

Proliferacije plazma ćelija

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Apstrakt

Plazmociti su terminalno diferentovane efektorne ćelije B-ćelijske linije. Cilj ovog rada je sveobuhvatni prikaz relevantnih podataka o fenotipu plazmocita, reaktivnih i neoplastičnih. Savremena klasifikacija limfoproliferativnih bolesti po Svetskoj zdravstvenoj organizaciji se zasniva na koreliranju njihovih morfoloških, histoloških, imunofenotipskih, citogenetskih i kliničkih karakteristika. Primena imunohistohemije je neophodna ne samo u dijagnostici plazmocitnih neoplazmi, već i u određivanju prognoze, kao i evaluaciji rezidualne bolesti i relapsa. U ovom radu je istaknut značaj imunohistohemijske analize neoplastičnih i neoplastičnih proliferacija plazmocita u cilju lakše dijagnostike, sa posebnim osvrtom na savremene pristupe u njihovoj subklasifikaciji.

Ključne reči: plazma ćelije, proliferacije, klasifikacija

Plasma cell proliferations

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Abstract

Plasma cells (PC) are the terminally differentiated effector cells of the B-cell lineage. The aim of this review is to integrate relevant data on the phenotype of plasma cells, including reactive and malignant PC. The current World Health Organisation classification of lymphoid neoplasm is based on correlation of their morphologic, histologic, immunophenotypic, genetic and clinical features. The extensive application of immunohistochemistry is necessary in diagnosis of plasma cell neoplasm, but also in determining prognosis as well as in evaluating residual/relapsing disease. This review focuses on immunohistochemical analysis non-neoplastic and neoplastic plasma cell proliferation in facilitating the diagnosis and highlights the recent advances that have been made with regard to their stratifying.

Key words: plasma cell proliferation, classification

Plasma cells: a new light at the end of B cell development

As the final mediators of a humoral response, plasma cells play a critical role in adaptive immunity. However, the mechanisms that control the differentiation of germinal center (GC) B cells toward the plasma cell or memory B cell pathway are not known. Both cell types derive from antigen-activated B cells that have undergone the "GC reaction", in which they specifically modify their immunoglobulin through somatic hypermutation and class-switch recombination.¹

Klein et al² report that the transcription factor Interferon Regulatory Factor 4 (IRF4) is required for the generation of plasma cells. Transgenic mice with conditional deletion of IRF4 in germinal center B cells lacked post-germinal center plasma cells and were unable to differentiate memory B cells into plasma cells. In addition, IRF4-deficient B cells had impaired expression of activation-induced deaminase and lacked class-switch recombination, suggesting an independent function for IRF4 in this process.² These results identify IRF4 as a crucial transcriptional "switch" in the generation of functionally competent plasma cells. IRF4, also called MUM1, originally identified as the product of a proto-oncogene involved in chromosomal translocations in multiple myeloma, is capable of transforming cells in vitro and is often abnormally expressed in B cell lymphomas.³

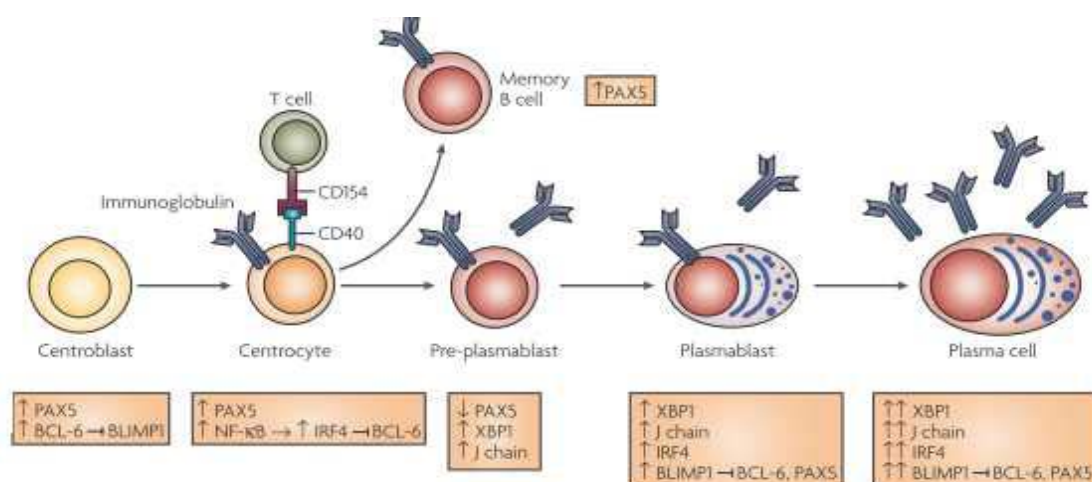


Figure 1. Termination of the GC transcriptional programme and post-GC B-cell development¹

