Caso Clínico

Paranasal sinuses lymphoma and past hepatitis B virus infection: possible association?

Linfoma dos seios perinasais e infeção prévia pelo vírus da hepatite B: uma possível

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**Resumo**

As neoplasias linfóides representam menos de 1% de todos os tumores da cabeça e pescoço. Tradicionalmente, são classificadas em linfomas Hodgkin e não-Hodgkin, sendo que este último grupo pode ser dividido nos subtipos células B maduras, células T maduras e células NK/T.

Neste artigo, os autores descrevem o caso clínico de um homem de 64 anos com queixas de obstrução nasal crónica, associado a edema da face e peri-orbitário bilateral e tumefação no palato duro com sinais inflamatórios. Ao exame físico apresentava edema da mucosa nasal, com abundantes secreções seromucosas. Os exames de imagem evidenciaram uma massa nos seios perinasais de grandes dimensões, agressiva, com sinais de erosão óssea das paredes dos seios maxilares e palato duro. A biópsia permitiu o diagnóstico de linfoma difuso de grandes células B, o subtipo mais prevalente de linfoma de células B.

Neste doente, o estudo serológico realizado revelou antecedentes de infecção prévia pelo vírus da hepatite B. Esta informação clínica foi importante para o planeamento do tratamento médico mas, realça também uma possível associação, descrita com crescente interesse na literatura, entre a infecção pelo vírus da hepatite B e o aumento do risco de linfoma de células B particularmente, o linfoma difuso de grandes células B.

**Palavras-chave**

Seios Perinasais; Linfoma Difuso de Grandes Células B; Hepatite B.
Abstract

Lymphoid neoplasms account for less than 1% of all head and neck cancers. They are divided into Hodgkin and non-Hodgkin lymphomas, this last group can be further divided into mature B-cell, mature T-cell and NK/T-cell subtypes.

The authors describe the clinical case of a 64-year-old man with complaints of chronic nose blockage, facial edema and swelling of the hard palate with inflammatory signs. On physical examination he presented nasal mucosa edema, with abundant seromucous secretions. The imaging exams revealed an aggressive sinonasal mass with significant erosion of the maxillary sinus walls and hard palate. The biopsy allowed the diagnosis of diffuse large B-cell lymphoma, the most prevalent subtype of B-cell lymphomas.

In this patient, the serological study revealed a history of previous hepatitis B virus infection. This clinical information was important for medical treatment planning, but also highlights a possible association, described with increasing interest in the literature, between the hepatitis B virus infection and the increased risk of B-cell lymphoma, particularly diffuse large B-cell lymphoma.

Keywords

Paranasal Sinuses; Lymphoma; Large B-Cell; Diffuse; Hepatitis B.
Introduction

Sinonasal malignancies have most frequently an epithelial origin, however, other etiologies such as lymphoid neoplasms can be found and account for less than 1% of all head and neck cancers. Traditionally divided into Hodgkin and non-Hodgkin lymphoma, the last group can be further divided into mature B-cell, mature T-cell and natural killer (NK)/T-cell subtypes. Among the B-cell lymphomas, the most prevalent subtype is the Diffuse Large B-Cell Lymphoma (DLBCL) which is more prevalent in white males after the sixth decade of life.

The authors describe an uncommon case of paranasal sinuses DLBCL in a patient with a previous hepatitis B virus infection. In addition to the description of the case, a literature review was conducted to understand the possible association between these two entities.

A 64 year-old man, caucasian, with a medical history of non-insulin dependent diabetes, hypertension, obesity, dyslipidemia and obstructive sleep apnea, was observed on the Otorhinolaryngology emergency department with complaints of nose blockage during the last four months. The patient was previously observed by his family physician who prescribed oral antibiotics for an acute rhinosinusitis, with no symptomatic improvement. In fact, the nasal complaints of obstruction, serous rhinorrhea, sinus pressure and rhinolalia clausa were progressively worst. He also referred an intra-oral swelling at the level of the palate, as well as, asthenia and unintentional weight loss. The patient denied other nasal symptoms, facial hypoesthesia or dysesthesia, fever or night sweats.

