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A New Observation of Bone Marrow Involvement by Diffuse Large B-Cell Lymphoma Mimicking Myelofibrosis

Fall Seynabou[1], Alioune Badara Diallo[1], Dibor Niang[2], El Hadji Daouda Niang[1], Khadim Sarr[1], Marième Lolita Camara[1], Abibatou Sall[1], Fatou Samba Ndiaye[1]

[1]Department of Hematology, Cheikh Anta Diop University, Dakar, Senegal
[2]Department of Pathology, Gaston Berger University, Saint-Louis, Senegal
Email: liounebd@gmail.com

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Abstract

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma, characterized by high clinical and biological heterogeneity. Patients typically present with progressive lymphadenopathy, extranodal disease and may also experience fever, night sweats and unexplained weight loss. We report here the case of a 16-year-old female with osteoarticular pain, dizziness, and dyspnea on exertion. Clinical examination showed no lymphadenopathy. Complete blood count (CBC) revealed pancytopenia and marrow smears found to be hypocellular. Initial diagnosis favored secondary myelofibrosis. Diagnosis of bone marrow involvement by DLBCL was retained on bone marrow histology and immunohistochemistry which showed infiltration of large B lymphoid cells. The patient was treated by immunochemotherapy R-CHOP regimen. This case highlights a very rare and atypical circumstance of discovery of DLBCL with myelofibrosis as an initial symptom. Prognosis value of this presentation and management difficulties are also discussed.

Keywords

Diffuse Large B-Cell Lymphoma, Myelofibrosis, Rituximab

1. Introduction

Diffuse large B cell lymphoma (DLBCL) is an aggressive lymphoma characterized by a diffuse malignant proliferation of mature large B-cells. It is the most common non-Hodgkin lymphoma, with an estimated 150.000 new cases annually worldwide [1]. Its incidence is less well unknown in Sub-Saharan Africa with few studies [2].

DLBCL is highly heterogeneous in regard to clinical manifestations, biological features, and prognosis. Patients typically present with progressive lymphadenopathy, extranodal disease and may also experience fever, night sweats and unexplained weight loss.

Bone marrow (BM) involvement occurs approximately in 11% - 34% of patients when DLBCL is initially diagnosed [3]. Secondary myelofibrosis may be caused by a variety of diseases such as hematologic malignancies, auto-immune diseases, infections or other nonhematologic disorders [4].

The association between myelofibrosis and lymphoproliferative disease is a very rare event with few reported cases [5].

We present here a case of DLBCL with myelofibrosis as an initial symptom treated by immunochemotherapy R-CHOP regimen.

2. Case Presentation

A 16-year-old female was referred to our unit for the investigation of cytopenias. The patient complained with a four months history of diffuse osteoarticular pain predominantly in the hip and spine and a recent history of epistaxis, dizziness, palpitations and dyspnea on exertion. She also mentioned feeling of fever, night sweats and unexplained weight loss.

There was no specific past medical story, including no specific medications.

On clinical examination, she was pale and tachycardic and present a hepatosplenomegaly; there was no lymphadenopathy and no bleeding, locomotor system examination was normal.

Her complete blood count (CBC) revealed pancytopenia (**Table 1**). Peripheral blood smear showed anisopoikilocytosis and large lymphocytes, without circulating blast cells.

Serum parameters showed positive C-reactive protein, hepatic cytolysis predominantly on SGOT, elevation of lactate dehydrogenase (LDH) 4x the upper limit of normal. Auto-immune tests (antinuclear antibodies) and viral serologies (HIV, HCV, HBV) were negative.

Abdominal ultrasound showed hepatosplenomegaly without focal lesions and hilar adenopathies. Chest X-ray was normal, with no objectified mediastinal mass.

A bone marrow aspirate was “dry tap” and found to be hypocellular, without extra hematopoietic cells, which led us to perform a bone marrow biopsy.

The microscopic examination by hematoxylin eosin of the bone marrow biopsy showed six osteomedullary spaces. The hematopoietic lineages were inexistent and were replaced by areas of eosinophilic fibrosis, which could lead to suspicion of myelofibrosis (**Figure 1**). However, the reticulin framework was not disturbed.

