Doença de Behçet e linfoma. Associação fortuita?

Behçet disease and lymphoma. Casual association?

João Pedro Ferreira, Fabienne Gonçalves, João Araújo Correia, Luciana Xavier, Pedro Farrajota

Resumo

A doença de Behçet (DB) caracteriza-se, classicamente, por uma tríade sintomática de úlceras orais recorrentes, úlceras genitais e uveíte.

A DB é sistémica, com desenvolvimento de lesões vasculíticas ou vasculopáticas nas áreas afectadas. Estas áreas podem apresentar evidência microscópica de infiltração tecidual com células T e neutrófilos.

A associação com Linfoma não-Hodgkin tem sido reportada em raros casos, não permitido afirmar relação causal.

Reportamos um caso de Linfoma não-Hodgkin em doente com doença de Behçet, com revisão de literatura neste contexto.

Palavras-chave: doença de Behçet, linfoma não-Hodgkin, associação.

Abstract

Behcet's disease (BD) is characterized by a triple-symptom complex of recurrent oral aphthous ulcers, genital ulcers, and uveitis. Systemic involvement of multiple organs is observed in Behcet's disease, based primarily in the development of vasculitis or vasculopathies lesions in the affected areas. These areas may demonstrate microscopic evidence of inflammatory tissue infiltration with both T cells and neutrophils.

Association with Non-Hodgkin Lymphoma has been reported in few cases, but does not allow establishing causal relationship.

In this paper we report a case of Non-Hodgkin Lymphoma in a patient with Behcet's disease and literature review.

Key words: Behcet's disease, non-Hodgkin lymphoma, association.

INTRODUÇÃO

Behcet's Disease (BD) is characterized typically by a symptomatic triad of recurrent oral ulcers, genital ulcers and uveitis.

Hippocrates has described the disease in the 5th century BC, however the first description of the syndrome was attributed to the Turkish dermatologist, Hulusi Behçet in 1924. Since then, such syndrome has been referred as Behcet's Disease.[1]

Theories regarding BD pathogenesis, suggest an autoimmune etiology. Recent researches suggest that exposure to an infectious agent can trigger a crossed immunologic reaction. The proposed agents include *Herpes simplex virus* and the bacteria *Streptococcus spp, Staphylococcus spp* and *Escherichia coli*. All living in the oral cavity.

Internal Medicine Service, Unit A, of Porto Hospital Centre (PHC)

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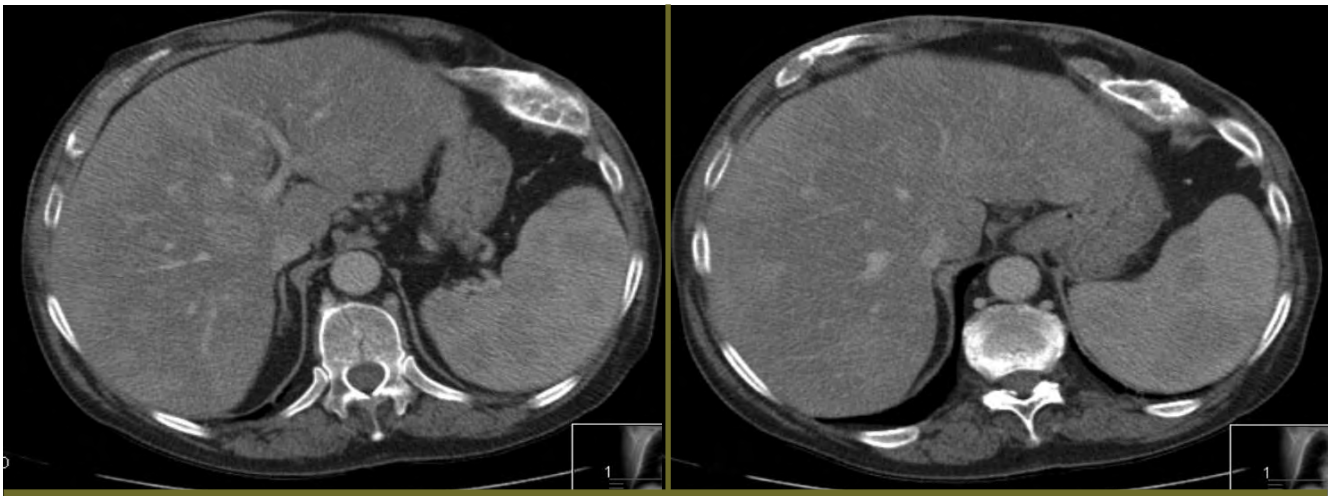
BD is a systemic disease. The presence of vasculitis or vasculopathies lesions was verified in the affected areas. These areas can show microscopic evidence of key issue infiltration with T cells and neutrophils.[2]

