Academic Journal of Cancer Research 2 (1): 40-50, 2009
ISSN 1995-8943

Significance of Immunologic Markers in the Diagnosis of Lymphoma

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Abstract: The malignant lymphomas with indolent course present numerous diagnostic controversies, the frequent involvement of viral etiopathogeny, which can be followed up serologically, making these lymphomas an ideal topic for further study. The phenotypical and genetic heterogenity of the lymphomas make it difficult to elucidate the molecular mechanisms which concur in initiation and growth of these neoplasms. Therefore, the classification, diagnosis and therapeutic management of these patients have been frequently controversial and inadequate. Lymphocytes are characterized by membrane markers which, in part, reflect biological and functional activity. This is particularly true for T lymphocyte subsets identified by monoclonal antibodies. The B lymphocytes can be identified but in a more general manner. It has been proposed that the use of these markers will aid in the differential diagnosis of a variety of lymphomas. In this context, the existing new cytogenetic and immunological findings were discussed.

Key words:

INTRODUCTION

What is lymphoma?: Lymphoma, a cancer of the lymphocytes, occurs when cells grow abnormally and out of control. Lymphoma usually begins in a lymph node, but it can also begin in the stomach, intestines, skin or any other organ [1,2]. The World Health Organization recognizes three major categories of lymphoid neoplasms: [1] B-cell neoplasms; [2] T-and natural killer (NK)-cell neoplasms; and [3] Hodgkin's lymphoma [3].

Hodgkin's disease: This type of cancer can spread throughout the lymphatic system, affecting any organ or lymph tissue in the body. Hodgkin's disease usually affects people in their late 20s or older than 50. Males get the disease more often than females, and whites are affected more often than people of other races. The disorder strikes about 5 in every 100,000 people. Hodgkin's disease (HD) is characterized by malignant cells known as multinucleated Reed-Sternberg (RS) and mononucleated Hodgkin (H) cells, which comprise less than 1% of the tumor mass and the remaining cells are benign infiltrating T-and B-lymphocytes, monocytes, eosinophils, macrophages and dendritic cells (DC).[4] Molecular studies have shown that the majority of H and RS cells are derived from the germinal center B lymphocytes and in rare cases, Tlymphocytes [5,6]. This is considered to be the most curable of all the blood cancers. With proper treatment, about 80 % of patients survive five years or longer. Patients diagnosed with Stage I disease have more than a 90 % chance of living 10 years or more. Those diagnosed in Stage IV have a 50 % chance of living 10 years or more [7].

Non-Hodgkin's Lymphoma: Non-Hodgkin's Lymphoma (NHL) are a heterogeneous group of malignancies of the lymphoid system that account for approximately 55,000 to 60,000 new cases and approximately 19,000 deaths per year. Non-Hodgkin's lymphoma is the fifth most common cancer in the United States. It is the eighth most common cause of cancer deaths in males and the seventh most common cause of cancer deaths in females [8]. The incidence of NHLs has nearly doubled during the past three decades. NHLs are divided primarily into two main categories based on their rate of growth ie aggressive and indolent. Within these two groups are various subtypes that have various clinical features [9].

Most lymphoma are Non-Hodgkin's lymphoma. In adults, non-Hodgkin's lymphoma affects males more than females and often occurs between the ages of 60 and 70. Whites are affected more often than people of other races [8]. The disorder affects about 16 in every 100,000

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people or about 45,000 people in the United States alone. For unknown reasons, this cancer has been becoming more common. [10]

For patients with NHL, the chance of survival depends on the grade and stage of cancer, overall health, and response to treatment. Between 50% and 80% of patients survive five years or more. The higher-grade aggressive types of lymphoma are more likely to be cured with chemotherapy, but this form of cancer can be fatal. Lower-grade lymphomas, while usually not curable, often have longer average survival times, with mean survival reaching 10 years in some cases. Most children respond well to treatment, even though children tend to have the higher-grade, aggressive types of non-Hodgkin's lymphoma. As many as 70% to 90% of children survive five years or more [11].