The GC transcriptional programme culminates in the differentiation of a centroblast into a centrocyte through the stimulation of CD40 mediated by GC T cells that leads to repression of B-cell lymphoma 6 (BCL-6) by IRF4 (Figure 1).¹ This centrocyte stage could represent the common precursor of memory B cells and plasma cells. Inactivation of PAX5 (paired box protein 5) by an unknown stimulus and mechanism appears to be the first step towards plasma-cell differentiation. The pre-plasmablast stage is characterized by low-levels of immunoglobulin secretion, which results from the release of the repression of the genes encoding XBP1 (X-box binding protein 1) and J (joining) chain. The subsequent upregulation of BLIMP1 (B-lymphocyte-induced maturation protein 1) and IRF4, during a plasmablast stage, then establishes the characteristic plasma-cell phenotype. BCL-6 and BLIMP1 establish a mutual suppression loop between the centroblast and the plasmablast and/or plasma cell, respectively. BLIMP1 represses PAX5 in plasmablasts and plasma cells; evidence suggests that PAX5 might also repress positive-regulatory-domain-containing 1 (Prdm1), which encodes BLIMP1.⁴ Continued signalling through CD40 may be crucial in driving the centrocyte towards memory B-cell differentiation, and continued PAX5 expression maintains B-cell identity in memory B cells.¹

Because they are terminally differentiated, end-stage cells, plasma cells do not divide. However, “plasmablasts” in extrafollicular regions or exiting GCs do undergo cell division just before they become plasma cells.^{1, 5} The lifespan of nondividing plasma cells varies from a few days to many months. Numerous B cell-specific surface proteins are down-regulated upon plasma cell differentiation, including major histocompatibility complex (MHC) class II, B220, CD19, CD21 and CD22.⁶ The proteoglycan syndecan-1 (CD138), which recognizes extracellular matrix and growth factors, is induced on antibody-secreting B cells and is often used as a marker of plasma cells.⁷ Most normal plasma cells express CD138, CD38, VS38, cIg, CD19, CD10, EMA, CD27, CD31, hTPD52, MUM1, CD20^v, CD45^v and HLA-DR antigens, although there is extensive antigenic heterogeneity reflecting a spectrum of differentiation that ranges from the immature plasmablast to the mature plasma cell. Among integrin family proteins, which mediate cell-matrix and cell-cell adhesion functions, VLA-4 (very late antigen 4) is most predominant on plasma cells. Perhaps most important for differential homing of plasma cells, the chemokine receptors CXCR5 and CCR7 are decreased, which reduces responsiveness to the B and T cell zone chemokines CXCL13, CCL19 and CCL21.⁸ In contrast, expression of CXCR4, which recognizes CXCL12 present in splenic red pulp, lymph node medullary cords and in bone marrow, remains high.⁸ These changes mediate movement of plasma cells from the follicles to other locations, including the bone marrow.

The signaling pathways that normal B cells utilize to sense antigens are frequently derailed in B cell malignancies, leading to constitutive activation of prosurvival pathways.⁹ A better understanding of these issues will provide major insights into the mechanisms that regulate humoral immunity, as well as in those that lead to its pathological manifestations such as B-cell lymphomas.

