

# Plasma Cell Myeloma and Related Neoplasms

Robert B. Lersbach, MD, PhD,<sup>1</sup> Eric D. Hsi, MD,<sup>2</sup> Ahmet Dogan, MD, PhD,<sup>3</sup> and Falko Fend, MD<sup>4</sup>

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

DOI: 10.1309/AJCPENJ68FFBRIYB

## 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.<sup>1,2</sup> 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.<sup>3,4</sup> 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 **Table 1** and **Table 2**. In practice, typical PCM rarely poses a diagnostic dilemma. Nevertheless, PCM cases with atypical clinical, morphologic, and phenotypic features may be difficult to distinguish from other PC neoplasms or other lymphoma types. This review summarizes the discussions and conclusions of the session on PCM and related neoplasms held at the 2009 Workshop of the Society for Hematopathology/European Association of Haematopathology. It is not our intention to provide a comprehensive review of PC neoplasms, but to highlight areas of special interest and diagnostic challenges as reflected by the spectrum of interesting and difficult cases submitted to the workshop.

### 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.<sup>5-7</sup> 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).<sup>8-10</sup> 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.<sup>7,11</sup> 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 **Image 1**, 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  $\kappa$  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,<sup>11</sup> 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

---

|                                                                                                                                 |
|---------------------------------------------------------------------------------------------------------------------------------|
| Monoclonal gammopathy of unknown significance                                                                                   |
| Plasma cell myeloma                                                                                                             |
| Variants                                                                                                                        |
| Asymptomatic myeloma                                                                                                            |
| Nonsecretory myeloma                                                                                                            |
| Plasma cell leukemia                                                                                                            |
| Plasmacytoma                                                                                                                    |
| Solitary osseous plasmacytoma                                                                                                   |
| Extramedullary plasmacytoma                                                                                                     |
| Immunoglobulin deposition diseases                                                                                              |
| Primary amyloidosis                                                                                                             |
| Systemic light and heavy chain deposition diseases                                                                              |
| Osteosclerotic myeloma (POEMS [polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes] syndrome) |

---

**Table 2**  
World Health Organization Diagnostic Criteria for Plasma Cell Myeloma

---

|                                                                                                    |
|----------------------------------------------------------------------------------------------------|
| Monoclonal gammopathy of unknown significance                                                      |
| Serum M protein present, <30 g/dL                                                                  |
| Bone marrow                                                                                        |
| Clonal plasma cells comprising <10% of nucleated cells in aspirate                                 |
| Interstitial infiltration present in biopsy sample                                                 |
| No lytic bone lesions                                                                              |
| No myeloma-related end-organ injury or impairment*                                                 |
| No evidence of other B-cell lymphoproliferative disorder                                           |
| Plasma cell myeloma                                                                                |
| Symptomatic                                                                                        |
| Serum or urine M protein present                                                                   |
| Presence of clonal plasma cells in bone marrow or plasmacytoma                                     |
| Myeloma-related end-organ injury or impairment*                                                    |
| Asymptomatic                                                                                       |
| Serum M protein present, >30 g/L                                                                   |
| and/or                                                                                             |
| Presence of clonal plasma cells in bone marrow, >10% of nucleated cells                            |
| No myeloma-related end-organ injury or impairment*                                                 |
| Plasma cell leukemia†                                                                              |
| Presence of clonal plasma cells in peripheral blood, >2 × 10 <sup>9</sup> /L or >20% of leukocytes |

---

\* End-organ damage due directly 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.

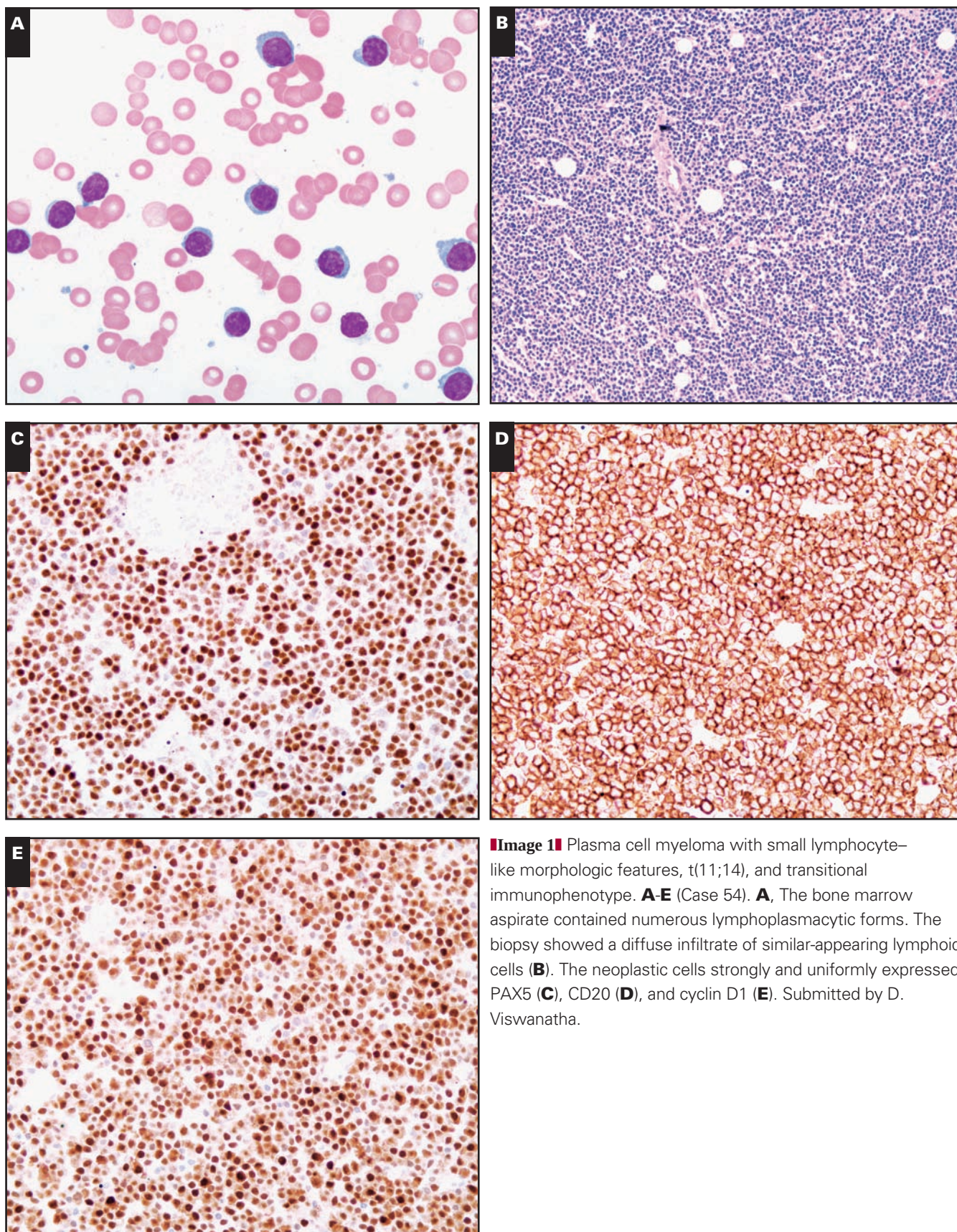


**Image 1** Plasma cell myeloma with small lymphocyte–like morphologic features, t(11;14), and transitional immunophenotype. **A–E** (Case 54). **A**, The bone marrow aspirate contained numerous lymphoplasmacytic forms. The biopsy showed a diffuse infiltrate of similar-appearing lymphoid cells (**B**). The neoplastic cells strongly and uniformly expressed PAX5 (**C**), CD20 (**D**), and cyclin D1 (**E**). Submitted by D. Viswanatha.