Different Types of non Hodgkin's Lymphoma and Their Occurrence: NHLs are broadly classified as B-cell or T-cell lymphomas, depending on the lymphocyte lineage that gave rise to the malignancy. B-cell lymphomas represent approximately 90 % of NHLs, whereas T-cell lymphomas represent approximately 10 % [12]. NHL occurs more commonly in males, and whites are affected more often than blacks. The incidence of NHL increases with age. Approximately 2.4 cases per 100,000 people occur in 20-to 24-year-old individuals. The rate increases more than 18 times to 44.2 cases per 100,000 by age 60 and 40-fold to more than 100 cases per 100,000 persons after age 75.[8] NHL is known to be associated with chronic inflammation diseases such as Sjogren syndrome, celiac disease, and rheumatoid arthritis [13]. Immune suppression has also been associated with an increased risk of developing lymphoma. Following a solid organ transplant, the risk of lymphoma is associated with the duration of immunosuppression and the drugs and dosages used.[14] In addition, infections with the human immunodeficiency virus (HIV) have been associated with a significantly elevated risk of NHL [15,16].

Because NHL is not a single disease, but a group of diseases, the specific type of lymphoma must be classified given that treatment varies with each type of lymphoma. Lymphomas are classified with the use of the World Health Organization (WHO) classification system. This classification system is based on cytology, immunophenotype, and genetic and clinical features. The WHO recognizes three major categories of lymphoid neoplasms: [1] B-cell neoplasms; [2] T-and natural killer (NK)-cell neoplasms; and [3] Hodgkin's lymphoma. Both lymphomas and lymphoid leukemias are included in the WHO classification. The WHO classification primarily stratifies these neoplasms by lineage. Even within a designated histopathologic classification there is considerable biologic and clinical heterogeneity [3]. NHLs are broadly classified as B-cell or T-cell lymphomas, depending on the lymphocyte lineage that gave rise to the malignancy. B-cell lymphomas represent approximately 90% of NHLs, whereas T-cell lymphomas represent approximately 10% [12].

NHLs covers a far more broad range of cancer cells. There are about 30 different types of non-Hodgkin's lymphoma. These types of lymphoma can be difficult to diagnose as there are so many types. The most common subtypes of non-Hodgkin's lymphopma are T-cell lymphomas and B-cell lymphomas.[17] The T-cell lymphomas are further classified into extranodal natural killer/T-cell lymphoma, nasal type, cutaneous T-cell lymphoma, enteropathy type T-cell lymphoma, angioimmunoblastic T-cell lymphoma, anaplastic large T/null-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma and unspecified T-cell lymphoma. B-cell lymphomas are further classified into diffuse large B-cell lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, extranodal marginal zone B-cell lymphomas-mucosa-associated lymphoid tissue lymphomas, follicular lymphoma, mantle cell lymphoma, nodal marginal zone B-cell lymphoma, Burkitt's lymphoma, hairy cell leukemia, primary central nervous system lymphoma, splenic marginal zone B-cell lymphoma, lymphoplasmocytic lymphoma and primary mediastinal B-cell lymphoma.

In adulthood, adult non-Hodgkin's lymphoma is classified by the size, type and distribution of cancer cells in the lymph nodes. The three types are low grade (slower growing), intermediate grade, and high grade (aggressive). Low-grade lymphomas include small-lymphocytic lymphoma, follicular small-cleaved-cell lymphoma, and follicular mixed-cell lymphoma. Intermediate-grade lymphomas include follicular large-cell lymphoma, diffuse small-cleaved-cell lymphoma, diffuse mixed lymphoma, and diffuse large-cell lymphoma. High-grade lymphomas include immunoblastic lymphoma, lymphoblastic lymphoma, and small noncleaved (Burkitt's and non-Burkitt's) lymphoma.

In childhood, childhood NHLs include lymphoblastic lymphoma, large-cell lymphoma, and small-noncleaved-cell lymphoma (including Burkitt's and non-Burkitt's lymphomas). It is notable that high-grade (aggressive) non-Hodgkin's lymphomas usually affect children and young adults.

