ARCHIVES OF HELLENIC MEDICINE: ISSN 11-05-3992

CONTINUING MEDICAL EDUCATION
ΣΥΝΕΧΙΖΟΜΕΝΗ ΙΑΤΡΙΚΗ ΕΚΠΑΙΔΕΥΣΗ

Hematology Quiz – Case 27

ARCHIVES OF HELLENIC MEDICINE 2011, 28(6):856–857
ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2011, 28(6):856–857

L. Papageorgiou,
V. Karali,
A. Kanellopoulos,
G. Gainarou,
P. Flevari,
G. Boutsikas,
K. Petevi,
T. Dalagiorgos,
E. Koutsi,
V. Telonis,
Z. Galani,
A. Bilalis,
E. Sinni,
G. Georgiou,
M.K. Angelopoulou,
T.P. Vassilakopoulos,
J. Meletis

Department of Hematology and Bone Marrow Transplantation Unit, National and Kapodistrian University of Athens, School of Medicine, "Laiko" General Hospital, Athens, Greece

A previously healthy 24-year-old man presented at the emergency department with cervical lymphadenopathy, dyspnea and leukocytosis. The patient also complained of weight loss and night sweats during the preceding two months. Physical examination revealed bilateral crepitations and palpable bilateral cervical and supraclavicular lymphadenopathy. At room air ABGs (arterial blood gas) were as follows: pH=7.4, PO_2=68.5 mmHg, PCO_2=30.4 mmHg, HCO_3^-=20.3 mEq/L, SpO_2=95%.

His full blood count was as follows: Ht=40.7%, Hb=13.5 g/dL, RBC=4.88×10^{12}/L, WBC=33.95×10^9/L (neutrophils=68%, lymphocytes=15%, monocytes=4%, atypical lymphocytes=13%), PLT=456×10^9/L. Serum biochemistry showed elevated LDH levels (358 IU/L). Peripheral blood cell morphology is shown in figure 1. The bone marrow aspiration revealed the presence of atypical lymphoid cells, similar to those found in the peripheral blood, albeit at a low percentage (fig. 2). Immunophenotypic study showed an expression of cytCD3, CD4, CD2, CD30 to 83% of lymphocytes while being negative for CD7, CD5 and sCD3. CT scan of the thorax revealed multiple enlarged mediastinal lymph nodes, interstitial lung disease and bilateral pleural infusions. A cervical lymph node biopsy was performed that revealed the presence of large and medium-sized cells with round or kidney-shaped nuclei and prominent nucleoli (fig. 3). Immunohistochemistry was as follows: 100% positivity for LCA, ALK, CD30, EMA, CD43, CD2, CD4, CD25, 10% positivity for granzyme B, 20% positivity for CD3 and TIA1. Blood and bone marrow immunophenotype and lymph node histology were diagnostic.

