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Case Series

Plasma Cell Neoplasms with Unusual Anatomic Locations, Morphology, Phenotype, and Review of Literature: A Case Series

Azal Alani, Jui Choudhuri, Ryan J. Malonis, Oleksii Iakymenko, Yang Shi, Qing Wang, Xuejun Tian, Yanan Fang and Yanhua Wang*

Department of Pathology, Montefiore Medical Center/Albert Einstein College of Medicine, New York, USA

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Abstract

Background and objectives: Plasma cell neoplasms are well-known for having diverse morphological and phenotype presentations and less commonly unusual immunophenotypical profiles. Such unexpected immunophenotypical variability could lead to inaccurate impressions upon initial assessment, thus delaying an accurate diagnosis. Here, the authors report seven plasma cell neoplasm cases with unusual morphology, immunophenotype, or unusual anatomic locations from the archives of Montefiore Medical Center Hematopathology department to highlight key considerations involved in diagnosing plasma cell neoplasms. ***Methods:*** The authors reviewed the 2015 to 2022 electronic medical records at Montefiore Medical Center and identified seven plasma cell neoplasm cases with unusual immunophenotypes as well as anatomic localization. Clinical information including demographics, patient history, clinical presentation, and treatment was retrieved along with pertinent laboratory data. Cell morphology and immunohistochemistry were evaluated from formalin-fixed, paraffin-embedded biopsy specimens stained with hematoxylin and eosin (H&E). Morphologic features and immunophenotype determined by flow cytometry and immunohistochemistry were reviewed, along with molecular and cytogenetic studies. ***Results:*** The analysis of the cases underscores the diagnostic complexity associated with the diverse array of morphological and immunophenotypic features of plasma cell neoplasms and offers insight into overcoming diagnostic challenges while avoiding potential pitfalls. ***Conclusions:*** Awareness of the spectrum of morphological and immunophenotypic variability in plasma cell neoplasms is key to avoiding misdiagnosing variants and delaying clinical workup. Due to the rarity of most variants described in this study, the authors find themselves short of providing an accurate incidence rate and the prognostic impact of these variants. Correlation with clinical and laboratory findings and evaluation by immunostaining to confirm plasma cell origin is necessary to reach a correct diagnosis.

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Introduction

Plasma cells are the final stage of mature differentiation of B cells. Mature plasma cells usually show eccentric nuclei, clock face chromatin, and pinkish cytoplasm on Hematoxylin and Eosin (H&E) stained slides. A plasma cell neoplasm is defined as an abnormal clonal plasma cell proliferation invading bone marrow, blood, and other organs or tissues.[1] Depending on the clinical presentations and laboratory findings, plasma cell neoplasms, according to the 2022 World Health Organization (WHO) Classification, are usually classified as monoclonal gammopathies, light or heavy chain diseases, mass-forming plasmacytoma, plasma cell myeloma, or plasma cell leukemia with their associated paraneoplastic syndromes.[2]

Unusual plasma cell neoplasm cases can be diagnostically challenging. Therefore, accurately distinguishing it from its mimics, including both hematopoietic and non-hematopoietic tumors is important to avoid delay in diagnosis and patient care.[3] Here, the authors present a series of cases that display unusual patterns of morphology, immunophenotype, and localization of plasma cell neoplasms to describe the critical considerations leading to an accurate diagnosis. The CARE guideline has been applied.

Material and methods

A retrospective search of cases from 2015 to 2022 electronic medical records at Montefiore Medical Center identified seven plasma cell neoplasm cases with unusual

Keywords: Multiple myeloma; CD138; Plasma cell; Morphology; Immunophenotype; A Case series.

Abbreviations: 1IRF4, interferon regulatory factor 4; BCL1, Cyclin D1; CD20, B-lymphocyte antigen; CD38, cluster of differentiation 38; CD43, leukosialin; CD45, protein tyrosine phosphatase, receptor type, C; CD56, neural cell adhesion molecule; CD79a, B-cell antigen receptor complex-associated protein alpha chain; CD138, syndecan-1; H&E, hematoxylin and eosin; kappa, light chain kappa; lambda, light chain lambda; MM, multiple myeloma; MUM1, multiple myeloma; MyoD1, myoblast determination protein 1; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; P53, tumor protein p53.

