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ΣΥΝΕΧΙΖΟΜΕΝΗ ΙΑΤΡΙΚΗ ΕΚΠΑΙΔΕΥΣΗ

Hematology Quiz – Case 62

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2022, 39(3):430–432

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In May 2021, a 71-year-old man presented to the emergency department with a 2-month history of progressive fatigue, fever, nocturnal diaphoresis, and weight loss. Twelve years previously, he had received a diagnosis of immunoglobulin heavy-chain variable region (IGHV)-mutated chronic lymphocytic leukemia (CLL). During the next years he was well but in April, 2015, disease progression occurred and he was treated with fludarabine, cyclophosphamide, and rituximab (FCR) chemoimmunotherapy for 5 cycles. Disease reappeared in December 2018, with generalized lymphadenopathy, splenomegaly, and anemia. In February 2019, he began treatment with ibrutinib. Fluorescence *in situ* hybridization (FISH) analysis was negative for deletion of chromosome 17p13 and 11q22.3.

Physical examination revealed left supraclavicular lymphadenopathy measuring 10×6 cm (fig. 1) and slight splenomegaly. Laboratory tests revealed a white-cell count of 13×10^9/L (50% neutrophils, 47% lymphocytes, 3% monocytes), hemoglobin concentration 11.4 g/L, platelet count 80×10^9/L, C-reactive protein 8.13 mg/dL (0–5), and lactate dehydrogenase 290 U/L (120–246). Renal and liver function tests were normal. A peripheral-blood smear disclosed small lymphocytes with clumped chromatin and smudge cells. Broad spectrum antibiotics were started empirically but no improvement was seen. Cultures of blood, urine, and sputum, a PCR of the peripheral blood for cytomegalovirus, and a tuberculin skin test were negative. The peripheral-blood Epstein-Barr virus (EBV) DNA viral load was 50 copies/mL. Needle aspiration of the left supraclavicular lymph node yielded abundantly cellular aspirate smears comprised of small and medium sized lymphocytes, neutrophils and histiocytes (fig. 2) admixed with giant mononuclear (fig. 3), binucleated (figures 4 and 5), or multinucleated (fig. 6) neoplastic cells with huge nucleoli, coarsely reticulated chromatin, and pale cytoplasm.

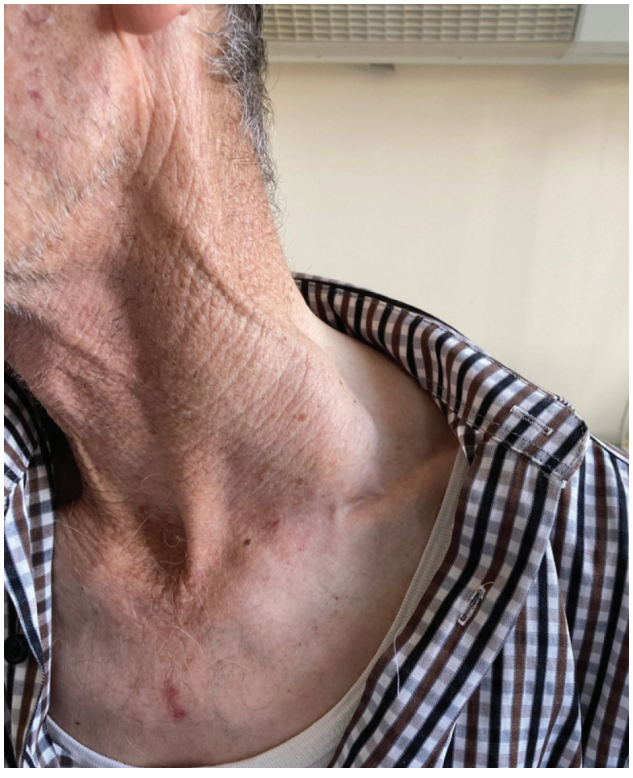

Figure 1

Comment

The morphologic characteristics of the giant cells in the lymph node aspirates were typical of Hodgkin and Reed-Sternberg cells. The clinical presentation of rapidly growing asymmetric lymphadenopathy and prominent systemic symptoms in a patient with CLL, combined with the presence of cells with this morphologic pattern, is highly suggestive of the Hodgkin's lymphoma variant of Richter's transformation (HVRT). This diagnosis was confirmed through biopsy

