-CD20 therapy with rituximab was chosen. This treatment has shown promising efficacy in the 5 patients described by Arnautou et al.[4], both for HHV8-positive MCD flares and for auto-immune hypoglycemia. The patient responded well to rituximab treatment, with no relapse or adverse effects observed during the 6-month follow-up period.

In conclusion, we report a new case of anti-insulin receptor autoantibodies-associated hypoglycemia revealing a relapse of HHV8+ Castleman's disease. This type of autoimmune complication should be considered in cases of unexplained hypoglycemia in patients with MCD. In the context of HIV infection, they may occur even in cases with good immunovirological control. Rituximab is a treatment of choice to control severe hypoglycemia in this setting.

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