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Case Report

De Novo CD5-positive Diffuse Large B-cell Lymphoma in the leukemic phase: A case report and review of the literature

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ABSTRACT

Recent advances have led to major progress in the classification of lymphomas with better understanding of the cellular immunophenotyping and molecular biology. The expression of CD5 and presentation in the leukemic phase in patients diagnosed with diffuse large B-Cell lymphoma are usually stigmata of an aggressive disease with a poor prognosis. Controversy arises concerning the management of these aggressive forms of DLBCL with the absence of clear recommendations guiding the oncologist's choice. In this paper, we report the occurrence of a CD5-positive DLBCL manifesting in the leukemic phase in an elderly patient .

INTRODUCTION

Recent biological advances have led to major improvement in the classification of lymphomas. Cellular immunophenotyping and molecular biology allowed proper stratification of subgroups with different prognostic features. Diffuse large B-Cell Lymphoma (DLBCL) is the most commonly encountered (1). It often lacks the expression of the CD5 antigen that is usually expressed in chronic lymphocytic leukemia (CLL) and Mantle Cell Lymphoma (MCL). The expression of CD5 in DLBCL is usually a stigmata of an aggressive disease with a poor prognosis (2). The presentation of DLBCL patients in the leukemic phase is also associated with an aggressive disease that is resistant to conventional chemotherapy (3).The published literature reports rare cases of patients with such detrimental prognostic factors which render the treatment plan a real challenge. In this paper, we report the occurrence of a CD5-positive DLBCL manifesting in the leukemic phase.

Case report

A 78-year-old man was referred to our oncology department for fever, unintentional weight loss, and anorexia. The patient's medical history is remarkable for chronic obstructive pulmonary disease, chronic renal failure and chronic heart failure. Clinical examination

showed a thin, well-oriented man with diffuse lymphadenopathy on palpation. The blood test were relevant for elevated WBC=65,300/mm3 (lymphocytes 72%), decreased hemoglobin level 9.4 g/dL and platelets 140,000/mm3, and elevated creatinine levels (185 micromol/L). Older blood tests performed few months ago before performing cataract showed normal findings (WBC=15,000/mm3 with lymphocytes 50%) (Table 1). A complete body computed tomography scan (CT scan) revealed cervical, axillary, mammary, mediastinal, celiac, portal, mesenteric, pelvic and inguinal lymph nodes. The peripheral blood flow cytometry displayed leukemic involvement by lymphoid cells showing positivity for CD5, CD22, CD79b, and FMC7 with Kappa : Lambda ratio above 99:1. An axillary lymph node biopsy showed a diffuse lymphoid growth pattern with large atypical pleomorphic lymphoid cells with coarse chromatin and small nuclei, and displayed a high index of proliferation (Ki67 90%). These cells were positive for CD5, CD20, BCL2, IgM and IgD but negative for CD3, CD10, BCL6, CD21, CD23, Cyclin D1, SOX11 and MUM1. Thus, we retained the diagnosis of stage III CD5-positive DLBCL of non-germinal center subtype with an increased R-IPI score 4.

In view of the patient's chronic heart failure, the anthracyclines were omitted and the patient was then started on Rituximab 375 mg/m2 on day 1, Cyclophosphamide 750mg/m2on day 1, Vincristine 1.4mg/m2on day 1 and Prednisone 40mg/m2 from day 1-5 every 21 days (R-CVP). The patient tolerated well the first two cycles without major grade 3-4 toxicities. Thereafter, the patient was admitted through the emergency department for acute onset of hypotension and dyspnea. Comparative CT scan showed a progressive disease. Laboratory testing showed decreased low hemoglobin levels 8.7 g/dL and increased WBC count 36,500 / mm3 with blast cells 55%. The patient succumbed to his disease after suffering from acute septic shock and died after nearly two months of diagnosis.

Discussion

DLBCL with CD5-positive are of rare occurrence and altered prognosis. The majority of these patients have a history of a previous low-grade lymphoma with an actual Richter transformation. A small and newer proportion was defined as de novo CD5-positive DLBCL albeit the absence of accurate distinctive features (4). This entity occurs in the elderly with a female predominance and is characterized by an aggressive pattern with advanced stages (stage 3 and 4), lower performance status, extranodal involvement and higher IPI score. A characteristic immunophenotype expresses CD5, CD19, CD20 with a predominance of surface IgM Kappa (5). Biologically, CD5-positive DLBCL features a non-germinal center involvement, Bcl-2 positivity and high incidence of central nervous system involvement (6).

