CASE REPORT

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The unexpected evolution of a case of diffuse large B-cell non-Hodgkin lymphoma

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Abstract

The diffuse large B-cell lymphoma (DLBCL) represents the most common type of aggressive non-Hodgkin's lymphoma with a heterogeneous morphology, biology and clinical presentation. Gene expression profiling studies identified three distinct molecular subtypes of DLCBL arisen from B-cells at different stages of differentiation: germinal center B-cell-like (GCB) DLBCL, activated B-cell-like (ABC) DLBCL, primary mediastinal B-cell lymphoma (PMBL). The most relevant oncogenic pathways in diffuse large B-cell lymphoma are: deregulated B-cell receptor/proliferation signaling, BCL6 and NF-kB constitutive expression, defects in apoptosis and neoangiogenesis. The treatment of DLBCL has been completely modified in the last ten years by combination of anti-CD20 monoclonal antibody (rituximab) and CHOP chemotherapy, which is now the first line therapy. In the last years, there have been reported several cases of progressive multifocal leukoencephalopathy (PML) at patients with rheumatoid arthritis treated with rituximab. Progressive multifocal leukoencephalopathy is possible as an adverse reaction to rituximab at patients treated with R-CHOP for diffuse large B-cell lymphoma.

Keywords: diffuse large B-cell lymphoma, rituximab, progressive multifocal leukoencephalopathy.

Introduction

The diffuse large B-cell lymphoma (DLBCL) represents the most common type of aggressive non-Hodgkin's lymphoma (NHL), 35–40% of all cases. In the new *WHO Lymphoma Classification 2008*, there were presented the following subtypes of diffuse large B-cell lymphoma: primary mediastinal large B-cell lymphoma; T-cell histiocyte rich large B-cell lymphoma; intravascular large B-cell lymphoma; primary DLBCL of the CNS; primary cutaneous DLBCL, leg type; DLBCL associated with chronic inflammation; EVB + DLBCL of the elderly; lymphoma arising in HHVS-associated multicentric Castleman disease; plasmablastic lymphoma; ALK positive DLBCL; primary effusion lymphoma [1, 2].

Gene expression profiling studies identified three distinct molecular subtypes of DLCBL arisen from B-cells at different stages of differentiation [3]:

▪ Germinal center B-cell-like (GCB) DLBCL – originated from germinal center centroblasts and expressed the transcriptional repressor BCL6 that is required for the differentiation of mature B cells during immune response [4–6].

▪ Activated B-cell-like (ABC) DLBCL – have a gene expression profile of activated B-cells and derived from postgerminal center plasmabasts that are arrested during plasmacytic differentiation [7, 8]; express many genes characteristic of plasma cells, XBP-1(the key regulator of the secretory phenotype of plasma cells, PRDM1 (PR domain containing 1, the master regulator of plasmacytic differentiation) [9, 10].

▪ Primary mediastinal B-cell lymphoma (PMBL) – originated from a B-cell population in the thymus; arises in young female patients and the predominant site of manifestation is mediastinum [11]. Gene expression profiling revealed a molecular relationship between Hodgkin's lymphoma (nodular sclerosis) and PMBL [12, 13].

The most relevant oncogenic pathways in diffuse large B-cell lymphoma are: deregulated B-cell receptor/ proliferation signaling, BCL6 and NF-kB constitutive expression, defects in apoptosis and neoangiogenesis [14–16].

The prognosis of these subtypes of DLBCL is different in morphology, immunohistochemistry, gene expression profiling: the prognosis of DLBCL with immunoblastic morphology is worse than that of DLBCL with centroblastic morphology; the expression of BCL6, CD10, LMO2 have been associated with a favorable prognosis and BCL2, X-linked inhibitor of apoptosis (XIAP), TP53, cyclin D2, cyclin D3, IRF4/Mum1, CD5, FOXP1, PKC-β, ICAM1, c-FLIP, HLA-DR with an adverse outcome; the presence of MYC rearrangement and the mutations in the TP53 DNA binding domain are associated with an unfavorable prognosis [1].

The treatment of DLBCL has been completely modified in the last ten years by combination anti-CD20 monoclonal antibody (rituximab) and CHOP chemotherapy, which is now the first line therapy [17]. Salvage chemotherapy followed by high dose therapy and autologous stem cell transplantation is the standard

treatment for chemosensitive relapses in diffuse large B-cell lymphoma [18, 19].

Patient, Methods and Results

We are presenting the case of a male patient, 55-year-old, hospitalized in September 2007 in the Clinic of Hematology, "Filantropia" Hospital, Craiova, with the diagnosis of diffuse large B-cell non-Hodgkin's lymphoma, stage IIIB.

First symptoms appeared one month ago, when the patient presented fatigue, irregular fever, weight loss, diffuse abdominal pain. Physical examination revealed a tumor in the left hypochondrium and left flank of the abdomen.

Laboratory findings revealed: hemoglobin value 13.3 g/dL, leukocyte count 8500/cmm (neutrophils 73%, lymphocytes 15%, eosinophils 2%, monocytes 10%); platelet count 368 000/cmm. Inflammatory tests revealed: erythrocyte sedimentation rate (ESR) 29 mm/hr, fibrinogen 604 mg/dL; lactate dehydrogenase (LDH) 449 U/L.

