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Editorial

Gray Zone Lymphoma: Diagnosis and Treatment

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Gray zone lymphoma is a disease at the interface of Hodgkin's and Non-Hodgkin's lymphomas. Considerable progress has been made regarding the origin of the neoplastic cell in classical Hodgkin's disease, the Reed-Sternberg cell. Recent studies show it is a B cell in almost all cases [1]. However, both clinical and biologic overlap should occur if Hodgkin's disease is derived from an altered B lymphocyte [2]. In a similar way, synchronous lymphomas of discordant histologies can involve a combination of Hodgkin's disease and Non-Hodgkin's lymphoma. Some of the first meta-chronous lymphomas described involved the late presentation of lymphoma after Hodgkin's disease. Hodgkin's disease and Non-Hodgkin's lymphoma have long been considered as distinct disease entities based on morphology, immunophenotyping, clinical course and response to therapy, however, recent observations suggest that these disorders may be more closely related than before. Therefore, the term gray zone should be limited to those cases in which morphologic, biologic and clinical features suggest overlap between Hodgkin's disease and Non-Hodgkin's lymphoma [3].

In gray zone lymphoma cases, the histologic and immunophenotypic features are transitional between nodular sclerosis Hodgkin's disease and mediastinal large B-cell lymphoma. In some case the histology is composite, with some areas resembling nodular sclerosis Hodgkin's disease and other areas showing sheets of large B cells characteristics of mediastinal large B-cell lymphoma. Immunophenotypically, the features also are intermediate. Scattered Reed-Sternberg like cells are CD30+, but CD15 positivity is more inconsistent. CD30 is also expressed in mediastinal large B cell lymphoma [4].

Nodular sclerosis Hodgkin's disease and mediastinal large B-cell Non-Hodgkin's lymphoma are negative for immunoglobulin expression; thus, studies of immunoglobulin are non-informative [5]. Nodular sclerosis Hodgkin's disease and mediastinal large B-cell lymphoma share a number of molecular characteristics, such as REL amplification and gain on chromosome 9 suggesting molecular overlap as well [6].

Synchronous lymphomas may be defined as the simultaneous occurrence of two lymphoma subtypes within a single patient. These may be further distinguished by presentations within the same anatomic site, termed composite lymphoma, and presentation in different sites, termed discordant lymphoma.

Regarding metachronous lymphoma, patients with a history of lymphoma are at increased risk of developing a second, clonally unrelated lymphoma. Most cases are lymphoma after Hodgkin's disease and EBV-positive diffuse large cell lymphoma after angioimmunoblastic T-cell lymphoma.

Treatment recommendations for gray zone lymphomas must be derived from an understanding of their biology and natural history, due to the lack of prospective clinical trials. Clinically, many cases present in mediastinal nodes, and as such, the clinical presentation is not helpful in the differential diagnosis of nodular sclerosis Hodgkin's disease and mediastinal large B-cell lymphoma [7]. However, a superior vena caval syndrome is more common in meiastinal large B-cell lymphoma. Based on the former findings, the Groupe d'Etudes des Lymphomes de l'Adultes (GELA) reviewed 2855 cases between 1987 and 1993 and found that Doxorubicin-based regimen is favorable for aggressive diffuse large cell lymphoma in combination with Rituximab [8]. GELA has had a successful experience with etoposide, vincristin, doxorubicin, cyclophosphamide

and prednisone (EPOCH)-Rituximab regimen without radiation in mediastinal gray zone lymphoma and mediastinal large B-cell lymphoma [9]. Methotrexate-leucovorin, adriamycin, cyclophosphamide, oncovin, prednisone and bleomycin (MACOP-B) is an alternative chemotherapy regimen with activity in mediastinal large B-cell lymphoma [10]. Although it is unknown whether radiation can be avoided in MACOP-B and Rituximab, however, radiation consolidation should be used in all cases with localized disease in which there is an inadequate response to chemotherapy, as judged by CT and PET scans.

In synchronous lymphomas, transformation of low grade lymphoma to an aggressive large B-cell lymphoma, best illustrated by follicular lymphomas, comprises the majority of composite and discordant lymphomas. In such cases, treatment is directed toward controlling the most aggressive lymphoma subtype by a doxorubicin-based regimen [11].

In Metachronous lymphomas, the most common event is the late development of Non-Hodgkin's lymphoma after the curative treatment of Hodgkin's disease, although the converse occurs as well. Clinically, treatment is directed toward the most recent lymphoma. Anecdotally, the clinical outcome of these late lymphomas appears worse than similar histologists that present de novo and raises the question whether more aggressive treatment should be used such as stem cell transplant consolidation.

In conclusion, Hodgkin's disease and Non-Hodgkin's lymphoma occur together more frequently than expected and these associations support the lymphoid origin for the malignant cell of Hodgkin's disease raising the question about the clonal relationship between certain forms of classical Hodgkin's disease and Non-Hodgkin's lymphoma. Data also support the concept that typical Hodgkin's disease may be an altered lymphoid malignancy, with secondary transformation by a virus such as EBV.

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