The major differential diagnosis includes Burkitt lymphoma and Richter transformation. Burkitt Lymphoma can be distinguished confidently from DLBCL using histopathological and immunohistochemical findings. In fact, typical Burkitt Lymphoma is characterized by CD10 (+), BCL-2 (-), BCL-6 (+) and Ki-67 >95% (7). Richter's transformation from a latent CLL diagnosis can be soundly eliminated due to several findings. The normal blood counts on previous blood tests exclude possible diagnosis of CLL. Moreover, CLL immunophenotyping usually express CD5 (+), CD20 (+), CD22 (-), CD23 (+) and CD43 (+). In view of these findings, we retained the diagnosis de Novo CD5-positive Diffuse Large B-Cell Lymphoma in the leukemic phase (Table 2).

The leukemic phase of DLBCL is rarely reported although it is a well-recognized complication among low grade lymphomas and terminal phase of refractory lymphomas (8,9). These cells suffer from a defective expression of adhesion molecules on their surface that leads to lymphocyte migration from their nest into the systemic circulation (10). This leukemic phase of DLBCL presents with a median age of 48 years, high IPI-Score, B symptoms and leukocytosis, and extranodal involvement. The majority co-expresses CD19, CD20, CD22, CD38, CD45, HLA-DR and FMC7 and lambda or kappa restriction with a limited CD5-positivity of 17%. Median progression-free (PFS) and overall survival (OS) were 11.5 and 47.5 months, respectively (3).

The combination of Cyclophosphamide, Adriamycin, Vincristine and Prednisone (CHOP) is the primary regimen in patients with DLBCL. However, more aggressive treatment options are adopted to overcome the negative effect of CD5 expression. First,

Table 1. Variation of the complete blood count at different time points

	Three months before diagnosis	At diagnosis	After 1st cycle	After 2nd cycle	After 3rd cycle	Before death
Hemoglobin (g/dL)	13.0	9.4	9.2	8.8	9.3	12.2
White blood cell count (/mm³)	15,300	65,300	71,500	75,200	31,200	50,000
Neutrophil (%)	38	20	15	20	20	29
Lymphocytes (%)	52	72	72	13	22	7
Blasts (%)	0	0	0	64	54	56
Platelets /mm³	283,000	140,000	108,000	150,000	140,000	70,000

Table 2. Comparison of the different clusters of differentiation of the different lymphoma subtypes

Type of Lymphocyte	CD5	CD10	CD20	CD22	CD23	CD43	BCL2	BCL6	Ki67
Our Patient	(+)	(-)	(+)	(+)	(-)	(-)	(+)	(-)	90%
Burkitt Lymphoma	(-)	(+)	(+)		(-)		(-)	(+)	>95%
Chronic lymphocytic lymphoma	(+)	(-)	(+)	(-)	(+)	(+)			

the addition of Rituximab to chemotherapy in CD5-positive DLBCL was assessed in 337 patients with CHOP being the most common chemotherapeutic backbone. The median OS and the complete response rate were significantly higher in the Rituximab subgroup (2-year OS rates of 70% vs 54% in the chemotherapy only subgroup). One important finding is the similar rate of central nervous system relapse between the two groups, thus shedding the light on the utmost need for an effective CNS prophylaxis and a better neurological control of the disease (11). Second, in one retrospective study, ninety percent of the patients diagnosed with leukemic phase DLBCL received Rituximab and Anthracycline-based regimen with complete response in more than 50% of the patients. However, it is worth mentioning that in this study, patients were young with a median age of 48 years and up to 14% of patients had an early morbidity and mortality upon the start of treatment. The latter category of patients were older (median age of 70 years) which could explain the lack of response to conventional therapy and the unexpected outcome of our patient (3).

In spite of the aggressive nature of this lymphoma subtype, more intensive management was not possible due to frailty and comorbidities of our patient. This frailty dictated a palliative treatment especially that the patient suffered from chronic heart failure (New York Heart Association 2) which rendered him ineligible for anthracycline-based treatment. All in all, there are no prospective data in frail patients with DLBCL. Experts recommend a Rituximab single agent pretreatment phase of one week (ORR 35%) followed by Bendamustine or Vinblastine upon condition improvement and discussion of the pros and cons with the patient and his family (12). Unfortunately, the patient succumbed to his disease before benefiting from further therapy.

Our case highlights an issue daily encountered by physicians who find themselves facing a complicated form of a hematological dilemma with different aspects of histopathological and immunophenotypic particularities in the absence of clear recommendations guiding their optimal decision. It would be fundamental to further elaborate on the molecular dissection of these hematological malignancies in order to properly stratify each subgroup according to their prognostic features.

Disclosure

The authors have stated that they have no conflicts of interest.

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13. been shown to induce cell death in many tumor models, including prostate, colon, and pancreatic cancer and multiple myeloma (MM) (Cusack et al., 2001; Hideshima et al., 2001).