F

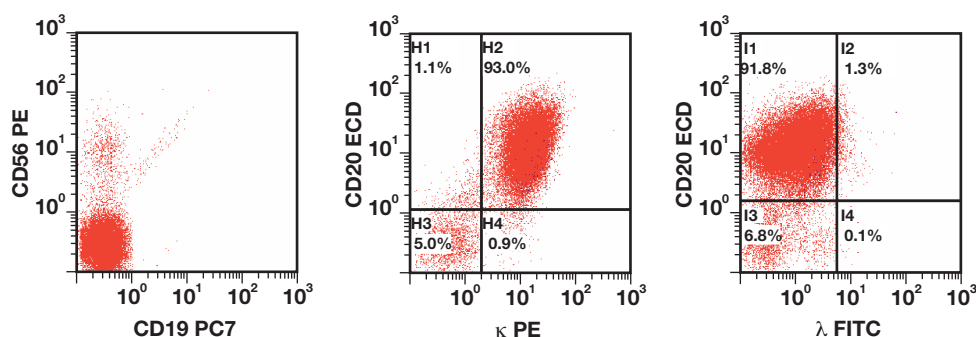


**Image 1** (cont) **F** (Case 63), The neoplastic cells were negative for CD19 and CD56 but strongly CD20+ with moderately bright surface  $\kappa$  light chain expression. Submitted by M. Xie and M. Smith.

## PCM With Uncommon Immunoglobulin Isotypes or Perturbed Immunoglobulin Secretion

### 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).<sup>12</sup> 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.<sup>9</sup> 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,<sup>13</sup> 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 **Image 2**. While the IgM paraproteinemia raises a differential diagnosis of other B-lymphoid malignancies clinically, most cases of IgM-expressing PCM are not usually diagnostically challenging from a pathologic perspective. Detection of the t(11;14) by FISH or demonstration of cyclin D1 positivity is diagnostically helpful in these cases. Finally, it should be remembered that because of the rarity of IgM PCM, most t(11;14)+ PCMs are associated with an IgG, IgA, or light chain paraprotein.

### PCM, Nonsecretory Variant

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.<sup>14</sup> However, many

nonsecretory PCMs maintain some minimal level of secretory activity because approximately 70% are associated with abnormal ratios of free  $\kappa$  and  $\lambda$  serum light chains.<sup>15</sup> 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.<sup>16,17</sup>

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 **Image 3**. Both cases had primary leukemic involvement and contained the t(11;14), which is associated with PC leukemia (PCL) and nonsecretory disease.<sup>18–20</sup> One patient had marked leukocytosis (case 280) with atypical lymphoid cells in the peripheral blood. By flow cytometry, these cells were CD45<sup>dim</sup> 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  $\mu$  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.<sup>21</sup> One case of PCM with associated CSH was submitted to the workshop (case 265). As is typical for this unusual myeloma variant,

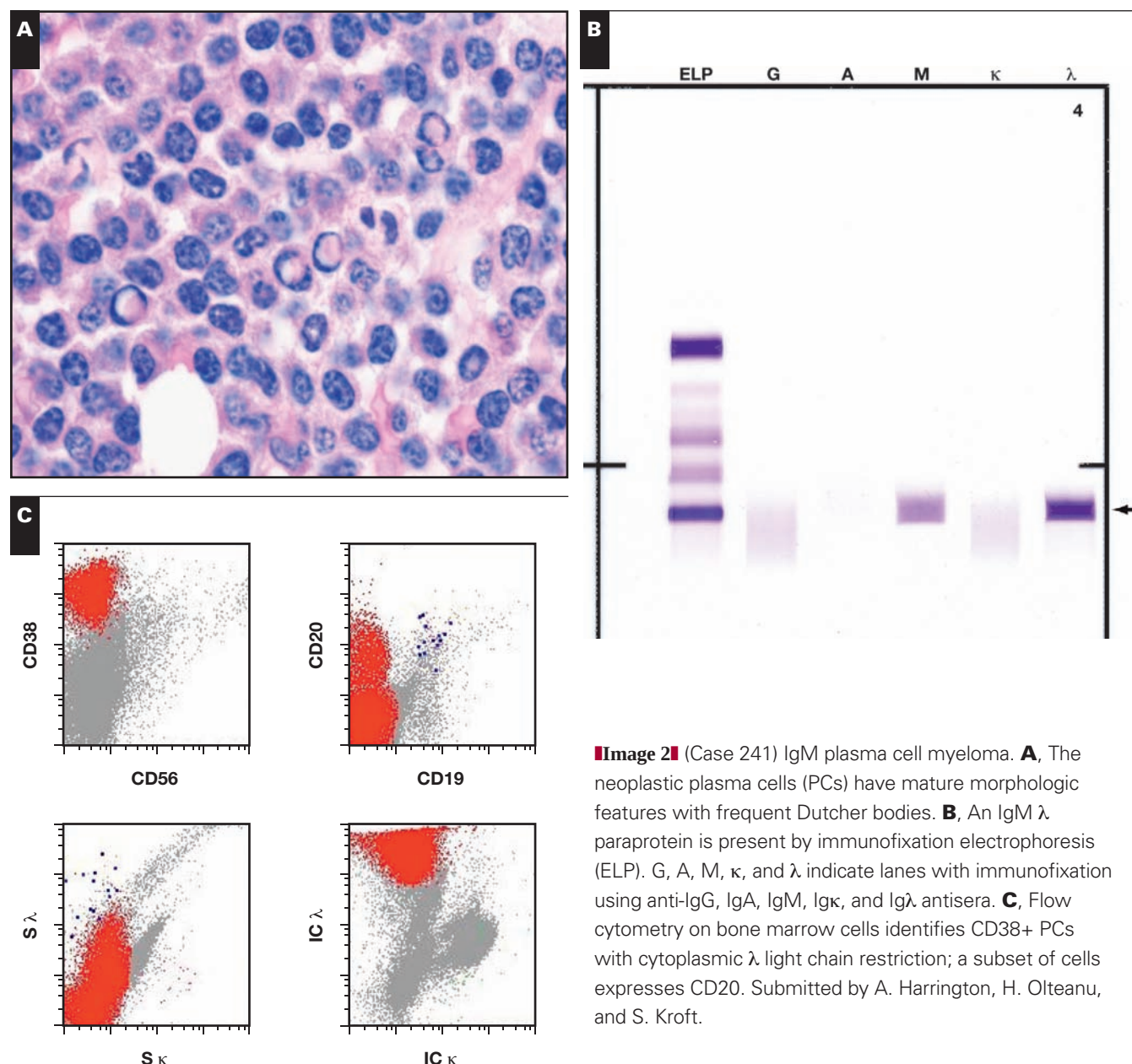


**Image 2** (Case 241) IgM plasma cell myeloma. **A**, The neoplastic plasma cells (PCs) have mature morphologic features with frequent Dutcher bodies. **B**, An IgM  $\lambda$  paraprotein is present by immunofixation electrophoresis (ELP). G, A, M,  $\kappa$ , and  $\lambda$  indicate lanes with immunofixation using anti-IgG, IgA, IgM, Ig $\kappa$ , and Ig $\lambda$  antisera. **C**, Flow cytometry on bone marrow cells identifies CD38+ PCs with cytoplasmic  $\lambda$  light chain restriction; a subset of cells expresses CD20. Submitted by A. Harrington, H. Olteanu, and S. Kroft.