Computed tomography (CT scans) of the whole abdomen including the pelvis, revealed a left retro-peritoneal tumor, 6.3/5.8 cm, irregular, homogenous, between left kidney, pancreas and spleen, and multiple lymphadenopathies with 1.4–2.7 diameter in the splenic hilum, left kidney hilum, mesenteric and latero-aortic lymph nodes (Figure 1).

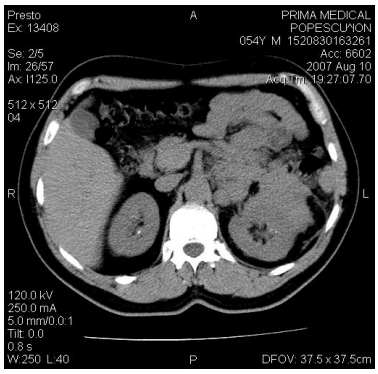

Figure 1 – ***CT scan of the left retro-peritoneal tumor.***

Nuclear magnetic resonance (NMR) imaging revealed a left retroperitoneal tumor and lymph nodes in the splenic hilum and in the median retroperitoneum (Figure 2).

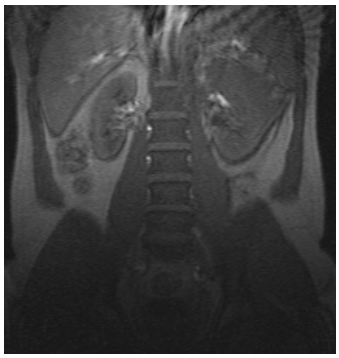

Figure 2 – ***NMR imaging of the left retroperitoneal tumor.***

Histopathologic exam of the retroperitoneal tumor biopsy revealed a diffuse large B-cell non-Hodgkin's lymphoma (Figure 3).

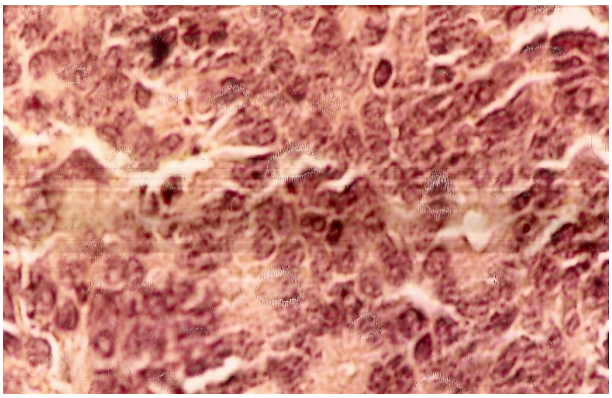

Figure 3 – ***Lymph node biopsy: diffuse large B-cell lymphoma (HE stain, ob. 40×).***

Immunohistochemically, the malignant cells were positive for CD20 (B-cell marker), UCHL1/CD45RO (T-cell marker), BCL2, Ki-67 (proliferation factor) and negative for vimentin, FVIII, cromogranin, EMA. Immunohistochemical procedure was made at Central Military Hospital of Bucharest.

Bone marrow smear revealed a hypercellular bone marrow with a granulocytes/erythrocytes ratio 100/30; erythroid series with light erythroblastic anisocytosis; rich granulocytic series with light deviation to the left; lympho-plasmocytic series: 10–12% lymphocytes; 2–4% plasmocytes; rich megakaryocytes series with frequent thrombocytogenic megakaryocytes.

The final diagnosis of the patient was diffuse large B-cell non-Hodgkin lymphoma stage IIIB.

The patient received eight cycles R-CHOP (rituximab + cyclophosphamide, doxorubicin, vincristine, prednisone); an abdominal ultrasound revealed the disappearance of retroperitoneal tumor after four cycles R-CHOP. At the ending of the eight cycles R-CHOP the patient was in complete hematological remission and a FDG-PET/CT (fluorodeoxyglucose-positron emission tomography) done in a hospital from Budapest revealed the total remission of disease (intra-cranially, head-neck region, supra and infraclavicularly, in the mammae and axillae, pathological FDG distribution or morphological alterations could not be detected; in the lungs the radiopharma distribution was normal, pathological alteration could not be seen; in the mediastinum and in the lung hila enlarged lymph nodes or other pathognomonic alterations were not represented. In the normal-sized liver focal accumulation could not be detected, and in the native scans circumscribed alteration in density was not represented. The gallbladder, spleen, pancreas and adrenal glands were without alteration; The FDG excretion of the kidneys was appropriate, symmetric, pyelectasia could not be seen. In the colon and in the rectum focal accumulation could not be identified; in the organs of the lesser pelvis pathological tracer accumulation could not be detected. In the mapped infradiaphragmatic lymph regions alteration in density referring to pathological lymph node, pathological FDG accumulation could not be detected. In the mapped bones, pathological FDG accumulation could not be seen) (Figure 4).

