Published in final edited form as:

Leuk Lymphoma. 2013 November ; 54(11): 2540–2542. doi:10.3109/10428194.2013.773995.

Spontaneous remission of chemo-immunotherapy related, non-transplant Epstein-Barr virus–associated lymphoproliferative disorder in a patient with chronic lymphocytic leukemia

Preetesh Jain¹, Ohad Benjamini¹, Sergej Konoplev², Mohamed Shamel Mohamed¹, Carlos Guillermo Romo¹, and Zeev Estrov¹

¹Departments of Leukemia, All from - The University of Texas, M.D. Anderson Cancer Center, Houston, Texas

²Hematopathology, All from - The University of Texas, M.D. Anderson Cancer Center, Houston, Texas

A 75-year-old man presented with a 1-month history of rapidly progressive cervical lymphadenopathy, swallowing difficulty and B symptoms (fever, night sweats and weight loss). Review of outside hospital records showed that one year ago, patient underwent a computerized tomography (CT) scan of the thorax which showed multiple enlarged lymph nodes above and below the diaphragm. His initial complete blood cell (CBC) count was hemoglobin 12.8 g/dL, white cell count of 6.1 K/uL (which rose to 29.8 K/uL after a month) and platelet count of 164,000. He then underwent a whole body positron emission tomography (PET-CT scan), which showed multiple enlarged retroperitoneal lymph nodes (maximum size 7.7 cm with a maximum standardized uptake value of 5.8). An axillary lymph node biopsy was suggestive of small lymphocytic lymphoma (SLL). It also showed lambda light chain restricted, CD19, CD23, dim CD5, dim CD20 expressing monoclonal B cells with negative FMC7 and CD10 and ill-defined proliferation centers. A bone marrow (BM) biopsy and peripheral blood flow cytometry were not performed at the time of diagnosis. Patient was diagnosed as chronic lymphocytic leukemia (CLL)/SLL. He then received 6 cycles of fludarabine, cyclophosphamide, and rituximab (FCR) at another hospital (last cycle of chemotherapy was administered three months prior to current presentation) and achieved a partial response (based on a two month old PET-CT scan report). Three years ago (2 years prior to the diagnosis of CLL/SLL) the patient received therapy with etanercept for 5 years for rheumatoid arthritis. His physical examination revealed an ulcerated growth in the right oropharyngeal area, bulky bilateral cervical lymphadenopathy (> 5 cm), and splenomegaly. His hemoglobin level was 9.2 g/dL, white cell count was 5.8K/uL, his platelet count was 60,000 /uL, and his serum lactate dehydrogenase (LDH) level was 665 IU/L (normal range, 313 to 618 IU/L). Peripheral blood polymerase chain reaction results for Epstein-Barr virus (EBV) were positive (58,475 copies/mL). Absolute numbers of CD3, CD4 and CD8 T cells were (1099, 228 and 882 UL respectively) with corresponding normal range (502-2373, 167-1672, 109-812 UL). Serum

