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CLINICAL CASE

# Primary immunodeficiencies and B-cell lymphomas

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**KEYWORDS**
Antitumor immunity;
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Epstein-Barr virus

**Abstract**
*Introduction:* In primary immunodeficiencies there is a failure in the anti-tumor defense. Common variable immunodeficiency (CVID) is one of the most common primary immunodeficiencies characterized by an alteration in the differentiation of B lymphocytes (BL). Epstein-Barr virus (EBV) is an ubiquitous virus that selectively infects the BL. In patients with immunodeficiency, uncontrolled proliferation of infected BL and the action of viral proteins promote the development of lymphomas.
*Clinical cases:* At the University Hospital Sant Joan de Deu, Barcelona, 28 patients were diagnosed with CVID from 2000 to 2013. This paper describes four patients who developed non-Hodgkin's lymphoma (NHL). The lymphoma was associated with EBV in two of the cases. Patients were < 18 years old, diagnosed with lymphoma between 4 and 13 years old. Two patients were treated with rituximab as monotherapy and achieved complete remission. Two patients were treated with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) and radiotherapy or rituximab and achieved complete remission.
*Conclusions:* Early detection of EBV infections and NHL in all patients diagnosed with CVID is recommended, regardless of age at diagnosis.


**PALABRAS CLAVE**
Inmunidad antitumoral;
Inmunodeficiencia variable común;
Linfomas B;
Linfoma no Hodgkin;
Virus Epstein-Barr

**Inmunodeficiencias primarias y linfomas de células B**

**Resumen**
*Introducción:* En las inmunodeficiencias primarias existe un fallo en la defensa antitumoral. La inmunodeficiencia variable común (IDVC) es una de las inmunodeficiencias primarias más frecuentes. Se caracteriza por una alteración en la diferenciación de linfocitos B (LB). El virus de Epstein-Barr (EBV) es un virus ubicuo que infecta de manera selectiva los LB. En pacientes con inmunodeficiencias, la proliferación incontrolada de LB infectados y la acción de proteínas virales promueve la aparición de linfomas.

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*Casos clínicos:* En el Hospital Universitario Sant Joan de Déu, Barcelona, se han diagnosticado 28 pacientes con IDVC del 2000 al 2013. En este trabajo se describen cuatro que desarrollaron linfoma no Hodgkin (NHL). El linfoma fue asociado a EBV en dos de ellos. Los pacientes eran menores de 18 años, con el linfoma diagnosticado entre los 4 y 13 años de edad. Dos de los pacientes fueron tratados con rituximab como monoterapia, y lograron la remisión completa. Dos fueron tratados con CHOP (ciclofosfamida, doxorrubicina, vincristina y prednisolona) y radioterapia o rituximab y también alcanzaron la remisión completa.
*Conclusiones:* Se recomienda realizar la detección precoz de las infecciones por EBV y los NHL en todos los pacientes con diagnóstico de IDVC, independientemente de la edad del diagnóstico.


## 1. Introduction

Immunodeficiencies are a very broad group of diseases with different pathogenetic mechanisms, which have in common a failure in the regulation of the immune defense against foreign aggressions. This failure in the regulation gives rise to diseases whose origin could be in the alteration of a receptor (for example, TOLL type), in the absence of an interleukin (IL), in the lack of function of the B lymphocytes (BL) or T lymphocytes (TL) or in the lack of a protein such as MBL *(mannose-binding lectin)*. In the end, whatever the inductor genetic failure, the predominant symptomatology is the presence of infections, although these patients also have cancers of lymphoid origin and autoimmune diseases.[1,2] Immunodeficiencies are classified into two categories: i) congenital or primary, almost always due to mutations or deletions of genes that tend to be hereditary but can also be *de novo* mutations; and (ii) acquired or secondary due to a disease that facilitates the loss of antibodies or lymphocytes. Primary immunodeficiencies are associated with the genetic deficiencies mentioned above. Examples of diseases that promote secondary deficiencies are persistent infections such as malaria, chronic diarrhea or nephrotic syndrome.[3] Currently there have been > 70 clinical forms of primary immunodeficiencies identified. Due to recent advances in molecular biology, the molecular defects responsible for an important part of the primary immunodeficiencies are known, with undeniable advantages in terms of the possibility of an accurate diagnosis, prenatal diagnosis in affected families, genetic counseling and, in some cases, the possibility of treatment through gene therapy (Table 1).[4,5]

### 1.1. Immunity and cancer

The relationship between immunity and cancer is well known. Tumor cell antigens induce effector immune responses that destroy tumor cells. An immunological approach is increasingly used for the diagnosis and treatment of cancer.

The immune defense against cancer is initially mediated by innate immunity, composed of natural killer (NK) cells capable of destroying tumor cells. This function potentiates with interleukins 2 and 12 (IL-2, IL-12) and interferons. Macrophages eliminate tumor cells using the same mechanisms that eliminate bacteria. Activated macrophages synthesize tumor necrosis factor (TNF) that produces thrombosis of the tumor blood vessels. Antitumor adaptive immunity is fundamentally mediated by LT CD8+, which are cytotoxic lymphocytes sensitized against tumor antigens capable of destroying cancer cells. This specific cytotoxic effector function starts with antigen-presenting cells (dendritic cells) and is potentiated by stimuli of the LT CD4+. Adaptive humoral immunity consists of specific IgG antibodies against tumor antigens, but usually has no effector function against the tumor and only serves for the diagnosis and control of tumor evolution.[6]

### 1.2. Epstein-Barr virus (EBV) and lymphomas

EBV is a double-stranded, ubiquitous DNA virus belonging to the herpesvirus family, which selectively infects BL, persisting in a latent state. EBV antigens are expressed differently, depending on the stage of differentiation of the BL and have different activity. These viral antigens are expressed in the nucleus, cytoplasm and surface of infected cells. The first antigens found in a latent infection are the Epstein–Barr nuclear antigens (EBNAs) of which EBNA-LP, EBNA-2, EBNA-3A,-3B and -3C are known and whose function is the stimulus of BL proliferation. Latent membrane proteins -1 and -2 (LMP-1 and LMP-2) have oncogenic properties because they facilitate genomic instability and promote the immortalization and transformation of the infected BL. EBV is a BL polyclonal activator, independent of the TL cooperating signals or dendritic cells. The *in vitro* BL infection promotes the formation of lymphoblastoid cell lines (LCL) immortalized due to the expression of the EBNA, LMP proteins and various non-coding miRNAs. LMP1 and LMP2A act as constitutively active receptors that imitate the CD40 signals of differentiation and of the BL antigen receptor, respectively. By this mechanism, EBV appropriates the physiological pathway of activation of the BL and promotes its proliferation and differentiation to memory cells in which the virus may persist for the lifetime of the infected individual.[7]

When a poor cytotoxic TL CD8+ response occurs due to an immunodeficiency of any type, an uncontrolled proliferation of infected BL takes place that increases the probability of errors occurring during DNA replication, including some that affect the oncogenes or tumor suppressor genes. The loci of the immunoglobulins are the most susceptible to suffer translocations. Translocation of the *MYC* gene to the