The cell population was largely composed of large cells with strongly nucleated nuclei. Immunohistochemistry revealed diffuse lymphomatous proliferation. Bone marrow cells showed positivity of CD20, CD10, MUM1 and BCL2. BCL6 was difficult to interpret, suggesting a weak positivity at the edge of the

sample. The Ki67 proliferation index was about 90% (Figure 2). The detection of c-myc was globally at 80%. There was negativity of cyclin D1 and presence of CD30 and EBV expression (EBERs).

Histological and immunohistochemical features favored diagnosis of bone marrow involvement of DLBCL, germinal center B-cell like (GCB) subtype, with double expression of MYC and BCL2. Thorough examination led to conclude diagnosis of DLBCL, Ann Arbor stage IV, International Prognosis Index (IPI) score of 4.

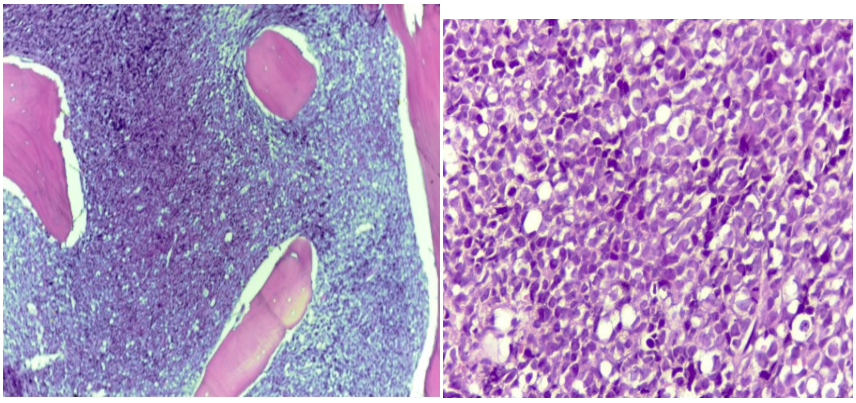
The patient underwent initially supportive care with transfusion of packed red cell and platelet concentrates. After staff concertation and evaluation of benefits versus risks, an immunochemotherapy was proposed with rituximab, reduced-dose R-COP regimen.

After 1 month of treatment, there was an improvement in the general condition with transfusion independence. Control of CBC revealed increase of hemoglobin, platelets and WBC levels (Table 1), which led us to prescribe subsequently R-CHOP regimen.

However, after 3 months of follow-up, we subsequently noted a deterioration of the general condition with a recurrence of osteoarticular pain and severe cytopenias that led to hospitalization. The patient succumbed to death with cardiovascular collapse induced by septic shock.

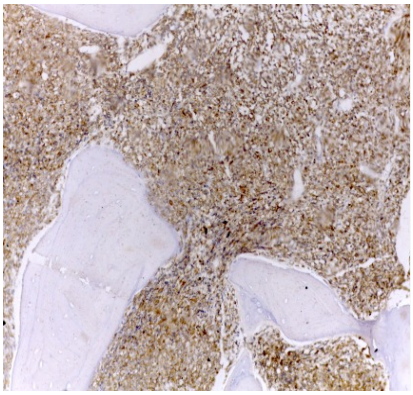
Table 1. Values of CBC (at diagnosis and follow-up).

Parameters	Initial	1 month after treatment	3 months after treatment	Normal
Hemoglobin (g/L)	64	85	56	120 - 160
White blood cells (10^9/L)	2.25	10.1	2.1	4 - 10
Neutrophils (10^9/L)	1.2	1.75	1	1.5 - 7
Platelets (10^9/L)	36	38	15	150 - 450
Reticulocytes (10^9/L)	16.6			80 - 120



(a) (b)

Figure 1. Bone marrow histology. (a) Diffuse lymphomatous proliferation occupying the medullary spaces composed of medium-sized cells sometimes clarified (b) (x400).