At physical examination he had a bilateral periorbital and left hemifacial swelling (figure 1A) and, on anterior rhinoscopy complemented with nasal endoscopy, besides mucosa hypertrophy and serous rhinorrhea no other alterations were found. Oral cavity examination revealed a soft tumefaction on the hard palate without fluctuation or drainage (figure 1B). Neurological examination showed no cranial nerves involvement.

The computed tomography (CT) scan performed (figure 2A) in the emergency department revealed a bilateral ethmoid and maxillary opacity, with signs of bone erosion of the maxillary sinus walls and hard palate. The blood sample analysis had an increased sedimentation rate and C-reactive protein.

The patient was admitted for medical treatment and etiological study since the imagiological exams could not differentiate between an aggressive acute inflammatory/infectious process and a neoplasm. During this period a magnetic resonance imaging (MRI) (figure 2B) confirmed the almost total opacity of the paranasal sinuses by a heterogeneous material (hyperintense in T2 and hypointense on T1) and erosion of the maxillary sinus, lamina papyracea and cribriform plate, with no intracranial invasion, as well as bilateral extension to the malar fat pad and extraconical orbital fat.

In order to obtain a histological diagnosis the patient was submitted to endoscopic sinus surgery with bilateral maxillary antrostomy and ethmoidectomy. The intraoperative findings revealed a hyperplasic mucosa with an inflammatory and friable mass exteriorized through the left ostium of the maxillary sinus, filling both ethmoid and maxillary sinuses (figures 3A and 3B). Multiple biopsies were sent in fresh for pathological study, which revealed nasal mucosa with large neoplastic lymphoid cells CD20 positive, Bcl6 positive, Bcl2 positive and CD10 negative (figures 4A-D). These finding were consistent with the diagnosis of DLBCL.

The collaboration of Haematology was requested and staging was completed with abdominal, pelvic and...
thoracic CT, cerebral MRI, bone marrow biopsy and echocardiogram, as well as serologic tests. The latter demonstrated a positive hepatitis B core antibody (anti-HBc) with all the others hepatitis B virus (HBV) specific antigens and antibodies negative, probably as a result of a past HBV infection (Table 1). Therefore, the patient was observed by the Infectiology department and started prophylactic treatment with lamivudine.

The DLBCL staging was Ann Harbour stage IV, R-IPI 4 (high risk) and CNS-IPI 4 (high risk), and the patient was started on standard chemotherapy based on the first-line regimen of R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone) completing a total of six cycles.

The MRI after treatment revealed a radiologic regression and all the previous findings of the physical exam disappeared (figures 5A and 5B). The patient reported no symptoms three months after treatment completion.
Discussão

The B-cell lymphomas are more prevalent in the Western countries and commonly arise from the paranasal sinuses\(^2\). On the other hand, NK/T-cell lymphomas are endemic neoplasias in some parts of Asia and South America; they are typically located in the nasal compartment and are considered to be more aggressive\(^2\).

DLBCL is regarded as less aggressive than other lymphoma subtypes, but frequently leads to inespecific symptoms consistent with benign inflammatory conditions, as a result of a mass effect and progressive mucociliary dysfunction, causing a delay on the diagnosis and treatment\(^3,4\). Patients can also present B symptoms such as fever and weigh loss\(^3\). Imaging exams normally reveal opacification of the sinuses with or without sinonasal mass therefore, without any pathognomonic signal\(^4\). For this reason, the histologic diagnosis is crucial\(^4\).

Non-surgical treatment is the gold standard, with most patients being treated with chemotherapy, usually with R-CHOP protocol\(^4\). Age younger than 60 years, earlier stages of disease and the absence of B symptoms are associated with higher complete response and overall survival rates\(^5\). It is also paramount to keep a long period of follow-up since the mean time for recurrence can be up to 40 months or longer\(^1\).

This clinical case was also challenging because the patient had a past HBV infection. Patients with resolved HBV infection under rituximab are at higher risk of developing HBV reactivation and hepatitis. Therefore, antiviral prophylaxis is recommended, as well as, monitorization of HBV DNA levels and liver function\(^6\).