Immunoglobulin Stains for Clonality Assessment

Staining for kappa and lambda light chains may help to identify the presence of an abnormal clonal population, particularly plasma cells. Immunohistochemistry is less sensitive than flow cytometry for the detection of immunoglobulin expression, as it does not detect surface immunoglobulin. Immunohistochemistry in fixed tissue relies on some degree of cytoplasmic immunoglobulin production. Plasma cells and immunoblasts strongly express cytoplasmic immunoglobulin, whereas only a small subset of other B-cell proliferations has detectable immunoglobulin expression by paraffin immunoperoxidase techniques.¹⁰

Non-neoplastic plasma cell proliferation

Benign polyclonal plasmacytosis (BPP) was first described in 1988 by Peterson et al. as benign polyclonal immunoblast proliferation.¹¹ The most common clinical presentations have been fever with leukocytosis and skin rash. Other presenting signs include lymphadenopathy, dyspnea, hepatosplenomegaly, jaundice, and autoantibodies. The BPP cases showed an association with bacterial sepsis (*Staphylococcus aureus*, *Pseudomonas aeruginosa*), viral infection (hepatitis C, infectious mononucleosis), serum sickness-like syndrome (streptokinase therapy) and immunological disorders and they can be interpreted as a dysregulated hyperactive immune response.¹² A reactive increase of polyclonal plasma cells is common and is associated with a variety of conditions including HIV and other infections, chronic inflammatory diseases, haemopoietic and non-haemopoietic malignant disease, angioimmunoblastic lymphadenopathy, systemic Castleman's disease, cirrhosis, diabetes mellitus, iron deficiency, megaloblastic anaemia and haemolytic anaemia.¹³ Pathologically, the plasma cells increased in number and accounted for 20–40% of nucleated cells of bone marrow. Cytological features must be assessed as well as plasma cell number. The presence of plasmablasts and marked plasma cell dysplasia, e.g. giant forms, striking nuclear lobulation and prominent nucleoli, are strongly suggestive of multiple myeloma. Reactive plasma cells showed mature cytomorphology. Immunoperoxidase studies of light chain determinants for plasma cells and their precursors demonstrated a polyclonal pattern.¹⁴ In reactive plasmacytosis immunocytochemistry shows that κ - and λ -expressing plasma cells are present in a ratio of approximately 2:1. About half the plasma cells express γ heavy chain, about a third α and the remainder μ .¹³

The plasma cell type of Castleman's disease (CD) is often associated with polyclonal gammaglobulinemia and increased serum levels of IL-6. Anemia and elevated erythrocyte sedimentation rate are frequent findings. The most frequent site of involvement is the abdomen, particularly in the small bowel mesentery.¹⁵ Lymph node sections show follicular hyperplasia with a well-defined mantle zone, surrounded by sheets of mature plasma cells and scattered immunoblasts. Vascular proliferation or hyalinization is usually absent. In approximately 40% of the cases the plasma cells are monotypic and express Ig lambda light chain. The plasma cell type resembles other follicular hyperplasias, such as those associated with rheumatoid arthritis, or other autoimmune disorders. Plasma cell variant of CD should be considered in the differential diagnosis of plasma cell neoplasms (primary lymph node plasmacytoma), polyclonal plasma cell-rich lymphoproliferative disorder (marginal zone lymphoma, lymphoplasmacytic lymphoma, Burkitt's lymphoma with plasmacytoid differentiation, plasmablastic lymphoma, angioimmunoblastic lymphadenopathy with dysproteinemia, Hodgkin's lymphoma), plasma cell granuloma, syphilitic lymphadenitis, etc.

Neoplastic plasma cell proliferation

Plasma cell neoplasms encompass a group of diseases with varying clinical manifestations but with at least one common feature, the production by neoplastic plasma cells with a monoclonal immunoglobulin protein (M-protein, or paraprotein). These diseases include monoclonal gammopathy of undetermined significance (MGUS), plasma cell myeloma (PCM) (and its clinical variants), plasmacytoma, the monoclonal

immunoglobulin deposition diseases (primary amyloidosis and monoclonal light and heavy chain deposition diseases) and osteosclerotic myeloma (POEMS syndrome).¹⁶

The diagnosis of a plasma cell neoplasm rests on the correlation of clinical and pathological findings. At one end of the spectrum of plasma cell dyscrasia is **monoclonal gammopathy of undetermined significance**, which is the most common and relatively indolent form of plasma cell dyscrasia; this contrasts with plasma cell myeloma, which is aggressive and requires treatment. Patients presenting with MGUS demonstrate no B-symptoms (e.g. weight loss, night sweats), no bone lesions, and no symptoms that indicate organ or tissue impairment. A low level of M-protein of <30 g/L in serum, and clonal plasma cells accounting for <10% of total marrow cellularity, are characteristic features in MGUS.¹⁷ Recent studies indicate that the diagnosis of symptomatic multiple myeloma is always preceded by monoclonal gammopathy for 2 or more years.