Factors That May Contribute to the Development of Lymphoma: Environmental factors: Recent studies show a possible link between lymphoma and exposure to certain chemicals, herbicides and insecticides. Genetic factors: Studies indicate that patients with certain genetic (inherited) immunodeficiency disorders, such as Wiskott-Aldrich syndrome, may have an increased risk of developing lymphoma. Viral infections: Research suggests links between lymphoma and certain viruses, such as the Epstein-Barr virus and HIV [18,20]. Patients infected with HIV, especially those with AIDS, also are more likely to get both Hodgkin's and non-Hodgkin's lymphoma [12,21,22].

Symptoms of Lymphoma and Diagnosis: The main symptom of both Hodgkin's and non-Hodgkin's lymphomas is swelling of lymph nodes in the neck, under the arms, or in the groin. Other symptoms can include fever, night sweats, fatigue, abdominal pain, unexplained weight loss and itchy skin. Because swollen lymph nodes caused by lymphoma usually are painless, lymph nodes may get larger slowly over a long time before the patient notices. Also, the fever commonly associated with lymphoma may appear and disappear for several weeks and the unexplained weight loss caused by certain lymphomas may continue for months before the patient seeks medical help [12,9].

When trying to diagnose lymphoma, doctors may use any of the following options: Examination of the patient's medical history, thorough physical examination looking for enlarged lymph nodes, liver and/or spleen, blood testing to determine liver and kidney functionality and biopsy (inserting a needle to withdraw a very small amount of tissue from internal organs) for further examination. If the physician suspects lymphoma based on medical history and the results of a physical examination then blood tests and a lymph node biopsy are needed. Other tests, including X-rays to look at the chest, bones, liver and spleen; a bone marrow biopsy; a gallium scan or a PET scan; and a computed tomography (CT) scan of the abdomen are also needed [23].

Diagnostic methods usually include chest x-ray; abdominal sonography; CT scans of the neck, thorax, abdomen, and pelvis; bone marrow aspiration; and bone marrow or skeletal radionuclide imaging. In some selected cases, additional procedures including MRI, positron emission tomography (PET), or a liver biopsy may be indicated [24].

The new technique now used is to look for particular molecules of a very specific type that are located on the surface of the cells. On the surface of the cells that carry the lymphoma, these cells are called lymphocytes, the molecules residing there are called CD markers (Cluster Differentiation). Researchers have so far managed to identify a little fewer than one hundred of these different types of cells and what makes them so useful is that when a normal lymphocyte change over time from newly built cells into mature cells, the markers also change. Cells that used to look the same when inspected under a microscope now were found to carry different CD markers leading to completely different behavior. A modern diagnose of lymphoma today always includes the identification of at least a few lymphoma markers. In order to group the actual lymphoma properly it is necessary to use a biopsy to grab a sample of the tissue and then perform a number of different CD marker trials on this. Expression of cell surface antigens and immunoglobulin proteins is dependent on the type of lymphocyte and its stage of differentiation or maturation. Analysis of these proteins in the malignant cells is useful diagnostically as well as for determining tumor histogenesis [9].

Chromosomal translocations and molecular rearrangements are commonly used to confirm the diagnosis. The most common chromosomal abnormality in NHL is the translocation of t(14;18)(q32;q21) that is found in 85 % of follicular lymphomas and 28 % of diffuse large B-cell lymphomas.[25] Additional oncogene rearrangements that can be diagnostically useful in lymphoma include t(8;14) or MYC in Burkitt's lymphoma, t(2;5), or ALK in anaplastic large-cell lymphoma, t(11;14) or bcl-1 in mantle cell lymphoma, and trisomy 3 or trisomy 18 in marginal zone lymphomas.

