A case of non-Hodgkin lymphoma in a patient with chronic myeloid leukemia

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Abstract
Chronic myeloid leukemia is a clonal expansion of hematopoietic progenitor cells characterized by exaggerated proliferation of granulocytic lineage, with chronic phase, accelerated phase and blast crisis. Accelerated phase and blast crisis may be associated with extramedullary disease. Extramedullary transformation of CML can be determined both in nodal and extranodal sites. Non-Hodgkin lymphoma is rare in chronic myeloid leukemia and may be misdiagnosed as an extramedullary lymphoid blast transformation; the majorities are T-cell lymphomas with an immature thymic phenotype, while peripheral B-cell lymphomas are rarer. We report the case of a 79-year-old woman carrier Ph+ chronic myeloid leukemia who developed at eight months of diagnosis an accelerated phase of CML associated simultaneous with a tumor of soft palate, which was initial considering an extramedullary disease. The patient was treated with specific chemotherapy for accelerated phase of CML (Cytosinarabinoside) + Anagrelide, and reversed to secondary chronic phase of CML, but soft palate tumor persists. The immunohistochemical findings of bone marrow trephine biopsy examination showed chronic phase of CML (negativity for immature cells such as CD34, Tdt) and the biopsy of soft palate tumor and immunohistochemical findings revealed a primitive non-Hodgkin lymphoma (NHL) with medium B-cells (CD20, CD79a positive) and excluding an extramedullary blast crisis (CD34 negative, Tdt negative). Cytogenetic analysis in tumor revealed absence of Philadelphia chromosome. The patient was treated with local radiotherapy for NHL, with a favorable evolution and Hydroxyurea 1 g/day for CML with hematological remission. A localized lymphoid neoplasm may be an extramedullary localized blast crisis of CML or a distinct malignancy, with distinguished therapy and prognosis. A correct diagnosis based on a complex investigation: immunohistochemistry, conventional cytogenetic analysis and fluorescence in situ hybridization (FISH), molecular analysis (Southern blot and RT-PCR) is necessary. Further studies are required to clarify the pathogenetic relationship between chronic myeloid leukemia and non-Hodgkin lymphomas.

Keywords: chronic myeloid leukemia, non-Hodgkin lymphoma, extramedullary disease, distinct neoplasm.

Introduction
Chronic myeloid leukemia (CML) is a clonal expansion of hematopoietic progenitor cells characterized by exaggerated proliferation of granulocytic lineage. The cytogenetic marker of disease is Philadelphia (Ph) chromosome (present in granulocytes, monocyto-macrophages, erythroblasts, megakaryocytes, B-lymphocytes) generated by a reciprocal translocation between the long arm of chromosome 9 and the long arm of chromosome 22 designated t(9;22)(q34;q11), recognized on the karyotype as a smaller chromosome 22, due to a shorter long arm. The translocation interests two cellular oncogene, c-ABL and c-SIS; c-ABL oncogene (which codifies a protein with tyrosine-kinase activity involved in normal cell growth and differentiation) is translocated on chromosome 22 in a small region called BCR (breakpoint cluster region) resulting a new fusion oncogene, the BCR-ABL. The product of this gene is bcr-abl P210 protein with enhanced tyrosine-kinase activity compared with normal abl-kinase, resulting a growth advantage for the hematopoietic clone [1]. It had been identified three different types of bcr-abl: the classic 210 kDa protein seen in almost all CML patients and approximately one-third patients with Ph+ acute lymphoblastic leukemia; a 190 kDa type seen in the remainder of Ph+ acute lymphoblastic leukemia patients and rarely Ph+ chronic neutrophilic leukemia, and a 230 kDa type associated with the rare Ph+ chronic neutrophilic leukemia [2, 3]. The aberrant bcr-abl signaling is linked to five events that play key roles in leukemogenesis and disease progression: induces cell proliferation through activation of a number of mitogenic pathways, inhibits the adhesion of hematopoietic progenitor cells to stromal cells and the extracellular matrix in the bone marrow, inhibits apoptosis, causes the degradation of regulatory protein (potentially including p53), impairs DNA repair [1, 2, 4]. The latter two effects have been hypothesized to cause or contribute to genetic instability in Ph+ CML in blast
discreet densification in reticulin fibers. Immunohisto-
perivascular loose cluster; Gömöri stain section revealed
G/E ratio 2/1, numerous megakaryocytes disposed in
Eosin staining sections) cellular bone marrow
Institute, Bucharest, Romania) showed (Hematoxylin–
approaches to the therapy of newly diagnosed chronic
abnormalities, extramedullary disease). Numerous
>20% basophils in peripheral blood, additional cytogenetic
not related to therapy or persistent thrombocytosis,
blast count in peripheral blood (15–30%), thrombocytopenia
splenomegaly, difficult control of leukocytosis, increasing
phase (fatigue, weight loss, abdominal pain, progressive
blastic phase may be done directly, or through accelerated
peripheral blood or bone marrow. The evolution to the
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anomalies, extramedullary disease). Numerous
approaches to the therapy of newly diagnosed chronic
phase CML is available: first generation tyrosine kinase
inhibitors (Imatinib mesylate) or second generation
tyrosine kinase inhibitors (Imatinib, Dasatinib, Bosutinib), allogeneic
stem cell transplantation or other therapeutic options
(Interferon alpha, conventional chemotherapy) [7–9].