***Correspondence to:** Yanhua Wang, Department of Pathology, Montefiore Medical Center, 111 E 210th Street, Bronx, NY 10467, USA. ORCID: https://orcid.org/0000-0002-7946-2843. Tel: 718-920-4976, Fax: 718-920-7611, E-mail: ywang@montefiore.org

Table 1. : Description of the spectrum of cases of plasma cell neoplasms seen in our institute

Case	Age (years)	Sex	Anatomic sites	Morphology feature	Phenotype	Clinical history
1	57	M	Bladder	Anaplastic morphology	Both kappa and lambda negative	Urinary bladder mass
2	75	F	Breast	Brush pen-like crystal inclusion	CD138+, MUM1+, lambda+	Breast invasive ductal carcinoma
3	65	F	Thyroid	Anaplastic morphology	CD138+, CD43+, lambda+, P53+	Thyroid mass
4	72	M	Bone marrow	Pseudo- rosette/ glandular pattern	CD138+, MUM1-, keratin-	Status post stem cell transplant for MM
5	72	F	Bone marrow	Mixed classic and blastoid	CD138, dim and strong	IgA MM status post stem cell transplant
6	68	F	Bone marrow	Erythroid precursor morphology	CD38-, CD138+, MUM1+, kappa+	Status post stem cell transplant for MM
7	50	M	Bone marrow	Classic plasma cell morphology	CD33+, CD117+, CD138+, kappa+	Lytic bone lesion
8[6]	69	M	Heart	Spindle cell morphology	CD138 negative	Right atrium mass
9[7]	9	M	Blood, bone marrow	Normoblast and monocytoid morphology	CD138 negative, P53+	Barth syndrome status post heart transplant
10[5]	85	M	Bone marrow	Small lymphocyte like	CD20+, BCL1+, CD138+, kappa+	Lytic bone lesion

1IRF4, interferon regulatory factor 4; BCL1, Cyclin D1; CD20, B-lymphocyte antigen; CD33, siglec-3; CD38, cluster of differentiation 38; CD43, leukosialin; CD45, protein tyrosine phosphatase, receptor type, C; CD56, neural cell adhesion molecule; CD79a, CD117, proto-oncogene c-KIT; B-cell antigen receptor complex-associated protein alpha chain; CD138, syndecan-1; H&E, hematoxylin and eosin; kappa, light chain kappa; lambda, light chain lambda; MM, multiple myeloma; MUM1, multiple myeloma; MyoD1, myoblast determination protein 1; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; P53, tumor protein p53.

immunophenotypes and anatomic localization. Clinical information including demographics, patient history, clinical presentation, and treatment was retrieved along with pertinent laboratory data. Cell morphology and immunohistochemistry were evaluated from formalin-fixed, paraffin embedded bone marrow biopsy specimens stained with hematoxylin and eosin (H&E). Morphologic features, as well as immunophenotype determined by flow cytometry and immunohistochemistry were reviewed, along with molecular and cytogenetic studies. All patient information was deidentified, and the study was approved by the Montefiore Institutional Research Board (IRB).

Results

The authors present a series of seven cases collected from 2015 to 2022 at Montefiore Medical Center with unusual morphology, phenotype, or anatomic locations. The cases were diagnosed according to the 5th edition of the WHO Classification.[4] Patient clinical information, anatomic sites, morphology and immunophenotype have been summarized in Table 1.[5,6,7]

Case 1

A 57-year-old male patient presented with acute renal failure secondary to obstructive uropathy and was found to have a urinary bladder mass and retroperitoneal lymphadenopathy on both cystoscopy and imaging studies. A retroperitoneal needle core biopsy was performed initially; however, the biopsy was inadequate due to fibrosis and a severely crushed artifact. Rare spindle-shaped malignant cells with eosinophilic cytoplasm were observed, suggestive of a malignant neoplasm with a broad differential diagnosis that includes plasma cell neoplasm, sarcoma, melanoma, as well as poorly differentiated carcinoma. Several immunomarkers were attempted including plasma cell markers, skeletal muscle markers, and cytokeratin, which were not conclusive. Subsequently, the bladder mass was excised and showed a non-cohesive, pleomorphic, plasmacytoid cell infiltration. Such observation suggested a differential diagnosis of urothelial carcinoma with plasmacytoid differentiation or a plasma cell neoplasm. Immunohistochemistry and flow cytometry showed that the neoplastic cells were positive for syndecan-1 (CD138), B-cell antigen receptor complex-associated protein alpha chain (CD79a), Immunoglobulin G (IgG), and multiple myeloma-1 (MUM1); myoblast determination protein 1 (MyoD1) showed cytoplasmic staining, while negative for cytokeratin, immunoglobulin light chains kappa or lambda, and T or B cell markers (Fig. 1).