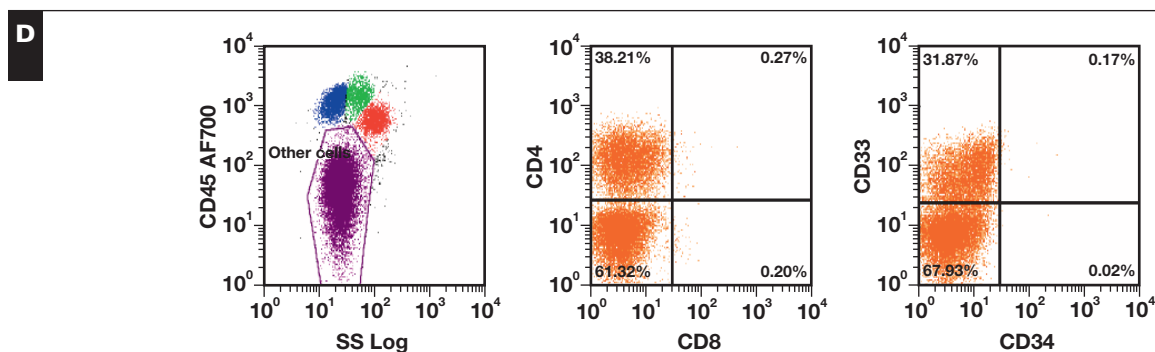
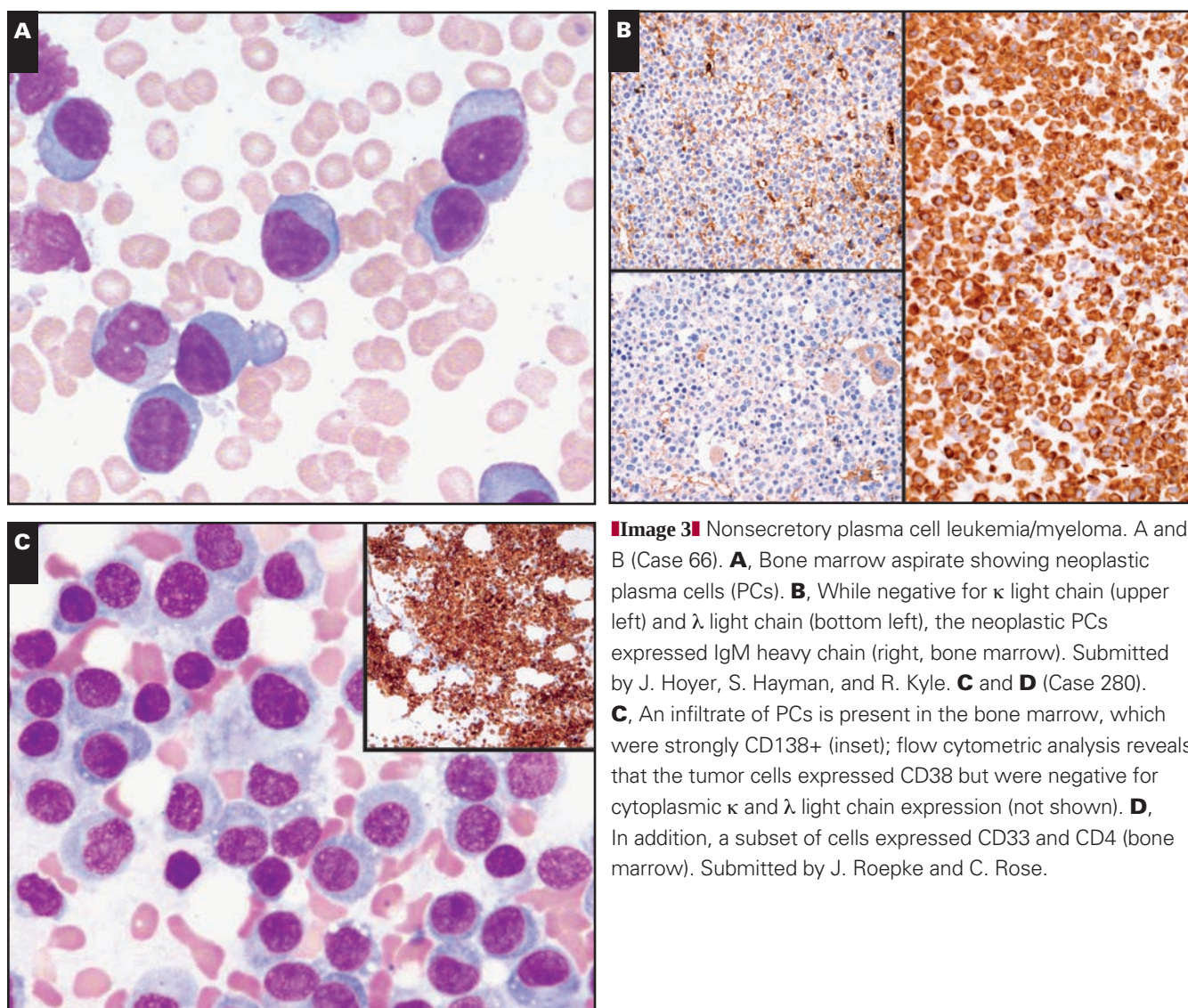
the neoplastic PCs also contain prominent immunoglobulin inclusions and express  $\kappa$  light chain **Image 4**. The molecular basis for the crystal formation has not been defined in most reported cases. In 1 study, proteomic analysis identified several  $\kappa$  light chain amino acid substitutions, including rare ones that may disrupt hydrophobic interactions within the light chain.<sup>22</sup>

