Non-Hodgkin's lymphoma and Hodgkin's disease: consequence or association?

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Abstract

The occurrence of non-Hodgkin lymphoma in patients previously treated for Hodgkin's disease has already been described and explained by an iatrogenic immunologic deficit.

The authors describe a 60 year-old patient with Hodgkin's disease (scleronodular) which in the course of the therapy with MOPP developed a superior vena cava syndrome due to an "explosive proliferation" of mediastinal and cervical adenopathies, histopathologically corresponding to a high-grade lymphoma B.

The authors discuss the possible direct association of both conditions, based on a common pathology. The conclusions clearly indicate the evidence of this association in the clinical case described, and emphasize the need to reevaluate concepts, nowadays given as acquired, concerning the immunology and pathogenesis of the lymphoproliferative syndromes.

Key words: Hodgkin's disease, non-Hodgkin lymphoma, lymphoma composite, simultaneous lymphoma, sequential lymphoma.

Introduction

The simultaneity of two neoplasias is a phenomenon that, although not particularly common, is referred to with some regularity in the literature. This simultaneity has attracted more careful attention when it occurs in the presence of a lymphoproliferative syndrome. The finding of the "genealogical proximity" of the mother cell in this type of neoplasm has led to the acknowledgment of a possible definite relationship between the various types of non-Hodgkin's lymphomas (NHL) and between these and Hodgkin's disease (HD).[1] The idea that NHL and HD are perfectly distinct entities has changed as a result of new data that show a closer relationship between them. Similarities have been identified between the cellular lineages found in the genesis of each type of neoplasm.[2]

The concept of composite lymphoma is most commonly defined as the coexistence of two distinct types of NHL, or as the rare association between an NHL and any type of HD in the same organ or tissue. The simultaneous presence of these two entities in distinct organs, or in two nodes, even in the same ganglionic chain, is called simultaneous lymphoma.[4]

The incidence of this phenomenon seems to vary between 1 and 4.7%, a variation that results from different interpretations of the histological findings or the classification systems used. Besides these factors, sequential lymphomas are also considered, whose conceptual boundary with lymphatic transformation (normally to a lesser extent for a greater degree of malignancy) is often ambiguous. The most frequent associations are between phenotype B NHL, known as small cell follicular lymphoma, and diffuse histiocytic lymphoma.[6]

The association of NHL with HD is less frequent and in most cases, consists of the association of lymphocyte predominant HD with large cell NHL.[7]

These concepts are of key importance in the early identification of the situation described, with the necessary therapeutic and prognostic implications.

Case report

J. N. M., 60 years old, Caucasian, born in Marvão and living in Lisbon, a retired policeman, was admitted

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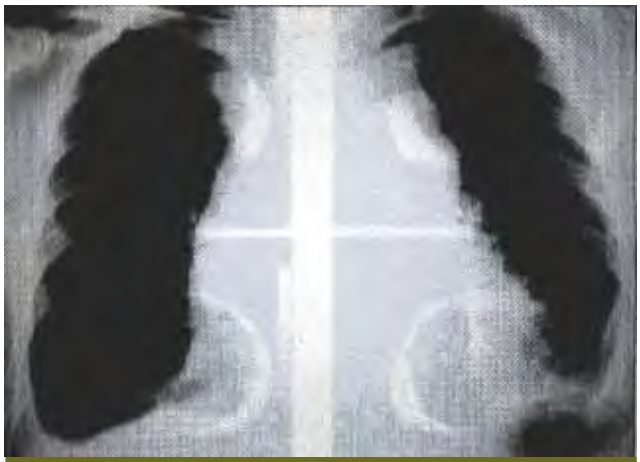


Posteroanterior chest teleradiography, showing enlargement of the mediastinum.

FIG. 1

to our hospital following the appearance of a cervical node on the right side. He described himself as always having been healthy until about two months before admission, when he noticed the appearance of a hard painless lump in the right side of his neck, with no other local changes or signs of inflammation.

He denied the existence of any systemic symptoms such as fever, increased sweating, weight loss, weakness or loss of appetite. He also systematically denied any and all other symptoms of either the organs or systems. A smoker of 40 cigarettes/day, he denied any significant use of alcohol or continuous medication. The remaining personal history was irrelevant and there was no known significant family history.

On physical examination, the patient was lucid and cooperative, without fever, hydrated with mucous membranes of normal color, and haemodynamically stable. Hair, skin and nails were normal. A hard, non-adherent, painless internal jugular chain adenopathy was identified, without signs of associated inflammation. There were no other palpable enlargements of lymph nodes in the superficial ganglion chains. There were no changes in cardiovascular symptomatology, nor was any abdominal swelling or mass identified. The neurological exam was normal.

