

CONTINUING MEDICAL EDUCATION ΣΥΝΕΧΙΖΟΜΕΝΗ ΙΑΤΡΙΚΗ ΕΚΠΑΙΔΕΥΣΗ

Hematology Quiz – Case 37

A 62-year-old male patient presented to our unit for further evaluation and treatment of a diffuse large B-cell lymphoma (DLBCL). Approximately one month ago, he experienced an abdominal pain and underwent a laparoscopic cholecystectomy, since physical examination revealed Murphy's sign and upper abdominal ultrasonography revealed sludge and gallbladder wall thickening. Preoperative computed tomography (CT) imaging was negative for lymphadenopathy or tumor lesions. Intraoperatively, the surgeon noticed multiple, "tiny", subcentimeter, white lesions on the surface of the liver. Biopsy of a lesion revealed DLBCL and the patient was referred to our department. Medical history was only remarkable for arterial hypertension and diverticulitis.

While the result of the histologic examination was pending, the patient developed low-grade fever, night sweats and rapid weight loss. His clinical condition deteriorated promptly. At presentation, ECOG (Eastern Cooperative Oncology Group) performance status was 3. He had no abnormal physical findings except of appearing ill. Laboratory evaluation revealed the following: Hematocrit 31.8%, hemoglobin 10.2 g/dL, RBC $3.6 \times 10^{12}/L$, WBC $16 \times 10^9/L$ with leukoerythroblastosis (poly 62%, lymphs 12%, monos 5%, metamyelocytes 6%, myelocytes 14%, blasts 1%, erythroblasts 7 per 100 WBC; figures 1–3), PLTs $80 \times 10^9/L$, ESR 132 mm/h, CRP 392 mg/L, normal serum glucose, sodium, potassium and bilirubin levels, mild renal insufficiency (urea 71

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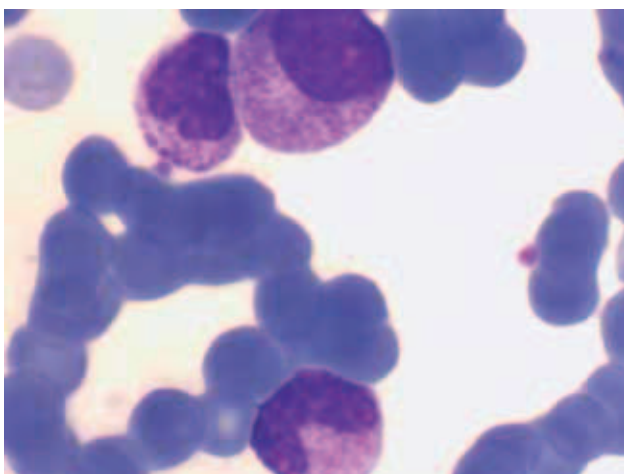