Patient, Methods and Results

The patient was a 79-year-old woman presenting in
March 2011 in the Clinic of Hematology, “Filantropia”
Municipal Hospital, Craiova, Romania, with chronic
phase Ph+ chronic myeloid leukemia.

Symptoms appeared two months ago, when the patient
presented fatigue, dyspnea, weight loss, abdominal
pain, low-grade fever. Physical examination revealed
splenomegaly (6 cm below costal margin), confirmed by
abdominal ultrasound (16 cm mild splenomegaly, without
any abnormality of the structure).

Laboratory findings showed: hemoglobin value 9.2 g/dL,
leukocyte count 112 000/mm³ (blasts 2%, promyelocytes
3%, myelocytes 11%, metamyelocytes 12%, neutrophils
48%, eosinophils 2%, basophils 5%, lymphocytes 14%,
monocytes 3%), platelet count 861 000/mm³ (Figure 1),
erythrocyte sedimentation rate (ESR) 140 mm/h, lactate
dehydrogenase (LDH) 784 U/L, uricemia 7.8 mg/dL. Bone
marrow smear revealed a hypercellular bone marrow,
increased granulopoiesis and megakaryopoiesis. Cytochemical
analysis revealed translocation t(9;22) in 40% of meta-
phases (Figure 2).

Conventional therapy was used: initial Hydroxyurea
2 g/day + Allopurinol 600 mg/day, than Hydroxyurea
1 g/day + Allopurinol 300 mg/day, with hematological
remission (disappearance of initial signs and symptoms
and normalization of blood count) after two months.

The patient did not show-up at clinic for a period of
four months and in October 2011 came with fatigue,
fever, weight loss, abdominal pain, important splenomegaly,
tumor of soft palate. Laboratory findings revealed
hemoglobin value 8.7 g/dL, leukocyte count 78 000/mm³
(blasts 18%, promyelocytes 13%, myelocytes 7%, meta-
myelocytes 8%, neutrophils 31%, eosinophils 2%, basophils
23%, lymphocytes 6%, monocytes 2%), platelet count
1 560 000/mm³ (Figure 3), ESR 160 mm/h, LDH 1176 U/L,
uricemia 7.3 mg/dL. CT scans revealed mild hepatomegaly
and important splenomegaly (20 cm).

It was considered a CML in accelerated phase and
the patient was treated with Cytosinarabinoside 100 mg/m²
×2/day, days 1–5 + Anagrelide 1.5 mg/day + Allopurinol
600 mg/day, transfusion of RBCs.

After treatment, hemoglobin value 11.4 g/dL, leukocyte
count 17 300/mm³ (blasts 1%, promyelocytes 3%,
myelocytes 10%, metamyelocytes 12%, neutrophils
62%, eosinophils 2%, basophils 1%, lymphocytes 6%,
monocytes 3%), platelet count 639 000/mm³, but persist
tumor of soft palate.

