Richter Syndrome: Chronic Lymphocytic Leukemia Transformation into Hodgkin's Disease

Ofir Zavdy MD[1], Gilad Twig MD PhD[1,2], Abraham Kneller MD[3], Gal Yaniv MD[4], Tima Davidson MD[5], Ginette Schiby MD[6] and Howard Amital MD MHA[1]

[1]Department of Medicine B, [2]Talpiot Medical Leadership Program, [3]Department of Hematology, [4]Department of Radiology, [5]Institute of Nuclear Medicine and [6]Institute of Pathology, Sheba Medical Center, Tel Hashomer, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

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For Editorial see page 646

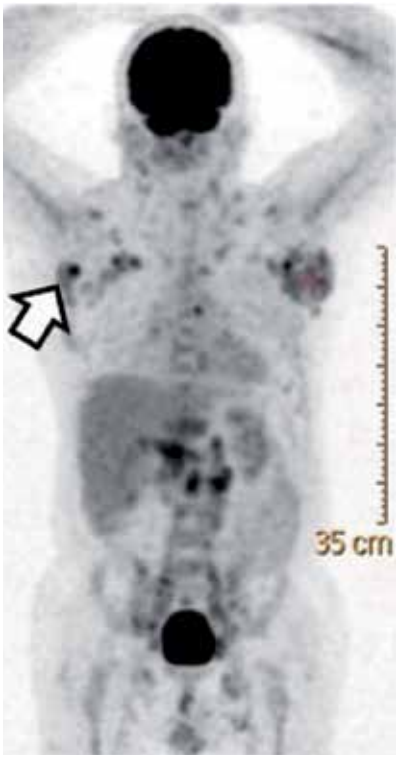
Richter syndrome is a clinical condition in which indolent chronic lymphocytic leukemia evolves into a more aggressive diffuse large B cell lymphoma. Maurice Nethaniel Richter first described this phenomenon in 1928, which was named the "Richter syndrome" in 1964 [1]. Due to the aggressive nature of the disorder, the clinical manifestations, prognosis and treatment differ from CLL [2]. Symptoms will usually include lymphadenopathy, the appearance of "B symptoms" and elevated levels of serum lactate dehydrogenase [2]. The incidence of Richter syndrome originating from CLL to diffuse large B cell lymphoma ranges between 2% and 8% of CLL patients [3].

Although uncommon, approximately 0.4% of CLL patients will experience transformation into Hodgkin's disease [3]. In the current communication we report on such an occurrence and elaborate on the possible effect of fludarabine therapy on this association.

PATIENT DESCRIPTION

A 53 year old Caucasian man was diagnosed with CLL in early 2005. The patient was asymptomatic and was not receiving any treatment until he underwent a splenectomy due to severe hemolytic anemia. Two years later his white blood cell count reached 300,000 cells/mm^3 and he presented with symptomatic axillary lymphadenopathy for which he received five courses of chemotherapy with fludarabine and cyclophosphamide. After 6 symptom-free months with a drop of his WBC level to 5000/mm^3, the patient reported the onset of excessive night sweats, intermittent nocturnal high fevers, and weight loss of more than 10 kg occurring within 5 months.

Figure 1. Coronal reformats of FDG-PET scan demonstrates enhanced metabolic activity in various lymph nodes and vertebrae bone marrow (big arrow)



An extensive infectious disease workup was negative. The blood tests revealed a normal WBC count, with a hemoglobin concentration below 7 g/dl, in the presence of a positive antiglobulin test (Coomb's assay) and elevated levels of serum lactate dehydrogenase. The patient began treatment with rituximab and corticosteroids. An F-FDG PET CT scan revealed a bilateral increase in the number and size of axillary lymph nodes with maximal nodes exceeding 20 mm in diameter with a marked uptake along the spine, sternum and several hypermetabolic areas of lymphadenopathy above and below the diaphragm [Figure 1].