immunoglobulin levels were normal and serology was negative for HIV. Bone marrow aspiration and biopsy were unremarkable. PET scan showed a FDG-avid mass at the base of the tongue extending inferiorly and occupying the vallecula. Extensive bulky FDG-avid lymphadenopathy was noted throughout the neck (more on the right side; **Fig 1A**) with a maximum standard uptake value (SUV) of 23. CT scan of the neck showed an exophytic lesion at the base of the tongue and left lateral oropharyngeal wall and bulky bilateral cervical lymphadenopathy (**Fig 1B**). CT scan of the abdomen showed enlarged preaortic lymph nodes (maximum diameter, 3 cm). An excisional biopsy of the oropharyngeal mass showed lymphoid tissue with large areas of geographic necrosis, a wide variation in cytological features: small lymphocytes, medium-size cells, large cells with irregularly shaped nuclei, numerous immunoblasts, and occasional Reed-Sternberg cells. Numerous histiocytes and small lymphocytes were present in the background (**Fig 1D**; Hematoxylin and eosin). No sheets of large cells were identified. In situ hybridization for EBV-encoded ribonucleic acid (EBER) showed strong, uniform EBER expression throughout the neoplasm (**Fig 1E**) especially in small lymphocytes and immunoblasts. LMP1 positive cells were infrequently seen (**Fig 1F**). Immunohistochemical staining showed CD30 positivity in immunoblasts and occasional Reed-Sternberg cells (**Fig 1G**). The Reed-Sternberg cells were negative for CD15 and strongly positive for CD20 (**Fig 1H**) and CD45. No aberrant co-expression of CD5 and CD20 was detected. Staining for CD79a and PAX-5 was positive, and staining for CD138 was negative. Flow cytometry immunophenotypic studies of the lymph node cell suspension showed a distinct population of B cells with immunoglobulin kappa light chain restriction (different from original CLL clone which was lambda restricted); these cells were also positive for CD22, CD38, and CD44 and negative for CD5, CD11c, CD10, CD20, CD43, CD200, FMC-7, and immunoglobulin lambda light chain. No morphological or immunophenotypic evidence of CLL was observed in the BM and LN analysis.

A working differential diagnosis of non-transplant, post FCR chronic immunosuppression-related EBV-associated polymorphous lymphoproliferative disorder (LPD) versus EBV-associated diffuse large B-cell lymphoma (DLBCL) was rendered. We recommended that the patient undergo chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) because of his acute presentation, severe symptoms and marked lymphadenopathy. However, the patient returned home. Nine days later, he experienced spontaneous regression of the B symptoms and bulky lymphadenopathy. Therefore, no treatment was given. CT scan after 3 months revealed further reduction in the size of the cervical lymph nodes (**Fig 1C**), and his performance status improved. A repeat PB for EBV RNA was not performed during remission. Patient is doing well and is under follow up for his CLL and LPD.

Patients with autoimmune diseases such as rheumatoid arthritis are prone to developing LPDs, ranging from lymphomas to atypical non lymphomatous LPD's.¹⁻⁴ In addition, the increasing use of biological agents (such as etanercept and rituximab) to treat autoimmune diseases and cancers may predispose patients to EBV-associated LPD.^{2,5} Defective germinal centers and follicular dendritic cells may predispose to lymphoid proliferation in these patients.⁶ In a study of 18 cases⁴ of immunomodulatory agent related LPD's, EBER

positivity was observed in 7/18 cases suggesting the association of EBV with atypical lymphoid tissue proliferation. However, all the 18 cases were receiving therapy with immunomodulatory agents for various autoimmune disorders at the time of development of LPD and none had a history of recent malignancy or chemo-immunotherapy. Histology of only one case out of seven from this series resembled our patient and this case (case-14) was receiving efalizumab therapy (anti-CD11a antibody) for psoriasis. In the present report we are emphasizing on chemo-immunotherapy related, non-transplant and non-lymphomatous EBV associated LPD in a patient with CLL. We are unclear whether a previous history of therapy with etanercept might have contributed to the current presentation. CLL is also strongly associated with immunosuppression⁷ and may predispose patients to EBV reactivation and accompanying LPDs. Our patient was treated with FCR recently and has also received etanercept in the past, both of which can predispose the patient for immunosuppression therefore creating a niche for EBV reactivation.

EBV-associated LPDs comprise the following conditions: EBV-associated DLBCL of the elderly, atypical iatrogenic immunosuppression-related LPD, infectious mononucleosis, post-transplant EBV-associated LPD, and EBV-associated Hodgkin lymphoma. It is critical to identify EBV-associated LPD early on, because of its similarity to age-associated DLBCL of the elderly.^{8,9} The prognosis and therapy of both the disorders is different. The histopathological features of both the conditions are similar and include predominant geographic necrosis and polymorphous morphology. Co-expression of CD10, IRF4/Mum1, and Bcl2 in the presence of monoclonal B cells points towards EBV-associated DLBCL of the elderly. In addition, EBV-associated DLBCL of the elderly is more frequent in immunocompetent patients, has higher CD20 expression in Reed-Sternberg cells, and is negative for CD15 and positive for CD30.^{10,11}

