

CONTINUING MEDICAL EDUCATION ΣΥΝΕΧΙΖΟΜΕΝΗ ΙΑΤΡΙΚΗ ΕΚΠΑΙΔΕΥΣΗ

Hematology Quiz – Case 32

A 20-year-old male of Albanian origin with no significant past medical history was admitted to the Hematology Department with painless bilateral axillary and cervical/supraclavicular lymphadenopathy and pitting right upper limb edema. On admission, his performance status was poor (4 in the ECOG scale), he was febrile (38.2°C), normotensive, tachycardic and tachypnoic, had whooping cough and could not move his right upper limb due to edema. Symptoms began approximately 45 days before admission and gradually worsened. He reported drenching night sweats and weight loss. Physical examination revealed absence of lung sounds at the middle and lower right chest auscultation with dullness to percussion, dull cardiac sounds, right chest wall cyanosis (fig. 1), no hepatosplenomegaly, no head or lower limb



Figure 1

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2012, 29(6):761–765

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edema and no stridor or hoarseness. The right axillary swelling was very bulky, apparently causing the posterior and anterior right chest wall, pitting upper limb, as well as right upper neck edema. Multiple, hard, painless, discrete lymph nodes up to 1.5 cm in diameter were also present in the left supraclavicular fossa and left axilla.

Laboratory findings revealed leukocytosis (neutrophils: $12.1 \times 10^9/\text{L}$), elevated ESR (82 mm/hour) and CRP (138 mg/L), marked hypoalbuminemia (22.3 g/L) and elevated LDH levels ($2.3 \times$ the upper normal limit).

The patient had a chest and abdomen CT scan revealing a large right axillary lymph node mass of 15 cm in diameter, infiltrating the frontal thoracic musculature up to the skin, enlarged left axillary, mediastinal and intraabdominal lymph nodes, significant right pleural effusion, small pericardial effusion and no signs of ascites. The upper limb triplex ultrasonography did not reveal signs consistent with deep vein thrombosis.

The patient had a right axillary lymph node biopsy done elsewhere approximately 15 days before admission, while he was still ambulating, which had been interpreted as lymphocyte depletion Hodgkin lymphoma. However, his clinical condition rapidly deteriorated and became bedridden.

After admission, a second left axillary and right cervical lymph

node biopsy was performed. Lymph node imprint cytologic findings are shown in figure 2. The right pleural effusion was drained. Pleural fluid cytology revealed large, bizarre cells, similar to those appearing at the lymph nodes, on a background of mesothelial cells (fig. 3). On immunophenotype, these cells were CD30 positive (fig. 4), as well as CD2, CD4 positive and