A higher prevalence of HLA-B51 has been demonstrated in populations in Turkey, the Middle East and Japan, corresponding to a higher incidence of Behcet's disease in such populations, however HLA-B51 does not influence the severity of symptoms.

BD prevalence in Portugal is of 2.4 cases per 100.000 inhabitants, similar to other European countries of the Mediterranean basin.[3]

Although the diagnostic triad has been classically reported, the diagnosis criteria have been changed. In 1990, the *International Study Group (ISG) for Behcet's Disease* proposed as diagnosis initial criteria the occurrence of at least three episodes of herpetiform or aphthous oral ulceration within a period of 12 months. To confirm the diagnosis, at least two of the following criteria must be demonstrated: 1) recurring genital ulcers; 2) Ophthalmic lesions, including posterior or anterior uveitis or retina vasculitis; 3) skin lesions, including erythema nodosum lesions *like*, papule, pustule or acne form; 4) positive results in pathergy test, characterized by the formation of erythematous papule or pustule (≥2 mm of higher



Liver and spleen solid foci lesions.

FIG. 1 e 2

diameter) appearing in the first 48 hours after the peak on forearm anterior face.

The association with non-Hodgkin lymphoma, has been reported in rare cases, and does not allow stating a causal relationship.

We report a case of non-Hodgkin lymphoma in the patient with Behcet's disease, with the revision of literature in this context.

CASE REPORT

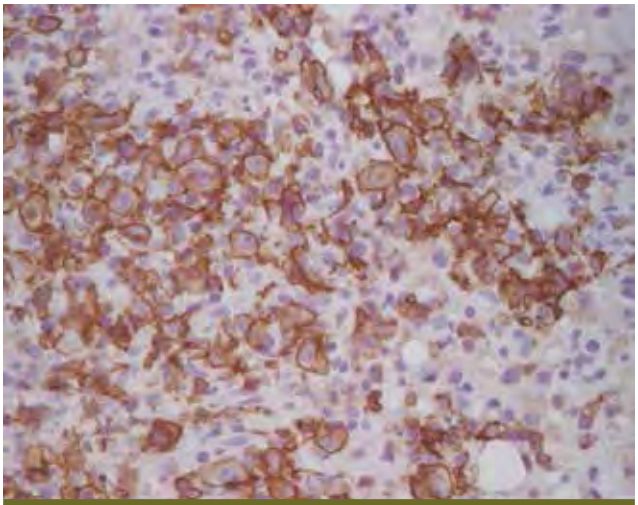
75 years-old man, a farmer and shoemaker, autonomous, with Behcet's disease (criteria: recurrent oral and genital ulcers and anterior uveitis) progressing for over 30 years, asymptomatic under low dosage chronic corticotherapy (Deflazacorte 6 mg/day). During the first couple of years after the diagnosis he took colchicine (1 mg/day) reducing aphthous crisis, but without a satisfactory resolution. He did not do immunosuppressant therapy.

In the six months preceding hospitalization, symptoms B of *Ann Arbor* (weight loss >10% of body weight, recurring fever and night sweating), sensation of fullness with post-prandial nausea and progressive worsening dyspnea.

In the week before admission to hospital here refers a sudden edema and pain in the right lower limb.

