

## CONTINUING MEDICAL EDUCATION ΣΥΝΕΧΙΖΟΜΕΝΗ ΙΑΤΡΙΚΗ ΕΚΠΑΙΔΕΥΣΗ

### Hematology Quiz – Case 26

An 81-year-old man presented with one-month history of disseminated, painless, brownish, maculopapular or nodular skin lesions of the trunk and extremities. Initially, the patient presented with a large dark-brown plaque at the inner surface of the left ankle, with a maximum diameter of 4.5 cm. He was also complaining of weakness, fatigue and weight loss of 8 kg during the last 4 months (12% of body weight). His medical history was remarkable for arterial hypertension and “arrhythmia”, treated with oral amlodipine and carvedilol, respectively.

Except of the skin lesions, physical examination revealed moderate splenomegaly (5 cm blcm), but no hepatomegaly. A complete blood count revealed normochromic-normocytic anemia, leukocytosis and thrombocytopenia, as follows: Hct 27.5%, RBC  $2.96 \times 10^{12}/L$ , Hb 9.4 g/dL, MCV 92.6 fL, MCH 31.6 pg, MCHC 34.2 g/dL, WBC  $17 \times 10^9/L$  (differential count: 35% neutrophils, 18% lymphocytes, 49% blast cells) and PLTs  $23 \times 10^9/L$  (figures 1, 2). Serum biochemistry was rather unremarkable, except of mild hyperuricemia, with the following values: Urea 82 mg/dL, creatinine 1.1 mg/dL, total bilirubin 1.4 mg/dL, SGOT 41 U/L, SGPT 27 U/L, LDH 442 IU/L (upper normal limit 460 IU/L), uric acid 8 mg/dL and total proteins 6.71 g/dL with a normal electrophoretic diagram. Skin biopsies were performed from two separate lesions. Both biopsies revealed a diffuse dermal blast cell infiltrate. Immunohistochemical staining demonstrated that the neoplastic cells were positive for CD56, CD4 (+/-), CD123, TCL1, CD43 and terminal deoxynucleotidyl transferase (Tdt; few cells positive), while they were negative for CD3, CD20, CD79a,

