Plasma Cell Myeloma and Related Neoplasms

Robert B. Lorsbach, MD, PhD, Eric D. Hsi, MD, Ahmet Dogan, MD, PhD, and Falko Fend, MD

Key Words: Plasma cell myeloma; Neoplasms; Lymphoid malignancies; t(11;14): Plasma cell leukemia; Nonsecretory plasmacytoma; Plasmablastic transformation

Abstract

Session 1 of the 2009 Workshop of the Society for Hematopathology/European Association of Haematopathology, Cleveland, OH, focused on plasma cell neoplasms. This report summarizes the salient diagnostic, clinical, and genetic features of plasma cell myeloma (PCM) and related neoplasms. Based on the cases submitted to the workshop, we highlight common diagnostic issues and unusual manifestations of plasma cell neoplasms, such as t(11;14)+ PCM, plasma cell leukemia, and nonsecretory plasmacytoma, as well as plasmablastic transformation of PCM. Additional issues repeatedly raised at the workshop included the differential diagnosis of extramedullary dissemination of PCM vs primary extramedullary plasmacytoma and plasmablastic lymphoma; systemic plasma cell neoplasms in immunocompromised people; and Epstein-Barr virus–associated plasma cell neoplasms. Difficult cases with borderline features presented by submitters emphasized the necessity of integrating clinical, immunophenotypic, and genetic features for appropriate classification of these disorders.

Plasma cell myeloma (PCM) and related plasma cell (PC) neoplasms are derived from a post–germinal center B cell that has undergone somatic hypermutation and productive immunoglobulin heavy chain class switching. Extensive cytogenetic and molecular characterization of PCM has identified 2 major genetic subtypes. Hyperdiploid PCM is characterized by trisomy or tetrasomy of primarily the odd-numbered chromosomes. The second major type of PCM involves the PCMs that harbor chromosomal translocations targeting the immunoglobulin heavy chain locus present at chromosome 14q32.1,2 However, these 2 groups show some overlap because a subset of hyperdiploid PCM contains immunoglobulin chromosomal translocations. These translocations targeting chromosome 14q32 are detected in approximately 50% of monoclonal gammopathy of uncertain significance (MGUS) and PCM cases, indicating that they are primary genetic abnormalities, usually acquired during heavy chain switch recombination in the germinal center. In contrast with most mature B-cell lymphomas, PCM shows a range of different translocation partners, which are often associated with specific clinical and prognostic features. Progressive genomic instability is a hallmark of the pathogenesis of PCM. As such, numerous cytogenetic abnormalities have been identified; their frequency is low in MGUS and low-grade PCM and increases with evolution to more aggressive disease.3,4 Moreover, whereas myeloma cell growth and survival in the initial stages of the disease are dependent on interactions with bone marrow stroma, disease progression in PCM is characterized by increasing independence from the bone marrow microenvironment.

PC neoplasms are included in the World Health Organization (WHO) classification and encompass clonal
PC proliferations with a wide range of clinical manifestations and behavior, which, in most cases, are associated with the production of a monoclonal immunoglobulin, or M protein, detectable in the serum and/or urine. In both cases. While CD20 positivity in PCM with t(11;14) is well described, these cases with a broader range of B-cell antigen expression illustrate that distinction of this myeloma subtype from B-cell lymphomas with plasmacytic differentiation may be very difficult in some cases. Cyclin D1 immunohistochemical studies and FISH to detect the IGH/CCND1 fusion, as well as recognition of the clinical features typical of conventional PCM, may be critical to making the appropriate diagnosis.

**PCM With t(11;14)(q13;q32)**

PCM harboring the t(11;14) is one of most common cytogenetic subtypes, comprising approximately 20% of all myelomas, and is characterized by cyclin D1 overexpression due to the translocation-mediated juxtaposition of the CCND1 gene and the immunoglobulin heavy chain enhancer. Although weak or moderate cyclin D1 expression may be seen in PCMs with polysomy of chromosome 11, strong cyclin D1 positivity is highly correlated with the presence of the t(11;14). Perhaps more than any other myeloma subtype, PCM with t(11;14) is associated with several morphologic and immunophenotypic peculiarities that may cause diagnostic problems and that were well reflected in the large number of cases submitted to the workshop (cases 22, 51, 54, 63, 66, 106, 241, 257, 280, 284, and 325).