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

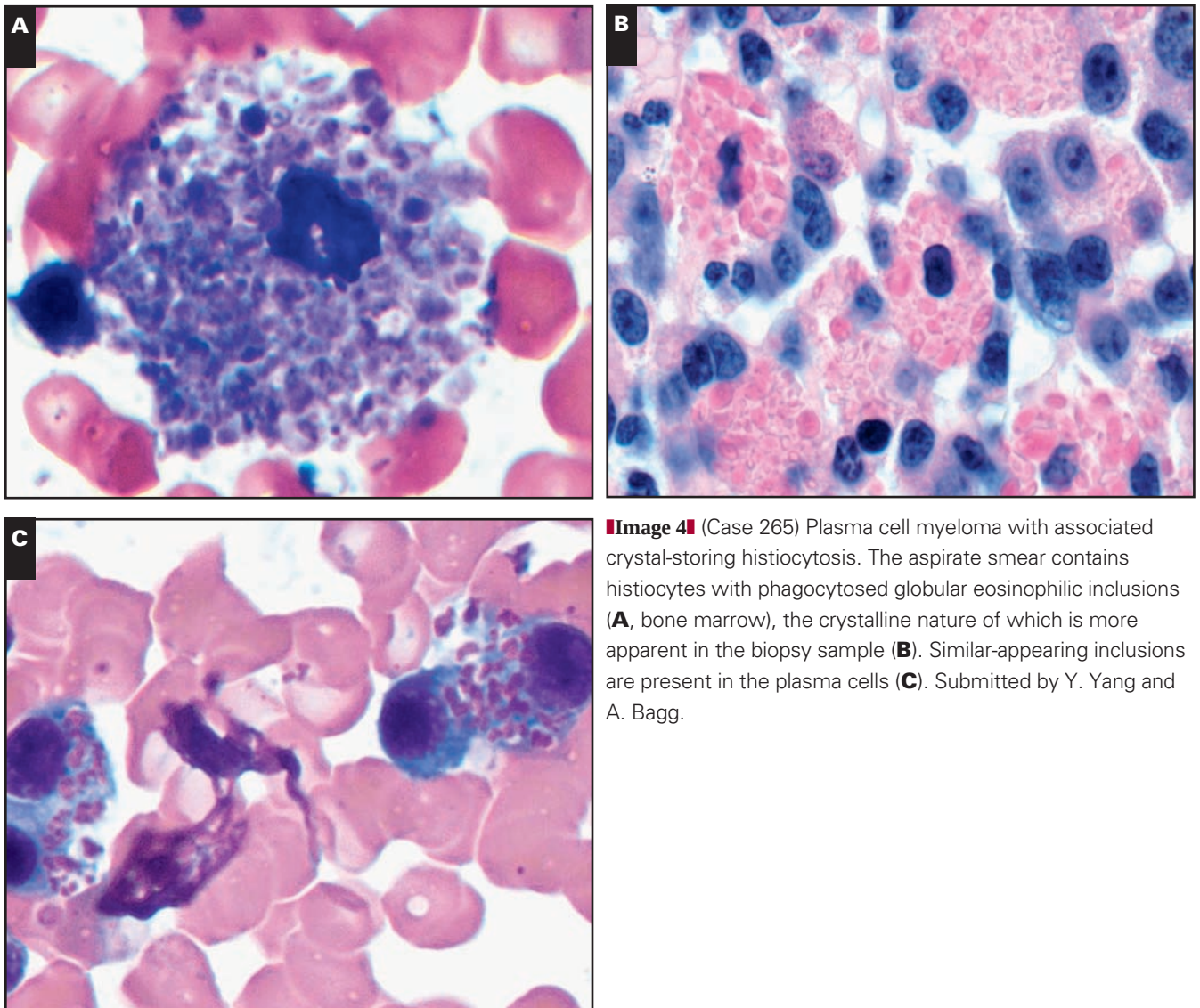


**Image 4** (Case 265) Plasma cell myeloma with associated crystal-storing histiocytosis. The aspirate smear contains histiocytes with phagocytosed globular eosinophilic inclusions (**A**, bone marrow), the crystalline nature of which is more apparent in the biopsy sample (**B**). Similar-appearing inclusions are present in the plasma cells (**C**). Submitted by Y. Yang and A. Bagg.

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.<sup>23,24</sup> Molecular analyses have confirmed that in most patients with CLL and PCM, the 2 neoplasms are clonally unrelated.<sup>25-29</sup>

## 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  $2 \times 10^9/L$  circulating PCs or more than 20% of nucleated peripheral blood cells.<sup>30</sup> 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.<sup>18,20,31-33</sup> 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 **Image 5**.<sup>34</sup> Immunophenotypically, PCL shows less frequent expression of CD56 (neural cell adhesion molecule) and more common CD20 expression than conventional PCM.<sup>32,35</sup> 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.<sup>18,20,36</sup> Aberrations of *MYC* are common in PCL and are associated with aggressive clinical behavior.<sup>37</sup> The specific features of PCL were also reflected in the cases

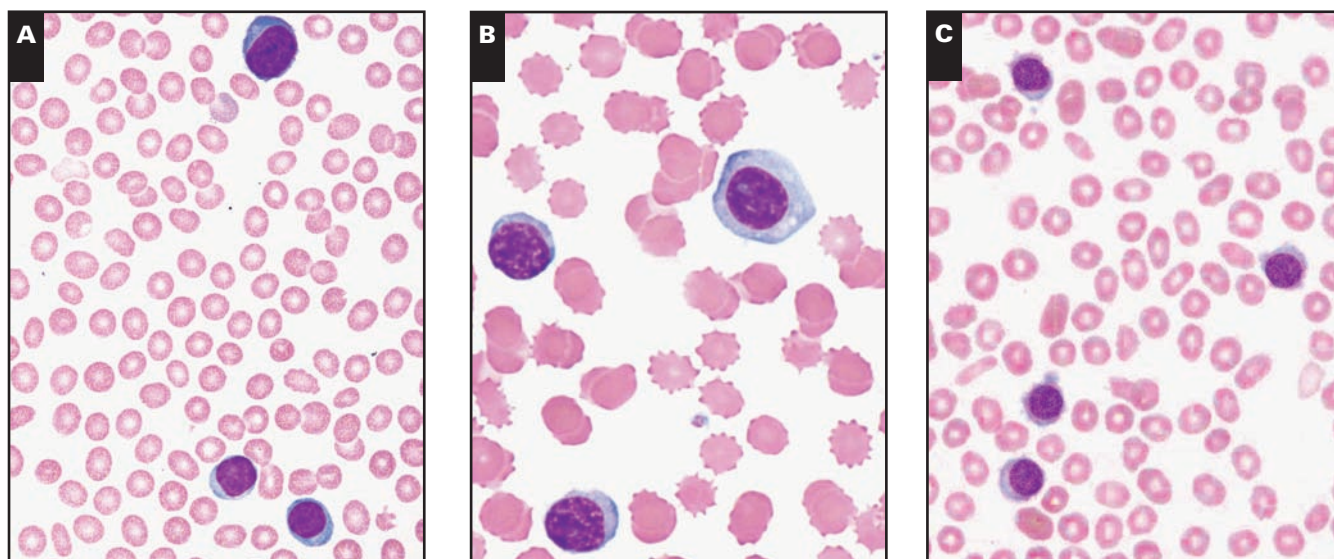


**Image 5** Morphologic spectrum of plasma cell leukemia (PCL). **A** (Case 66), Submitted by J. Hoyer, S. Hayman, and R. Kyle. **B** (Case 247), Submitted by S. Chen, T. Barry, V. Cruz, M. Hibbard, A. Hii, V. Chizhevsky, and D. O'Malley. **C** (Case 280), PCL with villous cytoplasmic projections. Submitted by J. Roepke and C. Rose.

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.

### 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).<sup>14</sup> SOPs primarily involve the axial skeleton and frequently progress to disseminated PCM.<sup>38-41</sup> 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.<sup>38</sup>

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.

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) **Image 6**. 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.<sup>42</sup> 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.<sup>43</sup> 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

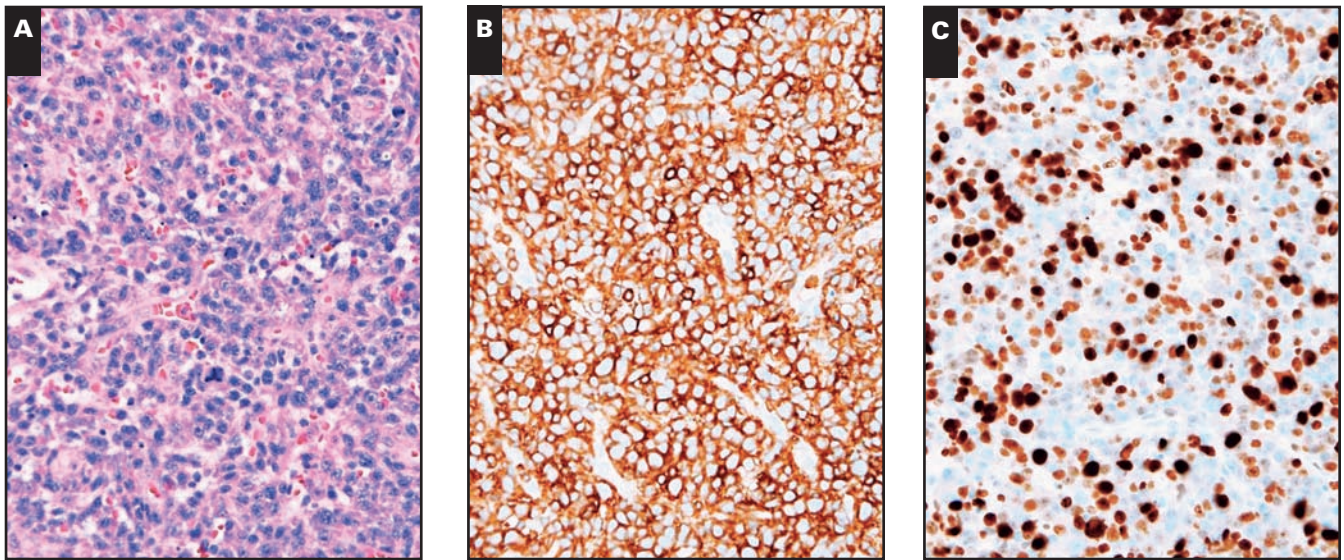


**Image 6** (Case 91) Primary extramedullary plasmacytoma. **A**, An infiltrate of atypical plasma cells is present in the nasal submucosa. These cells express CD45 (**B**) and CD138 but are negative for CD56. **C**, There is moderately high proliferative activity, with Ki-67 labeling of approximately 50% of neoplastic cells. Submitted by J. Frater and J. Klcó.

the presenting feature of PCM and, in such circumstances, may closely mimic B-cell lymphomas with plasmacytic differentiation such as MALT lymphoma. In both cases, the patients had gastric involvement. In 1 case (case 228), the neoplastic PCs strongly expressed cyclin D1, excluding MALT lymphoma. The second case (case 230) was more challenging in that it was negative for cyclin D1 and the appropriate diagnosis was indicated only by the lack of immunoglobulin heavy chain expression by the neoplastic PCs and the subsequent clinical course with rapid progression to PCM with multiple osteolytic lesions **Image 7**.

