Case Report

Acute myelomonocytic leukemia presenting as CD4+/CD56+ blastic plasmacytoid dendritic cell neoplasm

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Accepted 21 December, 2012

Blastic dendritic plasmacytoid cell neoplasm is a rare aggressive tumor of plasmacytoid dendritic cells. We report a 38-year-old female with nodular skin lesions on both legs at presentation which on immunohistochemical staining were CD4+ and CD56+ responding to blastic plasmacytoid dendritic cell neoplasm. Five months later the bone marrow analysis showed infiltration with 80% blasts which on flowcytometry had the immunophenotype suggesting acute myelomonocytic leukemia. Additional staining of skin lesions with CD123 was negative excluding blastic dendritic plasmacytoid cell neoplasm and suggesting the diagnosis of leukemia cutis. The patient achieved a complete remission after first course of standard induction chemotherapy, but relapsed 2 months later with leukemic manifestations and skin lesions. She died 13 months after initial diagnosis. This case illustrates the significance of immunophenotyping in differential diagnosis of blastic plasmacytoid dendritic cell neoplasm and myeloid leukemia cutis.

Key words: CD4+/CD56+ blastic plasmacytoid dendritic cell neoplasm, leukemia cutis, acute myelomonocytic leukemia, immunohistochemistry.

INTRODUCTION

CD4+/CD56+ blastic plasmacytoid dendritic cell neoplasm (BPDCN) typically presents in the skin and then rapidly progresses to a systemic disease affecting the blood, bone marrow and other organs (Herling and Jones, 2007; Cronin et al., 2012; Khoury et al., 2002). BPDCN cells show immunophenotypic similarities to monocytes and these cells have thus been termed plasmacytoid monocytes (Petrella et al., 2002). Acute myeloid leukemia (AML) localized in the skin-leukemia cutis (LC) and BPDCN are morphologically very similar making differential diagnosis between this two malignancies challenging. Leukemic variants of BPDCN should be examined with immunohistochemistry or flowcytometry demonstrating blast cells CD4+ and CD56+ but negative for myeloperoxidase (MPO), CD3 and CD20. Specific BPDCN associated immunomarker is CD123, which is interleukin-3 (IL-3) receptor α-chain and strongly positive in 90% of BPDCN, but it could also be found as dim positive in acute LC making the differential diagnosis between two diseases even more difficult (Herling and Jones, 2007; Cronin et al., 2012). CD56 marker, neural adhesion molecule which mediates tumor cell adhesion in tumor tissue and extramedulary sites, may be expressed in myeloid leukemias as well as in BPDCN (Herling and Jones, 2007; Cronin et al., 2012). Confusion can also arise as the CD4 antigen may be expressed in 82% by leukemic monocytes together with CD56 antigen which

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can be positive in up to 71% of monocytic blast cells. In such cases beside CD4 and CD56 specific dendritic cell markers CD123 and TcI-1, CD303 and CD2AP should be used to make differential diagnosis between these two entities (Herling and Jones, 2007; Cronin et al., 2012; Petrella et al., 2002; Herling et al., 2003; Tsunoda et al., 2012; Chang et al., 2010). The expression, at least three of those markers are necessary for the diagnosis of BPDCN. The optimal therapy for BPDCN and myeloid LC are different, so separating BPDCN from acute myeloid leukemia is very significant (Cronin et al., 2012).

We report the patient who presented with MPO negative LC but with some immunophenotypic features responding to BPDCN, who during the next few months developed AML M4 resistant to chemotherapy with a rapidly fatal course.