An axillary lymph node biopsy demonstrated lymphoid tissue comprising sheets of small lymphocytic cells admixed with medium-size cells resembling prolymphocytes. In addition, there were large abnormal cells scattered with irregular nuclei and prominent nucleoli consistent with Reed-Sternberg cells [Figure 2A]. On immunostaining these cells were positive for CD30 [Figure 2B] as well as for in situ Epstein-Barr virus [Figure 2C], but negative for CD20, CD45 and CD15. Polymerase chain reaction was performed separately for the different portions of the lymph node and was consistent with a monoclonal B cell population. The morphological changes together

CLL = chronic lymphocytic leukemia

WBC = white blood cells

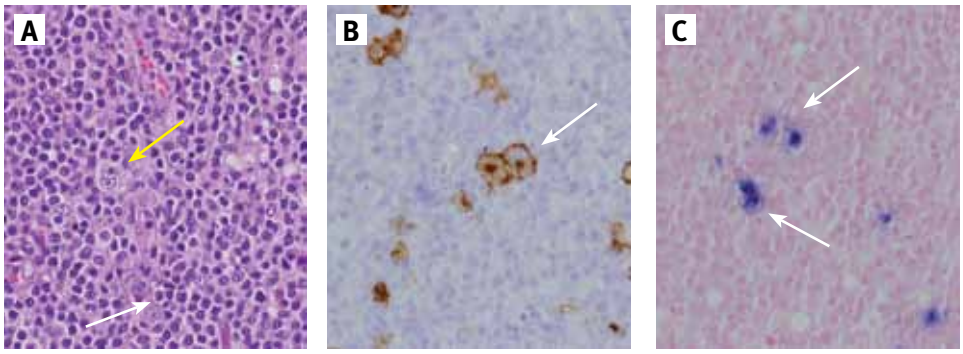


Figure 2. [A] A Reed-Sternberg Hodgkin's-like cell (marked by a yellow arrow) in the area of chronic lymphocytic leukemia which is rich in small B lymphocytes and prolymphocytes (green arrows) (H&E x400). **[B]** Hodgkin's cells immunostained positive for CD30 (membranous and Golgi stain) (CD30 x600). **[C]** Hodgkin's cells positive for in situ hybridization for EBV-encoded RNA (EBER) (nuclear stain). EBV in situ stain x600

with the phenotypical differences in the presence of EBV-positive Hodgkin's-like cells, established the diagnosis of CLL transforming into classical Hodgkin's lymphoma. Therapy with the ABVD protocol (adriamycin, bleomycin, vinblastine, dacarbazine) was begun and led to significant improvement of subsequent imaging findings.

COMMENT

In the past 40 years there have been fewer than 90 reported cases of the Richter syndrome Hodgkin's variant in the medical literature [3]. Several reports have underlined the possible causal relationship between Richter transformation and EBV infection, especially in the context of prior fludarabine treatment [3-5], which in itself increases the risk for transformation of CLL into Hodgkin's lymphoma [4]. One theory regarding this finding is that reduction of CD4+ and CD8+ T cells following therapy for CLL allows reactivation and proliferation of latent EBV infection, leading to the development of an aggressive lymphoma [5].

While the median reported half-time from diagnosis of CLL and Hodgkin's transformation was previously estimated to range between 2 and 4 years, our patient was diagnosed 7 years prior to the transformation [3]. However, he received five courses of fludarabine approximately 6 months before the transformation. This fact emphasizes the role of immunosuppression, EVB reactivation, and appearance of new systemic symptoms. This assumption is reinforced by the fact that the Hodgkin-like cells that were detected in the biopsy were CD30 positive and encoded EBV RNA. Interestingly, immunostaining and EBV studies that were performed on sections from a splenectomy that he underwent 4 years prior to the transformation failed to demonstrate similar findings, suggesting that the CD30-positive cells appeared in a later phase of his disease.

The findings in our report further strengthen the theory of a possible causality between fludarabine treatment, EBV and the Richter transformation to Hodgkin's lymphoma. Currently there are no formal guidelines on how to monitor the EBV viral load while administering fludarabine treatment to CLL patients. Clearly, further studies are necessary to address the role of preventive antiviral treatment based on viral load.

EBV = Epstein-Barr virus

Corresponding author:
Dr. H. Amital
Head, Dept. of Medicine B, Sheba Medical Center, Tel Hashomer 52621, Israel
Phone: (972-3) 530-2435, **Fax:** (972-3) 530-4796
email: Howard.Amital@sheba.health.gov.il

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"Force without wisdom falls of its own weight"

Horace (65-8 BCE) Roman poet and satirist during the time of Augustus

"A strong nation, like a strong person, can afford to be gentle, firm, thoughtful, and restrained. It can afford to extend a helping hand to others. It is a weak nation, like a weak person, that must behave with bluster and boasting and rashness and other signs of insecurity"

Jimmy Carter (born 1924), 39th U.S. President and Nobel laureate. He and his wife Rosalynn established the Carter Center in 1982, a non-governmental, not-for-profit organization that works to advance human rights. He travels extensively to conduct peace negotiations, observe elections, and advance disease prevention and eradication in developing nations