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CASE REPORT

PROTECTIVE LEVELS OF VARICELLA-ZOSTER ANTIBODY DID NOT EFFECTIVELY PREVENT CHICKENPOX IN AN X-LINKED AGAMMAGLOBULINEMIA PATIENT

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SUMMARY

We describe the case of an eight-year-old boy with X-linked agammaglobulinemia who developed mild varicella despite regular intravenous immunoglobulin (IVIG) therapy. He maintained protective antibody levels against varicella and the previous batches of IVIG that he received had adequate varicella-specific IgG levels. The case illustrates that IVIG may not prevent VZV infection.

KEYWORDS Chickenpox; Immunoglobulin; Intravenous; Agammaglobulinemia; Immunodeficiency disorders.

INTRODUCTION

Patients who have immunodeficiency disorders rely on immunoglobulin prophylaxis to prevent common infectious diseases. Intravenous immunoglobulin (IVIG) products are prepared from pools of plasma collected from a large number of healthy donors and, therefore, contain antibodies against many infectious agents preventing a variety of bacterial and viral infections, such as varicella, in patients with impaired antibody production[1,4,12].

X-linked agammaglobulinemia (XLA) is a hereditary immunodeficiency, characterized by absence of mature B cells, resulting in very low levels of all immunoglobulin isotypes. The mainstay of therapy for these patients is immunoglobulin replacement[9,13,16].

Varicella is a disease caused by the primary infection with the varicella-zoster virus (VZV). Clinical manifestations of the disease depend on age, immune and vaccination status, and type of exposure [2]. As a result of immunization, in some countries, chickenpox is no longer a common illness[11]. In Brazil, however, this disease is still endemic.

The majority of primary VZV infections involve uncomplicated chickenpox. However, in newborns and inadequately protected immunosuppressed patients, exposure to VZV can lead to severe illness[2,11,17].

In this study, we report a case of chickenpox in a child with XLA who is being treated with regular intravenous immunoglobulin. Although the patient developed a mild disease, this case shows that regular intravenous immunoglobulin therapy did not effectively prevent chickenpox.

CASE REPORT

An eight-year-old boy was diagnosed with XLA at the age of four, and presented 0.5% of B lymphocytes and serum IgG, IgA and IgM levels of 149 mg/dL, 1 mg/dL and 11 mg/dL, respectively. T lymphocyte numbers were normal. He started treatment with IVIG (600 mg/kg, every four weeks) with excellent compliance and good outcome, keeping IgG levels over 600 mg/dL.

He was admitted to our clinic with a one-day history of skin lesions on trunk and abdomen that had started 19 days after his last IVIG infusion and was diagnosed with a mild varicella (less than 50 lesions at various stages - red papules, vesicles and broken vesicles leaving a crust). There was no history of fever or other symptoms. He was treated with oral acyclovir for five days and received an extra dose of standard IVIG. He recovered without any complication.

Total serum IgG levels, varicella-zoster IgG levels, and avidity, assessed on day 1 of varicella, are presented in Table 1. VZV antibodies and VZV IgG avidity were also assessed from serum samples collected five, ten, sixteen and twenty months before varicella (Table 1). Varicella-specific IgG levels from the batch of IVIG that was administered to the patient for the last three months before varicella were determined (Table 1).

At the time of varicella infection, the patient's CD4+ and CD8+ T lymphocyte counts were 2388 cells/mm^3 and 1293 cells/mm^3,

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Table 1

(a) Varicella-specific IgG levels and its avidity, and total IgG levels obtained from the serum of the patient. (b) Varicella-specific IgG levels from the batch of IVIG that patient received over the last three months before VZV infection. Samples were tested for varicella-specific IgG levels by ELISA[5,14]

	Varicella-specific IgG titer (IU/mL)	Varicella-specific IgG avidity (%)	IgG (mg/dL)
Day 1 of varicella[(a)]	2.03	70.3	718
Five months before varicella[(a)]	1.2	62.4	
Ten months before varicella[(a)]	0.48	72.3	
Sixteen months before varicella[(a)]	0.79	66.9	
Twenty months before varicella[(a)]	0.87	70.9	
IVIG[(b)]	12.4	--	

Protective IgG levels are considered when higher than 0.1 IU/mL[8,9].

respectively. Fifteen days after infection, both CD4+ and CD8+ T cells expressed CD25 upon *in vitro* stimulation with VZV specific antigens[18] (Fig. 1).

DISCUSSION

The aim of IVIG replacement therapy in hypogammaglobulinemic patients is to protect them from potentially preventable infections.

However, it is well known that many factors may have an impact on the quality and quantity of antibodies in IVIG preparations, and there are differences in immunoglobulin content from brand to brand as well as from batch to batch[1,3,4,6,11,12].

Assessment of current IVIG preparations showed that they contain high levels of VZV specific IgG, despite the changing epidemiology of varicella due to vaccine introduction[11,12]. A study published in 2000 showed that patients receiving monthly IVIG at 400 mg/kg may be protected against varicella and probably do not require varicella-zoster immune globulin (VZIG) if the last dose of IVIG was given three weeks or less before exposure[8]. That is in agreement with the fact that antibodies for some virus and bacteria in IVIG preparations seems to have a half-life longer than 20 days[10].