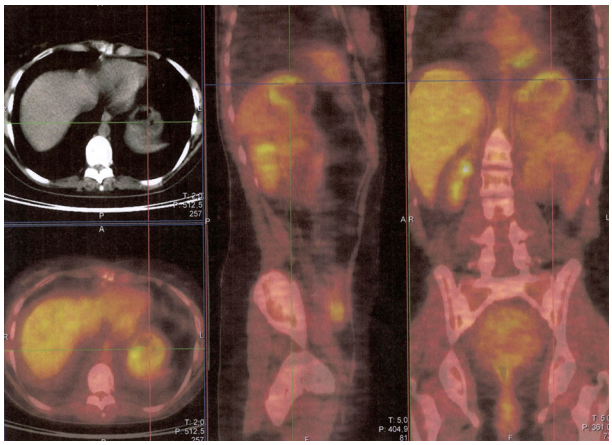

Figure 4 – ***FDG-PET/CT total remission at a patient with DLBCL after eight cycles R-CHOP.***

After a week after coming back from Budapest, the patient returned in the Clinic of Hematology presenting double visions, drowsiness, behavior disorders, euphoria.

Neurologic exam revealed a bradylalic patient, with a complete paresis of the right oculomotor and incomplete paresis of the left oculomotor nerve.

Cranial NMR revealed: unspecific areas with hypersemnal T2/PD and multiple demyelinating lesions of the anterior ponto-mesencephalon region and the right thalamus.

Laboratory findings: leukocytosis (white blood count 11 390/cmm) with neutrophilia (neutrophils 75.9%, lymphocytes 15.1%, eosinophils 2%, monocytes 7%); hemoglobin value 14.3 g/dL, Ht 42.9%, platelet count 169 000/cmm, erythrocyte sedimentation rate 3 mm/hr, fibrinogen 765 and than 244 mg/dL, lactate dehydrogenase 212 U/L. Bone marrow exam was normal. Lumbar puncture and cerebrospinal fluid exam revealed eosinophilia in cerebrospinal fluid. The parasitological tests done at N.C.D.M.I. Cantacuzino for cysticercosis (ELISA IgG), toxoplasmosis (ELISA IgG and IgM), borelliosis (ELISA IgG and IgM) were negative.

The patient received treatment with mannitol, corticosteroids, cephalosporins; the evolution was unfavorable and he died after two months from the beginning of neurological symptoms.

Discussion

All patients with DLBCL are now treated with R-CHOP as first line therapy [18]. Anti-CD20 monoclonal antibody (rituximab) is very effective in inducing complement dependent cytotoxicity, activate antibody dependent cellular cytotoxicity *in vitro*, have been direct effects including growth arrest and apoptosis in some non-Hodgkin's lymphoma cell lines, interaction with the host immune system [20, 21]. The addition of anti-CD20 monoclonal antibodies to chemotherapy has improved the survival of patients with DLBCL and eliminated the negative impact of the expression of BCL2 and the positive impact of BCL6 on clinical outcome [1]. Functional imaging using positron emission tomography (PET) with fluorodeoxyglucose (FDG) has demonstrated its usefulness to discriminate between active lymphoma lesions and true residual mass after induction therapy [22].

Rituximab is also used in the treatment of follicular lymphoma, chronic lymphocytic leukemia, mantle cell lymphoma, lymphocyte-predominant Hodgkin's disease or other CD20+ subtypes of Hodgkin's disease at first or subsequent relapse, Waldenström's macroglobulinemia, immune thrombocytopenic purpura, rheumatoid arthritis.

In the last years, there have been reported three cases of progressive multifocal leukoencephalopathy (PML) at patients with rheumatoid arthritis treated with rituximab. The first signs and symptoms which suggesting PML are visual perturbations, motor dysfunctions, behavior alterations, specific lesions at NRM scans; lumbar puncture for testing DNA of John Cunningham's virus in cerebrospinal fluid is necessary.

The features of the case, which we presented, were the atypical debut, fast remission of retroperitoneal tumor after four cycles of R-CHOP, total PET remission after eight cycles R-CHOP and appearance of neurological signs and symptoms after a week from the PET total remission associated with multifocal demyelinating lesions at cranial NRM scans. In the context of the treatment with rituximab we thought of the possibility of PML as an adverse reaction to the treatment with anti-CD20 monoclonal antibody. Unfortunately, the viral DNA of John Cunningham's virus in cerebrospinal fluid could not be detected.

Differential diagnosis was made with: cerebral determinations of NHL (lower probability in the context of PET total remission, low level of LDH); lymphomatous meningitis (absence of malignant B-cells in cerebrospinal fluid); cerebral parasitosis (negative tests for cysticercosis, toxoplasmosis, borelliosis).

Conclusions

In a case of a patient with diffuse large B-cell non-Hodgkin's lymphoma treated with rituximab in combination with chemotherapy and the PET complete remission, the presence of neurological dysfunctions, cranial multifocal demyelinating lesions revealed at NRM and viral DNA evaluation for John Cunningham's virus in cerebrospinal fluid, may suggest the existence of a progressive multifocal leukoencephalopathy as an adverse reaction to rituximab.

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