There were several PCMs with prominent, small lymphocyte-like or lymphoplasmacytoid features submitted to the workshop, morphologic features that are strongly associated with the presence of the t(11;14) and may closely mimic a B-cell lymphoma. This lymphoplasmacytic variant accounts for approximately 40% to 50% of t(11;14)+ PCMs. In addition to these “transitional” morphologic features, some cases manifested a similarly transitional immunophenotype with expression of mature B-cell and plasmacytic markers. Two cases were particularly instructive, both of which had prominent lymphoplasmacytic morphologic features. In case 54, the neoplastic cells strongly expressed MUM1, CD138, CD19, CD20, PAX5, cyclin D1, and manifested surface light chain restriction. In case 63, the tumor cells expressed CD138, CD45, CD20, and surface κ light chain but were negative for CD19 and CD56. Fluorescence in situ hybridization (FISH) confirmed the presence of the t(11;14) in both cases. While CD20 positivity in PCM with t(11;14) is well described, these cases with a broader range of B-cell antigen expression illustrate that distinction of this myeloma subtype from B-cell lymphomas with plasmacytic differentiation may be very difficult in some cases. Cyclin D1 immunohistochemical studies and FISH to detect the IGH/CCND1 fusion, as well as recognition of the clinical features typical of conventional PCM, may be critical to making the appropriate diagnosis.

**Table 1**

**World Health Organization Classification of Plasma Cell Neoplasms**

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<th>Category</th>
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<tbody>
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<td>Monoclonal gammopathy of unknown significance</td>
<td>Serum M protein present, &lt;30 g/dL</td>
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<td>Variants</td>
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<td>Primary amyloidosis</td>
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**Table 2**

**World Health Organization Diagnostic Criteria for Plasma Cell Myeloma**

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* End-organ damage due to destructive activity of the neoplastic plasma cells (eg, lytic bone lesions, hypercalcemia, or anemia) or indirectly secondary to deposition of or damage induced by the immunoglobulin M protein (eg, hypercalcemia, renal insufficiency, or anemia).

† Considered primary if present at initial diagnosis; secondary plasma cell leukemia develops during subsequent disease evolution.
Plasma cell myeloma with small lymphocyte–like morphologic features, t(11;14), and transitional immunophenotype. A–E (Case 54). A, The bone marrow aspirate contained numerous lymphoplasmacytic forms. The biopsy showed a diffuse infiltrate of similar-appearing lymphoid cells (B). The neoplastic cells strongly and uniformly expressed PAX5 (C), CD20 (D), and cyclin D1 (E). Submitted by D. Viswanatha.
IgM-Expressing PCM

IgM paraproteinemia is frequently associated with several types of B-cell lymphoma, most commonly lymphoplasmacytic lymphoma and B-cell chronic lymphocytic leukemia (CLL).12 By contrast, owing to the usual origin from post-switched germinal center cells, PCM associated with an IgM paraprotein is extremely rare, constituting fewer than 1% of myelomas.9 Several cases were submitted to the workshop (cases 22, 106, and 241) that illustrate the salient immunophenotypic features of IgM-expressing PCM. As has been reported,13 these cases are associated with the t(11;14) in more than 80% of cases, are typically negative for CD56 and CD117, and, in contrast with the majority of usual t(11;14)-associated non-IgM PCMs, do not coexpress CD20.

Nonsecretory PCM

Nonsecretory PCM historically constitutes 1% to 5% of all myelomas. With the advent of increasingly more sensitive serum protein analytic methods, including immunofixation electrophoresis and serum free light chain assay, the frequency of bona fide nonsecretory PCM is waning. Current WHO criteria define nonsecretory PCM on the basis of negative serum or urine immunofixation studies.14 However, many nonsecretory PCMs maintain some minimal level of secretory activity because approximately 70% are associated with abnormal ratios of free κ and λ serum light chains.15 The molecular basis for nonsecretory PCM is incompletely understood; however, alterations in messenger RNA splicing and frameshift mutations in the light chain genes have been identified, which may induce misfolding of the encoded light chain protein targeting them for proteasome-mediated degradation.16,17

