

Long Term Remission of a Primary Intracerebral Hodgkin Lymphoma in a Patient Previously Treated With Azathioprine

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Abstract

Background: primary central nervous Hodgkin Lymphoma is a very rare event that occurs in less than 0.2% of cases, most of them in immunosuppressed patients.

Case presentation: We describe a 59 year-old man with a 20 year history of ulcerative colitis treated with azathioprine during 6 years who developed a primary central nervous system Hodgkin Lymphoma. Immunohistochemical study was positive for Epstein-Barr virus showing a type II latency pattern. The patient was treated with chemotherapy regimen consisting on high dose methotrexate and cytosine arabinoside achieving complete remission that remains more than five years after diagnosis.

Conclusions: To the best of our knowledge we present the first case in the literature of a primary central nervous system Hodgkin lymphoma in a immunosuppressed patient due to azathioprine with a long remission after chemotherapy alone.

Keywords: Primary central nervous system; Hodgkin lymphoma; Epstein-barr virus; Azathioprine

Introduction

Primary central nervous system (CNS) lymphoma is a rare form of primary brain neoplasm, in which ninety percent of cases are diffuse large B-cell lymphoma. HL involving the CNS is a rare event happening most of them in the context of relapsed systemic disease [1,2]. Primary CNS-hodgkin lymphoma (CNS-HL) is very rare, occurring in less than 0.2% of all HL cases [3], and it has been poorly reported in the literature. Most of these few published cases refer to human immunodeficiency virus (HIV) patients [4,5]. Immunosuppressive therapy like azathioprine carries a well reported increase risk of developing lymphoma [3].

Here, we describe a unique case of a patient previously treated with azathioprine that develops a type II latency Epstein-Barr virus (EBV) primary CNS-HL in long remission after chemotherapy treatment.

Case Report

A 59 year-old man was admitted to our Hospital in February 2009 because of a history of holocranial headache, right palpebral ptosis, ataxia gait and diplopia. His past medical history showed that he had suffered with an ulcerative colitis for 20 years, which had been treated with azathioprine from February 2003 until February 2009. At his physical examination presented a left III cranial nerve palsy. There were no palpable lymph nodes, hepato or splenomegaly. Peripheral blood cell counts were as follows: white blood count $5.8 \times 10^9/L$ (67% neutrophils), platelets $226 \times 10^9/L$ and hemoglobin 13.2 g/dL. Serum biochemistry showed normal hepatic and renal function test, lactate dehydrogenase 1.5 uKat/L (normal range: < 3.4 uKat/L), β_2 -microglobulin 2.2 mg/L (normal range: < 2.2 mg/L) and erythrocyte sedimentation rate 15 mm/h. A cranial computed tomography revealed lesions at the right thalamic- mesencephalic and protuberant regions with marked contrast enhancement. The patient had stable vital signs. Treatment with azathioprine was stopped. He was initially treated with steroids. A magnetic resonance imaging showed a lesion in the right pontomesencephalic region. During the descent of steroids the patient showed clinical deterioration of the right ptosis and new

neurological symptoms like dysarthria and dysphagia. At this point the patient was hospitalized and treatment with intravenous steroids was initiated. A second magnetic resonance imaging showed expansive growth of the diencephalic lesion and the appearance of new lesions in the right cerebellum hemisphere and in the left temporobasal region. A positron emission tomography-computed tomography (PET-CT) revealed three hypermetabolic focuses localized in the right protuberance, the right cerebellar hemisphere and in the left temporo basal region. A cerebellar biopsy revealed a classic Hodgkin lymphoma. The tumor was necrotic and the cells were large, atypical and with large nuclei (Figure 1). Immunohistochemical study showed a characteristic profile: expression of cluster of differentiation (CD) 30 (Figure 2), CD15 and paired box 5. CD20, CD79a and B-cell specific octamer binding protein-1 were focally positive. Immunohistochemical studies demonstrate positive cells for the EBV antigens latent membrane protein -1 (Figure 3), being negative for Epstein-Barr virus nuclear protein- 2 and lytic protein BZLF1/ZEBRA. A chromogenic in situ hybridization showed the presence of viral ribonucleic acid (EBV) EBV virus encoded ribonucleic acid 1 and 2) in scattered lymphoid cells showing a type II latency pattern. Microbiological cultures were negative. Serologic test results indicated that several virus, including hepatitis B and C virus, syphilis (RPR and TP) and HIV were negative. Immunological tests including antinuclear antibodies and screening tumor markers were negative. Thoracic and abdominal computed tomography scans did not show enlarged lymph nodes. Bone marrow

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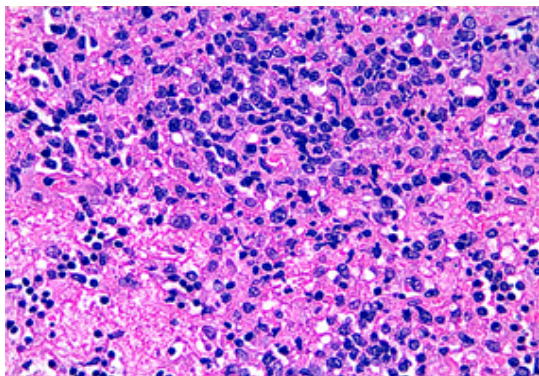


Figure 1: H&E. The brain parenchyma is involved by a lymphoid infiltrate comprised of small to large cells. The large cells are atypical. (Hematoxylin and Eosin, X10).