**CASE REPORT**

A 38-year-old female developed erythematous diffuse redish nodular skin lesions over her lower extremities and abdomen in April 2010, which gradually increased in number and size over the subsequent few months (Figure 1). Biopsy of the skin lesions taken 4 months after first appearance showed a diffuse infiltration of the dermis by monomorphic neoplastic medium sized cells with large, vesicular, round, and occasionally intended nuclei. The epidermis had been spared. Immunohistochemical analysis revealed the following cellular immunophenotype: Cytokeratin1, CD34+, CD117-, B marker-, LCA+, CD3-, CD5-, CD4+, CD8-, MPO-, Tdt-, CD43+, CD45Ro+, CD56+, CD30-, bcl-2-, bcl-6-, MUM-1-, CD10-, and Ki-67 40%, consistent with a CD4+/CD56+ BPDCN (Figure 2a, b, c, and d). Laboratory data were as follows: hemoglobin (Hb) of 59 g/L (reference range 125 to 170 g/L), a reduced white blood cell count (WBC) 1.3×10⁹ L⁻¹ (reference range 3.4 to 9.7×10⁹ L⁻¹) (differential leukocyte count: segmented 32%, lymphocytes 24%, monocytes 36%, and bands 8%), and platelets 242×10⁹ L⁻¹ (reference range 158 to 424×10⁹ L⁻¹). Biopsy of the bone marrow performed immediately after skin biopsy showed hypercellularity with mild dyshematopoesis and presence of 7% of blast cells which were performed additional immunohistochemical staining of skin lesions suggesting myelodysplastic syndrome, refractory anemia with excess of blasts (RAEB-I). The patient was transfused with packed red blood cells, however, her condition worsened and in September, 2010 she was referred to our institution, 5 months after the appearance of the skin lesions.

On abdominal ultrasound, a 15.8 cm splenomegaly was found, and papulonodular skin infiltrates over her legs and trunk measuring up to 2 cm in diameter. Morphologic analysis of bone marrow aspirate showed hypercellularity with 80% blast cells with a polymorphic and monoblastic appearance. Cytochemical staining showed MPO positivity in 30% of blast cells (Figure 3). Flowcytometry detected the following cellular immunophenotype (CD71, anti MPO, CD117, CD13, CD33, CD15, CD11c, CD4+) and (HLA-DR, CD3, CD20, CD34, CD11b, CD56)-.

Cytogenetics did not detect any clonal abnormalities (karyotype 46,XX [20]), molecular analysis found mutations of FLT3/ITD (tyrosine kinase internal tandem duplication) and NPM1 (nucleophosphin 1). HIV, HCV, and HbsAg were negative. We performed additional immunohistochemical staining of skin lesions for CD123 which was negative excluding the diagnosis of BPDCN and confirming the diagnosis of AML M4 with LC at presentation (Bennett et al., 1985). The patient was treated according to 3+7 protocol (doxorubicin 80 mg i.v. from day 1 to day 3; cytarabine 2×170 mg i.v. for 7 days). Complete remission was achieved after the first cycle, and she was given a further cycle for consolidation.

She remained well until December, 2010 when she developed some right lumbar discomfort. Ultrasound and magnetic resonance imaging (MRI) scans revealed a right adnexal tumor mass mea-
suring 6×5×4 cm and causing a grade I hydronephrosis. Blood tests found an Hb of 137 g/L, WBC 16.3×10^9 L⁻¹ and platelets 230×10^9 L⁻¹ (differential count normal). A bone marrow aspirate found 21% blast cells. The patient was treated with HiDAC protocol (cytosine arabinoside 2×5.0 g for 3 days), and following this treatment in bone marrow aspirate, 62% of the blasts was found. She was subsequently treated with a course of FLAG-Ida protocol (fludarabine 50 mg for 5 days, cytosine arabinoside 3.4 g for 3 days and idarubicin 20+10+10 mg i.v. for 3 days), after which blast cells disappeared from the peripheral blood and the right adnexal tumor mass regressed. Unfortunately, soon the WBC increased to 109×10^9 L⁻¹ with 93% blasts in the differential count. She was treated with mitoxantrone 15 mg and etoposide 160 mg for 5 days, however, her condition soon deteriorated and she died in May 2011, 13 months after the disease had first appeared.