Owing to the absence of an M protein and the frequent presence of osteolytic lesions, nonsecretory PCMs raise a broad differential diagnosis and may be diagnostically challenging for clinicians and pathologists alike. Two cases of nonsecretory PCM were submitted to the workshop (cases 66 and 280), both of which nicely illustrate the diagnostic challenges associated with this entity.18-20 One patient had marked leukocytosis (case 280) with atypical lymphoid cells in the peripheral blood. By flow cytometry, these cells were CD45dim and coexpressed CD33, CD56, and CD4 and were negative for CD20 and light chains by immunohistochemical studies. These immunophenotypic findings raise a broad differential diagnosis, including myeloid neoplasms and blastic plasmacytoid dendritic cell neoplasm. In the other case (case 66), the neoplastic cells expressed a μ heavy chain but with no detectable serum IgM paraprotein. Strong positivity for CD138 and the presence of the t(11;14) were diagnostic of PCL/PCM in both cases.

PCM With Associated Crystal-Storing Histiocytosis

PCM is rarely associated with a “crystal-storing histiocytosis” (CSH), a reactive histiocytic hyperplasia in which the histiocytes contain prominent crystalline cytoplasmic immunoglobulin inclusions.21 One case of PCM with associated CSH was submitted to the workshop (case 265). As is typical for this unusual myeloma variant,
the neoplastic PCs also contain prominent immunoglobulin inclusions and express κ light chain. Image 4. The molecular basis for the crystal formation has not been defined in most reported cases. In 1 study, proteomic analysis identified several κ light chain amino acid substitutions, including rare ones that may disrupt hydrophobic interactions within the light chain.22

Awareness of the association of PCM with CSH is important to avoid misdiagnosis. In some cases, the histiocytic hyperplasia may be sufficiently prominent as to mimic Gaucher disease or other storage disorders or may mask the underlying PC neoplasm. It is important to note that CSH may develop in association with other lymphomas (eg, lymphoplasmacytic lymphoma and mucosa-associated lymphoid tissue [MALT] lymphoma), nonlymphoid tumors such as inflammatory myofibroblastic tumors, and even reactive inflammatory conditions. Thus, when confronted with a suspected CSH, a thorough pathologic evaluation must be performed because the underlying disorder is not always a PC neoplasm. Furthermore, the CSH may be disseminated, involving the reticuloendothelial system, and, thus, may be encountered at extramedullary sites as well.

Association of PC Neoplasms With Other Lymphoid Malignancies

The PC neoplasms may coexist with other lymphoid malignancies, most commonly CLL and monoclonal B-cell lymphocytosis. Several such cases were submitted to
the workshop (cases 250, 258, 276, and 347). When the development of these malignancies is metachronous, they are usually diagnostically straightforward. However, the synchronous detection of a PC neoplasm and a lymphoid malignancy, particularly when both populations manifest the same light chain restriction, brings up a broad differential diagnosis that also includes lymphoid malignancies with plasmacytic differentiation, in particular, CLL/small lymphocytic lymphoma with plasmacytic differentiation, lymphoplasmacytic lymphoma, and marginal zone lymphoma. As was nicely demonstrated in case 276, the application of FISH or immunoglobulin heavy chain polymerase chain reaction to lymphoid and PCs purified by cell sorting can be helpful in assessing the clonal relatedness of the 2 populations.

**Image 3** Nonsecretory plasma cell leukemia/myeloma. A and B (Case 66). A, Bone marrow aspirate showing neoplastic plasma cells (PCs). B, While negative for κ light chain (upper left) and λ light chain (bottom left), the neoplastic PCs expressed IgM heavy chain (right, bone marrow). Submitted by J. Hoyer, S. Hayman, and R. Kyle. C and D (Case 280). C, An infiltrate of PCs is present in the bone marrow, which were strongly CD138+ (inset); flow cytometric analysis reveals that the tumor cells expressed CD38 but were negative for cytoplasmic κ and λ light chain expression (not shown). D. In addition, a subset of cells expressed CD33 and CD4 (bone marrow). Submitted by J. Roepke and C. Rose.
and, thus, determining whether one is dealing with concurrent malignancies or a B-cell lymphoma with plasmacytic differentiation. Flow cytometry may also be helpful because immunophenotypic differences have been identified between the PC neoplasms and the neoplastic PCs of lymphomas with plasmacytic differentiation.23,24 Molecular analyses have confirmed that in most patients with CLL and PCM, the 2 neoplasms are clonally unrelated.25-29