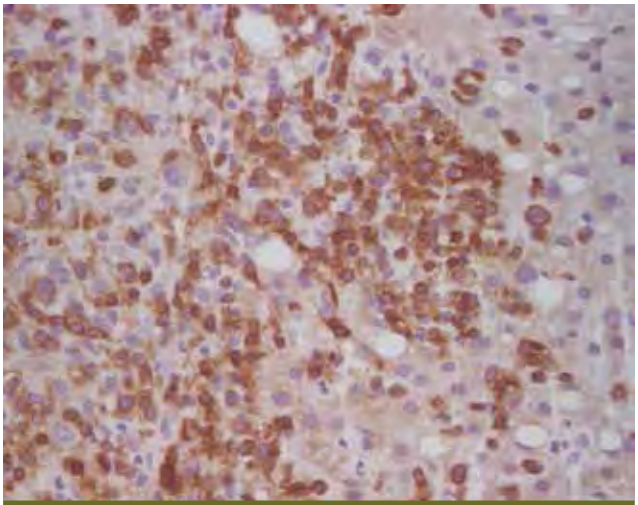
On admission he had no changes in the mental state, stable hemodynamically, apyretic, with tachypnea, abdominal pain triggered by deep palpation, liver edge palpable two fingers below the rib cage in deep inspiration, non-palpable spleen, no signs of peritoneal irritation; right lower limb edema up to the thigh root; painless adenopathy with around 2 cm of higher diameter, mobile with rubber consistency, palpable in the neck posterior triangle. Analytically, one could see hypoxemic respiratory insufficiency, normochromic and normocytic hypoproliferative anemia (HgB 11.7 g/dL), lymphopenia (170 x10^3/µL), mild thrombocytopenia (105 x10^3/µL), increase on transaminases (AST/ALT:253/205 UI/L), lactic dehydrogenase (679 UI/L) and beta-2 microglobulin (3475 ng/mL) increase. No particular data in the immunologic study. Negative viral markers (B, C hepatitis *Epstein-Barr* and *HIV*). Abdominal ultrasound showing numerous hypoechoic lesions affecting the liver, spleen and ganglia in the hepatic hilum conditioning mild hepatosplenomegaly. The thorax abdominal and pelvic angio CT scan showed central pulmonary thromboembolism and right and extensive venous thrombosis (iliac and femoral); anterior mediastinum adenopathy conglomerate; multiple liver and spleen solid foci lesions (*Fig.1 and 2*). Echocardiogram showing no evidence of right ventricle dysfunction.

The choice was to perform a biopsy of the liver lesion, with a pathoanatomical study compatible with non-Hodgkin lymphoma (NHL) B of big cells (*Fig.3, 4 and 5*- immunohistochemistry; *6*- hematoxylin and eosin). Without changes suggesting bone marrow involvement or peripheral blood by lymphoproliferative disease (immunophenotype/pathological anatomy).



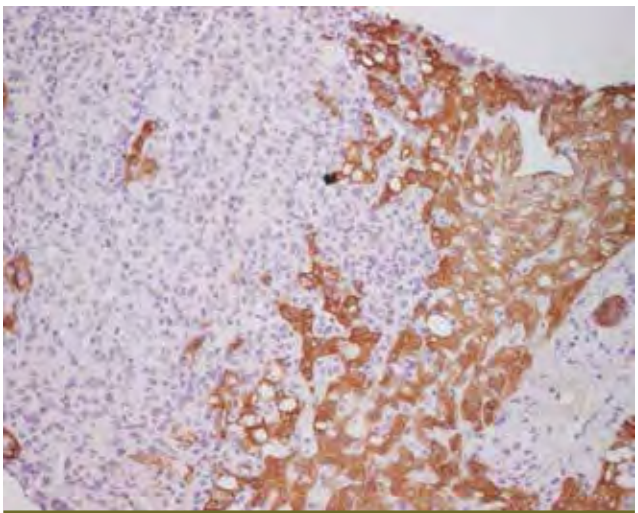
Immunoreactivity for CD20 in big cells.

