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CLL transformation after one cycle of FCR: Richter's or EBV-associated lympho-proliferation?

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Keywords

Richter's transformation; EBV

A 64-year-old man presented with rapid-onset cervical and axillary lymphadenopathy, B symptoms, and high serum lactate dehydrogenase (LDH) approximately 4 weeks after receiving first cycle of FCR chemo-immunotherapy as frontline treatment for chronic lymphocytic leukemia (CLL). The patient had been diagnosed with CLL 12 years ago and was under observation. He had low-risk prognostic factors, including mutated *IGVH* and 13q deletion. One month ago he presented with signs and symptoms suggestive of disease progression and therefore was started on FCR. One month ago he presented with disease progression, with anemia (hemoglobin: 8.4 g/dL), worsening leukocytosis (white blood count (WBC): 112.3 K/μL; 96% lymphocytes), and thrombocytopenia (platelets: 89 K/μL). At this time, his LDH was 486 IU/L. After the first cycle of FCR, his symptoms improved and his lymph nodes initially shrank. Approximately four weeks after finishing the first cycle of FCR, the patient started developing fevers, night sweats, fatigue and progressive lymphadenopathy, including a large cervical node measuring 6×3 cm. Laboratory studies revealed a hemoglobin of 8.9 g/dL, WBC 5.4 K/μL, ALC of 0.5 K/μL and platelets 110 K/uL. LDH increased to 1736 IU/L. PET-CT scan showed multicompartmental bulky hypermetabolic lymphadenopathy with a maximum standardized uptake value (SUV) of 18.1 (Figure-1A). Accordingly, Richter transformation was considered, and the patient underwent cervical lymph node biopsy. Histologic evaluation showed sheets of large lymphoid cells with area of necrosis. Figure-1B-C shows a proliferation of large lymphoid cells (arrowheads) with admixed small lymphocytes (short arrow). Inset shows necrosis (long arrow). (Hematoxylin and eosin stain; **B and inset: 100×, C: 600×)**. Mitotic figures were identified readily (4 per high-power field) within the large cell proliferation, and the

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Authorship Statement and Disclosures

P.J., J.B. and J.K. collected and analyzed pathology and wrote the paper. J.B. managed the patient.

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Ki-67 proliferation index was high (>90%) (Figure-1D). The large cells were positive for MUM-1 and CD38 and negative for PAX5, CD20 and CD79a, in keeping with plasmablasts. Notably, in situ hybridization showed extensive positivity for Epstein-Barr virus-encoded RNA in plasmablasts (200x; Figure-1E). CD5/PAX5 coexpression was detected in small lymphocytes, consistent with residual CLL, which was further confirmed with flow cytometry immunophenotyping. Based on these findings, the patient was initially considered to have Richter's transformation, and chemotherapy options were discussed. However, his LDH and lymphadenopathy spontaneously resolved, without intervention. Quantitative PCR for EBV subsequently showed elevated plasma levels of 36,958 viral copies/mL. The patient was therefore considered to have an EBV-positive lymphoproliferative reaction after the first cycle of FCR therapy; he was managed with observation and returned to the clinic a month later with resolution of lymphadenopathy and B symptoms. Now, 3 years later, the patient remains under observation and has maintained remission for CLL. EBV associated lymphoproliferation after immunosuppressive therapy is a well-known complication.[1,2] In the context of CLL, it is an essential differential diagnosis to Richter's transformation, given the similarities in presentation. This case also highlights the clinical relevance of recognizing EBV-associated lymphoproliferation after FCR therapy in CLL. High SUV values in PET-CT scan can be over-interpreted as Richter's transformation [3] but given the alternatives etiologies, generally viral or other infectious complications[4,5] mimicking Richter's transformation, histopathology workup with appropriate stains for infectious agents is essential for establishing the appropriate diagnosis, as the basis for treatment recommendation.