Plasma cell myelomas are more advanced neoplasms and classified as either asymptomatic (smouldering) myeloma or symptomatic myeloma. In the former, the patients have either an increase in M-protein (>30 g/L) or an increase in clonal plasma cells (>10%) in the bone marrow without end organ impairment, and lack symptoms and signs. Symptomatic myeloma is diagnosed when there is end-organ or tissue impairment (most classically defined as the “CRAB” findings: hypercalcemia, renal insufficiency, anemia and bone lesions) with the presence of M-protein in serum or urine and bone marrow clonal plasma cells or plasmacytoma¹⁷. When there are multiple bone lesions or the disease is systemic, the clinical term is multiple myeloma (MM), as opposed to plasma cell myeloma (plasmacytoma).

The risk that MGUS may evolve to a malignant state (MM, primary amyloidosis, macroglobulinaemia, chronic lymphocytic leukaemia or plasmacytoma) is about 1–2% of cases per year, and patients are at risk of progression even after 25 years or more of stable MGUS.¹⁸ The differences in follow-up, treatment, and survival between MM and MGUS necessitate discrimination between these two entities. Most normal plasma cells express CD138, CD38, CD19, CD10, CD27, CD45 and HLA-DR antigens¹⁹, although there is extensive antigenic heterogeneity reflecting a spectrum of differentiation that ranges from the immature plasmablast to the mature plasma cell. Benign plasma cells are typically negative for CD117 and CD56. Malignant plasma cells are usually positive for CD27dim, CD28, CD56, and negative for CD19, CD20, and CD45, or dimly positive for CD45.²⁰ However, CD45 and CD20 can be expressed at moderate or higher intensity in 10% and 20% of cases, respectively. CD56 is negative in about 40% to 45% of MM, as it has in association with progressive disease.²¹ CD117 is aberrantly expressed in 30% of cases and is a useful marker for malignancy. Myeloid markers CD13 and CD33 or CD10 can also be identified in a small subset of cases. Myelomatous plasma cells may express other antigens associated with different haematopoietic lineages such as CD45R, CD25, CD2, CD4²⁰. The monoclonal antibody CD56/NCAM (clone 1B6) seemed to have potential for discriminating between myelomatous, MGUS and reactive plasmacytosis cells in bone marrow sections and aspirates, especially in those cases with low infiltration.²⁰ Of the MM samples 78% were CD56+ in smears and 92% positive in biopsies. Martín et al. did not find strong CD56 expression in MGUS samples.²² One of five samples of polyclonal plasmacytosis was CD56+ (a case was considered to be positive for CD56 expression if >50% of the CD138+ plasma cells expressed NCAM with an intensity on a par with that of the osteoblasts).²²

All normal and malignant PC express CD38 and CD138. However, the level of expression is different and allows normal PC to be distinguished from malignant PC: myeloma cells express more CD138 but less CD38 than do normal PC²³. Bataille et al. have never observed viable CD138– myeloma cells whereas CD38– myeloma cells.²³

The normal ratio of plasma cells is 2–4 kappa-expressing cells to each lambda positive cell; a ratio of 8 (or more) kappa to 1 lambda strongly suggests a monoclonal kappa-positive population and can be readily visualised by ISH with a plasmacytosis of approximately 5% in trephine sections. Conversely, a ratio of even 4 lambda-expressing cells to 1 kappa-positive one indicates the presence of a monoclonal lambda-positive plasma cell population.

Cytologic features of plasma cells in the bone marrow smears may vary from normal-appearing mature plasma cells to immature and anaplastic forms. Plasmablasts show a high nuclear:cytoplasmic ratio, deep blue cytoplasm, with or without perinuclear hof, round or irregular nucleus, fine chromatin, and one or several prominent nucleoli. Multinucleated or multilobated plasma cells may be present. Cells with cherry-red,

round cytoplasmic (Russell bodies) or nuclear (Dutcher bodies) inclusions, as well as cytoplasmic crystals may be present. Some plasma cells may appear like grapes and demonstrate numerous, round, Ig-containing cytoplasmic structures (Mott and Morula cells). Blood smears may show rouleaux formation of the red blood cells or the presence of plasma cells in various proportions. In some patients with multiple myeloma, the neoplastic cells are so immature or atypical that they are cytologically indistinguishable from large cell lymphoma or other anaplastic tumours, including carcinoma, melanoma and acute leukaemias. Plasmablastic myeloma and large cell lymphoma with cells having the features of immunoblasts are particularly likely to be confused.

