CLINICAL AND EVOLUTIONAL PECULIARITIES OF A PATIENT WITH RICHTER'S SYNDROME

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Abstract: *Richter's transformation of chronic lymphocytic leukemia or nonHodgkin's malignant lymphoma with a low grade of malignancy considerably alters the evolution and prognosis of the patient. There are clinical and biological factors that may suggest the risk of Richter's transformation. We present the case of an elderly patient; the diagnosis of Richter's syndrome was done simultaneously with that of follicular lymphoma. Initial complications and those which have occurred during treatment and the solutions chosen for overcoming them are discussed. Richter's syndrome generally requires aggressive treatment, due to the presence of release risk, but it is important to take account of the age, performance status and concomitant diseases, like chronic lymphocytic leukemia behaviour, and as part of the personalization of the therapy.*

Cuvinte cheie: *limfom folicular, sindrom Richter*

Rezumat: *Transformarea richteriană a unei leucemii limfatice cronice sau a unui limfom malign nonHodgkinian cu grad mic de malignitate modifică considerabil evoluția și prognosticul pacientului. Există factori clinici și biologici care pot sugera riscul de transformare richteriană. Prezentăm cazul unui pacient vârstnic, la care diagnosticul de sindrom Richter s-a făcut simultan cu cel de limfom folicular. Sunt discutate complicațiile inițiale și cele apărute în timpul tratamentului și soluțiile alese pentru depășirea lor. Sindromul Richter impune în general un tratament agresiv, deoarece există riscul recidivelor, dar el trebuie să țină cont de vârstă, statusul de performanță și afecțiunile concomitente, asemănător conduitei din leucemia limfatică cronică, și ca parte a personalizării terapiei.*

INTRODUCTION

Richter's syndrome or Richter's transformation occurs in approximately 5-10% of patients with chronic lymphocytic leukemia (CLL) or small cells nonHodgkin's malignant lymphoma (NHL) and consists in developing of a NHL with high degree of malignancy (most commonly, diffuse large B-cell) (1) or a Hodgkin's lymphoma (2) which have aggressive evolution and a median survival of about 10 months (1), with variations depending on the stage of the disease at the time of transformation (in a recently published study - 34.5 months to those in Binet A and B stages and 10.3 months for those in Binet C stage).(2) The exact mechanism of Richter's transformation is not known, but several risk factors are known.

CASE PRESENTATION

The patient, aged 77 years old, found the emergence of bilateral inguinal and axillary lymph nodes for which a left axillary biopsy was carried out. He had no symptoms and signs at admission in hematology service, but he presented lymph nodes with a maximum diameter of 4 cm, slightly sensitive to palpation, lymphatic edema of lower limb and he was without hepato-splenomegaly. From the biological point of view, he had got leukocytosis (12130/mm^3), inflammatory syndrome (VSH 45 mm/1 hour, C-reactive protein 17,77 mg/dl), but with normal serum and lactate dehydrogenase, and with cholesterolemia 225 mg/dl; in addition-hypertriglyceridemia (215 mg/dl).

Computed tomography examination showed the presence of multiple lymph nodes disseminated at the underarm level, bilaterally, with axial dimensions up to 2.8 cm without mediastinal lymph nodes, but with coalescing blocks of lymph nodes that formed lymph node mass, paraaortic, paracaval, interaorto-caval, and along the common iliac vessels, deep and superficial, and inguinal. Masses of lymph node framed homonymous arterial and venous vessels, especially right iliac vein, producing a reduction of its diameter. There were no primary or secondary pulmonary masses or abdomino-pelvic parenchymas. Doppler ultrasound ruled out possible thromboses of iliac and femoral arterial and venous axis. The pericardium and the heart cavities were normal, and the ejection fraction of the left ventricle measured 80%; discrete mitral posterior ring calcifications had just been noticed.