### 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 al<sup>44,45</sup> and the cytologic features–based system proposed by Greipp and colleagues.<sup>46</sup>

Under the criteria of Greipp and colleagues,<sup>46</sup> plasmablastic myeloma cells are defined as having a large,

centrally placed nucleus (>10  $\mu\text{m}$  in diameter) or a nucleolus (>2  $\mu\text{m}$  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.<sup>46</sup>

By contrast, in the grading scheme of Bartl et al,<sup>44,45</sup> 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,<sup>44,45</sup> 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.<sup>44-46</sup>

In subsequent studies, the independent prognostic impact was confirmed also for patients treated with modern therapeutic strategies, including autologous bone marrow transplantation.<sup>47,48</sup> 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

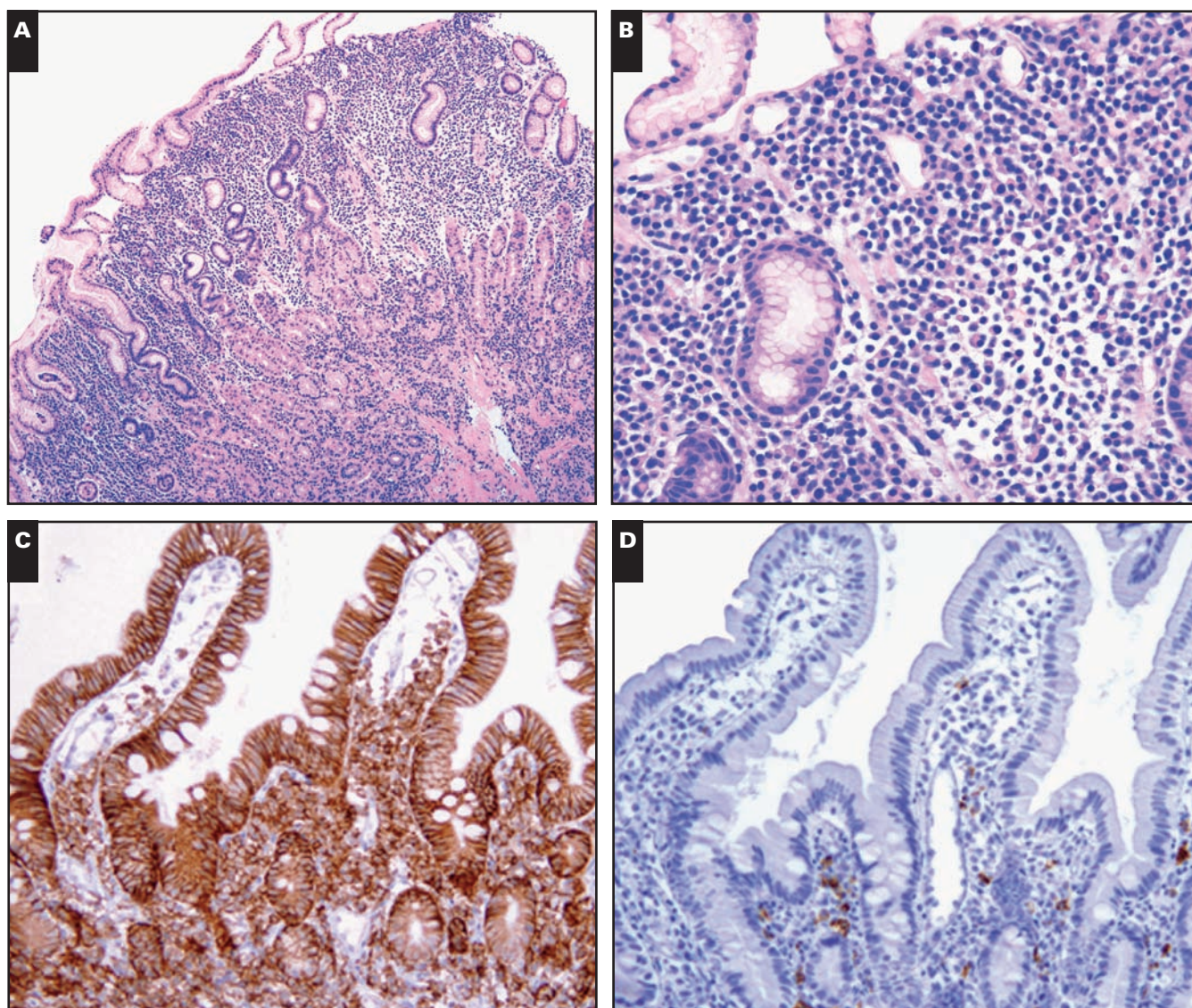


**Image 7** (Case 230) Extramedullary (gastric) manifestation of plasma cell myeloma (PCM) mimicking mucosa-associated lymphoid tissue lymphoma. Dense infiltrate of cells present in the gastric lamina propria (**A**) that, on higher power (**B**), is composed predominantly of mature-appearing plasma cells (PCs).

to which cytomorphic features correlate with other established risk factors is largely undefined.<sup>49</sup> It is important to note that both grading schema predate the advent of newer antimyeloma therapeutics such as thalidomide and bortezomib, which have been shown to profoundly affect the risk associated with individual cytogenetic aberrations.<sup>50,51</sup> Whether plasmablastic morphologic features will retain any prognostic importance for patients treated with these newer drugs is unknown.

A total of 19 cases diagnosed as plasmablastic PCM by the submitter were presented at the workshop, more than two thirds with extramedullary involvement. The criteria used for diagnosing plasmablastic PCM in the submitted cases reflected the lack of a clear-cut consensus in the literature. The workshop panel concurred with a diagnosis of plasmablastic

PC neoplasm/plasmablastic PCM in 13 of 19 cases (cases 87, 95, 101, 122, 125, 214, 232, 273, 312, 314, 317, 351, and 368)