Stages: The stage of lymphoma is determined with the use of the Ann Arbor Staging Classification System, based on the distribution and number of involved sites, the presence or absence of extranodal sites, and the presence or absence of constitutional symptoms (B symptoms). NHL does not spread in an orderly fashion. In addition, other prognostic factors are important in predicting outcome. Therefore, the Ann Arbor staging system is not as useful in NHL as it is in Hodgkin's disease [26,27].

Once a diagnosis of lymphoma is confirmed, more tests will be ordered to determine the stage of the disease. The stage of lymphoma indicates how far the cancer has spread. The stages range from Stage I, in which the cancer is limited to one area, such as only one lymph node, to Stage IV, in which the cancer has spread extensively outside the lymph system and possibly to the bone

marrow or other organs. Occasionally, a procedure called laparoscopic surgery is done to help to determine the cancer's stage.[28]

Treatment: Most widely accepted combined-modality treatment for Hodgkin's lymphoma consists of two to four cycles of ABVD followed by 30 Gy of IF-RT, as standard treatment for early favorable stages [29,24]. Treatment for non-Hodgkin's lymphoma depends on the grade of lymphoma (low, intermediate or high), the stage of the disease, and the age and health of the patient.

In very early stages, low-grade (slow-growing) lymphomas sometimes can be cured with a combination of radiation and chemotherapy. Otherwise, treatment is based on when the symptoms develop and how bad they are. Early, aggressive therapy is not thought to improve survival for most low-grade lymphomas. In some cases of early-stage, low-grade lymphoma, the disease will be monitored, but no treatment will be given unless the disease gets worse. If a patient with early-stage, low-grade (slow-growing) lymphoma has symptoms, or if the disease has spread significantly, it can be treated with radiation therapy [30].

Advanced-stage, low-grade lymphoma may be treated in a variety of ways, ranging from chemotherapy with or without radiation therapy to a bone marrow transplant. In a bone marrow transplant, the patient's bone marrow cells are killed and then cancer-free bone marrow cells are injected.

For higher-grade lymphomas, cure is possible in 40 % to 50 % of cases. The main treatment is chemotherapy. Radiation also is used sometimes. Intermediate-grade lymphoma may be treated with a combination of chemotherapy drugs. More advanced stages may require higher-dose chemotherapy and possibly a bone marrow transplant or stem cell transplant. In a bone marrow transplant, the patient's bone marrow cells are killed, and then cancer-free bone marrow cells are injected. Stem cells are immature cells that grow into blood cells. In a stem cell transplant, the patient's stem cells are removed and treated to kill the cancer before being injected back into the patient. Burkitt's lymphoma, a high-grade lymphoma, can be cured in 80 % of the cases with a combination of chemotherapy drugs.

If cancer returns in a person who has been treated for intermediate and high-grade lymphomas, he or she may be a candidate for a bone marrow or stem cell transplant. In recent clinical trials, radioimmunotherapy involves injecting antibodies with added radioactive iodine has been used to treat advanced, higher-grade lymphomas or those that keep returning after treatment [31].

Prevention: There is no definitive way to prevent Hodgkin's or non-Hodgkin's lymphoma. Taking precautions to avoid becoming infected with HIV may lower the risk [15,16]. It is not known whether avoiding certain chemicals will prevent lymphoma.

The Use of Immunologic Markers in the Diagnosis of Lymphoma: On the surface of lymphocytes, the cells that are transformed to lymphomas have been found to have unique and different molecules on their surface. These surface molecules are called markers, or more specifically, CD markers.[32] It was found that lymphomas that previously looked similar under the microscope had different markers on their surface.[33,35] When that happened, they acted like different diseases altogether. The work is still going on to catalog these and around 80 different markers have so far been found.

In the evaluation of a patient suspected of having lymphoma, lymphocyte marker studies may be essential for a correct diagnosis.[36]Although the histologic features are well described, there is considerable morphologic overlap with reactive lymphoid proliferations and other lymphomas. The specific phenotypic or molecular markers have been identified so far to assist the diagnosis that lead to right histologic diagnosis, providing the patient the chance of early treatment. CD 20 a transmembrane protein found on B-cell is found to be associated with 95 % of malignant lymphomas and CLL [37].