The lymph node biopsies were anatomo-pathologically examined in two university centres (one in each place). Microscopic examination showed the presence of a lymph node modified structure by lymphomatous infiltration with follicular aspects, with relatively uniform sized follicles, consisting of small cells with cleaved nuclei, without nucleoli, and a few medium-sized cells (centroblasts) + areas with Castelman-like issues, fibrosis, and peri-lymph node tissue infiltration (figure no. 1). Immunohistochemistry examination showed: CD20+ uniformly in lymphoid population, CD3+ in the population of reactive T lymphocytes, CD5- and CD10+ in tumour follicles, CD23+ especially in dendritic cells, CD30 + in rare activated B lymphocytes, Bcl2+ uniform in the lymphoid population, Ki-67+ in 30-35% on tumour follicles. The described aspect advocated for a follicular NHL of grade I-II,

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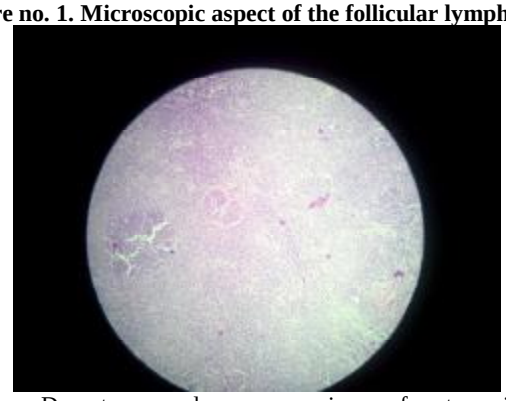
CD20 +. The lymph node analyzed in the other university centre advocated for a large B-cell NHL, CD20 +, and there doctors have validated the accuracy of the first anatomo-pathological examination, as the two advocated for a transforming follicular lymphoma (with low grade of malignancy) in a diffuse one, with large cell (with high grade of malignancy), so, the existence of a Richter syndrome.

The patient does not have markers of infection with hepatitis viruses B and C, HTLV or HIV virus and had got antibodies of type immunoglobulin G anti-CMV.

Figure no. 1. Microscopic aspect of the follicular lymphoma



Due to vascular compressions of retroperitoneal blocks of lymph nodes and the presence of lymphoma and periods of immobilization in bed (at least during chemotherapy), it has been opted for prophylactic anticoagulation with dalteparinum-5000 IU/day s.c. The patient was treated with 6 polychemotherapy cycles type CHOP + 8 administration of rituximab (365 mg/m^2). He was additionally treated with a granulocyte colony stimulating factor due to the risk of febrile neutropenia.

At computed tomography control carried out after 3 courses of polychemotherapy, lymph nodes have not been seen, but there was merely an amorphous mass of maximum transverse diameter of 1.2 cm that extends caudally from the fork of the iliac and evolve between the deep and superficial iliacs vesels; the weak iodophilia of described tissue did not allow the differentiation between a possible outstanding lymphoid tissue and pelvic fibrosis. Common iliac vessels were embedded in the described tissue, but they presented flow after i.v. administration of contrast agent. After 3 more courses of polychemotherapy computed tomography aspect did not changed, but the amorphous deep iliac tissue described above was this time noniodofil. At the end of the therapy the patient was asymptomatic, without identifiable lymph nodes, with the usual biochemical tests and blood count within the normal range, except a mixed dyslipidemia. Cholesterolemy, located slightly above the superior limit of normal values from the onset, remained almost the same (215 mg/dl), but triglyceridemia has increased progressively up to 403 mg/dl (after 6 courses of polychemotherapy) and required fenofibrate therapy (145 mg/day and with doubling of the dose later) after adjusting the diet has been proven to be ineffective.

During treatment, he presented a reactive thrombocythosis with a maximum value of 735000/mm^3, which reaffirmed the usefulness of anticoagulant prophylaxis treatment, and a decrease in immunoglobulin G up to 700 mg/dl. The sedimentation rate of erythrocytes remained increased throughout the first courses of polychemotherapy and reached 104 mm/1 hour after the third, when he returned for a febrile syndrome (39^{0}C) without bacteriological or micological documentation, despite manifold determinations that have been made. Before that, he presented a positive uroculture with E coli, sensitive to all antibiotics which it has been tested, treated with cefuroxim. Fever proved to be resistant to the combination of ertapenem with voriconazole and amikacin, as well as to meropenem + vancomycin, but disappeared after the association of polymyxin E (to meropenem). Subsequently, inflammatory syndrome has disappeared progressively, and the number of platelets was normalized (342000/mm^3). After about a month of feverish, under anticoagulation prophylaxis he presented an episode of left facio-brachial paresthesias, without motor deficiency. Cranial computed tomography exam showed only an old lacunar infarct. The evolution was favourable under dalteparinum, clopidogrel, piracetamum and vitamins B1 and B6.