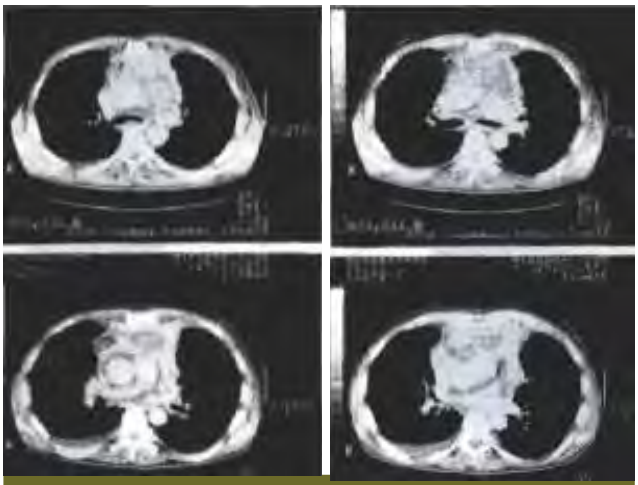
Results of the tests ordered at that time were: RBC 3.990.000/mm^3; Hgb 3.4 gr/dL; WBC 8600/mm^3; ESR 46 mm during the first hour; coagulation normal; fibrinogen 469mg/dL. The biochemical blood study was normal, with the exception of LDH of 415 mg/dL. Protein electrophoresis was normal. The immunoelectrophoresis and the b2-microglobulin were normal. Mantoux 10 U was non-reactive.

Chest X-Ray normal; the CT of the neck, chest, abdomen and pelvis revealed cervical adenopathies of the right paratracheal lymph node chain. None of the nodes was larger than 20 mm in diameter.

Excisional biopsy of the cervical lymph node showed scleronodular HD. The bone marrow biopsy was normal, and the disease was classified as stage II a.

He began chemotherapy with MOPP (mechlorethamine 6 mg/m^2 , vincristine 1,4 mg/dL, IV on 1st and 8th days and procarbazine 100 mg/m2 and prednisone 40 mg/m^2 PO from 1st to 14th day) every 28 days. An overall assessment was planned following the 4th cycle, with two subsequent consolidation cycles. During this period, tingling was noted in the extremities of all four limbs, justifying a reduction and subsequent cessation of vincristine in the 3rd and 4th cycles respectively.

Study following the 4th cycle showed no changes other than the disappearance of the adenopathies identified in the previous exam. The appearance of an isolated, infracentimetric perihilar adenopathy in the left lung was described, but was not considered important due to its possible relationship to a recent pulmonary infection. Due to the apparent good response to the treatment, maintenance with biweekly radiological monitoring was prescribed. The patient continued to appear to be doing well after the 5th and 6th cycles, but was admitted to the emergency room eighteen days after completion of the 6th cycle with superior vena cava syndrome (*Fig. 1*). An emergency cervicothoracic CT revealed multiple cervical adenopathies of the right external jugular and axillary chains; accentuated enlargement of the mediastinum, with multiple adenopathies located in anterior and superior spaces, as well as fatty infiltration adjacent to and compromising the vascular structures and brachiocephalic trunk (*Fig. 2*). The axillary lymph node (the only lymph node of the surface chains with increased volume and capable of being excised via minor surgery) only showed fibrosis and a reduction of adipose tissue. Therapy with methylprednisolone, 1 gr/day, IV, was started, without significant improvement. An excisional biopsy of the supraclavicular adenopathy conglomerate was scheduled for surgery in the operating room due to its characteristics (size and inflammation).



Cervicothoracic computed axial tomography, illustrating superior vena cava syndrome, due to compression of the mediastinal structures by multiple adenopathies

FIG. 2

A review of the initial histological components confirmed the diagnosis of Hodgkin's disease, and treatment with ADVB (doxorubicin 25 mg/m^2, bleomycin 10 mg/m2, vinblastine 6 mg/m^2 and dacarbazine 375 mg/m^2) was begun, IV, on the 1st and 15th days of a 28-day cycle.

On the 11th day after starting ABVD, the vena cava syndrome had worsened, with the appearance of light dyspnea associated with dysphonia (ENT – recurrent paresis of the left nerve).

Analytically, the myelogram showed pancytopenia, and the bone biopsy showed a bone marrow aplasia, without lymphomatosis infiltration.

Biopsy of the supraclavicular mass showed centroblastic phenotype B non-Hodgkin's lymphoma of a high degree of malignancy.

MACOP-B (methotrexate, leucovorin, doxorubicin, cyclophosphamide, vincristine, prednisone, co-trimoxazole, bleomycin) was begun.

The clinical situation continued, with a progressive increase of dyspnea and the onset of dysphagia, and the patient died from the progression of the disease in the 2nd month of MACOP-B treatment.

Discussion

HD and NHL are considered to be distinct nosological entities in all the currently used classifications of lymphoproliferative syndromes.[1,3,8] The coexistence of these two diseases is widely documented, whether occurring in the same anatomical area (composite lymphoma) or in separate locations (sequential and simultaneous HD and NHL).[4] From a histopathological perspective, the most common association combines lymphocyte predominant HD with large cell NHL.[7,9,10] Given the inherent characteristics of each of these entities, this association led some authors to postulate that lymphocyte predominant HD reflects the existence of a malignant B clone (the Reed-Sternberg cell possibly being an altered B lymphocyte), and that its "evolution" to histology of type B large cell NHL[11] would therefore be possible. However, this hypothesis is not made for the association of HD and other types of B-cell lymphoproliferative syndromes, such as follicular lymphoma,[12] chronic lymphocytic leukemia,[13,14] or even T-cell NHL.[15] As regards the association of scleronodular HD with large cell NHL, it is less frequent than forms involving the lymphocyte predominant subtype, but even so, it shows a much higher incidence than expected, given the frequency of each of the pathologies involved.[4]

Given the mediastinal location of the tumor in the case study presented, it was not possible to confirm whether it was a case of composite or simultaneous lymphoma. A hypothesis of sequential lymphoma did not seem reasonable in light of the lack of a free interval between the two neoplastic processes.