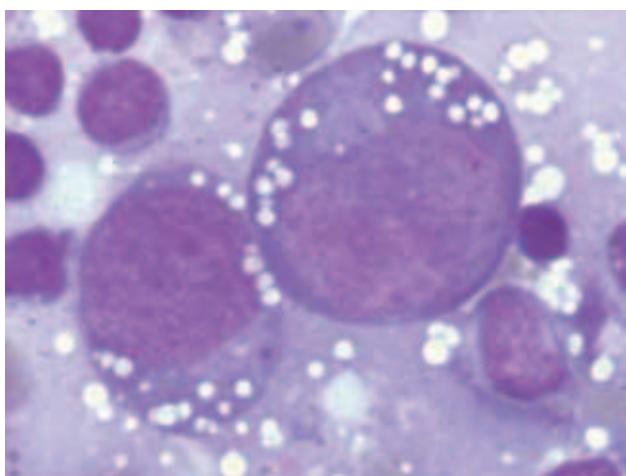


Figure 2

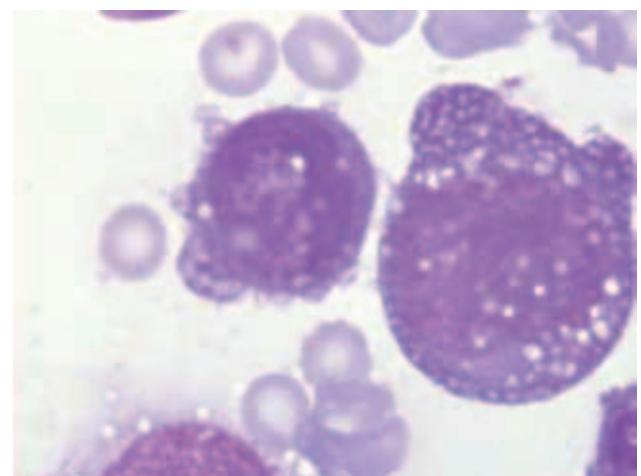


Figure 3

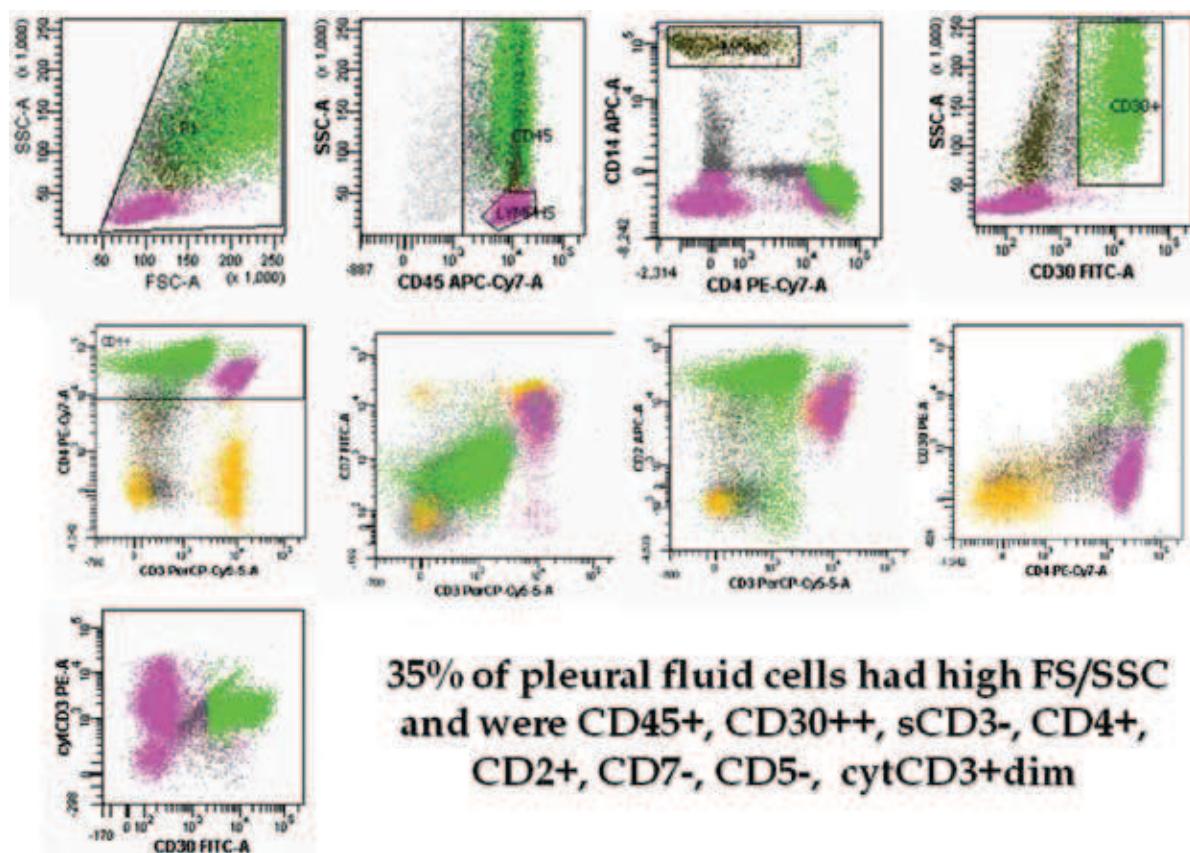


Figure 4

cytoplasmic CD3 positive (dim). Other T-cell markers (CD5, CD7 and surface CD3) were negative. A bone marrow biopsy revealed only reactive changes with no evidence of malignancy.