**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.<sup>52</sup>

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

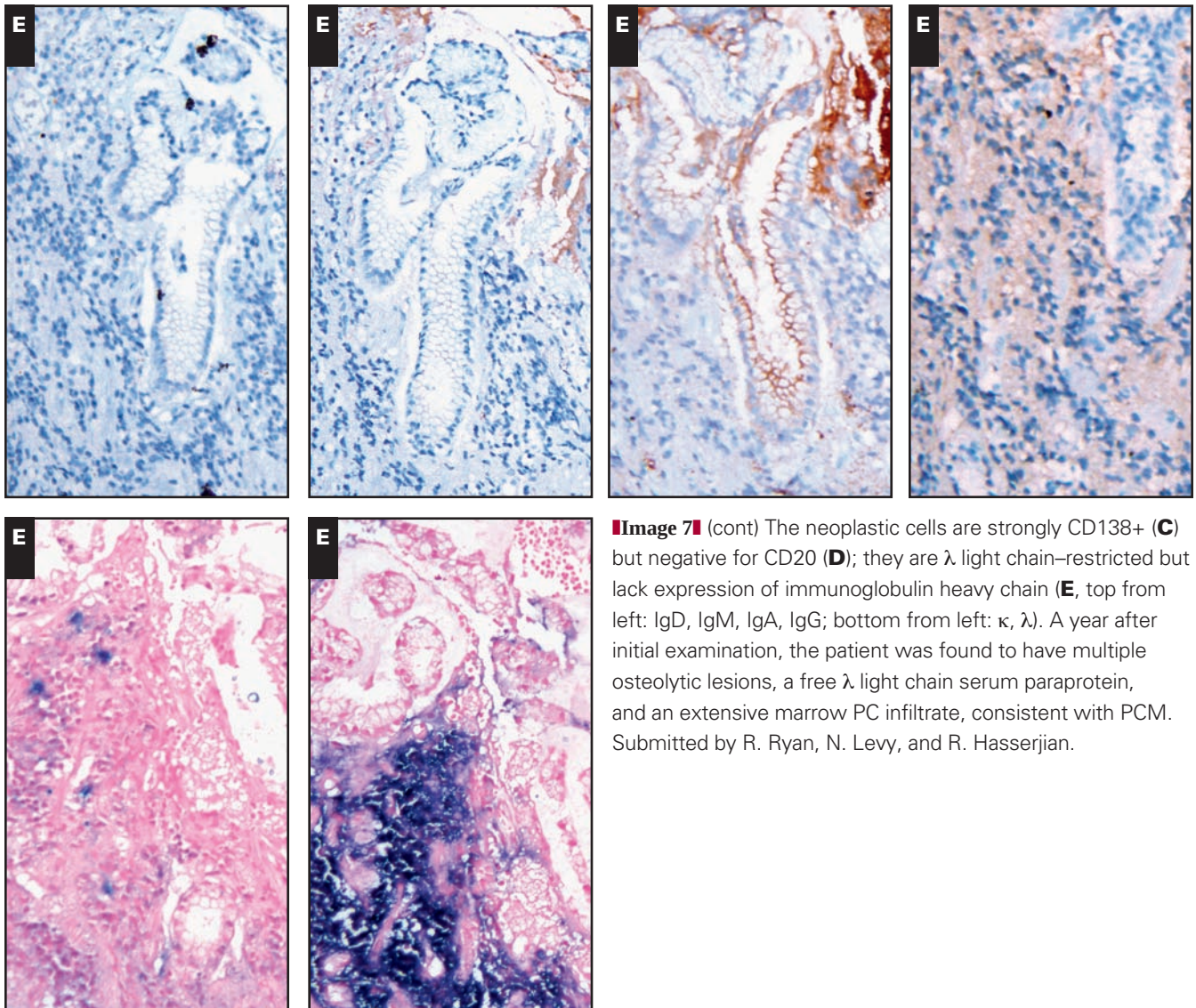


**Image 7I (cont)** The neoplastic cells are strongly CD138+ (**C**) but negative for CD20 (**D**); they are  $\lambda$  light chain–restricted but lack expression of immunoglobulin heavy chain (**E**, top from left: IgD, IgM, IgA, IgG; bottom from left:  $\kappa$ ,  $\lambda$ ). A year after initial 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.<sup>53</sup> 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*.<sup>3,4,37,54-62</sup>

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.<sup>3</sup> 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

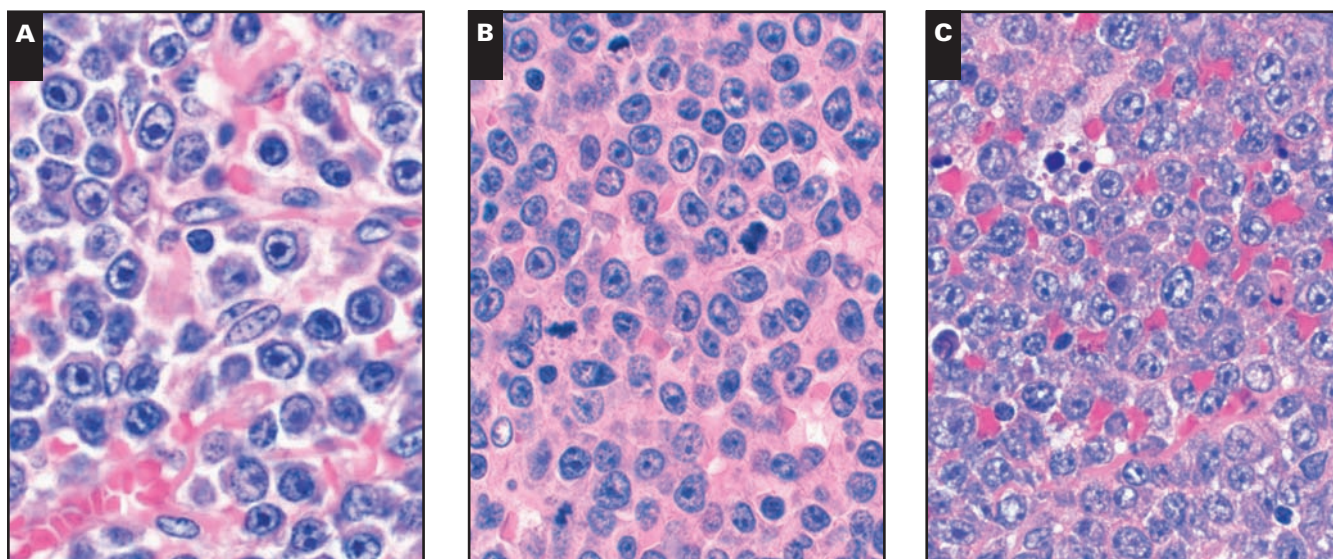


**Image 8** Morphologic spectrum of plasmablastic plasma cell myeloma (PCM). **A** (Case 95), Extramedullary PCM in a cervical node with a complex karyotype with t(8;14). Submitted by C. Wilson. **B** (Case 314), Extramedullary PCM involving the skin. Submitted by J Burke. Fluorescence in situ hybridization (FISH) confirmed a translocation targeting *c-MYC*. **C** (Case 351), Intracranial extramedullary PCM. Cytogenetics revealed a complex karyotype; this case was positive for a *c-MYC* rearrangement by FISH. Submitted by M. Djokic. All 3 cases showed concomitant or antecedent bone marrow infiltration by PCM. Note the large, immunoblast-like nuclei with large central nucleoli and the narrow, sometimes basophilic cytoplasm without prominent perinuclear hofs.

*MYC* expression is associated with clinical behavior.<sup>4,63,64</sup> 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.<sup>65</sup> PBL was subsequently shown to encompass tumors with a broader range of plasmacytic differentiation than was initially appreciated.

Colomo et al<sup>66</sup> 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

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.<sup>67</sup> 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,<sup>68</sup> 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 al<sup>68</sup> 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.<sup>69</sup> Furthermore, Taddesse-Heath et al<sup>70</sup> 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).<sup>71</sup> 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.