FIG. 3



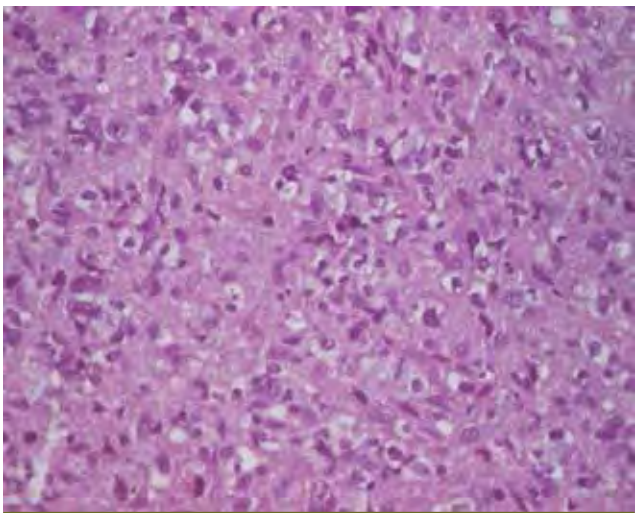
Immunoreactivity for CD3 observed in lymphocytes – infiltrate of a reactive nature.

FIG. 4



Immunoreactivity of hepatocyte for CAM 5.2 (cytokeratin of low molecular weight) – border between the neoplasm and the hepatocyte trabeculae

FIG. 5



Neoplasm of big cells laid out in " towel" observing mitosis pictures.

FIG. 6

In summary, a prothrombotic condition in the context of big cells NHL B, stage IV-B: IPI 4 (*ECOG 1*). Once the chemotherapy cycle was started (Cyclophosphamide, Vincristine, Prednisolone), without Anthracycline due to age and respiratory insufficiency; therapeutic dosage and half compressive Enoxaparin. Verified a progressive resolution of respiratory insufficiency and open reduction of the right lower limb edema.

He was discharged in a good general condition and able to carry on all his daily life activities. He is still under the chemotherapy regime as an outpatient.

DISCUSSION AND CONCLUSIONS

NHL is a heterogeneous group of lymphoproliferative neoplasms, with several patterns of behavior and

response to therapy.[1] Usually they are originated in the lymphoid tissues with metastases spreading for other organs. Conversely from Hodgkin disease, NHL is much less predictable and has a higher preference for spreading in extra nodular places. The prognosis depends on the histological type, stage and implemented therapy. Most (i.e. 80-90%) NHL has origin in B cells.[4]

NHL can divide themselves in two big prognosis groups – indolent and aggressive. Indolent lymphoma has a relatively good prognosis, with an average survival of 10 years. Most indolent lymphomas have a nodular or follicular morphology. The aggressive type NHL have a worst prognosis however in a significant number of such patients (around 30%) can be cured with chemotherapy.[4]

In general, the average survival at five years is about 50 – 60%. Most recurrences occur in the first couple of years of treatment.

NHL incidence has gradually increased around 3% year, however such data can be confused by the constant evolution of diagnosis additional means. At present, NHL corresponds to 5% of new neoplasms in men and 4% in women.

Several etiologies are proposed for NHL: genetic anomalies with chromosomal translocation or molecular reorganization; environmental factors (pesticides, herbicides, paintings, oil, plastics and synthetic products); exposure to chemotherapy or radiotherapy; virus (e.g. *Epstein-Barr virus, HTLV-1, HHV-8*); conditions of immunodeficiency (acquired and congenital); pathologies of the connective tissue, including Sjogren syndrome, rheumatoid arthritis, chronic lymphocytic thyroiditis and systemic erythematous lupus; gastrointestinal tract lymphomas in patients with coeliac disease and intestinal inflammatory disease; gastric MALT lymphoma, often observed in association with infection by *Helicobacter pylori*.[4]

In the particular case of BD, it is rarely associated with malignant neoplasms. In most cases the autoimmune nature of the disease and/or pharmacological immunosuppression have been identified as causal factors.[5-12]

There are 53 cases of BD associated with lymphoma described in *Pubmed*. 30 results are found when the crossing is made with NHL of B big cells. There is no other case described in CHP.

The meta analysis carried out do not show any evidence that the exposure to corticosteroids or non-steroids anti-inflammatory drugs are risk factors for NHL.[7]

BD association with NHL is rare and therefore does not allow to establish any links. However we should be attentive to the possibility of its occurrence. ■

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