The diagnosis was established based on lymph node biopsy morphologic and immunohistochemical findings.

Comment

According to the 2001 and 2008 World Health Organization (WHO) classification of lymphoid neoplasms, Hodgkin lymphoma is divided into the rare nodular lymphocyte predominant subtype (5% of all cases) and the common form of classical Hodgkin lymphoma (95% of all cases), which is further subclassified as nodular sclerosing (70%), mixed cellularity (20%), lymphocyte rich (5%) and lymphocyte depleted (<1%) classical Hodgkin lymphoma. In the previously applicable Lukes-Batler classification, established in 1966, "Hodgkin's disease" was subdivided in four sizeable histologic subtypes, namely lymphocyte predominance (20% of all cases), nodular sclerosis (35%), mixed cellularity (30%) and lymphocyte depletion (15%). Thus, there is a marked discordance between the reported frequencies of lymphocyte-depleted Hodgkin lymphoma according to the Lukes-Batler or WHO classification. Indeed, it was retrospectively shown that most cases of the so-called "lymphocyte-depleted Hodgkin's disease" according to the Lukes-Batler classification were in fact either nodular sclerosing Hodgkin lymphomas (syncytial variant) or anaplastic large cell lymphomas.

Based on the above information, any histologic report of lymphocyte depleted Hodgkin lymphoma should be interpreted with caution, since true cases of this specific subtype appear to be very rare. In the case reported here, there are some clinical clues favoring the modification of the initial diagnosis from "lymphocyte-depleted Hodgkin lymphoma" to "anaplastic large cell lymphoma": (a) The clinical growth rate of the tumor was very rapid, which is not a common feature of Hodgkin lymphoma; (b) the tumor produced marked compressive manifestations and skin infiltration; (c) clinically significant pleural effusions are infrequent in Hodgkin lymphoma; if present, the existence of neoplastic cells within the pleural fluid is extremely rare, and (d) serum LDH levels exceeding >2 times the upper normal limit are observed in only 2% of Hodgkin lymphoma cases.

Systemic anaplastic large cell lymphoma is an aggressive NHL (non-Hodgkin's lymphoma) with a clinical course depending on presence of translocations involving ALK (anaplastic lymphoma kinase). The t(2;5)(p23;q35) translocation is the most common genetic aberration, which results to the expression of the ALK protein. CD30 is present in all cases and may play a role in the pathogenesis by influencing the growth and survival of T-cells as a member of the TNF receptor family. CD15, a marker of Hodgkin lymphoma, can be rarely positive. Approximately 60% of cases express one or more T-cell markers, but they are negative for B-cell markers. However, approximately 40% of cases do not express T- or B-cell markers (null cell type). Their T-cell origin can be usually demonstrated by molecular methods.

The morphologic findings in the present case were also more compatible with anaplastic large cell lymphoma rather than lymphocyte-depleted Hodgkin lymphoma. Lymph node imprint cytology revealed the presence of a monotonous population of very large, bizarre cells (fig. 2). The presence of a very high number of neoplastic cells and the complete absence of any reactive cellular background favors the diagnosis of anaplastic large cell lymphoma. The expression of CD30, the hallmark of both anaplastic large cell lymphoma and classical Hodgkin lymphoma was rapidly demonstrated on pleural fluid immunophenotype (fig. 4), along with some T-cell marker expression. Cytogenetic analysis of the pleural fluid revealed the presence of t(2;5)(p23;q35) in the context of a complex karyotype, as follows: 48, XY, t(2;5)(p23;q35), add(7)(p22), +16, +22 [3] / 96, Idemx2, +i(q10)x2, +add(8)(q24), +add(16)(p21) [cp19]. ALK stain was positive on lymph node immunohistochemistry.