Although this is a controversial topic, some studies describe a possible association between HBV infection and the development of B-cell lymphoma\(^7\). HBV infection is able to directly infect B lymphocytes and may be related to the development of such neoplasms\(^7\). Despite most studies report this association regarding patients with current HBV infection, past infection may also increase the risk of B-cell lymphoma, particularly DLBCL\(^8\). Past HBV infection was associated with an almost two-fold elevated odds ratio for B-cell lymphoma\(^8\).

In this report, the author presented a complex clinical case, with long-standing evolution due to the patient’ non-specific symptoms. Also, in this case, the history of past HBV infection placed new questions and reinforced the importance of a multidisciplinary approach.

Conflicts of interest

No conflicts of interest were declared by the authors.
References:


Figures:

Figure 1:
A) Patient bilateral periorbital and left hemifacial swelling; B) Soft tumefaction of the hard palate.
Figure 2:
A) CT shows a bilateral ethmoid and maxillary opacity, with signs of bone erosion of the maxillary sinus walls and hard palate; B) MRI reveals an almost total opacity of the paranasal sinuses with erosion of the maxillary sinus, lamina papyracea and cribiform plate and bilateral extension to the malar fat pad and extraconical orbital fat.
Figure 3A and 3B:
The intraoperative aspect of the left maxillary sinus occupied with an inflammatory and friable tissue.

Figure 4:
A) Hematoxylin and eosin staining (2x): respiratory mucosa, dense atypical lymphoid infiltrate with tissue destruction; B) CD20 (2x): sheet of large cells with B-cell phenotype; C) CD3 (2x): T-cells in smaller number; D) Ki67 (2x): B-cells with high proliferative index.
### Table 1. Interpretation of Hepatitis B Virus serologic test results.

<table>
<thead>
<tr>
<th></th>
<th>HBsAg</th>
<th>anti-HBc</th>
<th>anti-HBs</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptible</td>
<td>negative</td>
<td>negative</td>
<td>negative</td>
<td></td>
</tr>
<tr>
<td>Immune due to natural infection</td>
<td>negative</td>
<td>positive</td>
<td>positive</td>
<td></td>
</tr>
<tr>
<td>Immune due to hepatitis B vaccination</td>
<td>negative</td>
<td>negative</td>
<td>positive</td>
<td></td>
</tr>
<tr>
<td>Acutely infected</td>
<td>positive</td>
<td>positive</td>
<td>positive</td>
<td></td>
</tr>
<tr>
<td>Chronically infected</td>
<td>positive</td>
<td>positive</td>
<td>negative</td>
<td></td>
</tr>
<tr>
<td>Interpretation unclear; four possibilities:</td>
<td>positive</td>
<td>positive</td>
<td>negative</td>
<td></td>
</tr>
<tr>
<td>1. Resolved infection (most common)</td>
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<td>positive</td>
<td>negative</td>
<td></td>
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<tr>
<td>2. False-positive anti-HBc, thus susceptible</td>
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<td>positive</td>
<td>negative</td>
<td></td>
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<tr>
<td>3. “Low level” chronic infection</td>
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<td>positive</td>
<td>negative</td>
<td></td>
</tr>
<tr>
<td>4. Resolving acute infection</td>
<td>negative</td>
<td>positive</td>
<td>negative</td>
<td></td>
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</table>

Legends: HBsAg - Hepatitis B surface antigen; anti-HBc - hepatitis B core antibody; anti-HBs - Hepatitis B surface antibody; IgM anti-HBc - IgM antibody to hepatitis B core antigen.
Figure 5A (T1-weighted image) and 5B (T2-weighted image): MRI after treatment revealed T2-hyperintense tissue occupying maxillary sinuses and some ethmoidal cells which had a central component with discrete spontaneous hypersignal at T1; these aspects were compatible with residual inflammatory alterations, neglecting the hypothesis of residual lymphoma. There was also hypointensity on T1-weighted in the alveolar and hard palate arches, without associated masses, which may reflect secondary changes due to the previous tumor presence. No meningeal involvement or tumoral lesion was found in the adjacent intracranial compartment.