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Richter syndrome: pathogenesis and management

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ABSTRACT

Richter syndrome (RS) is the development of an aggressive lymphoma in patients with a previous or concomitant diagnosis of chronic lymphocytic leukemia (CLL). The incidence rate RS is ~0.5% per year of observation. Two biomarkers (*NOTCH1* mutations and subset 8 configuration of the B-cell receptor) may help identifying CLL patients at risk of RS to be considered for close monitoring and a careful biopsy policy. In the presence of clinical features suspicious of RS, diagnosis of transformation and choice of the site of biopsy may take advantage of fluorine 18 fluorodeoxyglucose (^{18}FDG) positron emission tomography (PET)/computed tomography (CT). Molecular lesions of regulators of tumor suppression (*TP53*), cell cycle (*CDKN2A*), and cell proliferation (*NOTCH1*, *MYC*) overall account for ~90% of RS and may be responsible for the aggressive clinical phenotype observed in this disease because of the combined effect of chemoresistance and rapid disease kinetics. The prognosis of RS is generally highly unfavorable. However, the pattern of survival is not homogeneous and the most important prognostic factor is the clonal relationship between the CLL and the aggressive lymphoma clones. Rituximab-containing polychemotherapy represents the backbone for induction treatment in RS. Younger patients who respond to induction therapy should be offered stem cell transplant (SCT) to prolong survival.

1. Definition of Richter syndrome

The 2008 World Health Organization (WHO) Classification of Hematopoietic Tumors defines Richter syndrome (RS) as the development of an aggressive lymphoma in patients with a previous or concomitant diagnosis of chronic lymphocytic leukemia (CLL) [1]. The WHO classification recognizes two distinct pathologic variants of RS, namely the diffuse large B-cell lymphoma (DLBCL) variant and the Hodgkin lymphoma (HL) variant [1].

Morphologically, the DLBCL variant of RS consists of confluent sheets of large neoplastic B lymphocytes resembling either centroblasts (60%–80% of cases) or immunoblasts (20%–40% of cases) [2–4]. Importantly, CLL cases presenting with numerous proliferation centers and an increased proportion of prolymphocytes and paraimmunoblasts, but lacking clear cut features of DLBCL, should not be diagnosed as RS [5]. Phenotypically, tumor cells invariably express CD20, while CD5 expression is present in only a fraction (~30%) of cases, and CD23 expression is even more rare (~15% of cases) [2]. Based on immunophenotypic markers of de novo DLBCL, most cases of the DLBCL variant of RS (90%–95%) have a post-germinal center phenotype (IRF4-positivity), whereas only 5%–10% display a germinal center phenotype (CD10 and/or BCL6 expression) [2–4].

The HL variant of RS can be further subdivided in two pathologic types [6,7]. Type 1 usually mimics the pathologic features of classical HL, being characterized by the presence of mononuclear Hodgkin cells and multinuclear Reed-Sternberg cells residing in a polymorphous background of small T cells, epithelioid histiocytes, eosinophils, and plasma cells. In type 1, the Hodgkin-Reed-Sternberg cells show the typical CD30$^+$/CD15$^+$/CD20$^-$ phenotype. In contrast, type 2 is characterized by the presence of Hodgkin-Reed-Sternberg-like cells in a background of CLL cells lacking the polymorphous reactive infiltrate of classic HL. In type 2 transformation, Hodgkin-Reed-Sternberg-like cells express both CD30 and CD20 but lack CD15.

Based on the analysis of the rearrangement of *IGHV-D-J* genes, most (~80%) of the DLBCL variants of RS are clonally related to the preceding CLL phase, thus representing true transformation [2–4]. In contrast, only a fraction (~40%–50%) of the HL variants of RS are clonally related to CLL [2,8–10]. Consistently, a number of RS (~20% showing a DLBCL morphology and ~50%–60% showing a classical HL morphology) harbor distinct *IGHV-D-J* rearrangements compared to the paired CLL, representing de novo lymphomas arising in a CLL patient [2–4,8–10].

2. Epidemiology of Richter syndrome

Information about the prevalence of RS in unselected CLL populations mainly derives from analyses of retrospective cohorts of patients. The large variation in the prevalence of RS (1%–23%) in

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