The appropriate staging and management of lymphomas greatly depend on an accurate pathological diagnosis and classification.[38] A modern diagnose of lymphoma symptoms will always include establishing the presence of at least a few lymphoma markers. In order to do this we need to inspect the molecules rather than the cells as was the case earlier. With the older method of inspecting cells in a microscope, only a few types of lymphomas could actually be distinguished. But as it showed to be the case, the same tumor type would behave different in different patients, which is what led research to move from cellular inspection down to molecular.

Today, the diagnosis of lymphoma simply isn't complete unless a couple of lymphoma markers are first identified. To put a particular lymphoma in the proper group, doctors often have to put biopsy tissue to a series of marker tests called 'immunohistochemistry'. The over expression of D1 cyclin is usually encountered in most human cancers.[39] Tumor cells had classical histomorphology as well as expression patterns of the tumor marker CD30, which is a cell surface antigen

expressed on HL.[40] OX40/CD134 expression was characteristic of tumors composed of activated CD41 T cells and was not seen in small cell T-cell lymphomas, lymphoblastic lymphomas, or other tumor types, including B-cell lymphomas or carcinomas suggesting that immunostaining for OX40/CD134 may be helpful in subclassification of peripheral T-cell lymphomas and that the patterns of TNF receptor family expression in these tumors may parallel those seen within non-neoplastic helper T-cell subsets.[72]

Immunologic Markers in the Diagnosis of Hodgkin's Lymphoma: The tumor necrosis factor receptor (TNFR) family member CD30 has been identified as a cell surface antigen expressed on Hodgkin's and Reed Stanberg cells.[42,43] HD tumor cells show constitutive nuclear factor (NF)-κB activity as their characteristic feature, suggesting a role for NF-κB in the pathogenesis of HL. Development of novel therapies and study of the pathophysiology of this disease requires a reliable tool for the diagnosis of HL derived from both B and T cells. Despite the diversity in clinical manifestations of HL, strong and constitutive NF-κB activation is a unique and common characteristic of HL cells in patients [44]. Previous studies in HD have demonstrated the association of elevated serum levels and expression of IL-6 with unfavorable prognoses, as well as associating advanced stage and presence of 'B' symptoms with poor survival[.45,46] Although expression of mCD83 by Hodgkin's cells has been reported [47] little is known concerning its expression by other malignant populations.

Immunologic Markers in the Diagnosis of non Hodgkin's Lymphoma: The biological markers of NHLs are distinguished into three categories: serological, immunophenotypic, and molecular markers. The clinical importance of biological markers in NHL is based on their support of morphologic diagnosis, their role in staging and prognostic assessment, and their contribution to monitoring minimal residual disease (MRD). The most important serological markers reflect the tumor load (beta-2 microglobulin, β2-M), proliferative activity (lactic dehydrogenase, LDH), and invasive potential of lymphomas (CA 125). LDH and β2-M are included as important prognostic parameters in widely used staging systems. Immunophenotypic analysis identifies specific markers of lineage (B or T-cells), maturation level, cell proliferation, and clonality. Results of immunophenotyping are particularly useful in low to intermediate-grade NHLs to support the morphologic diagnosis and facilitate the detection of MRD after treatment. The molecular markers are genetic lesions involved in the pathogenesis of some categories of NHL. Their use as markers for diagnosis is justified by the selective association with specific lymphoma categories: follicular, mantle cell, diffuse large cell, and anaplastic large cell lymphomas. Molecular lesions are the most specific and sensitive markers for evaluating MRD. Today the biological markers of NHL are widely employed for diagnosis, staging, and prognostic assessment. Their systematic use may complement clinical parameters in the stratification of NHL patients, who may thus become candidates for treatments of different intensity. The detection of MRD after first-line treatment identifies patients at high risk of relapse who require additional therapy to cure their disease.[48]