Initial presentation for our patient was similar to Richter's transformation. However, lack of large prolymphocytic cells in the BM or in lymphoid tissues, clonally unrelated lymphoid proliferation, mildly elevated LDH in serum and spontaneous remission of the lymph node mass excluded this diagnosis. Furthermore, histological differentiation between EBV-associated DLBCL of the elderly and EBV-associated immunosuppression-related LPD was difficult. Spontaneous remission of the LPD without therapy favored the diagnosis of immunosuppression and FCR related EBV-associated LPD. The slightly elevated LDH level and the negative CD10 also supported this diagnosis. EBV reactivation can closely masquerade a lymphoma (both clinically and histologically due to presence of monoclonal B cell expansion and multiple reactive immune cells in the lymphoid tissues). Another disorder that resembles both of these diseases is classic Hodgkin lymphoma in which CD15 is commonly expressed and CD20 is rarely detected.

Immunomodulatory agent related LPD in autoimmune disorders and post-transplant LPD are well described in the literature. However, post chemotherapy or chemo-immunotherapy related EBV associated LPD are hardly reported. We believe that with the increasing use of various monoclonal antibodies in combination with chemotherapy (e.g. FCR) in patients with cancer, clinicians and pathologists may more frequently observe this. Chemo-immunotherapy may further precipitate the preexisting quantitative and qualitative aspects of immune system of cancer patients and thus may propagate the EBV driven lymphoid

proliferation. Moreover, EBV-associated LPD should also be considered in the differential diagnosis for Richter's transformation. Early identification of EBV-associated LPD is essential because it closely resembles EBV-associated DLBCL of the elderly, for which chemo-immunotherapy is needed; furthermore, administration of chemo-immunotherapy may further aggravate the symptoms of EBV-associated LPD. Latency status of EBV in the affected lymphoid tissue is needed in large cohort of patients in further characterizing this type of EBV-associated LPD, akin to post-transplant LPD. EBER-positive cells significantly outnumbered LMP-1-positive cells indicating that the majority of cells have type I latency in this case while in patients with PTLD, LMP1 is positive along with EBER and other latency markers suggesting a type III latency. Our case highlights the significance of diagnosing EBV-associated LPDs, determining the need for therapeutic interventions and finally identifying post chemo-immunotherapy EBV associated LPD's. Precise mechanisms of this type of EBV associated lymphoid proliferation are not well understood.

Acknowledgments

Sarah Bronson for editing the report

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Figure 1. (A-H) – Diagnostic imaging and histopathologic features of iatrogenic EBV associated lymphoproliferative disorder in a patient with CLL

A) Positron emission tomography (PET) Scan of the patient at the time of initial presentation showing extensive bulky fludeoxyglucose (FDG)-avid lymphadenopathy (Right side>left side; see arrow) throughout the neck with a maximum standard uptake value (SUV) of 23 in the neck nodes. **B)** CT scan of the neck at the level of mandible showing bulky cervical lymph nodes and oropharyngeal lymphoid tissue and compression of trachea. **C)** CT scan of the neck after the patient achieved spontaneous remission showing marked reduction in the size of oropharyngeal lymphoid tissue and visible tracheal opening **D)** Hematoxylin and eosin (500 X magnification) of the cervical lymph node mass showing geographic necrosis, numerous polymorphous lymphocytes, occasional Reed-Sternberg cells and histiocytes. **E)** EBER (EBV encoded small RNA) by *in-situ* hybridization) showing diffuse EBER positivity in the lymph nodes (200 X magnification) **F)** LMP1 (latent membrane protein -1) stain was positive only in few cells in the lymph nodes (200X

magnification) **G**) Diffuse CD30 positivity on immunohistochemistry of the lymph nodes (500 X magnification) **H**) Occasional CD20 positive cells seen in the lymphoid tissue (500 X magnification).