Cytogenetics and molecular genetics are not essential for diagnosis of PCM. Conventional cytogenetic analysis is frequently unsuccessful but it appears that the detection of deletions of 13q by metaphase analysis may have prognostic value, along with t(4;14) and deletion of TP53 by FISH²⁴. Translocations involving chromosomes 4, 14, and 16 as well as del17p13 (*TP53*) have been associated with a poor prognosis.²⁴ DNA aneuploidy is observed in more than 90%; these are predominantly hyperdiploid, with less than 10% being hypodiploid, and the latter carries a poor prognosis. The t(11;14) abnormality is found in 10-15% of cases, resulting in over-expression of cyclin D1.

Different surface molecules could be targeted as individual therapies for either well-defined MM entities i.e., CD19, CD20, CD27 or CD117, or subpopulations of MM i.e., CD33, CD52.²³ Half of MM retain CD27 and its expression is associated with a better prognosis. CD27 expression is lost with myeloma progression.²³ The expression of CD117 seems to be restricted to patients with indolent MM.²³ Clinical grade monoclonal antibodies exist for CD20, CD33 and CD52 and clinical trials are ongoing for some of them.

Non-secretory myeloma, which accounts for 1% to 5% of all myelomas, is characterized by the absence of detectable M-protein in serum and urine. The presenting features of nonsecretory myeloma are similar to those in patients with a detectable M-protein, except for the absence of renal function impairment and hypercalcemia. The response to therapy and survival of patients with nonsecretory myeloma are similar to those of patients with measurable M-protein.

Plasma cell leukaemia (PCL) is also a rare form of plasma cell dyscrasia (2% to 4% of all myelomas). It is a variant of multiple myeloma characterized by greater than or equal to 2×10^9 circulating plasma cells in one litre of peripheral blood. Patients can present with primary PCL, or it can evolve from previously recognized multiple myeloma (secondary PCL). The primary form accounts for 60% of the cases. In primary PCL, the constellation of adverse biologic prognostic factors in patients with advanced aggressive myeloma is already present at diagnosis. Immunohistochemically, PCL tends to be positive for CD20 (50%) but negative for CD117 and CD56 compared to myeloma. Approximately 90% of secondary PCL cases express CD28 as compared with 30% in primary PCL. The plasma cells express cytoplasmic but not surface Ig light chain. Primary PCL has a more aggressive clinical presentation than MM, with a higher frequency of extramedullary involvement, anemia, thrombocytopenia, hypercalcemia, and renal failure.

Plasmacytoma

Solitary bone plasmacytomas (SBP) are tumors of neoplastic plasma cells localized to a single bone and represent 3% of plasma cell neoplasms. Some patients with SBP present with a single painful bone lesion due to a monoclonal plasma cell infiltrate, and further studies show no evidence of myeloma elsewhere. In other cases, SBP may be discovered during roentgenographic studies for another condition or the patient presents with a painless swelling of the sternum, rib, or other bone. Electrophoresis of serum and urine samples reveals monoclonal protein in 24% to 72% of patients with SBP, although levels of the protein are much lower than those patients with MM. In true solitary or multifocal osseous plasmacytomas, trephine biopsy show no plasmacytosis and have no demonstrable clonal population of plasma cells. Most patients (70%) eventually develop systemic disease at a median of 2 to 4 years.