The bone marrow trephine biopsy examination (executed in
Department of Hematopathology, “Fundeni” Clinical
Institute, Bucharest, Romania) showed (Hematoxylin–
Eosin staining sections) cellular bone marrow ≈30–40%,
G/E ratio 2/1, numerous megakaryocytes disposed in
perivascular loose cluster; Gömöri stain section revealed
discreet densification in reticulin fibers. Immunohisto-
chemistry: CD34 negative (low percentage of CD34+); Tdt negative (Figures 4 and 5).

Soft palate tumor biopsy showed fibrous connective
tissue with diffuse lymphoid infiltration with medium/
large cells, little necrosis areas, rare granulocytes. Immuno-
histochemical findings (executed in Department of Hemato-
pathology, “Fundeni” Clinical Institute) in proliferation
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was: MPO negative, CD34 negative (positive in vessels), Tdt negative, CD20, CD79a diffuse positive, CD3 negative, CD5 negative, Cyclin D1 negative, CD10 negative, Ki67 positive in 50% of cells (Figures 6–9) establishing diagnosis of medium B-cell non-Hodgkin lymphoma primary of soft palate. Cytogenetic analysis in tumor revealed absence of Philadelphia chromosome.

Discussion

Chronic myeloid leukemia is a phasic disease with chronic phase, accelerated phase and blast crisis.
and excluding an extramedullary blast crisis Hodgkin lymphoma (NHL) with medium B-cells (CD20, CD34, Tdt) and the biopsy of soft palate tumor and phase of CML (negativity for immature cells such as marrow trephine biopsy examination showed chronic medullary transformation of CML can be determined both in nodal and extranodal sites, the majority are T-cell lymphomas with an immature thymic phenotype, while peripheral B-cell lymphomas are rarer [15–17]. We report the case of a 79-year-old woman carrier Ph+ chronic myeloid leukemia who developed at eight months of diagnosis an accelerated phase of CML with persistent thrombocytosis, associated simultaneous with a tumor of soft palate, which was initial considering an extramedullary disease. The patient were treated with specific chemotherapy for accelerated phase of CML (Cytosinarabinoside) + Anagrelide and reversed to specific chemotherapy for accelerated phase of CML (reverse transcription polymerase chain reaction) cannot distinguish an extramedullary lymphoid blast crisis by a synchronous lymphoma in a patient with CML [11]. The cell morphology phenotype of blast cells in B-lymphoid crisis cannot be distinguished from those of acute lymphoblastic leukemia [12]. The morphology of the cells of typical B-cell lymphoid crisis of CML in bone marrow or extramedullary sites has an immature aspect similar to lymphoblastic lymphoma [13, 14]. Extramedullary transformation of CML can be determined both in nodal and extranodal sites, the majority are T-cell lymphomas with an immature thymic phenotype, while peripheral B-cell lymphomas are rarer [15–17]. We report the case of a 79-year-old woman carrier Ph+ chronic myeloid leukemia who developed at eight months of diagnosis an accelerated phase of CML with persistent thrombocytosis, associated simultaneous with a tumor of soft palate, which was initial considering an extramedullary disease. The patient were treated with specific chemotherapy for accelerated phase of CML (Cytosinarabinoside) + Anagrelide and reversed to specific chemotherapy for accelerated phase of CML (reverse transcription polymerase chain reaction) cannot distinguish an extramedullary lymphoid blast crisis by a synchronous lymphoma in a patient with CML [11]. The cell morphology phenotype of blast cells in B-lymphoid crisis cannot be distinguished from those of acute lymphoblastic leukemia [12]. The morphology of the cells of typical B-cell lymphoid crisis of CML in bone marrow or extramedullary sites has an immature aspect similar to lymphoblastic lymphoma [13, 14]. Extramedullary transformation of CML can be determined both in nodal and extranodal sites, the majority are T-cell lymphomas with an immature thymic phenotype, while peripheral B-cell lymphomas are rarer [15–17].

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