ALK-positive anaplastic large cell lymphoma is more prevalent than its ALK-negative counterpart in children and young adults. ALK-positive cases probably carry a much better prognosis. More intensive chemotherapy with the addition of etoposide (CHOEP-21 or CHOEP-14) may be superior to CHOP, even in ALK-positive disease. Apart from anti-CD30 targeted therapy, which is applicable in both ALK-positive and ALK-negative cases with very encouraging results, ALK inhibition using the small molecule inhibitor crizotinib may prove a promising therapeutic option for patients with relapsed

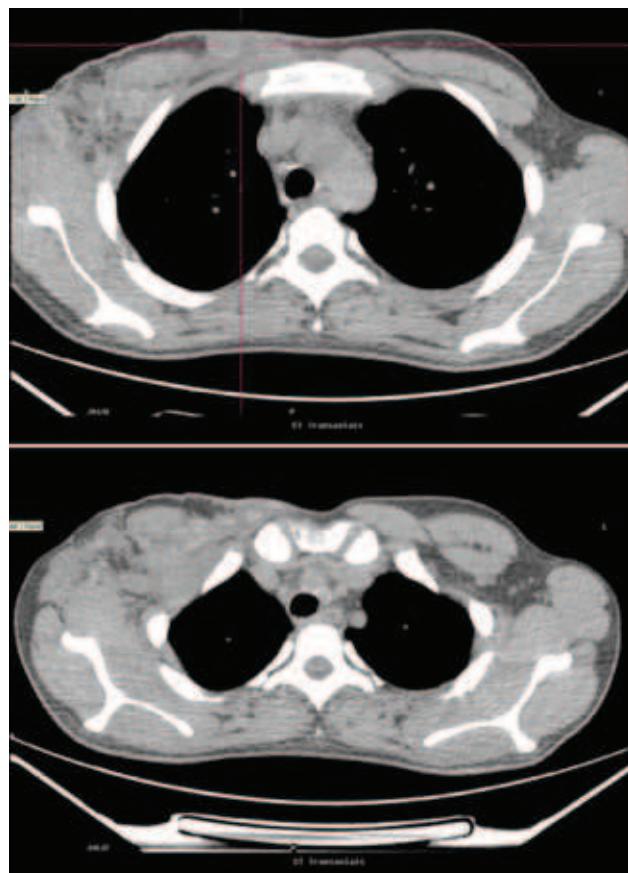


Figure 5

or refractory ALK-positive disease.

The patient reported here received six cycles of intensive chemotherapy with the CHOEP-14 combination. He achieved a partial radiographic remission with a significant residual abnormality at the right supraclavicular, subclavian and axillary area (fig. 5). However, positron emission tomography revealed only a mild, focal positivity (SUV_{max} 3.6) at the right parasternal region (fig. 6). An excisional biopsy of the corresponding anatomic finding revealed only necrosis of the underlying lymphoma. The patient subsequently received radiotherapy at a dose of 4,200 cGy to the residual mass and

remains in remission 3 months later. Consolidation with high dose therapy and stem cell support is not encouraged as consolidation of the first remission in the specific case of ALK-positive anaplastic large cell lymphoma regardless the baseline risk classification.

This case underlines the need of the review of any histologic material by expert hematopathologists, especially when rare lymphoma subtypes are described or the whole clinical and laboratory profile of the patient raises diagnostic concerns. Furthermore, the successful application of modern techniques, such as immunophenotype and conventional cytogenetics is highlighted.