Solitary extramedullary (extraosseous) plasmacytomas tend to be localized to the head and neck regions, where 80% of cases occur, although they can occur in many other parts of the body such as the gastrointestinal tract, central nervous system, and skin. The majority of the tumors do not produce detectable serum

paraprotein (less than 25%) and the tumors rarely spread (less than 30%). **Primary lymph node plasmacytomas (PLNPs)** represent 2% of all extramedullary plasmacytomas and 0.5% of lymph node malignant neoplasms. PLNPs can be diagnosed only after exclusion of metastatic multiple myeloma (which metastasizes to lymph nodes in up to 40% of cases of advanced-stage disease) and metastatic upper respiratory tract plasmacytomas (which represent 76% of extramedullary plasmacytomas and infiltrate cervical lymph nodes in approximately 15% of cases).²⁵ A total of 33 PLNPs have been described, primarily as single case reports, 7 of them arising in Castleman disease, plasma cell type. Because most PLNPs and other types of extramedullary plasmacytomas show mature plasma cell morphologic features relatively often and because reactive plasmacytoses form dense tumefactive plasma cell infiltrates simulating plasmacytoma in multiple body sites, as previously reported in the upper respiratory tract.²⁵

Monoclonal immunoglobulin deposition diseases (MIDD)

Primary amyloidosis

In this condition there is deposition of a fibrillary protein in the liver, kidneys, heart, gastrointestinal tract, peripheral nerves and other tissues resulting in organ impairment. Diagnosis is dependent on demonstration of amyloid protein and exclusion of secondary (non-immunoglobulin) amyloidosis. The protein binds Congo Red dyes with apple-green birefringence when viewed under polarised light. The light chain type in primary amyloidosis is usually lambda, presumably reflecting easier conversion of this protein, compared with kappa, into beta-pleated sheet structures. Primary amyloidosis is always the result of a clonal plasma cell neoplasm, but symptoms because of the amyloid deposition usually become clinically evident at a time when the plasma cell tumor burden is relatively low; most cases have < 10% bone marrow plasma cells with low M-protein levels (< 30 g/L), similar to that seen in MGUS.¹⁶ If the plasma cell count and M-protein level are consistent with MGUS and the patient's symptoms are entirely attributable to organ damage from amyloid deposition, the resulting organ failure does not constitute a criterion for the diagnosis of symptomatic PCM, and the diagnosis remains primary amyloidosis. Amyloidosis may also occur in the presence of a larger plasma cell burden and other symptoms of myeloma ($\leq 10\%$ of patients with myeloma); if the level of M-protein or the plasma cell count is sufficient for a diagnosis of asymptomatic myeloma, the diagnosis is amyloidosis and PCM.²⁶

Light and heavy chain deposition disorders

These may present with features resembling primary amyloidosis but the protein is non-fibrillary as seen by electron microscopy and does not bind Congo Red. Abnormal protein comprising heavy or light chains (or both) is deposited in tissues such as the heart and liver leading to organ dysfunction. As with primary amyloidosis, the associated tumor burden is usually low. In light chain deposition disease, the light chain type is usually kappa and neoplastic cells, if identifiable, are usually plasma cells. Heavy chain diseases (mu and gamma) usually affect older individuals and involve lymph nodes, marrow, spleen and peripheral blood, with varying lymphocytic, lymphoplasmacytoid and mature plasma cell morphology in cellular components. Occasional examples appear to be variants of diffuse large B-cell lymphoma. Alpha chain disease differs in presenting typically with small intestine and mesenteric lymph node involvement causing malabsorption in younger individuals. The small bowel in alpha chain disease has histological features resembling those seen in extranodal marginal zone B-cell lymphomas of MALT type.

Osteosclerotic myeloma is a rare form of plasma cell neoplasm (less than 1%) usually seen in POEMS (polyneuropathy, organomegaly, endocrinopathy, M component, and skin changes) syndrome. The bone changes are characterized by osteosclerosis rather than lytic lesions. The monoclonal protein is usually IgG or IgA type (with a marked predominance of lambda light chain) and generally less than 3 g/dL. Lymph nodes may show Castleman disease.

