Angioimmunoblastic T-Cell Lymphoma (AILT): A Unique Clinical and Pathobiological Entity

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While cardiac involvement by lymphoma is relatively uncommon, cardiac tamponade as the presenting primary manifestation of lymphoma – as described in the case reported by Lafras et al. in this journal [1] – is extremely rare. For both B- and T-cell lymphomas, cardiac involvement at initial diagnosis almost always occurs in patients with widely disseminated disease and in those whose tumor biology is associated with extranodal involvement [2]. This case of cardiac tamponade is interesting in that the underlying histology was angioimmunoblastic T-cell lymphoma (AILT) and the co-existence of malignant mesothelioma is also intriguing. AILT is a complex lymphoproliferative disorder that represents a distinct type of peripheral T-cell lymphoma (PTCL) and is characterized by unique clinical and biological features. Cardiac involvement by lymphoma is more common with diseases that involve extranodal sites and are associated with immunodeficiency – both are features of AILT.

Characteristic features of AILT at presentation include lymphadenopathy, hepatosplenomegaly, skin rash, constitutional symptoms and often bone marrow infiltration [3]. The disease tends to afflict older patients as is the case with other peripheral T-cell lymphomas. Signs of B-cell hyperactivity such as polyclonal hypergammaglobulinemia as well as hematological abnormalities such as Coombs-positive hemolytic anemia are also often present. AILT is associated with immunodeficiency and patients frequently (as reported in this case) succumb to infectious complications rather than progressive lymphoma. While Epstein Barr virus (EBV) and B-cell dysregulation are implicated in the pathogenesis of this disease, their exact mechanistic roles are not fully understood and indeed, the putative cell of origin of AILT remains a controversial question. Recently, the chemokine CXCL13 has been demonstrated to be over-expressed by the cells of AILT and this, in addition to the fact that the neoplastic T cells of AILT express CD4, CD10 and sometimes BCL-6 suggests that it is derived from follicular helper T cells (T_{FH}) [3–6]. This derivation is also sup-

ported by the results of recent gene expression profiling studies that demonstrate over-expression of several genes characteristic of follicular T helper cells [7].

Regarding the role of EBV in the pathogenesis in AILT, what is interesting is that EBV positive B cells are almost universally present within AILT [8]. While it was originally believed that EBV reactivation in AILT was a result of decreased immune surveillance, the fact that EBV positive B cells are found very early in the course of the disease is against this hypothesis. It is possible that EBV may play a pivotal role in the early pathogenesis of AILT by activating T_{FH} cells [3].

Another recent interesting development in the understanding of the biology of AILT has been the demonstration that vascular endothelial growth factor A (VEGF-A) is highly expressed in this disease [9]. VEGF-A has been shown to play an important role in tumor angiogenesis, particularly in solid tumors. A recent small study showed that high VEGF-A levels were related to extranodal involvement and correlated with an adverse clinical outcome in AILT [9].

The outcome of patients with AILT receiving conventional chemotherapy has been very disappointing with median survivals of only 36 months and 5-year survival rates of between 30 and 35% [3]. These poor outcomes have led to interest in the development of novel approaches for this disease, that use immunomodulatory and antiangiogenic agents. For example, there have been promising responses to single-agent cyclosporine – cyclosporine may mediate its effect by the inhibition of deregulated T-cell activation through the calcineurin – nuclear factor of activated T-cell signaling pathway [10]. The effects of this may be to reduce the production of various cytokines including interleukin 2 and tumor necrosis factor and in this way cyclosporine may alter the immune dysregulation associated with this disease. Angiogenesis inhibition is also an interesting strategy for this disease and one report demonstrated good efficacy of bevacizumab [11].

In conclusion, novel therapeutic approaches including the interesting efficacy of immunomodulation in AILT highlight the important role of immune deregulation in the disease's pathogenesis. Though much of the pathobiology of AILT remains to be unraveled, there has been considerable recent progress in

the understanding of this disease, and it is likely that optimal therapy of this disease will ultimately require a combination of conventional chemotherapy with the addition of novel immunomodulatory strategies.

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