**PC Leukemia**

PCL is a rare malignancy, constituting 2% to 5% of PCMs at primary diagnosis. PCL is defined by the presence of more than 2 × 10⁹/L circulating PCs or more than 20% of nucleated peripheral blood cells.30 It can manifest as primary disease or, more frequently, as secondary PCL arising during the terminal stage of PCM. Adverse clinical and laboratory features and organomegaly are common, and the prognosis of PCL is poor, especially for secondary PCL and PCL developing in older patients.18,20,31-33 Light chain–only expression, rare immunoglobulin isotypes, and nonsecretory cases, as described, are overrepresented among cases of PCL. The cytologic spectrum of PCL is broad, including cases with a villous or hairy appearance, as illustrated by case 280.34 Immunophenotypically, PCL shows less frequent expression of CD56 (neural cell adhesion molecule) and more common CD20 expression than conventional PCM.32,35 Most cases of PCL show complex cytogenetic aberrations, with a higher incidence of t(11;14) and t(14;16) translocations and 13q deletions than is detected in typical PCM.18,20,36 Aberrations of MYC are common in PCL and are associated with aggressive clinical behavior.37 The specific features of PCL were also reflected in the cases.
One case of PEMP was submitted to the workshop (case 91). This lesion developed as a nasal polyp and was composed of a submucosal infiltrate of atypical PCs with focal ulceration. The neoplastic cells were strongly positive for CD138, CD45, and CD79a with \(\lambda\) light chain restriction and were negative for CD20, CD56, and Epstein-Barr virus–encoded RNA (EBER). Of note, this lesion had significant proliferative activity.

PEMPs have a broad differential diagnosis that includes reactive disorders, such as the PC variant of Castleman disease, and other lymphoid malignancies, in particular MALT lymphoma and extramedullary involvement by PCM. Confirmation of light chain restriction eliminates most reactive causes from the differential diagnosis. MALT lymphomas can usually be excluded by their characteristic histologic features and identification of a clonal mature B-cell component, although this may be challenging in cases manifesting extreme plasmacytic differentiation. PEMP cannot be distinguished from extramedullary myelomatous involvement on a morphologic basis alone, although there seem to be diagnostically useful immunophenotypic differences. Whereas extramedullary PCM is frequently CD56+ and not infrequently cyclin D1+ and p53+, PEMP are rarely positive for these markers. Interphase FISH studies have confirmed the absence of t(11;14) translocations in PEMP, whereas the cytogenetic profile of PEMP is otherwise very similar to that of PCM. Proliferative activity is not a useful discriminant because both PEMP and extramedullary PCM may have rather high mitotic rates, as illustrated by the workshop case.

As nicely exemplified by 2 workshop cases (cases 228 and 230), extramedullary involvement may rarely be

**Solitary Osseous and Extramedullary Plasmacytoma**

In the absence of disseminated bone marrow involvement, the WHO recognizes 2 types of plasmacytoma: solitary osseous plasmacytoma (SOP) and extramedullary plasmacytoma (EMP). SOPs primarily involve the axial skeleton and frequently progress to disseminated PCM. Diagnosis of SOPs is usually straightforward because most lesions are composed of sheets of neoplastic cells with overt plasmacytic differentiation. The diagnosis of SOP should be made only when there is a negative bone marrow result and no clinical or radiologic evidence of more widely disseminated disease, ie, PCM.