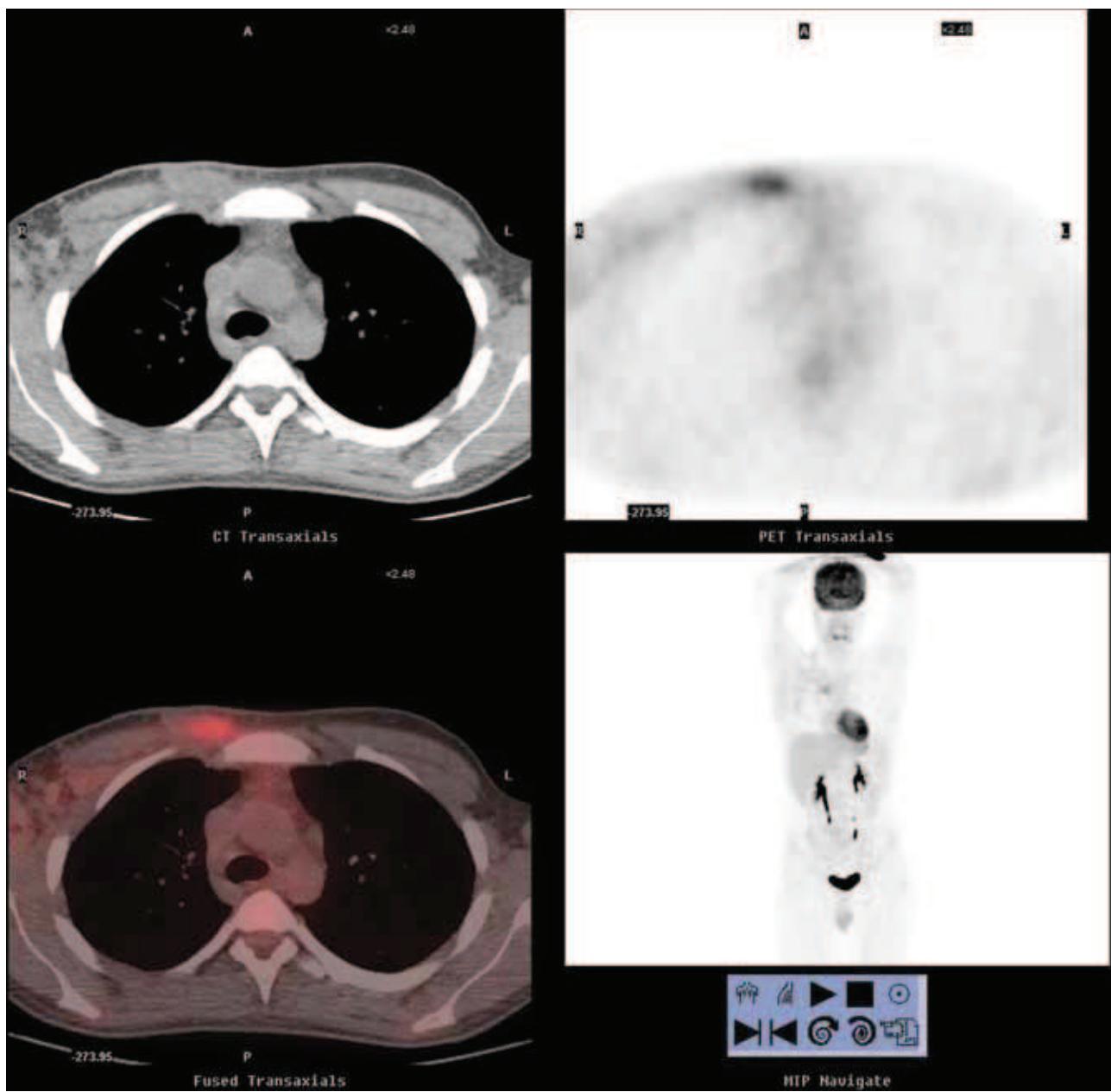


Figure 6

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