DISCUSSIONS

The negative prognostic factors for the presented patient are advanced age, smoking and voluminous tumour mass (bulky disease) at the time of diagnosis. There are studies which advocates for involvement of smoking in the Richterian transformation, by the absence of enzymes involved in DNA damage repair, made by it (MLH1 or MSH2).(3) Positive prognostic factors are: normal serum level of lactate dehydrogenase, the absence of medulary lymphomatous determinations at diagnosis (absence of an equivalent stage Binet C from CLL), the absence of possible suffering of vital organs (heart, kidney, brain, liver, etc.) and the absence of hypocholesterolemia. Decreased serum cholesterol levels at diagnosis calls for an aggressive lymphoma (lymphomatous cell uses serum cholesterol for its own replication); if patients are responding to treatment, cholesterol increases; if not – it decreases even more.(4) In addition, it is known that CD5 is involved in the synthesis of cholesterol, and cells of CLL (CD5+) and CD5+ lymphomas undergoe continuous stimulation and survive due to activation of CD5.(5)

Response to treatment was quick, although initial tumour mass was voluminous. This may suggest that lymphoma was mostly with large cells; aggressive lymphomas generally respond quickly to treatment, but they have also tendency to relapse. The question whether the patient has or not indication for maintenance therapy with rituximab arises. If we accept that the majority of tumour mass was with large B-cells, he has no indication. Rituximab has proved to be effective as a maintenance treatment (a dose at 2 or 3 months for 2 years) in CD20+ lymphomas with low-grade malignancy (including the follicular one). But considering that our patient is elderly and, therefore, cannot benefit from the intensification therapy with peripheral blood stem cells transplantation, a way to prevent the relapse of component with low grade of malignancy of the initial mass (follicular lymphoma) would be rituximab treatment. In a recent communication presented to ASH (December 2013) it was showed that rituximab in maintenance treatment was also effective (it significantly prolongs event free and progression free survival) to male patients with large B-cells lymphoma, contrary to the present guides of treatment.(6)

Although thrombotic risk score calculated according to the formula proposed by Khorana (7) was only 2, the presence of compressions produced by the iliac lymph node mass and edema present initially in the lower limb, which persisted until the 3rd cycle of polychemotherapy required prophylactic anticoagulation therapy, so that thrombotic accidents could be avoided. In addition it was required as the patient has developed a trombocythosis which was reactive to chemotherapy and infectious episode. The left faciobrachial paresthesias occurred during therapy with dalteparinum were not due to any thrombotic accident (he did not have recent injuries at computed tomography), but they were likely an adverse effect

of vincristine. A statin did not has been associated, although the patient had hypercholesterolemia (and it is known that statins have platelet antiaggregant and antithrombotic effect) because it can produce conformational changes of CD20 antigen in the patient's lymphocytes, so that rituximab could recognize with difficulty its target cellular receptor.(8)

The febrile episode of infectious etiology without bacteriological or micological documentation (including from repeated hemocultures) was probably due to the selection of an E coli strain (responsible for the previous urinary infection), which under cefuroxim treatment became resistant to multiple antibiotics. In such cases, we usually associate polymyxin E, to which multidrug resistance is exceptionally rare.

The diagnosis of NHL was done in the stage of Richter's transformation to the presented patient. But what are the risk factors with prognosis role concerning the Richter's transformation of a NHL with low grade of malignancy or CLL (previously diagnosed)? Fever in the absence of any infection or thrombophlebitis, rapid growth in the volume of a lymph node (9), the appearance of a viral infection (for example with Epstein-Barr virus) (10), lactate dehydrogenase increase (9), Binet stage C (in which it seems that the serum level of β2-microglobulin and lactate dehydrogenase are greater than in the early stages, as the expression of CD38 and ZAP70 and unmutated IgVH) (2), the absence of del 13q (11), appearance of trisomy 12 (12), of chromosome 11 and 14 abnormalities (9, 10), the presence of multiple cell-cycle disruptions regulator (10), and tumour suppressor gene defects involving p21, and p27, p53 (8), dysregulation of MYC pathway (although genomic lesions are heterogeneous and they suggest the possibility of multiple mechanisms involved in transformation) (13), telomere length $\leq$ 5000 bp (14) are indicators for a possible richter's transformation of the NHL. A lymph node biopsy is necessary to confirm the suspicion, and positron emission tomography might contribute to chose the lymph node that has to be biopsied (hypercaptant, so more active metabolically), although the use of this technique is not yet standardized in Richter's syndrome.(11)

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