Primary EMPs (PEMPs) are rare, constituting fewer than 5% of all PC neoplasms, in which there is no associated bone marrow or systemic disease. Progression to disseminated PCM is infrequent, occurring in approximately 15% of cases. PEMP are exquisitely radiosensitive, and external beam radiation provides excellent disease control in most cases. For unknown reasons, PEMP have a striking propensity for involvement of the upper aerodigestive tract.

submitted to the workshop (cases 51, 66, 247, 257, and 280). Of 5 submitted PCLs, 3 carried a t(11;14), including case 257 (submitted by L. Taddesse-Heath), which also contained a MYC translocation, and 3 of 4 cases with reported protein studies were nonsecretory, highlighting the potential diagnostic difficulties that may arise in the absence of a detectable paraprotein, as described.
Plasmablastic and Other High-Grade Variants of PCM

PCM shows a broad cytologic spectrum, ranging from small, lymphoplasmacytic variants and mature Marschalko-type PCs to large cells with prominent central nucleoli and immature cytoplasm, commonly designated as plasmablasts. Based on this morphologic variability and observations that the cytologic features in PCM correlate with clinical behavior and prognosis, several schemes for the identification of high-risk PCM based on cytologic grading have been proposed. Of these, 2 have gained more widespread acceptance and have been evaluated in clinical studies, namely the histologic features–based grading system by Bartl et al44,45 and the cytologic features–based system proposed by Greipp and colleagues.46

Under the criteria of Greipp and colleagues,46 plasmablastic myeloma cells are defined as having a large, centrally placed nucleus (>10 μm in diameter) or a nucleolus (>2 μm in diameter) and a high nuclear/cytoplasmic ratio; the cytoplasm is scant and lacks a prominent perinuclear hof. To be classified as plasmablastic PCM, plasmablasts must comprise 2% or more of nucleated cells in the bone marrow aspirate.46

By contrast, in the grading scheme of Bartl et al,44,45 designation as plasmablastic PCM requires that plasmablasts represent the predominant cell type in the bone marrow biopsy specimen, with no further specification of plasmablast percentage. Under the criteria of Bartl et al,44,45 plasmablasts are defined as having large, immunoblast-like nuclei with prominent nucleoli and a moderate amount of basophilic cytoplasm.

Although different diagnostic criteria are used in these 2 systems, plasmablastic PCM was diagnosed in a similar percentage of cases, 5% to 15%, irrespective of which criteria were used. Furthermore, plasmablastic morphologic features conferred a poor clinical prognosis, suggesting that morphologic evaluation is useful in identifying cases that will manifest aggressive clinical behavior.44-46

In subsequent studies, the independent prognostic impact was confirmed also for patients treated with modern therapeutic strategies, including autologous bone marrow transplantation.47,48 Despite the apparent prognostic significance of plasmablastic morphologic features, risk stratification in PCM relies primarily on clinical staging parameters, such as the international staging system for myeloma, and the identification of high-risk cytogenetic abnormalities. While evaluation of histologic or cytologic features may have some prognostic impact, the degree
PC neoplasm/plasmablastic PCM in 13 of 19 cases (cases 87, 95, 101, 122, 125, 214, 232, 273, 312, 314, 317, 351, and 368) because panel members thought that this diagnosis should be based on the morphologic features of the neoplastic cells rather than on other features of clinical aggressiveness, such as widespread extramedullary dissemination or high proliferation rate as assessed by MIB-1 staining. The sites of extramedullary involvement included lymph nodes, the upper aerodigestive tract, a common site of PEMP, and the central nervous system. Involvement of the central nervous system is associated with high-risk cytogenetics, plasmablastic morphologic features, and an aggressive course, as demonstrated in case 351.\textsuperscript{52}

Biologically, extramedullary involvement and dissemination of PCM reflect independence from bone

\textbf{Image 7} Extramedullary (gastric) manifestation of plasma cell myeloma (PCM) mimicking mucosa-associated lymphoid tissue lymphoma. Dense infiltrate of cells present in the gastric lamina propria (A) that, on higher power (B), is composed predominantly of mature-appearing plasma cells (PCs).