Figure 1

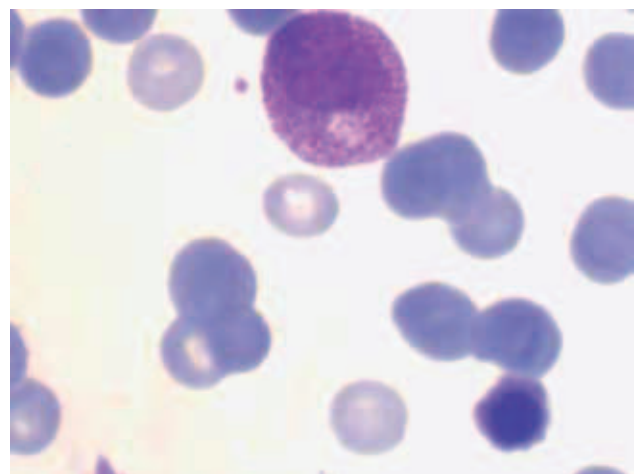


Figure 2

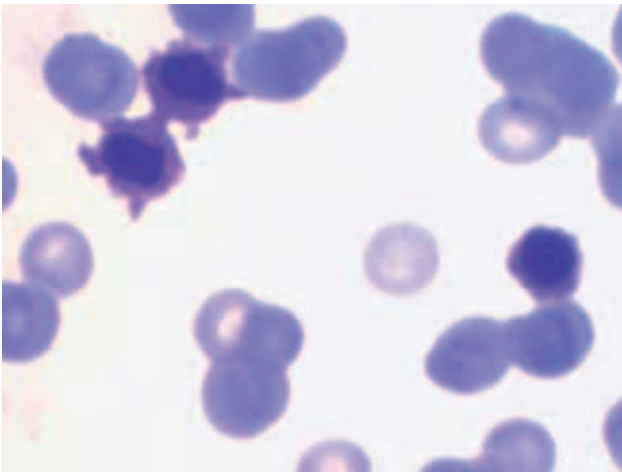


Figure 3

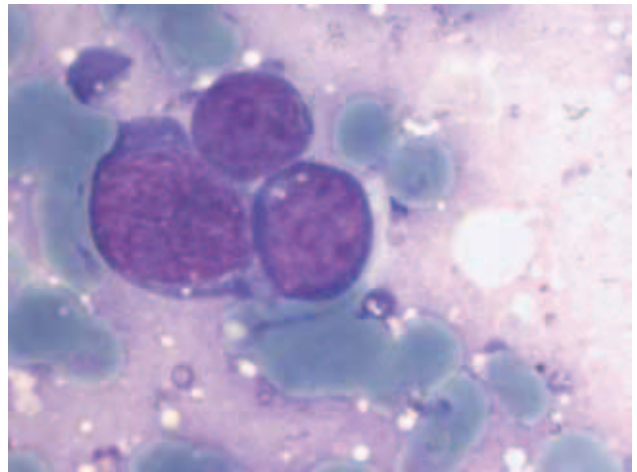


Figure 4

mg/dL, creatinine 1.6 mg/dL, hypercalcemia 12.9 mg/dL, hyperphosphatemia 4.7 mg/dL, hyperuricemia 12.9 mg/dL, abnormal liver function tests [AST 52 U/L (upper normal limit, UNL 31 U/L), ALT 52 U/L (UNL 34 U/L), serum alkaline phosphatase 570 U/L (UNL 141 U/L), γ GT 537 U/L (UNL 36 U/L)], hypoproteinemia 5.7 g/dL with slightly reduced albumin levels (3.4 g/dL), and highly elevated serum lactate dehydrogenase levels (1,973 U/L versus UNL 220 U/L or approximately 9 \times).

Liver biopsy histologic report described a DLBCL-not otherwise specified (DLBCL NOS) with the following immunophenotype: CD20+, CD10+, bcl6+, bcl2-. The proliferation index Ki67 was highly elevated reaching 98%. Bone marrow aspiration was not possible (dry tap), but bone marrow touch preparations revealed extensive monomorphic infiltration (figures 4–6). An urgent pathologic review was performed within few hours and further diagnostic tests were ordered.

Comment

If a diagnosis of DLBCL-NOS is accepted, the case presented here had several peculiar features: Clinical deterioration was very rapid and serum LDH was highly elevated (9 \times), indicating a rapid cellular turnover. Bone marrow involvement is rather infrequent, since it is observed in approximately 15% of the patients, but only half of them have “concordant” involvement; i.e. infiltration by large cells (the remaining patients have small cell –“discordant” infiltration).¹ Bone marrow infiltration is not usually so heavy to cause leukoerythroblastosis and thrombocytopenia, which are very features in DLBCL. Finally, the combination CD10+, bcl6+, bcl2- and very high Ki67 strongly raise the strong suspicion of Burkitt's lymphoma (BL).

An immediate pathology review of liver biopsy specimens by an expert hematopathologist confirmed the diagnosis of BL at the morphologic and immunohistochemical level. Bone marrow flow