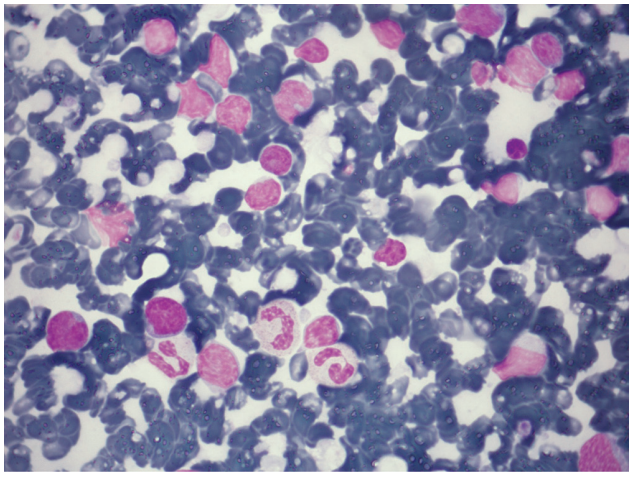

Figure 2

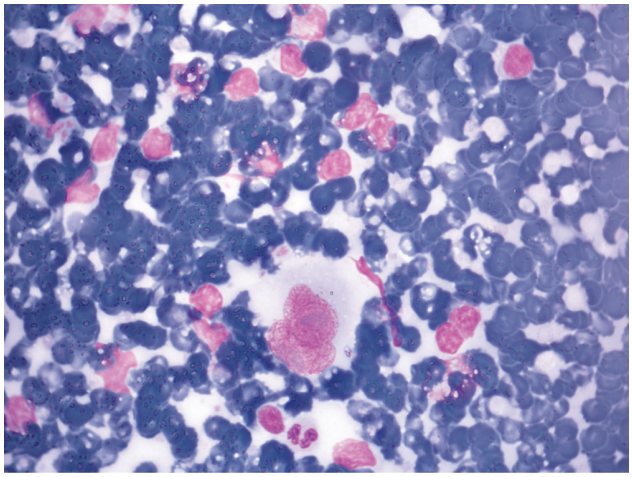

Figure 5

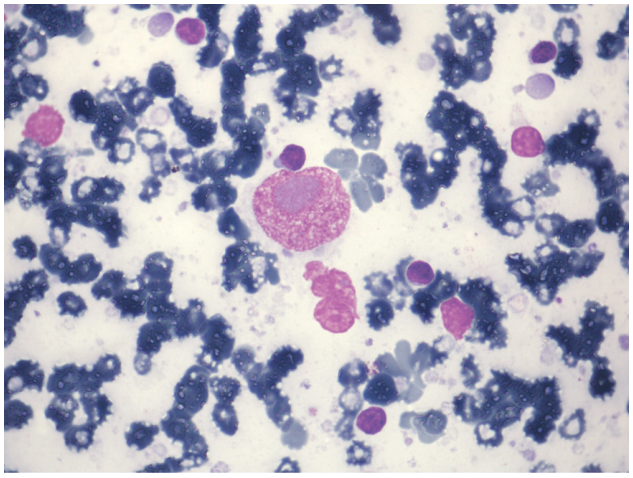

Figure 3

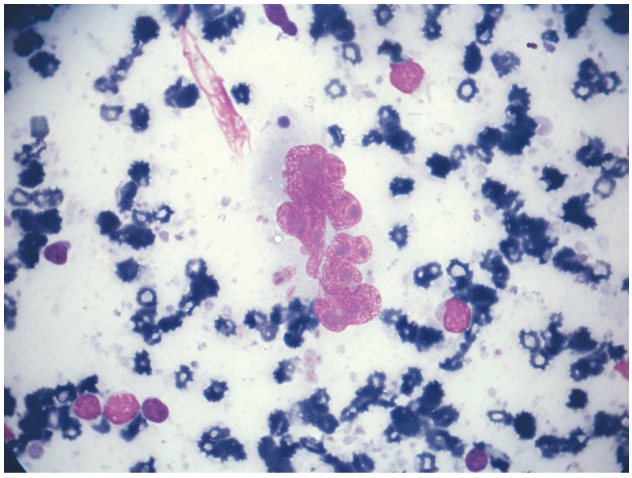

Figure 6

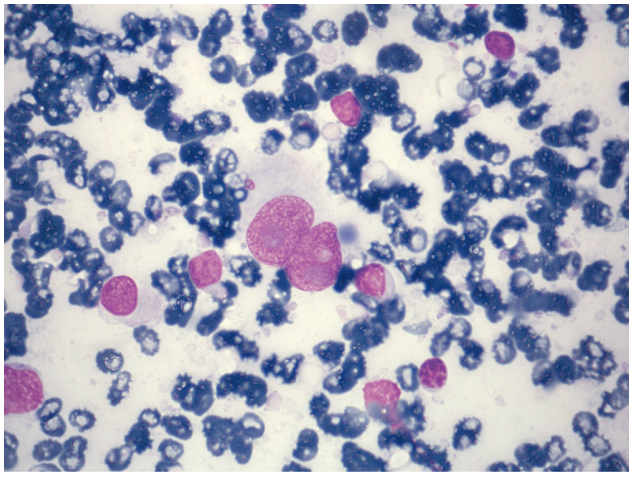

Figure 4

of a left supraclavicular lymph node which revealed distortion of the normal architecture by abnormal tissue consisting of numerous T-lymphocytes, histiocytes, fibrous tissue, and scattered Hodgkin and Reed-Sternberg cells (CD30+, CD15+, PAX5+). The Reed-Sternberg cells and their variants were positive for EBV (EBER+). Patchy infiltration with CLL was also noted. A bone-marrow biopsy revealed 20% involvement with CLL; features of Hodgkin's lymphoma or diffuse large B-cell lymphoma (DLBCL) were not seen.

Richter's transformation is a syndrome in which the activated B-cell (ABC) subtype of DLBCL (90–95% of cases), or in rare cases classic Hodgkin's lymphoma (5–10% of cases), arises in a patient with CLL. It was first described in 1928 by Maurice Richter who reported a case of "reticular cell sarcoma of the lymph nodes" in a 46-year-old man with lymphatic leukemia. Richter's transformation occurs in approximately 2–10% of patients with CLL with an annual transformation rate of 0.5–1% and is most likely to develop

2–4 years after the diagnosis of CLL, although it may occur at any time during a patient's disease course. The median time to HVRT is 6.2 years since diagnosis. Most patients with HVRT (78–80%) have heavily pre-treated CLL. The incidence of Richter's syndrome has not decreased in the era of novel agents.

Two types of HVRT in CLL have been described in the literature. In type 1 HVRST, the Reed-Sternberg cells are found within a background of CLL cells. It has been postulated that most cases of type 1 HVRT are directly clonally related to the underlying CLL. Type 2 HVRT is similar to classic Hodgkin's lymphoma, in which the neoplastic Reed-Sternberg cells are surrounded by a variable mixture of mature non-neoplastic inflammatory cells such as T-cells, neutrophils, plasma cells, and histiocytes, as in our patient. The two types have similar survival rates and treatment. Most cases of HVRT (67–76%) are positive for latent EBV infection. Median survival for HVRT is 39.5 months, with about a third of the patients being alive at 5 years of follow-up. In contrast, transformation to DLBCL is usually associated with poor median overall survival (6–8 months).

HVRT is treated similar to de novo classic Hodgkin's lymphoma. ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) is the most commonly used chemotherapy regimen. CVPP (cyclophosphamide, vinblastine, procarbazine, and prednisolone) is useful for older patients and patients with compromised cardiac function. More recently, the combination of bendamustine-brentuximab vedotin has emerged as a promising strategy to treat HVRT in patients with CLL without chromosome 17/17p deletion. Treatment with ABVD resulted in rapid clinical improvement in our patient.

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