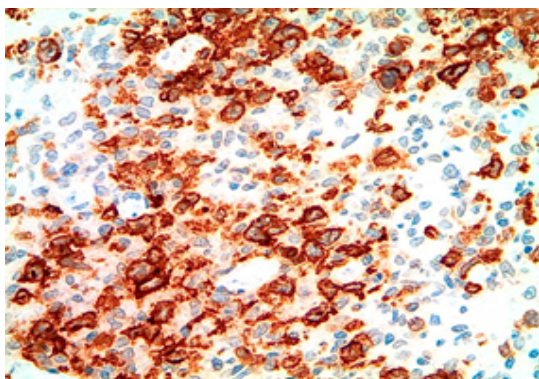


Figure 2: Neoplastic cells are strongly positive for CD30 (x10).

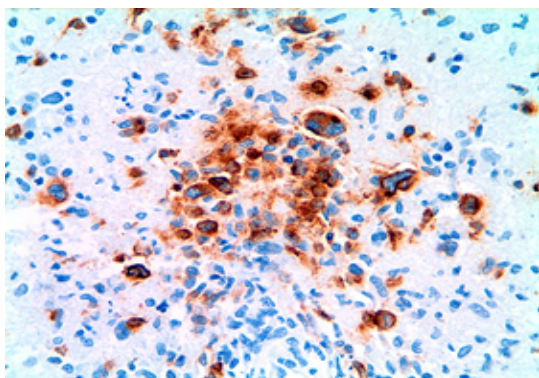


Figure 3: LMP-1 is positive for the neoplastic cells (x10).

biopsy did not show infiltration. No lymphoid cells were observed in cerebrospinal fluid. As a result of all these examinations, diagnosis of a primary intracerebral CNS classic HL was established. The patient was included in a therapeutic chemotherapy regimen based in methotrexate 2 g/m² and cytosine arabinoside 3 g/m². He received 6 cycles, and after that, a magnetic resonance imaging and a PET-CT confirmed an absence of lesions. Currently, sixty-five months after diagnosis, the patient remains in complete remission and with an excellent performance status.

Discussion

Primary CNS lymphoma is a rare form of primary brain neoplasm that in ninety percent of cases histological characteristics are of diffuse large B-cell lymphoma [6]. However, in very few cases the biopsy shows Hodgkin lymphoma [7-9]. It occurs in less than 0.2% of all HL cases. Most of them are in immunosuppressed patients, normally HIV patients or after transplantation. But in a very low number of cases like ours, immunosuppression is caused by immunomodulatory therapies like methotrexate, infliximab or azathioprine [10,11-13]. Lymphomas related with these immunosuppressors are described and well defined in the WHO 2008 classification and called iatrogenic immunodeficiency-associated lymphoproliferative disorders (ILPD) [14].

Reviewing the literature, only two isolated case reports with primary CNS-HL previously treated with azathioprine has been published. A 66-year-old female treated during 12 years with azathioprine due to a myasthenia gravis [8]. And a 47-year-old male treated with azathioprine during 20 years due to a multiple sclerosis and treated with the combination of chemo and radiotherapy achieving a remission during nine months [15]. A few important differences comparing with our case we want to remark: previous disease was an ulcerative colitis and was treated with azathioprine for significant less time, 6 years.

It is well described the effect decreasing T lymphocytes in patients treated with azathioprine during a not well defined long time [16]. This treatment causes a T cell immunosuppression and increases the risk of getting a lymphoma [3].

This T cell immunosuppression helps EBV to transcript high viral levels and facilitates the development of the lymphoma [17]. The ability of the virus to establish life-long persistent infection and induce growth transformation is in most of the cases related to the viral proteins that are variously expressed in normal and malignant cells [15]. In our case report, a type II EBV latency pattern was well defined [18].

Moreover, our patient is the case with a longer remission after chemotherapy treatment described in the literature, more than five years after diagnosis [19].

An interesting point difficult to explain is the affinity of CNS in this kind of patients. A retrospective paper published by Gerstner et al. [13] analyzing 6 cases with CNS HL involvement observed that 5 of 6 patients previously treated with immunosuppressors had disease limited to the brain. In this paper, authors suggest the predilection in this kind of patients for the CNS. ILPD should be considered in the differential diagnosis in patients with iatrogenic immunodeficiency presenting with neurological symptoms or/and intra-axial mass lesions. The fact that this immunosuppressed patient diagnosed of type II latency EBV intracerebral HL with a long remission after chemotherapy alone makes this case almost unique.

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