\textbf{Image 8} Because panel members thought that this diagnosis should be based on the morphologic features of the neoplastic cells rather than on other features of clinical aggressiveness, such as widespread extramedullary dissemination or high proliferation rate as assessed by MIB-1 staining. The sites of extramedullary involvement included lymph nodes, the upper aerodigestive tract, a common site of PEMP, and the central nervous system. Involvement of the central nervous system is associated with high-risk cytogenetics, plasmablastic morphologic features, and an aggressive course, as demonstrated in case 351.\textsuperscript{52}
additional cases by FISH. In total, alterations of \( MYC \) were observed in 8 (50%) of 16 evaluable workshop cases with plasmablastic features. This rate is significantly higher than the 15% observed for typical PCMs observed in a large series and indicates that translocations involving \( MYC \) might be associated with more aggressive behavior and extramedullary disease, although this latter study failed to identify clear-cut prognostic significance.\(^3\) This might be because only 25% of cases in this series showed a t(8;14) or a t(8;22) with involvement of immunoglobulin heavy or light chain loci, indicating that other translocation partners may not have the same biologic impact. The detection of \( MYC \) alterations in 50% of end-stage PCMs and more than 90% of human PCM cell lines, which are commonly derived from extramedullary sites in patients with terminal disease, further suggests that aberrant

**Image 7** (cont) The neoplastic cells are strongly CD138+ (C) but negative for CD20 (D); they are \( \lambda \) light chain–restricted but lack expression of immunoglobulin heavy chain (E, top from left: IgD, IgM, IgA, IgG; bottom from left: \( \kappa \), \( \lambda \)). A year after initial examination, the patient was found to have multiple osteolytic lesions, a free \( \lambda \) light chain serum paraprotein, and an extensive marrow PC infiltrate, consistent with PCM. Submitted by R. Ryan, N. Levy, and R. Hasserjian.

marrow stroma–derived growth factors such as interleukin-6 and others that are essential for the growth and survival of myeloma cells during the initial phase of the disease. This acquisition of stromal independence is accompanied by the progressive accumulation of secondary genetic alterations and has been integrated into a multistep model of disease evolution from MGUS to terminal PCM with extramedullary disease.\(^{53}\) Among genetic alterations associated with tumor progression are mutations of \( NRAS \) and \( KRAS \), \( TP53 \) mutations and deletions, chromosome 1p deletions and amplifications of 1q21 involving \( CKS1B \), and translocations involving \( MYC \).\(^3,4,37,54-62\)

Given the high frequency of c-\( MYC \) rearrangements in the cases of aggressive PC neoplasms submitted to the workshop, the occurrence of \( MYC \) breaks was further investigated in additional cases by FISH. In total, alterations of \( MYC \) were observed in 8 (50%) of 16 evaluable workshop cases with plasmablastic features. This rate is significantly higher than the 15% observed for typical PCMs observed in a large series and indicates that translocations involving \( MYC \) might be associated with more aggressive behavior and extramedullary disease, although this latter study failed to identify clear-cut prognostic significance.\(^3\) This might be because only 25% of cases in this series showed a t(8;14) or a t(8;22) with involvement of immunoglobulin heavy or light chain loci, indicating that other translocation partners may not have the same biologic impact. The detection of \( MYC \) alterations in 50% of end-stage PCMs and more than 90% of human PCM cell lines, which are commonly derived from extramedullary sites in patients with terminal disease, further suggests that aberrant
resemble immunoblasts, rather than cells with plasmacytic/plasmablastic differentiation, despite their expression of PC markers such as MUM1/IRF4, CD38, and CD138 and negativity for the B-cell markers CD20 and CD79a.65 PBL was subsequently shown to encompass tumors with a broader range of plasmacytic differentiation than was initially appreciated.

Colomo et al66 studied a series of cases of B-cell neoplasms with plasmablastic differentiation with low or absent expression of CD20 and CD79a and identified 3 main tumor subtypes. The first consisted of classical PBL of the oral mucosa type with monotonous large tumor cells with immunoblastic features. Half of the patients showed involvement of the oral cavity, most patients were HIV+, and 74% of the tumors were positive for EBV by EBER. The second subtype of PBL was composed predominantly of immunoblastic/plasmablastic cells but contained a subset of cells that manifested frank plasmacytic differentiation. These cases showed lower rates of immunosuppression and EBV association. The third subtype was morphologically indistinguishable from this second group and included tumors from patients with a history of an antecedent or a synchronous PC neoplasm, mainly PCM but also rare cases of osseous plasmacytoma and PEMP. Of note, the immunophenotypes of all 3 groups were similar, but with a higher incidence of CD56 expression in PBL with plasmacytic differentiation (46% vs 5%) and in the cases with coexistent PCM (75%). EBV MYC expression is associated with clinical behavior.4,63,64 Whether the biologic impact of c-MYC alterations applies only to translocations involving immunoglobulin loci or also to other partners needs further systematic studies.