Other plasma cell proliferations

Lymphoplasmacytic lymphoma (LPL) is a slowly progressive, clonal disorder of mature B cells, with features of plasma cell differentiation. In some patients this can be associated with peripheral neuropathy. Splenomegaly is frequent but not usually massive and lymphadenopathy, when present, is not usually prominent. **Waldenström's** macroglobulinemia (WM) is the term used to describe cases of LPL in which there is an IgM paraprotein, which may be associated with hyperviscosity. Trephine biopsy histology shows irregular nodular and paratrabeular infiltrates, with or without additional diffuse interstitial infiltration. Intrasinusoidal infiltration is uncommon, in contrast with splenic marginal zone and mantle cell lymphomas. Plasma cells may contain PAS-positive inclusions of immunoglobulin, which may appear in the cytoplasm (Russell bodies) or indenting the nucleus (Dutcher bodies). The proportions of lymphocytes, lymphoplasmacytoid cells and plasma cells vary widely. There may also be scattered larger blast cells but no true para-immunoblasts or proliferation centres. Accompanying reactive mast cells are often abundant.²⁷ The lymph nodes contain diffuse or vaguely nodular infiltrates of mixed lymphoid cells encompassing the spectrum described above. Absence of neoplastic follicles, expanded marginal zones or infiltrates of monocytoid B cells is important in differentiating lymphoplasmacytic lymphoma from other types of small B-cell lymphoma. Immunophenotype of LPL is Sm IgM+ CD5- CD10- CD19+ CD20+ CD22+ CD23- CD25+ CD27+ FMC7+ CD103- CD138-. Cases with little evidence of plasma cell differentiation may be confused with other small B-cell lymphomas; immunophenotyping can exclude chronic lymphocytic leukaemia, mantle cell lymphoma and follicular lymphoma, but not splenic or extranodal marginal zone lymphomas.²⁸

Plasmablastic lymphomas or lymphomas with plasmacytic differentiation

Plasmablastic tumors are composed of large cells with abundant, often eosinophilic cytoplasm and immunoblastic, anaplastic, or plasmacytoid morphology. The classification of tumors with plasmablastic morphology has become increasingly complex.²⁹ Important features to subclassify these neoplasms include the clinical site (oral cavity, body cavity, etc), morphologic spectrum (pure immunoblasts vs mixture of immunoblasts, plasmacytoid cells, and plasma cells), differential antigen expression (CD20, CD138, immunoglobulin, CD30, and CD56), and association with viruses¹⁰. Tumors with plasmablastic morphology typically occur in patients with an abnormal immune state (HIV positive, posttransplantation, or the elderly). These tumors often arise in the oral cavity or other mucosal sites of the head and neck, or body cavity (PEL), or in association with multicentric Castleman disease.³⁰ In addition, a Kaposi sarcoma-associated herpesvirus-positive solid lymphoma/ extracavitary PEL/human herpesvirus 8-associated DLBCL has been described, predominantly in HIV-positive patients and shows coexpression of EBV. Atypical BL with plasmacytoid differentiation is seen in HIV-positive patients, representing approximately 20% of AIDS-related NHL. Other tumors with plasmablastic morphology and less association with an immunocompromised state include PBL with plasmacytic differentiation defined by Colomo et al³¹ as prominent immunoblasts or plasmablasts but with some admixed smaller cells with plasmacytic differentiation and by little or weak expression of CD20, DLBCL with prominent plasmablastic/secretory differentiation, pyothorax-associated lymphoma, and PCM with a dysplastic, plasmablastic appearance. Morphologically, the PBL of the oral cavity and the rare ALK-positive DLBCL are composed of a very monomorphic, sheetlike proliferation of immunoblasts. PBL with plasmacytic differentiation and DLBCL with secretory differentiation (immunoblasts and plasmacytoid cells) are distinguished by the presence of centroblasts in the latter.¹⁰ CD138 and MUM-1, markers of post germinal center/terminal B-cell/plasmacytic differentiation, are useful in identifying the B-cell origin of these tumors that show variable or negative expression of CD20 and CD79a.¹⁰ Expression of Pax-5 has not been investigated in a significant number of cases to be informative at the present. Non HIV patients with plasmablastic lymphoma may present with nodal, soft tissue or bone marrow disease.³¹ The distinction from myeloma may be problematic. The immunophenotype can be difficult due to lack of the B antigens with weak/ absent CD19 and

CD20, PAX5 negative, CD138 positive, CD79 variable, MUM1 positive, CD56 positive (most), CD45 negative (usually) with a few cases expressing ALK1.³²

Open questions and future challenges

The 2008 WHO classification of lymphoid neoplasms has been a major consensus effort in updating new knowledge, concepts, and criteria in the taxonomy of plasma cell neoplasms. However, many questions still remain.

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