Are Patients with X-Linked Agammaglobulinemia at Increased Risk of Developing Acute Lymphoblastic Leukemia?

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In the current issue of Journal of Clinical Immunology, Hoshino et al. describe a patient with X-linked agammaglobulinemia (XLA) who developed acute lymphoblastic leukemia at 10 years of age [1]. It is worth noting that this patient did not have a null mutation in BTK; instead he had an amino acid substitution at codon 307, within the SH2 domain. This mutation has been described previously in a patient with typical XLA [2]. As is often true in XLA patients with amino acid substitutions, the patient described by Hoshino et al. had somewhat milder disease characterized by slightly higher serum IgM than is typical, and slightly more B cells than is usually seen in patients with XLA [3]. The coincidence of XLA and ALL brings up the possibility that impaired or absent BTK function plays a role in the initiation or progression of ALL, a leukemia originating in B cell precursors.

Somatic activating or inactivating mutations in BTK are rarely seen in untreated patients with any type of leukemia. Mice that are transgenic for a constitutively active variant of BTK, E41K, do not have leukemia but instead have a block in B cell differentiation that is more severe than that seen in BTK deficient mice [4]. Nevertheless, there is no question that normally expressed, non-mutant BTK plays a major role in most leukemias and lymphomas that involve later stages of B cell development. Small molecule inhibitors of BTK have proven to be very useful in the treatment of most patients with chronic lymphocytic leukemia, and some patients with non-Hodgkins lymphoma, mantle cell lymphoma or myeloma [5, 6]. The mechanism of action of these drugs appears to be the combined effects of inhibition of the BCR and NFκB pathways,

disruption of integrin mediated adhesion, and diminished responses to cytokines, culminating in apoptosis. Minimal side effects have been reported.

It has been suggested that BTK might act as a tumor suppressor in ALL [7–10]. Abnormally spliced BTK has been seen in primary leukemic cells from patients with newly diagnosed ALL [7, 8]. Mice that are deficient in BLNK, a scaffold protein that links BTK to its downstream target, PLCγ2, have an increased incidence of leukemia [9], and mice that are doubly mutant in BLNK and BTK have an even higher incidence of leukemia [10]. However, it is important to look at the epidemiologic features of both ALL and XLA. The incidence of ALL is estimated to be approximately 1 in 2000 children under 20 years of age [11]. Although XLA is a rare disorder, occurring with a frequency of about 4 per million births [12, 13], it is a well characterized immunodeficiency that has been recognized for more than 60 years [14]. Over 600 different mutations in BTK have been reported [15] and it is likely that several thousand patients have been identified since BTK was recognized to be the causative gene in XLA in 1993 [16]. The patient described by Hoshino et al. represents the first reported case of ALL in XLA. By contrast, at least 10 cases of adenocarcinoma of the gastrointestinal tract have been reported in patients with XLA, mostly in adolescents or young adults [17]. The increased incidence of gastrointestinal malignancy, which probably occurs in less than 1% of patients with XLA, is likely to be due to chronic infection and increased cell turn over rather than a direct effect of the mutations in BTK. If the lack of BTK predisposed to ALL, one might expect that patients with the most severe mutations, might be more vulnerable than the patient with a milder mutation in BTK described by Hoshino et al. Taken together, these observations suggests that if there is an increased risk of ALL in patients with XLA, the increase must be very small.

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