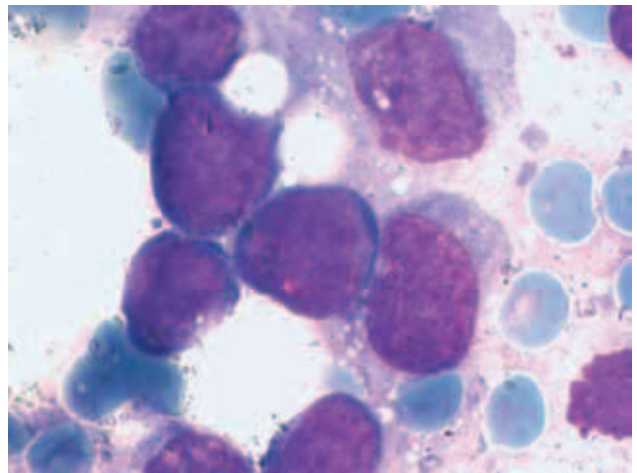


Figure 5

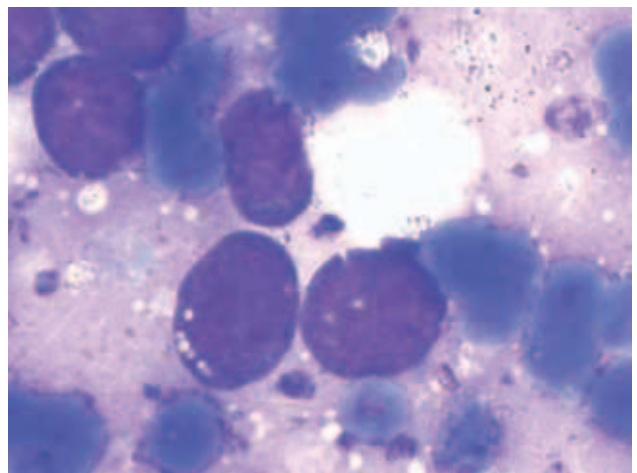


Figure 6

cytometry was not possible to perform, since aspiration was "dry tap", but blood immunophenotype revealed a very small monoclonal B-cell population. Indeed, lymphocytes consisted 18% of blood cells and 4% of them (0.7% of total blood cells) had moderate, monoclonal kappa (κ) surface immunoglobulin light chain expression, additionally being CD20+, CD10+, FMC7+ (moderate), CD79b+ (moderate), CD43+, CD38+. Interestingly, a similar percentage of 0.9% of the total blood cells had immunophenotypic features of myeloid blast cells (CD34+, CD33+), obviously in the context of leukoerythroblastic blood picture. The bone marrow biopsy confirmed the near 100% infiltration by Burkitt cells and FISH (fluorescent in situ hybridization) performed on bone marrow touch preparations confirmed the presence of *c-myc* rearrangements.

The patient was immediately treated with the pre-phase of the GMALL B-ALL/NHL 2002 regimen, including cyclophosphamide and prednisone. Subsequently, he received chemotherapy under the above protocol (modified for patients >55 years) and rituximab and achieved a complete remission.

Treatment of BL with the GMALL protocol is based on high-dose methotrexate in 24-hour infusion and administration of anthracyclines, alkylators (cyclophosphamide, ifosfamide), topoisomerase inhibitors (etoposide, teniposide), vinca alkaloids, cytarabine in various schedules and steroids.^{2,3} Treatment cycles are administered as rapid as possible. Good results have also been reported with other intensive chemotherapy regimens, such as CODOX-M/IVAC, HyperCVAD alternating with high-dose of methotrexate and cytarabine or dose-adjusted EPOCH.^{4,5} Central nervous system prophylaxis with intrathecal drug administration (methotrexate, cytarabine, dexamethasone) is also essential in addition to intravenous high-dose methotrexate, as well as high-dose cytarabine, which penetrate the blood-brain barrier.

With the addition of rituximab to these protocols, young BL patients (<55 years) are now cured in 85–90% of cases. Treatment results are also very satisfactory, although inferior to younger ones, in patients >55–60 years, who were difficult-to-treat with intensive chemotherapy, if baseline performance status is 0 or 1.^{2,6} Although patients >55–60 years old with impaired performance status can still be cured, treatment results are much less satisfactory due to high treatment-related mortality.²

The early recognition of BL and Burkitt leukemia (L3 acute lymphoblastic leukemia) is essential, since disease turnover is so rapid, that can lead to death in a few days. Abdominal presentations are frequently leading to extensive surgical interventions, which delay the initiation of the appropriate treatment. A high index of suspicion is required in order to recognize clinical presentations, laboratory

findings (highly elevated serum LDH, severe hyperuricemia) and immunophenotypic (and morphologic) characteristics associated with BL, which will permit prompt diagnosis and timely institution of the appropriate supportive and antineoplastic treatment.

With the advent of intensive chemotherapy and rituximab, the capability of rapid recognition of the disease and the appropriate supportive care, an extremely aggressive disease has been converted to a highly curable condition.

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