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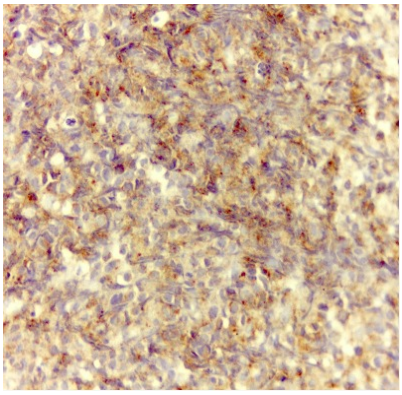

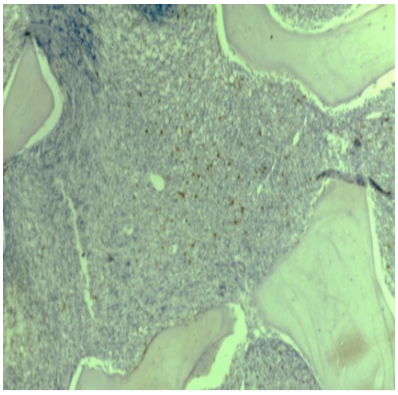

(b) (c)

Figure 2. Immunohistochemistry. (a) Positive CD20 labeling of large cells confirming the B phenotype of the lymphoma; (b) Expression of BCL2 and CD10; (c) Nuclear labeling by Ki67 of many neoplastic cells in mitotic phase (x400).

3. Discussion

Bone marrow (BM) involvement of DLBCL, defined by medullary invasion of lymphoma cells, occurs approximately in 11% - 34% of patients when DLBCL is initially diagnosed [3].

Secondary myelofibrosis may be associated with a large subset of diseases such as myeloproliferative neoplasms, acute megakaryoblastic leukemia, autoimmune disorders or lymphoproliferative diseases. Lymphoid myelofibrosis represents a particular and rare entity in which medullary fibrosis associated with abnormal lymphoproliferation replaces normal hematopoiesis. Hairy cell leukemia is one of the most known lymphoma in which myelofibrosis is frequently encountered; however, the association with other lymphoproliferations is rarely described. Rare cases have been reported in multiple myeloma, T-cell lymphoma, marginal cell, and lympho-plasmatoid cell lymphoma [6] [7] [8] [9].

Myelofibrosis as initial symptom of DLBCL is a very rare event, with few very case reports. A literature review found only one similar case report by Yan-Feng *et al.* [5]. Therefore, we report here the first case in Sub-Saharan Africa setting.

In our case, histological features mimicked strongly myelofibrosis; however, the reticulin framework was not disturbed.

The pathogenesis of secondary myelofibrosis is not well understood. Some growth factors such as platelet-derived growth factor (PDGF), megakaryocyte-derived growth factor (MKDGF), epidermal growth factor (EGF), transforming growth factor-β (TGF-β) may promote the proliferation of fibroblasts in megakaryocytes, which may induce myelofibrosis [5] [10].

In our patient, other etiologies of secondary myelofibrosis were considered. There was no past medical history and auto-immune tests were negative.

Bone marrow involvement of DLBCL is clinically recognized as advanced disease. It adversely impacts overall and progression-free survival, probably independent of the International Prognostic Index (IPI) score and cell-of-origin [3].

Our patient presented several poor prognostic factors, including advanced stage of disease (Ann Arbor stage IV), IPI high risk, double expression of MYC and BCL2. Bone marrow involvement surely impacted the prognosis due to severe induced cytopenias.

Primary management of DLBCL relies on immunotherapy, with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) immunochemotherapy recommended as first line therapy [1] [11].

Reduced-dose R-COP regimen was initially proposed to our patient considering severe cytopenias, with initially good response.

Yan-Feng *et al.* [5] reported a case of 73-year-old male initially treated with reduced-dose R-COP regimen and subsequently R-CHOP with complete remission.

In our case, such treatment was not successful as remission was not achieved. Death occurred at 3 months after the diagnosis due to severe cytopenias.

4. Conclusion

Myelofibrosis as an initial symptom of DLBCL is a very rare event complicating bone marrow invasion of large B-cells. It is associated with a poor prognosis, independently of the IPI-score and cell-of-origin. Management is difficult due to severe induced cytopenias.

Consent Statement

We confirm that the patient's parents have given their consent for the documentation of this case for scientific purposes.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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