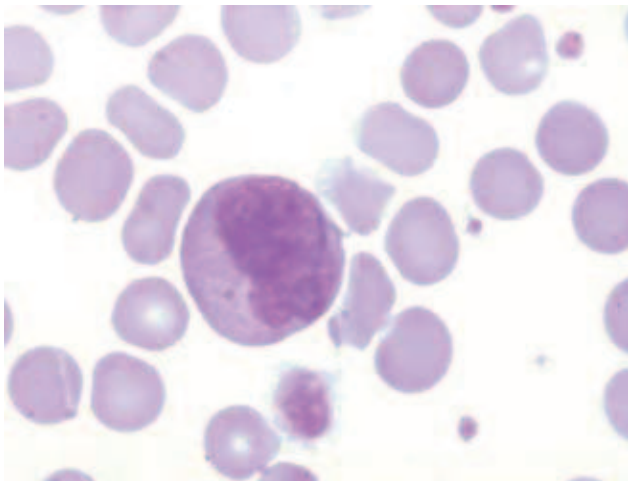

Figure 1

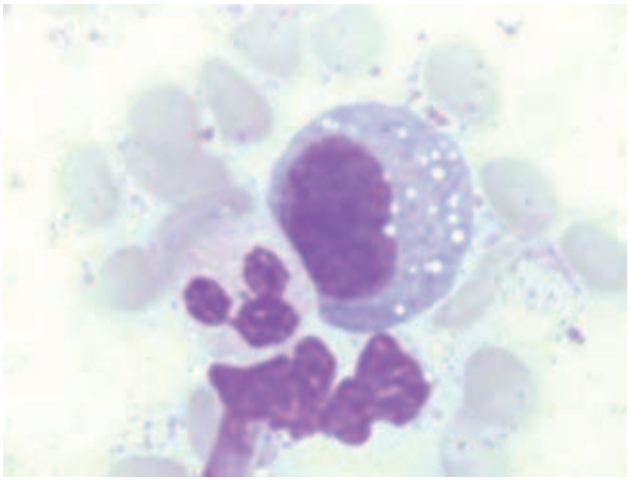

Figure 2

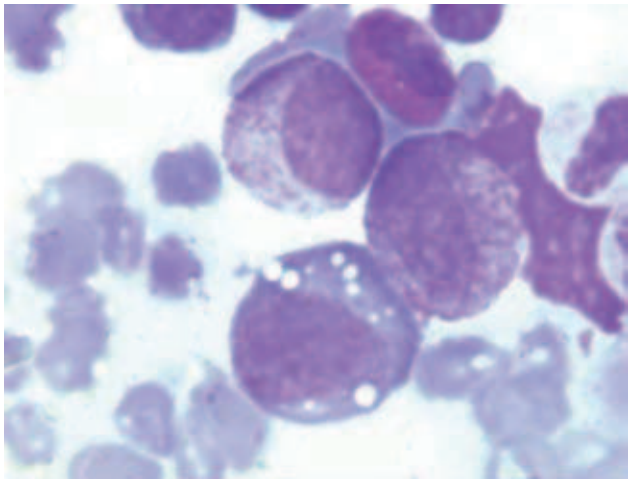

Figure 3

Comment

Anaplastic large cell lymphoma (ALCL), anaplastic lymphoma kinase (ALK) positive is a T-cell lymphoma. Five patterns can be recognized, according to morphologic features. The common type (60%) is characterized by large cells with abundant cytoplasm and pleomorphic, often horseshoe-shaped nuclei (hallmark cells). Hallmark cells are always present in all subtypes. In the lymphohistiocytic pattern, tumour cells are admixed with a large number of reactive histiocytes. In the small cell pattern, cells are small or medium sized with irregular nuclei. This variant may have a leukemic presentation with peripheral blood involvement. Other rare subtypes include Hodgkin-like pattern, ALCL with signet ring cells, sarcomatoid, hypocellular, rich in giant cells neutrophils or eosinophils.

Patients present with lymphadenopathy as well as extranodal involvement. Common sites included are the lungs, skin, bone, soft tissue and liver. Bone marrow involvement can be underdiagnosed when only H&E is used (10% of cases). Both neutrophilic leukemoid reaction due to G-CSF production and leukemic dissemination may contribute to leukocytosis in ALCL, ALK+; the latter being usually observed in the context of the small cell variant of the disease.

The characteristic chromosomal abnormality is t(2;5)(p23;q35), generating a chimeric transcript, NPM-ALK. The latter acts as an oncogenic protein through activation of numerous pathways. Immunohistochemistry can reveal bone marrow involvement in up to 20–30% of cases. In most cases that have the t(2;5) translocation, ALK staining of cells is both cytoplasmic and nuclear with the exception of small cell variant where ALK positivity is nuclear. Cases with variant translocations show either cytoplasmic or membranous positivity. An aberrant cytoplasmic expression of NPM is seen in most cases while the expected nuclear-restricted expression is observed in patients carrying variant translocations.

Tumour cells universally express Ki1 (CD30), a marker also present in Reed-Sternberg cells but, unlike these, ALCL are usually CD15 negative. Cells usually have a T-cell phenotype, while some cases are characterized as "null" (non-B, non-T) phenotype.

ALCL, ALK+ is an aggressive T-non-Hodgkin lymphoma. First line therapy consists of 6–8 cycles of CHOP combination chemotherapy. Recent studies suggest that adding etoposide (CHOEP) might benefit ALCL, ALK+ patients aged <60. Second-line therapy includes combinations such as ESHAP and ICE, followed by autologous stem cell transplantation in younger patients. Targeted therapy against CD30 or ALK has provided very promising results in relapsed/refractory patients. With respect to prognosis, ALCL, ALK+ is the most favorable subtype of mature T-cell lymphomas, but the rare leukemic cases are usually very aggressive.

References

1. DELSOL G, FALINI B, MULLER-HERMELINK HK, CAMPO E, JAFFE E, GASCOYNE RD ET AL. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H et al (eds) *WHO classification of tumours of haematopoietic and lymphoid tissues*. 4th ed. International Agency for Research on Cancer, Lyon, France, 2008:312–316
2. ΡΑΣΙΔΑΚΗΣ ΓΖ, ΒΑΣΙΛΑΚΟΠΟΥΛΟΣ ΘΠ. Αναπλαστικό λέμφωμα από μεγάλα κύτταρα. *Haema* 2010:1:29–41
3. ONCIU M, BEHM FG, RAIMONDI SC, MOORE S, HARWOOD EL, PUI CH ET AL. ALK-positive anaplastic large cell lymphoma with leukemic peripheral blood involvement is a clinicopathologic entity with an unfavorable prognosis. Report of three cases and review of the literature. *Am J Clin Pathol* 2003, 120:617–625
4. SCHMITZ N, TRÜMPER L, ZIEPERT M, NICKELSEN M, HO AD, METZNER B ET AL. Treatment and prognosis of mature T-cell and NK-cell lymphoma: An analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. *Blood* 2010, 116:3418–3425

Corresponding author:

J. Meletis, Department of Hematology and Bone Marrow Transplantation Unit, National and Kapodistrian University of Athens, School of Medicine, "Laiko" General Hospital, Athens, Greece, tel.: +30 210 74 66 902, fax: +30 210 7456698, e-mail: imeletis@med.uoa.gr

Diagnosis: *Anaplastic large cell lymphoma ALK+ (ALCL ALK+)*