The majority of NHLs are of B-cell lineage, with less than 20% of cases being of T-cell lineage. The B-cell NHLs phenotypically correspond to normal cells in the mid stages of normal differentiation. More specifically, by their expression of B-cell activation antigens, these tumors are the neoplastic counterparts of normal activated B cells. The follicular lymphomas-including the small cleaved, mixed small and large cell, and large cell types, as well as the small non-cleaved cell (Burkitt's) lymphomas-represent malignant expansions of normal germinal center B cells by their expression of pan-B cell antigens, B-cell activation antigens, and CD10 (CALLA). The diffuse lymphomas also correspond to normal activated B cells. The small lymphocytic lymphomas express the low-affinity IL-2 receptor and CD5, both of which are induced on normal B cells following mitogen stimulation. The other diffuse B-cell NHLs similarly express activation antigens and resemble "transformed" B cells. The T-cell NHLs generally correspond to normal activated CD4+ T cells. These tumors-which include most peripheral T-cell lymphomas, cutaneous T-cell lymphomas, and HTLV-I-associated adult T-cell leukemias/lymphomas-express antigens induced on activated T cells, including IL-2 and transferrin receptors (CD25 and CD71, respectively), as well as HLA-DR. The lymphoblastic lymphomas, which are generally of T-cell lineage, phenotypically correspond to stages of intrathymic differentiation, often by their coexpression of CD4 and CD8, as well as expression of CD1. It remains controversial whether the immunophenotype of lymphoblastic lymphoma differs significantly from T-cell acute lymphoblastic leukemia. Since immunologic heterogeneity of NHL was first observed, attempts have been made to employ the data as a prognostic variable. Earlier studies suggested that lineage derivation or expression of markers of proliferating cells affected outcome in NHL. However, many of the

reports were often retrospective, included various histologies, and did not treat patients uniformly. More recent prospective studies with relatively uniformly treated patients, predominantly involving DLCL, suggest that certain immunologically defined subgroups may have significantly different clinical outcomes [49].

Recent studies have reported that in order to formulate a molecular diagnosis of mantel cell lymphomas (MCL), D1 cyclin expression real time testing is much more sensitive than t(11;14) rearrangements diagnosis, because the localization of the breakpoints on chromosome 11 in t(11;14) is highly variable [50].

Reproducible categorization of peripheral T cell lymphoma (PTCL) has been problematic, given the morphological and immunophenotypic heterogeneity typical of these tumors. Among nodal-based tumors, the most recent classification schemes recognize only anaplastic large-cell lymphoma (ALCL) and angioimmunoblastic lymphoma (AIL) as distinct subtypes of PTCL. The majority of the remaining PTCLs are composed of cases having a mature T-helper cell phenotype (CD45RO1CD41) with variable expression of markers of cellular activation. To date, immunophenotypic characterization of these tumors has not identified consistent differences that would be helpful in sub classification. The use of OX40/CD134 antibody (ie, ACT35) showed strong staining in paraffin embedded material processed in a variety of fixatives, making it a useful marker for the routine diagnosis of PTCLs. In contrast to some other commonly used antibodies directed against T-cell-associated markers (eg, CD45RO and CD43), ACT35 staining appears highly restricted to T cells. OX40/CD134 staining is likely to be particularly useful diagnostically in putative T-cell lymphomas in which the widely used pan-T-cell marker, CD3, is negative [51].

Flow cytometry is useful in classifying the specific subtype of lymphoma present. Core flow cytometry panel for the investigation of surface antigen expression in suspected mature B-cell malignancies include surface immunoglobulin-heavy and-light chains, CD79a, CD19, CD20, and CD22.[52] Additional antibodies (CD5, CD10, CD23, cyclin D1) are used to further delineate the subtype of lymphoma [12].