Initial treatment of HD in supradiaphragmatic stage I or IIa depends on the patient's age, the histological type of the tumor, the number of sites involved, and the erythrocyte sedimentation rate.[16] According to the European Organization for the Research and Treatment of Cancer (EORTC), patients under 40 with lymphocyte predominant or scleronodular forms of the disease documented in 1 or 2 sites and ESR<70 may be treated with radiotherapy (RT).

In the case described, aside from age, other factors led us to opt for chemotherapy as the 1st line treatment: the absence of a staging laparotomy (considered necessary for patients with stage II who will undergo radiotherapy) and, in particular, the existence of cervical and mediastinal disease. In such cases, the inefficacy of RT as the sole form of treatment is well-documented,[17] including the publication of some series in which, if we consider patients with tumors larger than a third of the thoracic diameter ("bulky disease"), the recurrence rates were as high as 50%.[18]

The initial treatment option (MOPP x 4[19], with

restaging at the end of the 4th cycle, followed by 2 or 4 more cycles to reach full remission and occasional consolidation RT localized in the mediastinum) seemed more appropriate to us.

The appearance of a left perihilar adenopathy in the staging CT performed following the 4th cycle raised suspicion of a chemo-resistant tumor, but the impossibility of surgical access to this region, and the documented regression of adenomegalies involved, justified the "wait and see" attitude adopted, and the maintenance of the protocol initially implemented. The rapid progression of the disease immediately following the 6th MOPP confirmed chemo-resistance to the quadruple therapy instituted and, for the 1st time, required a review of the histological diagnosis and the assumption of a poor prognosis. Misdiagnosis was ruled out as an important cause of this lack of response, since the protocol instituted was composed of drugs with proven efficacy against HD and also against NHL.

A review of the microscopic slides by a second team of independent anatomopathologists (at the Portuguese Institute of Oncology) confirmed the diagnosis of scleronodular HD, therefore they opted for ABVD, an alternative 1st line protocol including 4 drugs without cross-resistance to MOPP, and with which many prolonged disease-free survivals, even with patients resistant to MOPP, have been reported.[20,21]

Documentation of the progression of the disease under ABVD coincided with a diagnosis of phenotype B NHL with a high degree of malignancy. These new data once again forced a review of the therapeutic strategy and for the first time, showed the existence of two simultaneous histological diagnoses. The resistance to the multiple drugs previously administered, the existing low tolerance of the bone marrow, and the peripheral neuropathy induced by vincristine in the initial MOPP cycles had significantly limited the treatment alternatives considered. Hence the decision to use MACOP-B[22]. This protocol uses 6 drugs administered alternately in a weekly regime over 12 weeks. It was designed with the goal of optimizing the antineoplastic effect of cytoplastics, diversifying their toxicity and so permitting maximum therapeutic intensity. This expectation, common to the so-called "2nd generation protocols", such as MACOP-B, m-BACOD, ProMACE-CytaBOM, ProMACE-MOPP and COP-BLAM among others, led to their widespread use in the 1980s. Subsequently, comparative studies conducted with CHOP (previously considered the protocol of reference for treatment of NHL with medium to high levels of malignancy) showed that the earlier protocols offered no real advantage in terms of disease-free or mean survival time[23,24] and that at the same time, they showed higher morbidity.

In this specific case, in light of the previously recorded multi-chemical resistance, resorting to MACOP-B for the inclusion of new drugs in the protocol, since it was clearly identified as a neoplasia with a high proliferation rate, and the need for intensive treatment is justified. The vinca alkaloid was substituted by another non-neurotoxic one (vinblastine) and the dosages of myelosuppressive drugs were reduced. Supportive treatment with haematopoietic growth factors was also administered, in order to meet the timetable proposed for this protocol. Autotransplantation was considered, but this idea was rejected due to the absence of chemosensitivity, the patient's general condition, and the lower tolerance of the bone marrow. Once again, we did not obtain a response to the prescribed therapy, and the patient died in the 9th week of MACOP-B due to the progression of the disease.

Final considerations

This case describes the existence of a relatively rare composite/simultaneous lymphoma, a histological subtype of HD. The history of this disease shows that the HD component displayed a predictable behavior (with response to the chemotherapy administered), emphasizing the rapid and inexorable progress of the NHL, in spite of the successive treatments attempted. This behavior suggests that in composite lymphomas, the two nosological entities in question can present different biological behaviors, regardless of a possible clonal relationship and their temporal or spatial coexistence. ■

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