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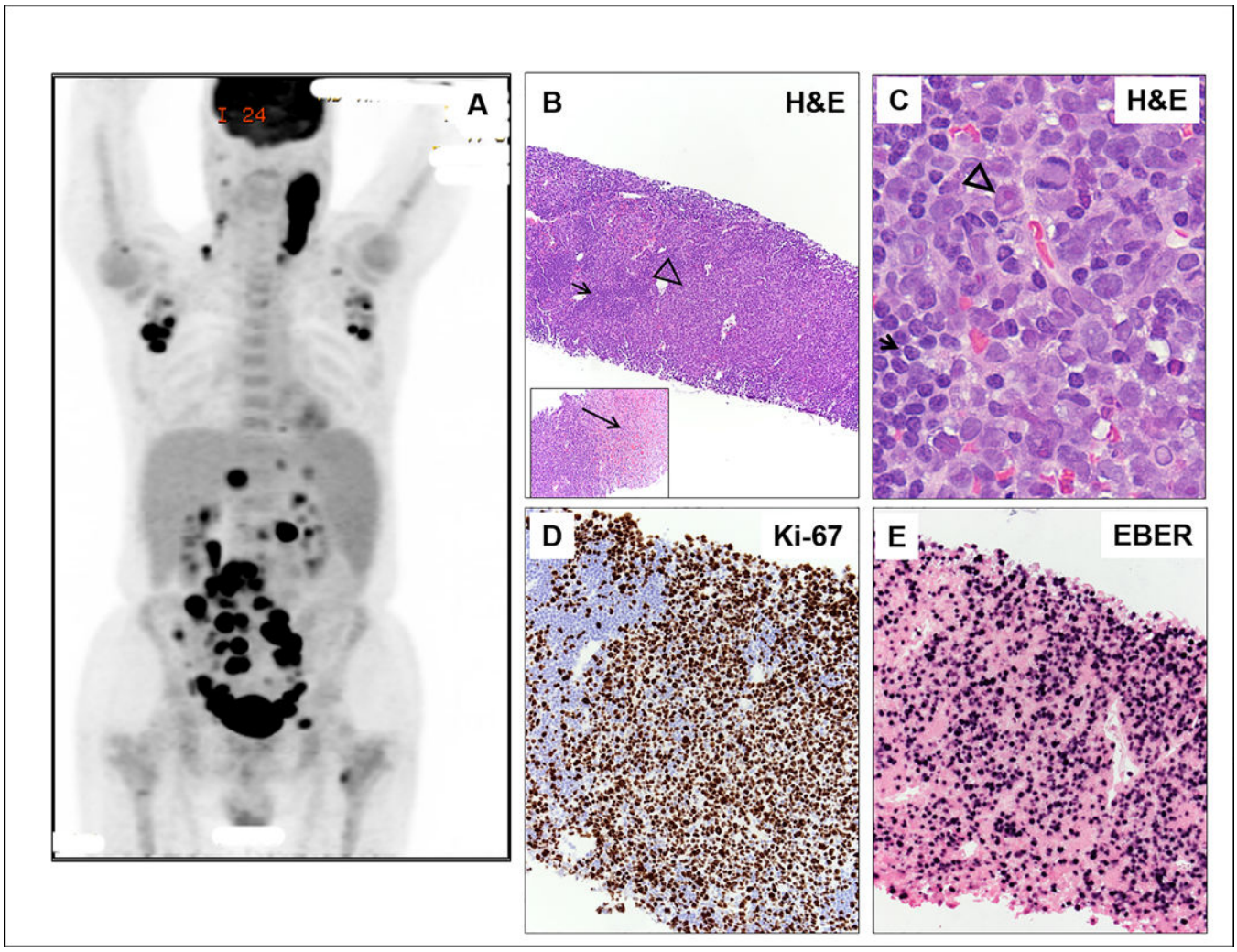

Figure 1. (A-E). Whole body PET-CT and histopathological features of a lymph node biopsy specimen involved by chronic lymphocytic leukemia (CLL) and EBV associated lymphoproliferation

PET-CT scan showed multicompartmental bulky hypermetabolic lymphadenopathy with a maximum standardized uptake value (SUV) of 18.1 **(A)**. Cervical lymph node biopsy showed sheets of large lymphoid cells with area of necrosis. **(B-C)** showing a proliferation of large lymphoid cells (arrowheads) with admixed small lymphocytes (short arrow). Inset shows necrosis (long arrow). (Hematoxylin and eosin stain; **B and inset: 100x, C: 600x)**. Mitotic figures were identified readily (4 per high-power field) within the large cell proliferation, and the Ki-67 proliferation index was high (>90%) **(D)**. The large cells were positive for MUM-1 and CD38 and negative for PAX5, CD20 and CD79a, in keeping with plasmablasts. Notably, in situ hybridization showed extensive positivity for Epstein-Barr virus-encoded RNA in plasmablasts (200×; **E).**