Earlier findings demonstrated that freshly isolated B cells from a subset of chronic lymphocytic leukemia (CLL) cases constitutively express CD40 ligand (CD40L, CD154), a member of the tumor necrosis factor family which is normally expressed by activated CD41 T cells and mediates T-cell-dependent B-cell proliferation and antibody production.[53] Recently the diagnosis of CLL is confirmed by fluorescence flow cytometry of the lymphocytes, which characteristically expresses cell surface antigens CD5, CD19, and CD23.[54] It has been found that the presence of elevated levels of CD83 is associated with a number of hematologic malignancies [76]. As most of the NHLs express CD22, it can be a promising target for immunotherapy [55].

Reports have shown that the neoplastic cells in most cases of AITL can be identified by aberrant expression of CD10. The presence of such a marker has provided the opportunity to establish objective criteria for the diagnosis of this disease, even in its early stage of evolution, as well as the ability to investigate the biologic characteristics of the neoplastic T cells [56].

A large number of studies have highlighted the expression of CD30 in ALCL, Reed Stanberg cells in Hodgkin's disease, and a minority of cases of large B-cell lymphoma and germ cell tumors [57,60].

The tumor necrosis factor (TNF) receptor family includes several important growth regulators that are expressed on T cells (eg, CD30, CD27, OX40/CD134, 4-1BB, FAS/CD95, and TNFRII/p80.[61,63] With the exception of CD30, the expression of these receptors in peripheral T-cell lymphomas has been studied in only a limited number of cases.[64,66] CD27, 4-1BB, and TNFR II are expressed on a number of different cell types and may therefore be diagnostically less useful in lymphomas. In contrast, OX40/CD134 is a receptor whose expression appears highly restricted to activated T cells [67,68].

Studies have been performed to evaluate the use of monoclonal antibodies (MAb-s) and surface immunoglobulin (sIg) analysis in a cell flow cytometer (CFC) as methods to identify and classify lymphomas. Results showed that the variety of hyperplasias and reactive follicular lymphadenopathies could not be characterized by the technique or application of CFC alone. Both B cell and T cell lymphomas could be recognized and differentiated by MAb-s and/or light chain monotypism using sIg's in a CFC, but morphologic and clinical information were required for diagnostic confirmation. Hodgkin's disease could not be identified by CFC because of the lack of a specific identifiable marker. Cell flow cytometry provides an easy and rapid adjunct to the diagnosis of a variety of lymphomas. At the present time, membrane markers in cell suspensions from tissues (lymph nodes) identified by MAb-s and sIg's in a CFC cannot be used to provide definitive diagnoses for reactive lymphadenopathies, Hodgkin's disease or some classes of lymphomas.[69]

Gene rearrangement analysis has emerged as a precise laboratory aid in the diagnosis and classification

of malignant lymphoma and leukemia. Both clonality and lineage can be identified in lymphoid neoplasms by the demonstration of rearrangements of antigen receptor genes of the immunoglobulin supergene family-immunoglobulin and T-cell receptor genes. Rearrangement analysis is not only useful in differential diagnosis and classification, but also serves as a sensitive unique clonal marker to detect early occult recurrence in patients after therapy. In a similar manner, chromosomal translocations associated with specific disease types can be detected with DNA probes in Southern blot analysis without the use of conventional cytogenetics. Using this approach, one may diagnose specific chromosomal translocations associated with histologic types of lymphoma and leukemia. When appropriately applied, DNA rearrangement analysis complements conventional histology, immunophenotyping, and cytogenetics [70].

The possibility of marker diagnosis of malignant lymphoma, especially non-Hodgkin lymphoma has been studied using paraffin section. The features of marker antigen and identification method based on marker analysis of infant non-Hodgkin lymphoma (lymphoblast type, Burkitt's, large cell type and undifferentiated large cell system lymphoma) and to explain analysis and identification method of the characteristic marker of non-Hodgkin lymphoma (follicular, mantle cell and chronic tuberculous empyema part backside lymphoma) observed in adults. The marker diagnosis with paraffin section enabled application of the antibody which could not be used in the conventional method, and was shown to be useful [71].