In 2009, we had two other patients, one with common variable immunodeficiency (CVI) and another with XLA who also presented with mild varicella while on regular IVIG replacement therapy, similar to the patient in this case. In this current report, we showed that the previous-batches of IVIG that the patient received had adequate varicella-specific IgG levels and our patient maintained protective antibody levels against

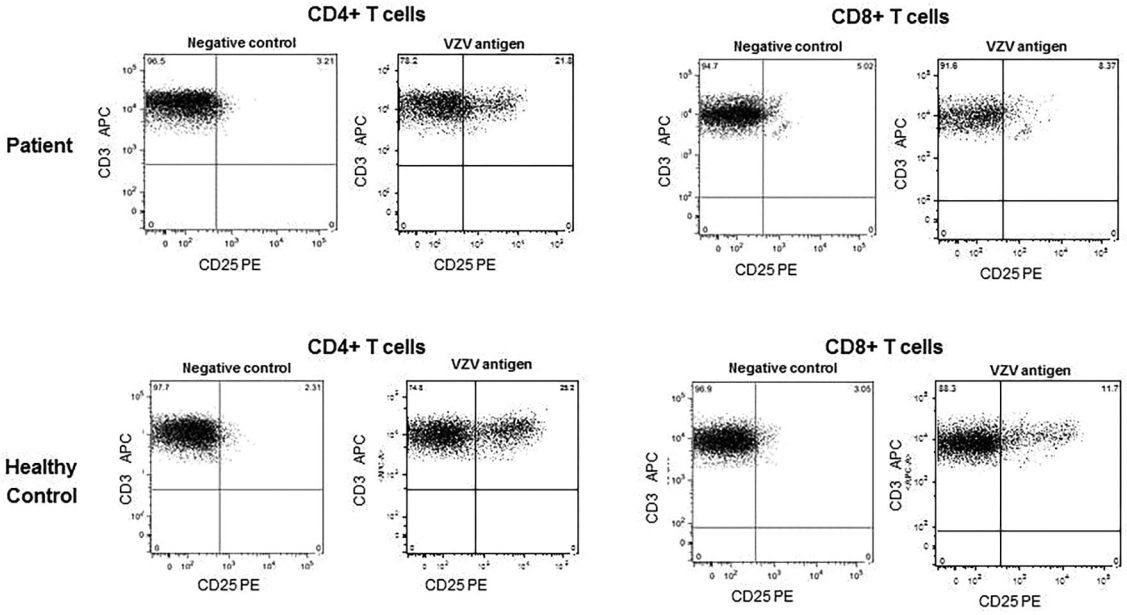

Fig. 1 - CD25 expression on CD4+ and CD8+ T lymphocytes after incubation with VZV specific antigens. The final value of positive cells was obtained by subtracting the percentage of cells stimulated with cell supernatant of non-VZV-infected cells (negative control) from the percentage of cells from the culture in presence of the stimulus (VZV antigen). Adapted from VIANA *et al*., 2010[18].

varicella during the previous months (Table 1).

Specific antibody levels have been correlated with protection against several diseases. Antibody levels that correlate with protection are generally derived from studies with healthy population wherein observations have been shown that individuals with a certain level of antibody are always or nearly always protected from disease[15]. However, these protective levels are usually determined after active immunization. There has been no study that has defined what level of varicella-specific antibody provides adequate protection in passive prophylaxis usage. What would be the protective antibody levels for a patient who does not produce antibodies?

Humoral immunity is very important for VZV neutralization of the cell-free virus and cellular immunity is essential for limiting the extent of primary infection with VZV[2,7]. XLA patients have normal T cells function and these cells from our patient responded to VZV (Fig. 1) which could explain his favorable evolution. However, certain groups of patients, such as those with impaired T cell-mediated immunity or with antibody deficiency but taking immunosuppressive drugs can develop severe complications[7] and must be protected.

Although the efficacy of IVIG in the prevention of several diseases is well established[1,4], we have to be aware that this therapy cannot be totally effective for some diseases in certain situations. Maybe IVIG is effective in modifying varicella infection but not in preventing the disease.

RESUMO

Nível sérico adequado de anticorpo contra o vírus da varicela-zoster não foi suficiente para prevenir a infecção em criança com agamaglobulinemia ligada ao X

Relatamos o caso de uma criança com agamaglobulinemia ligada ao X, sexo masculino, oito anos de idade, que desenvolveu quadro de varicela leve, apesar do tratamento regular com imunoglobulina intravenosa (IVIG). O paciente mantinha níveis adequados de imunoglobulina (IgG) contra varicela, assim como, os últimos lotes de IVIG por ele recebido também apresentavam níveis adequados do anticorpo específico. O caso ilustra que o tratamento regular com IVIG não é suficiente para prevenir a infecção pelo vírus da varicela-zoster.

CONFLICT OF INTEREST

None declared.

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ETHICAL APPROVAL

Not required.

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