

Hodgkin's Lymphoma as a Unique Variant of Richter Syndrome

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Chronic lymphocytic leukemia is the most common type of adult leukemia in western countries. The clinical course of CLL patients is heterogenic. While some patients enjoy an almost normal life expectancy, others will suffer from a steep downhill course [1]. In the past, patient prognosis was based on clinical staging, but today the ability to predict the clinical outcome of patients with CLL has improved with the use of novel prognostic factors such as specific cytogenetic abnormalities, serum beta-2 microglobulin levels, immunoglobulin variable heavy chain mutation status, CD38 positivity and ZAP 70 positivity [2]. A fludarabine-containing chemoimmunotherapy regimen was shown to improve progression-free survival and overall survival in CLL and became the standard frontline therapy for physically fit patients [3].

Since CLL patients live longer, there is growing interest in the long-term adverse outcome of the disease and in the possible role that specific chemotherapy agents may have in promoting them. This includes Richter transformation. The transformation of CLL into an aggressive lymphoma was first described by M.N. Richter in 1928. Richter syndrome involves an aggressive clinical course that consists of sudden

progression in lymphadenopathy, the appearance/worsening of "B" symptoms, and elevated levels of lactate dehydrogenase, as well as histological features requiring a new tissue biopsy. The incidence of Richter syndrome in patients with CLL is 2% to 9%. Most frequently, CLL transforms into diffuse large B cell lymphoma, while in only 0.4% of patients will CLL transform to Hodgkin's lymphoma [4].

In the current issue of *IMAJ*, Zavdy et al. [5] describe a 53 year old CLL patient who was diagnosed with Hodgkin's lymphoma as a rare variant of Richter syndrome. In the classic Richter syndrome, the large B cells of the lymphoma are usually clonally related to the CLL, representing a true transformation of the indolent disease into an aggressive phase [6]. The Hodgkin variant of Richter syndrome, in contrast, is almost always unrelated to the CLL clone. Nevertheless, since the incidence of Hodgkin's lymphoma among patients with CLL is approximately eight times higher than in the general population [7], this suggests a causal relationship between the two diseases.

The case described by Zavdy et al. raises another interesting question: the role of fludarabine in the course and development of Richter syndrome. CLL has an inherent immune-suppressive nature, which can be further augmented by chemotherapy. This immune suppressive state is considered a plausible pathobiological explanation for the increased risk of Hodgkin's lymphoma among CLL patients. Studies that evaluated Epstein-Barr virus status in Hodgkin's transformation of CLL, either by staining for latent membrane protein 1 (LMP1) on immunohistochemistry or by in situ

hybridization of EBV-encoded RNA transcripts, demonstrate that most cases of this "secondary" Hodgkin's lymphoma (~70%) are EBV-positive. EBV-LMP1 activates multiple signaling pathways to inhibit apoptosis and transform B cells, including the NF- κ B pathway [8].

It is interesting that the majority of Hodgkin variants of Richter syndrome are of the mixed cellularity and lymphocyte-depletion histological subtypes, which are strongly associated with immune deficiency and are EBV-associated, while these subtypes comprise only a minority of de novo Hodgkin's lymphoma cases [8].

Fludarabine, a pivotal drug in the treatment of CLL patients, is a purine analog with a potent and lasting inhibitory effect on T cells. Thus, although causality is hard to establish due to the rarity of Richter syndrome, fludarabine may promote the transformation of CLL to Hodgkin's. The clinical outcomes and prognosis of this variant of Richter syndrome are worse than seen in de novo Hodgkin's lymphoma, with an overall response rate of 44% and a median overall survival duration of 0.8 years [4].

Since many CLL patients today are followed in the community, the treating physicians are advised to be alert to possible changes in the indolent course of the disease. Early detection of Richter syndrome and prompt intervention are crucial and may affect patients' outcome.

The present discussion also highlights the current dilemma: novel therapies hugely improve the disease course and prognosis, but long-term iatrogenic adverse effects are emerging with greater vigor. This

CLL = chronic lymphocytic leukemia

EBV = Epstein-Barr virus

calls for a concerted effort to seek a more effective and less toxic treatment for CLL.

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Capsule

Activation of the Nlrp3 inflammasome in infiltrating macrophages by endocannabinoids mediates beta cell loss in type 2 diabetes

Type 2 diabetes mellitus (T2DM) progresses from compensated insulin resistance to beta cell failure resulting in uncompensated hyperglycemia, a process replicated in the Zucker diabetic fatty (ZDF) rat. The Nlrp3 inflammasome has been implicated in obesity-induced insulin resistance and beta cell failure. Endocannabinoids contribute to insulin resistance through activation of peripheral CB₁ receptors (CB₁R) and also promote beta cell failure. Jourdan et al. show that beta cell failure in adult ZDF rats is not associated with CB₁R signaling in beta cells, but rather in M1 macrophages infiltrating into pancreatic islets, and that this leads to activation of the Nlrp3-ASC inflammasome in

the macrophages. These effects are replicated in vitro by incubating wild-type human or rodent macrophages, but not macrophages from CB₁R-deficient (*Cnr1*^{-/-}) or *Nlrp3*^{-/-} mice, with the endocannabinoid anandamide. Peripheral CB₁R blockade, in vivo depletion of macrophages or macrophage-specific knockdown of CB₁R reverses or prevents these changes and restores normoglycemia and glucose-induced insulin secretion. These findings implicate endocannabinoids and inflammasome activation in beta cell failure and identify macrophage-expressed CB₁R as a therapeutic target in T2DM.

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Eitan Israeli

Capsule

Bacteria activate sensory neurons that modulate pain and inflammation

Nociceptor sensory neurons are specialized to detect potentially damaging stimuli, protecting the organism by initiating the sensation of pain and eliciting defensive behaviors. Bacterial infections produce pain by unknown molecular mechanisms, although they are presumed to be secondary to immune activation. Chiu et al. demonstrated that bacteria directly activate nociceptors, and that the immune response mediated through TLR2, MyD88, T cells, B cells, and neutrophils and monocytes is not necessary for *Staphylococcus aureus*-induced pain in mice. Mechanical and thermal hyperalgesia in mice is correlated with live bacterial load rather than tissue swelling or immune activation. Bacteria

induce calcium flux and action potentials in nociceptor neurons, in part via bacterial *N*-formylated peptides and the pore-forming toxin α -hemolysin, through distinct mechanisms. Specific ablation of Nav1.8-lineage neurons, which include nociceptors, abrogated pain during bacterial infection, but concurrently increased local immune infiltration and lymphadenopathy of the draining lymph node. Thus, bacterial pathogens produce pain by directly activating sensory neurons that modulate inflammation, an unsuspected role for the nervous system in host-pathogen interactions.

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Eitan Israeli

“Anyone who has ever struggled with poverty knows how extremely expensive it is to be poor”

James Baldwin (1924- 1987), American novelist, essayist, playwright, poet and social critic, whose essays, such as the collection *Notes of a Native Son*, explore palpable yet unspoken intricacies of racial, sexual, and class distinctions in western societies, particularly in mid-20th century America