The tumor necrosis factor (TNF) receptor family includes several important markers of activation in T cells. Examination of the expression patterns of two T-cell-associated members of these receptors, namely CD30 and OX40/CD134, in 148 cases of T-cell lymphoma to identify possible objective immunohistochemical criteria for subclassification of these tumors. CD30 expression was characteristic of tumors with an anaplastic (46/47 cases [98 %]) or large-cell (10/21 [48%]) morphology and was seen in only scattered cells in other tumor types. In contrast, large numbers of OX40/CD134(+) tumors cells were typical of angioimmunoblastic lymphoma (15/16 [94%]), angiocentric lymphoma (4/4), a subset of large-cell lymphomas (10/21 [48%]), and lymphomas with a prominent histiocytic component (6/7 [86 %]). Strong OX40/CD134 and CD30 coexpression was seen in only 4 % of tumors, typically those with an anaplastic/ Hodgkin's-like appearance. OX40/CD134 expression was characteristic of tumors composed of activated CD4(+) T cells and was not seen in small-cell T-cell lymphomas, lymphoblastic lymphomas, or other tumor types, including B-cell lymphomas or carcinomas. Suggesting that immunostaining for OX40/CD134 may be helpful in subclassification of peripheral T-cell lymphomas and that the patterns of TNF receptor family expression in these tumors may parallel those seen within nonneoplastic helper T-cell subsets [72].

Utilization of Cd Markers for Assessment of Prognosis: Tumor markers are valuable in monitoring the response of stage IV patients receiving hormonal or chemotherapy[73,75] and some special markers (one of them called bcl-2) can even tell the doctor how well the disease will fare. Some others (like CD20) are a pointer to whether a particular treatment will work. Some of these markers can show the prognosis of the lymphoma in question and there are even markers that will show how certain treatments will perform if applied to the actual case. The CD markers offer a vast improvement to the treatment of lymphoma. Previous attempts to correlate cytokine expression with tumor type and prognosis have been hampered by cell-to-cell variability and the difficulty in quantitating expression of secreted proteins in tissue sections. Earlier reports indicate that the elevated levels of soluble CD86 (sCD86) in some leukemia patients[76] and that elevated sCD86 levels are a marker of poor prognosis in acute myeloid leukemia (AML) [77]. Soluble CD83 (sCD83), a potent immunosuppressive agent, circulates at elevated levels in some chronic lymphocytic leukemia (CLL) patients[78] and reported that CLL patients with elevated plasma sCD83 levels had significantly shorter ($P = 0.038$) treatment free survival [79]. Previous findings also demonstrate that the regulation of Th1 and Th2 subclasses is dynamic, with some stimuli leading to intermediate (Th0) patterns of cytokine expression that may vary greatly over the course of disease[80] In the future, an approach based on examination of multiple sets of signaling receptors may lead to identify additional distinct subtypes of lymphoma as well as clinically important prognostic factors.

Similarly surface markers of prognostic significance have been reviewed in multiple myeloma patients. Multiple myeloma (MM) is characterized by increased numbers of malignant plasma cells. Plasma cells, that represent the terminal differentiation of B lymphocytes, have considerable heterogeneity of surface markers expressed on them. Some studies showed the prognostic significance of several immunophenotypic molecules on MM cells. CD56-negative MM is the unique entity characterized by poor prognosis with high incidence of extramedullary disease, protein, renal insufficiency, thrombocytopenia and plasmablastic morphology [81].

CONCLUSION

The studies reported in literature indicate the fact that, considering the outline of therapeutic strategies and prognostic evaluations, differential diagnosis of these lymphomas has to be backed up by a large selection of immunological, molecular and cytogenetic research. As more and more research goes into these markers, new uses are coming up all the time. In conclusion, early and accurate diagnosis of lymphomas utilizing the expression pattern of specific markers gives us the opportunity to investigate the biology of this disease with a view to devise novel therapeutic approaches. However, additional clinical studies will be necessary before treatment options are based upon immunologic markers.

ACKNOWLEDGMENT

The authors are thankful to the University Grant Commission, Government of India for financial support through the UPE (University with Potential for Excellence) Project under the focused Area: Microbial Plant and Animal Diseases.

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