*From the Departments of <sup>1</sup>Pathology, University of Arkansas for Medical Sciences, Little Rock; <sup>2</sup>Clinical Pathology, Cleveland Clinic, Cleveland OH; <sup>3</sup>Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN; and <sup>4</sup>Institute of Pathology, University Hospital Tuebingen, Eberhard-Karls University, Tuebingen, Germany.*

*Address reprint requests to Dr Lorsbach: RLorsbach@uams.edu; or Dr Fend: Falko.Fend@med.uni-tuebingen.de.*

*Acknowledgments: We thank the workshop participants for their case submissions and use of images.*

## References

1. Chng WJ, Glebov O, Bergsagel PL, et al. Genetic events in the pathogenesis of multiple myeloma. *Best Pract Res Clin Haematol.* 2007;20:571-596.
2. Bergsagel PL, Kuehl WM. Molecular pathogenesis and a consequent classification of multiple myeloma. *J Clin Oncol.* 2005;23:6333-6338.
3. Avet-Loiseau H, Gerson F, Magrangeas F, et al. Rearrangements of the c-myc oncogene are present in 15% of primary human multiple myeloma tumors. *Blood.* 2001;98:3082-3086.
4. Shou Y, Martelli ML, Gabrea A, et al. Diverse karyotypic abnormalities of the c-myc locus associated with c-myc dysregulation and tumor progression in multiple myeloma. *Proc Natl Acad Sci U S A.* 2000;97:228-233.
5. Liang W, Hopper JE, Rowley JD. Karyotypic abnormalities and clinical aspects of patients with multiple myeloma and related paraproteinemic disorders. *Cancer.* 1979;44:630-644.
6. Chesi M, Bergsagel PL, Brents LA, et al. Dysregulation of cyclin D1 by translocation into an IgH gamma switch region in two multiple myeloma cell lines. *Blood.* 1996;88:674-681.
7. Hoyer JD, Hanson CA, Fonseca R, et al. The (11;14) (q13;q32) translocation in multiple myeloma: a morphologic and immunohistochemical study. *Am J Clin Pathol.* 2000;113:831-837.
8. Cook JR, Hsi ED, Worley S, et al. Immunohistochemical analysis identifies two cyclin D1+ subsets of plasma cell myeloma, each associated with favorable survival. *Am J Clin Pathol.* 2006;125:615-624.
9. Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc.* 2003;78:21-33.
10. Slotta-Huspenina J, Koch I, Richter M, et al. Cyclin D1 positive multiple myeloma: predominance of the short, 3'UTR-deficient transcript is associated with high cyclin D1 mRNA levels in cases with t(11;14) translocation, but does not correlate with proliferation rate or genomic deletions. *Leuk Res.* 2008;32:79-88.
11. Robillard N, Avet-Loiseau H, Garand R, et al. CD20 is associated with a small mature plasma cell morphology and t(11;14) in multiple myeloma. *Blood.* 2003;102:1070-1071.
12. Lin P, Hao S, Handy BC, et al. Lymphoid neoplasms associated with IgM paraprotein: a study of 382 patients. *Am J Clin Pathol.* 2005;123:200-205.

13. Feyler S, O'Connor SJ, Rawstron AC, et al. IgM myeloma: a rare entity characterized by a CD20–CD56–CD117–immunophenotype and the t(11;14). *Br J Haematol*. 2008;140:547-551.
14. Swerdlow SH, Campo E, Harris NL, et al, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. Lyon, France: IARC Press; 2008.
15. Drayson M, Tang LX, Drew R, et al. Serum free light-chain measurements for identifying and monitoring patients with nonsecretory multiple myeloma. *Blood*. 2001;97:2900-2902.
16. Dul JL, Argon Y. A single amino acid substitution in the variable region of the light chain specifically blocks immunoglobulin secretion. *Proc Natl Acad Sci U S A*. 1990;87:8135-8139.
17. Coriu D, Weaver K, Schell M, et al. A molecular basis for nonsecretory myeloma. *Blood*. 2004;104:829-831.
18. Avet-Loiseau H, Daviet A, Brigaudeau C, et al. Cytogenetic, interphase, and multicolor fluorescence in situ hybridization analyses in primary plasma cell leukemia: a study of 40 patients at diagnosis, on behalf of the Intergroupe Francophone du Myelome and the Groupe Français de Cytogenetique Hematologique. *Blood*. 2001;97:822-825.
19. Avet-Loiseau H, Garand R, Lode L, et al. Translocation t(11;14)(q13;q32) is the hallmark of IgM, IgE, and nonsecretory multiple myeloma variants. *Blood*. 2003;101:1570-1571.
20. Tiedemann RE, Gonzalez-Paz N, Kyle RA, et al. Genetic aberrations and survival in plasma cell leukemia. *Leukemia*. 2008;22:1044-1052.
21. Jones D, Bhatia VK, Krausz T, et al. Crystal-storing histiocytosis: a disorder occurring in plasmacytic tumors expressing immunoglobulin kappa light chain. *Hum Pathol*. 1999;30:1441-1448.
22. Lebeau A, Zeindl-Eberhart E, Muller EC, et al. Generalized crystal-storing histiocytosis associated with monoclonal gammopathy: molecular analysis of a disorder with rapid clinical course and review of the literature. *Blood*. 2002;100:1817-1827.
23. Seegmiller AC, Xu Y, McKenna RW, et al. Immunophenotypic differentiation between neoplastic plasma cells in mature B-cell lymphoma vs plasma cell myeloma. *Am J Clin Pathol*. 2007;127:176-181.
24. Morice WG, Chen D, Kurtin PJ, et al. Novel immunophenotypic features of marrow lymphoplasmacytic lymphoma and correlation with Waldenström's macroglobulinemia. *Mod Pathol*. 2009;22:807-816.
25. Brouet JC, Feraud JP, Laurent G, et al. The association of chronic lymphocytic leukaemia and multiple myeloma: a study of eleven patients. *Br J Haematol*. 1985;59:55-66.
26. Feraud JP, James JM, Herait P, et al. Associated chronic lymphocytic leukemia and multiple myeloma: origin from a single clone. *Blood*. 1985;66:291-293.
27. Kaufmann H, Ackermann J, Nosslinger T, et al. Absence of clonal chromosomal relationship between concomitant B-CLL and multiple myeloma: a report on two cases. *Ann Hematol*. 2001;80:474-478.
28. Chang H, Wechalekar A, Li L, et al. Molecular cytogenetic abnormalities in patients with concurrent chronic lymphocytic leukemia and multiple myeloma shown by interphase fluorescence in situ hybridization: evidence of distinct clonal origin. *Cancer Genet Cytogenet*. 2004;148:44-48.
29. Pantic M, Schroettner P, Pfeifer D, et al. Biclinal origin prevails in concomitant chronic lymphocytic leukemia and multiple myeloma. *Leukemia*. 2010;24:885-890.
30. Kyle RA, Maldonado JE, Bayrd ED. Plasma cell leukemia: report on 17 cases. *Arch Intern Med*. 1974;133:813-818.
31. Dimopoulos MA, Palumbo A, Delasalle KB, et al. Primary plasma cell leukaemia. *Br J Haematol*. 1994;88:754-759.
32. Garcia-Sanz R, Orfao A, Gonzalez M, et al. Primary plasma cell leukemia: clinical, immunophenotypic, DNA ploidy, and cytogenetic characteristics. *Blood*. 1999;93:1032-1037.
33. Saccaro S, Fonseca R, Veillon DM, et al. Primary plasma cell leukemia: report of 17 new cases treated with autologous or allogeneic stem-cell transplantation and review of the literature. *Am J Hematol*. 2005;78:288-294.
34. Tanioka F, Tamashima S, Shimizu S, et al. A case of primary plasma cell leukemia with hairy-cell morphology and lambda-type Bence-Jones protein: immunohistochemical and molecular analysis. *Jpn J Clin Oncol*. 2003;33:232-237.
35. Pellat-Deceunynck C, Barille S, Jego G, et al. The absence of CD56 (NCAM) on malignant plasma cells is a hallmark of plasma cell leukemia and of a special subset of multiple myeloma. *Leukemia*. 1998;12:1977-1982.
36. Gutierrez NC, Hernandez JM, Garcia JL, et al. Differences in genetic changes between multiple myeloma and plasma cell leukemia demonstrated by comparative genomic hybridization. *Leukemia*. 2001;15:840-845.
37. Chiecchio L, Dagrada GP, White HE, et al. Frequent upregulation of MYC in plasma cell leukemia. *Genes Chromosomes Cancer*. 2009;48:624-636.
38. Soutar R, Lucraft H, Jackson G, et al. Guidelines on the diagnosis and management of solitary plasmacytoma of bone and solitary extramedullary plasmacytoma. *Br J Haematol*. 2004;124:717-726.
39. Dore G, Landgren O, McGlynn KA, et al. Plasmacytoma of bone, extramedullary plasmacytoma, and multiple myeloma: incidence and survival in the United States, 1992-2004. *Br J Haematol*. 2009;144:86-94.
40. Knobel D, Zouhair A, Tsang RW, et al. Prognostic factors in solitary plasmacytoma of the bone: a multicenter Rare Cancer Network study. *BMC Cancer*. 2006;6:118. doi:10.1186/1471-2407-6-118.
41. Ramsingh G, Mehan P, Morgensztern D, et al. Prognostic factors influencing survival in solitary plasmacytoma. *Br J Haematol*. 2009;145:540-542.
42. Kremer M, Ott G, Nathrath M, et al. Primary extramedullary plasmacytoma and multiple myeloma: phenotypic differences revealed by immunohistochemical analysis. *J Pathol*. 2005;205:92-101.
43. Bink K, Haralambieva E, Kremer M, et al. Primary extramedullary plasmacytoma: similarities with and differences from multiple myeloma revealed by interphase cytogenetics. *Haematologica*. 2008;93:623-626.
44. Bartl R, Frisch B, Burkhardt R, et al. Bone marrow histology in myeloma: its importance in diagnosis, prognosis, classification and staging. *Br J Haematol*. 1982;51:361-375.
45. Bartl R, Frisch B, Fateh-Moghadam A, et al. Histologic classification and staging of multiple myeloma: a retrospective and prospective study of 674 cases. *Am J Clin Pathol*. 1987;87:342-355.
46. Greipp PR, Raymond NM, Kyle RA, et al. Multiple myeloma: significance of plasmablastic subtype in morphological classification. *Blood*. 1985;65:305-310.
47. Greipp PR, Leong T, Bennett JM, et al. Plasmablastic morphology: an independent prognostic factor with clinical and laboratory correlates: Eastern Cooperative Oncology Group (ECOG) Myeloma Trial E9486 report by the ECOG Myeloma Laboratory Group. *Blood*. 1998;91:2501-2507.