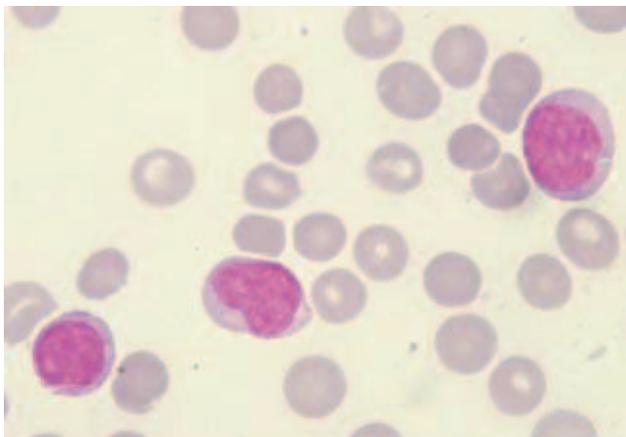


Figure 1

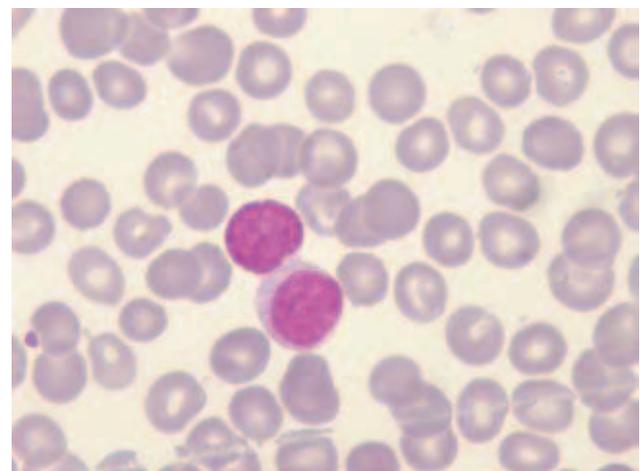


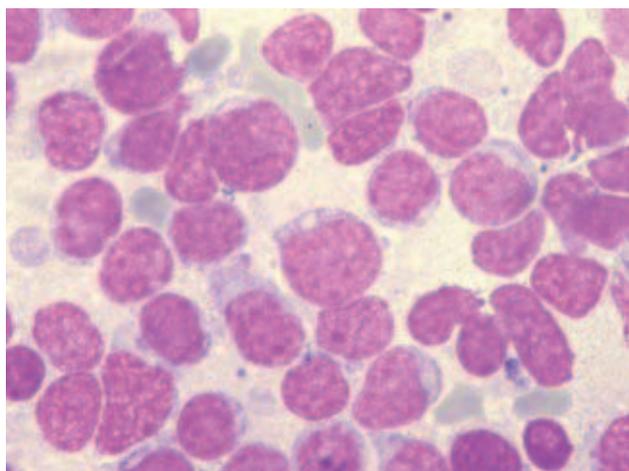
Figure 2

myeloperoxidase (MPO) and PGM1. A bone marrow aspiration and biopsy was performed. Bone marrow aspiration revealed extensive infiltration by medium-sized, monomorphous blast cells with irregular nuclei (Fig. 3). Blood and bone marrow immunophenotype confirmed and extended the findings of skin immunohistochemistry, as follows: CD56+, CD4 fully positive, CD123+, HLA-DR+, CD45RA+, 85k+ and Tdt+ (40% of cells). There was also positivity for CD7 and CD33 and weak positivity

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**Figure 3**

for CD117 and CD22, while CD3 and MPO were negative. Conventional cytogenetic analysis revealed a normal karyotype.

### Comment

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a clinically aggressive tumor derived from the precursors of plasmacytoid dendritic cells. Prior to the recent 2008 WHO classification, the same neoplasm had been reported under the terms “NK blastic leukemia/lymphoma, CD4+CD56+ hematodermic tumor” etc. The main clinical, pathologic and immunophenotypic features of this entity have been summarized by Herling and Jones. It is a very rare hematologic neoplasm, presenting mostly in elderly patients (median age approximately 65 years), with a clear male predominance of 2.5–3:1. The disease tends to involve multiple sites, with a predilection for skin (almost 100% of cases), followed by bone marrow and peripheral blood (60–90%) and lymph nodes (40–50%). Splenomegaly is less frequently observed (approximately 20% of patients). Patients usually present with asymptomatic, solitary or multiple skin lesions that can be nodules, plaques or bruise-like areas. Peripheral blood and bone marrow involvement can be minimal at presentation, but invariably develops during disease evolution. Cytopenias may occur at diagnosis as a result of bone marrow failure and may be severe in a sizeable minority of cases, as seen in the present one. About 10–20% of cases evolve into acute myeloid or myelomonocytic leukemia. BPDCN is usually characterized by a diffuse, monomorphous infiltrate of medium sized blast cells with irregular nuclei, fine chromatin and one to several nuclei. The neoplastic cells typically express CD4, CD56 and CD45RA, as well as the plasmacytoid dendritic cell-associated antigens CD123, BDCA-2/CD303, TCL1, and CLA (cutaneous lymphocyte-associated antigen). Tdt is expressed in one third of cases. Other markers, such as CD68 (normal plasmacytoid dendritic cells), CD43, CD36, CD7 and CD33 may be expressed in various proportions of cases. Lineage-specific markers (MPO, CD3, CD79a, CD20 etc), CD34, CD117 and EBV (present in most NK-cell tumors) are absent. Notably, CD117 was positive in the present case. Two thirds of patients with BPDCN have an abnormal karyotype. Specific chromosomal aberrations are

lacking, but complex karyotypes are common. The clinical course of the disease is aggressive, with a median survival of 12–24 months, irrespective of the initial pattern of the disease. Most cases (80–90%) show an initial response to multiagent chemotherapy, CHOP-like, AML-like or ALL-like, but relapses with subsequent drug resistance are typically observed. At present, there is no consensus regarding the optimal treatment of BPDCN, although ALL-like therapy might be more effective in a small series. The rate of complete remission may increase with more intensive therapy, but only myeloablative treatment with allogeneic bone marrow transplantation during first remission may provide a chance of long-term survival for the subgroup of younger patients.

After a diagnosis of BPDCN was made according to the 2008 WHO classification, it was decided the patient to be treated with a modified low dose cyclophosphamide, doxorubicine, vincristine and prednisone regimen (mini-CHOP). Due to severe baseline cytopenias and extensive bone marrow infiltration, the patient initially received a “pre-phase” with steroids, a single 1 mg dose of vincristine and 200 mg of cyclophosphamide intravenously for 3 days, prior to the main chemotherapy regimen. The skin lesions almost disappeared after the first cycle of mini-CHOP, while the ankle lesion disappeared after the third cycle. Chemotherapy was complicated by recurrent episodes of febrile neutropenia, anemia requiring erythropoietin treatment and red cell transfusions and moderate to severe thrombocytopenia (up to grade 3). By the end of the 4th cycle of mini-CHOP, the patient entered a clinical and bone marrow complete remission, which was maintained after the completion of the 8th cycle.

BPDCN is a rare but aggressive disease. The clinician should be alert to recognize the disease in patients presenting with cutaneous lesions and cytopenias, with or without leukemic picture.

### References

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**Diagnosis:** Blastic plasmacytoid dendritic cell neoplasm (BPDCN)