**Differential Diagnosis of Neoplasms With Plasmablastic Differentiation and Systemic PC Neoplasms in Immunodeficient People**

As exemplified by several workshop cases, distinction of PCM with plasmablastic morphologic features or with extramedullary involvement, particularly when present at initial diagnosis, from other neoplasms with plasmablastic differentiation can be difficult. In particular, plasmablastic lymphoma (PBL) and high-grade PEMP show significant morphologic and immunophenotypic overlap with plasmablastic PCM. In many cases, the clinical features of the disease, such as osteolytic lesions, diffuse bone marrow involvement, and the presence of an M protein in the case of PCM or the frequent association with HIV infection, common manifestation in the oral cavity, and Epstein-Barr virus (EBV) positivity in PBL aid in arriving at the correct diagnosis. However, cases of PCM or PBL with atypical clinical features can pose significant diagnostic challenges.

In the original description of PBL of the oral cavity, it was emphasized that the tumor cells morphologically resemble immunoblasts, rather than cells with plasmacytic/plasmablastic differentiation, despite their expression of PC markers such as MUM1/IRF4, CD38, and CD138 and negativity for the B-cell markers CD20 and CD79a.65 PBL was subsequently shown to encompass tumors with a broader range of plasmacytic differentiation than was initially appreciated.

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positivity was identified in 2 of 9 nodal cases with concurrent differentiated PC neoplasia.

EBV association has also been detected in 15% of cases of extramedullary plasmacytoma of the head and neck in immunocompetent patients, highlighting the fact that EBV status alone is insufficient to distinguish between PBL and other PC neoplasms.65 For EMP in the nasopharyngeal region, this might be related to the fact that this region is the primary site of entry of the virus. That EBV positivity may also rarely occur in systemic PC neoplasms of immunocompetent people was documented by Chang et al,68 who identified 4 PC neoplasms, including 1 EMP and 3 (6%) of 54 PCMs, with positive EBER staining in virtually all tumor cells. One of these original cases published by Chang et al68 was presented at the workshop (case 20). This 51-year-old man had multiple bone lesions, and extramedullary involvement developed, but he lacked a serum M protein. Besides the EBV positivity, the phenotype otherwise was that of typical PCM. All other 8 workshop cases of plasmablastic PCM in patients without a history of immunosuppression tested for EBV were negative, whereas 2 HIV+ patients with systemic plasmablastic neoplasms (cases 321 and 368) were EBV+. From a practical viewpoint, it can be concluded that the identification of EBV in a PC neoplasm alone is insufficient to make a diagnosis of PBL.

There is fairly limited information on cytogenetic features that may aid in the differential diagnosis of plasmablastic neoplasms. As mentioned, the high frequency of c-MYC alterations in PCM with extramedullary extension may be an additional aid for separating it from PEMP. On the other hand, the differential diagnosis between extramedullary plasmablastic PCM and PBL remains difficult; a recent study demonstrated the occurrence of a c-MYC/IGH rearrangement in 3 of 9 cases of PBL.69 Furthermore, Taddesse-Heath et al70 recently reported 4 cases of systemic, EBV-associated plasmablastic neoplasms in HIV+ patients with overlapping features between PCM and systemic PBL, which all showed a MYC translocation. Similar cases of systemic plasmablastic neoplasms in the setting of HIV infection with some features reminiscent of PCM, such as osteolytic lesions or high levels of M protein, have been documented by other authors and were also presented at the workshop (cases 321, 368, and 377).71 The best approach for the classification of these aggressive systemic neoplasms with plasmacellular and plasmablastic differentiation in immunocompromised hosts and the roles of EBV and c-MYC alterations in their pathogenesis will require further study.

The first session of the workshop provided a good overview of current diagnostic issues in PC neoplasms. Most important, its cases highlighted problematic areas in which more work is required for arriving at a biologically meaningful classification, such as systemic PC neoplasms in immunocompromised hosts and EBV-associated PC tumors.

References

Lorsbach et al / Plasma Cell Myeloma and Related Neoplasms