48. Rajkumar SV, Fonseca R, Lacy MQ, et al. Plasmablastic morphology is an independent predictor of poor survival after autologous stem-cell transplantation for multiple myeloma. *J Clin Oncol*. 1999;17:1551-1557.
49. Weh HJ, Bartl R, Seeger D, et al. Correlations between karyotype and cytologic findings in multiple myeloma. *Leukemia*. 1995;9:2119-2122.
50. Kapoor P, Kumar S, Fonseca R, et al. Impact of risk stratification on outcome among patients with multiple myeloma receiving initial therapy with lenalidomide and dexamethasone. *Blood*. 2009;114:518-521.
51. Reece D, Song KW, Fu T, et al. Influence of cytogenetics in patients with relapsed or refractory multiple myeloma treated with lenalidomide plus dexamethasone: adverse effect of deletion 17p13. *Blood*. 2009;114:522-525.
52. Fassas AB, Muwalla F, Berryman T, et al. Myeloma of the central nervous system: association with high-risk chromosomal abnormalities, plasmablastic morphology and extramedullary manifestations. *Br J Haematol*. 2002;117:103-108.
53. Hallek M, Bergsagel PL, Anderson KC. Multiple myeloma: increasing evidence for a multistep transformation process. *Blood*. 1998;91:3-21.
54. Neri A, Murphy JP, Cro L, et al. *Ras* oncogene mutation in multiple myeloma. *J Exp Med*. 1989;170:1715-1725.
55. Portier M, Moles JP, Mazars GR, et al. *p53* and *RAS* gene mutations in multiple myeloma. *Oncogene*. 1992;7:2539-2543.
56. Liu P, Leong T, Quam L, et al. Activating mutations of N- and K-*ras* in multiple myeloma show different clinical associations: analysis of the Eastern Cooperative Oncology Group Phase III Trial. *Blood*. 1996;88:2699-2706.
57. Drach J, Ackermann J, Fritz E, et al. Presence of a *p53* gene deletion in patients with multiple myeloma predicts for short survival after conventional-dose chemotherapy. *Blood*. 1998;92:802-809.
58. Avet-Loiseau H, Li JY, Godon C, et al. *p53* deletion is not a frequent event in multiple myeloma. *Br J Haematol*. 1999;106:717-719.
59. Bezieau S, Devilder MC, Avet-Loiseau H, et al. High incidence of N and K-*Ras* activating mutations in multiple myeloma and primary plasma cell leukemia at diagnosis. *Hum Mutat*. 2001;18:212-224.
60. Chang H, Qi C, Yi QL, et al. *p53* gene deletion detected by fluorescence in situ hybridization is an adverse prognostic factor for patients with multiple myeloma following autologous stem cell transplantation. *Blood*. 2005;105:358-360.
61. Chiecchio L, Dagrada GP, Protheroe RK, et al. Loss of 1p and rearrangement of MYC are associated with progression of smouldering myeloma to myeloma: sequential analysis of a single case. *Haematologica*. 2009;94:1024-1028.
62. Fonseca R, Bergsagel PL, Drach J, et al. International Myeloma Working Group Molecular Classification of Multiple Myeloma: spotlight review. *Leukemia*. 2009;23:2210-2221.
63. Bergsagel PL, Kuehl WM. Chromosome translocations in multiple myeloma. *Oncogene*. 2001;20:5611-5622.
64. Chesi M, Kuehl WM, Bergsagel PL. Recurrent immunoglobulin gene translocations identify distinct molecular subtypes of myeloma. *Ann Oncol*. 2000;11(suppl 1):131-135.
65. Delecluse HJ, Anagnostopoulos I, Dallenbach F, et al. Plasmablastic lymphomas of the oral cavity: a new entity associated with the human immunodeficiency virus infection. *Blood*. 1997;89:1413-1420.
66. Colomo L, Loong F, Rives S, et al. Diffuse large B-cell lymphomas with plasmablastic differentiation represent a heterogeneous group of disease entities. *Am J Surg Pathol*. 2004;28:736-747.
67. Aguilera NS, Kapadia SB, Nalesnik MA, et al. Extramedullary plasmacytoma of the head and neck: use of paraffin sections to assess clonality with in situ hybridization, growth fraction, and the presence of Epstein-Barr virus. *Mod Pathol*. 1995;8:503-508.
68. Chang ST, Liao YL, Lu CL, et al. Plasmablastic cytomorphologic features in plasma cell neoplasms in immunocompetent patients are significantly associated with EBV. *Am J Clin Pathol*. 2007;128:339-344.
69. Bogusz AM, Seegmiller AC, Garcia R, et al. Plasmablastic lymphomas with MYC/IgH rearrangement: report of three cases and review of the literature. *Am J Clin Pathol*. 2009;132:597-605.
70. Taddesse-Heath L, Meloni-Ehrig A, Scheerle J, et al. Plasmablastic lymphoma with MYC translocation: evidence for a common pathway in the generation of plasmablastic features [published online ahead of print March 26, 2010]. *Mod Pathol*. 2010;23:991-9999. doi:10.1038/modpathol.2010.72.
71. Dong HY, Scadden DT, de Leval L, et al. Plasmablastic lymphoma in HIV-positive patients: an aggressive Epstein-Barr virus-associated extramedullary plasmacytic neoplasm. *Am J Surg Pathol*. 2005;29:1633-1641.