RESULTS AND DISCUSSION

BPDCN is a rare hematopoietic tumor which expresses CD4 and CD56 antigens. The disease typically involves the skin at presentation, later spreading to the bone marrow, lymph nodes and blood (Herling and Jones, 2007; Cronin et al., 2012). The cutaneous nodules normally express CD4+/CD56+, and are usually negative for CD3, CD20, MPO, CD13, and CD33 (Herling and Jones, 2007; Cronin et al., 2012; Khoury et al., 2002; Tsunoda et al., 2012; Chang et al., 2010). Though a disease of the elderly, CD4+/CD56+ BPDCN can also occur in younger patients and even children. Immunohistochemical analysis is critical for the diagnosis with a specific immunophenotypic profile (CD4, CD56, CD123, and TCL1)+.

BPDCN and MPO negative acute myeloid LC with aberrantly expression of CD56 marker (as was also the case in our patient) and cutaneous localization as an extramedullary manifestation prior to bone marrow involvement is of important consideration in differential diagnosis. The distinction between an acute myeloid LC and BPDCN, can be extremely difficult in view of the
similarities in the clinical presentations, morphologic appearance of tumor cells and immunophenotypes. The problem of establishing a diagnosis can be compounded further with a possible loss of CD4 and CD56 antigens in cases of BPDCN (Petrella et al., 2002; Ascani et al., 2008; Sano et al., 2008; Kimura et al., 2001). According to Cronin et al. (2012), about 30% of myelod leukemias localized in the skin do not express MPO, but on flowcytometry are positive for this marker. The bone marrow blasts in our patient were MPO+ and CD117+ on the contrary from neoplastic cells in the cutaneous lesions, which were negative for both markers. This difference in MPO expression could be due to different sensitivity of flowcytometry and immunohistochemistry or due to immunophenotypic variations between different anatomic sites (Herling and Jones, 2007; Cronin et al., 2012). Ultimately, the differentiation between BPDCN and an acute myeloid LC is based on the application of specific CD myeloid markers CD33, MPO and lysozyme and specific dendritic cell-associated antigens CD123, CD303, CD2AP and Tcl-1 (Cronin et al., 2012). The expression of at least 3 of the markers CD4, CD56, CD123, CD303, CD2AP and Tcl-1 are necessary for the diagnosis of BPDCN (Cronin et al., 2012).

Cytopenia is present in 5 to 10% of these patients and is occasionally accompanied by bone marrow megalo-blastoid erythroid maturation and monocytosis, in keeping with myelodysplastic syndrome; this was the case in our patient who was also cytopenic on presentation misleading to diagnosis of BPDCN (Herling et al., 2003).

FLT3/ITD and NPM1 mutations have been shown as prognostic factors important in acute myeloid leukemias (Colovic et al., 2007). NPM1 mutation may help in distinguishing acute myeloid leukemia from BPDCN as NPM1 mutation is restricted to compartment of myeloid cells and can be found only in myeloid leukemias and not in BPDCN and lymphoid malignancies (Facchetti et al., 2009).

After the diagnosis of acute AML, M4 was established on bone marrow cytology and flowcytometry, we used additional staining biopsy of the skin with CD123 immunomarker which showed negativity. So, it was concluded that the patient had AML, M4 which at onset was presented as MPO -, CD4+, and CD56+ myeloid LC.

Our patient had an initially very good response to treatment, with complete remission lasting around 2 months. However, the disease soon progressed and she died with refractory myelomonocytic leukemia 12 months after the initial diagnosis.

CD4+/CD56+ BPDCN is a relatively rare aggressive disease with a predilection for the skin. The main differential diagnosis is acute myelomonocytic leukemia with...
skin involvement. The only way to make the diagnosis of BPDCN, is the usage of immunophenotyping as a powerful diagnostic technique to demonstrate the expression of plasmacytoid dendritic cell markers such as CD123, CD303, CD2AP or Tc1-1, requiring at least three positive of those markers. Negativity of MPO is important but not discriminating marker.

ACKNOWLEDGEMENTS

This study was supported by the project No. 41004 financially supported by the Ministry of Education and Science Republic of Serbia.

REFERENCES