The key diagnostic challenge for this case was that the light chains tests were negative. Additionally, there were no bone lesions seen in imaging studies, nor serum monoclonal protein on electrophoresis, and MyoD1 showed cytoplasmic staining. Urothelial carcinoma with plasmacytoid differentiation can mimic plasma cell neoplasm morphologically, and CD138 is also usually positive, leading to further misdiagnosis. An extensive work-up was done to exclude poorly differentiated plasmacytoid variant urothelial carcinoma, which included cytokeratins and GATA-3 immunohistochemical stains, which were found to be negative.

The supportive immunohistochemical markers for plasma cell neoplasms showed positive for MUM-1 and CD79a. Additional lymphoid markers for T and B cells were negative. The final diagnosis of the case was plasma cell myeloma with negative immunoglobulin light chains.

Case 2

A 75-year-old female with a history of invasive ductal carci-

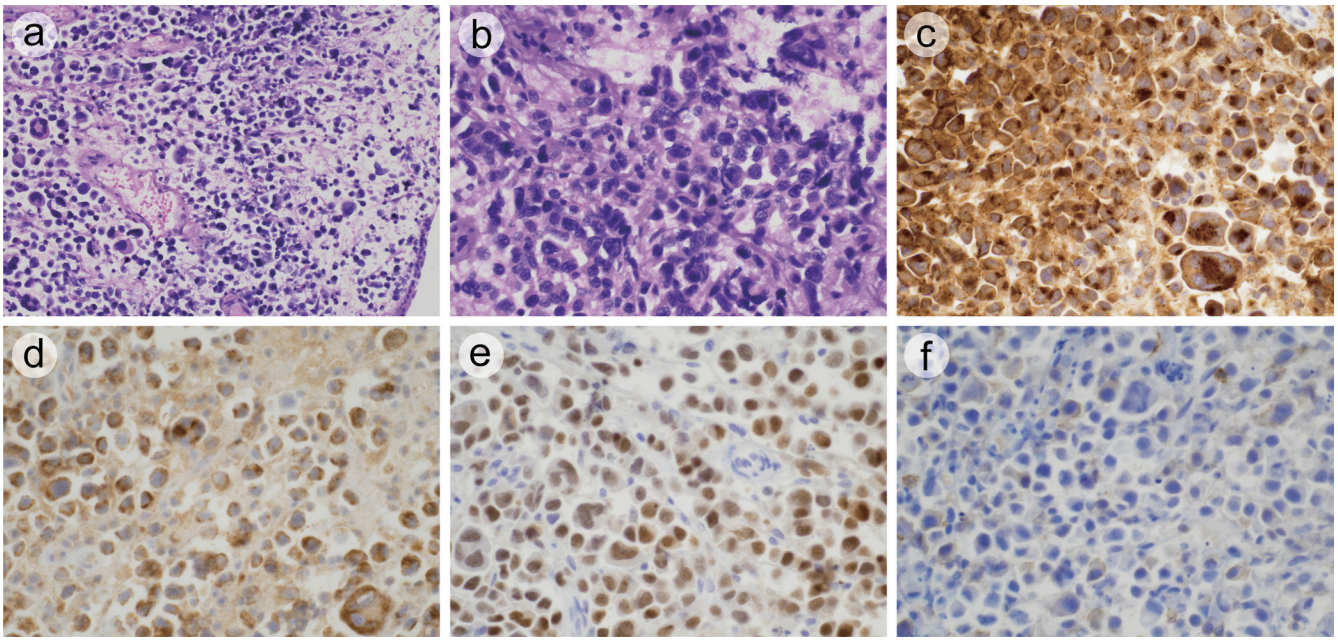

Fig. 1. Bladder mass excisional biopsy. (a) Hematoxylin and Eosin (H&E) 20×. (b). H&E 40X. (c) CD138 40X. (d) MyoD1 with cytoplasmic stain 40×. (e) MUM1 nuclear stain 40×. (f) CD56 40×. CD56, neural cell adhesion molecule; CD138, syndecan-1; H&E, hematoxylin and eosin; MUM1, multiple myeloma; MyoD1, myoblast determination protein 1.

noma of breast status at post-surgery and neoadjuvant therapy, presented one and a half years later with a new palpable mass near the original surgery site. Analysis of an additional lumpectomy specimen showed ductal carcinoma *in situ* and a nearby spindle-shaped lesion with longitudinal striation. The differential diagnosis included histiocytic lesion, muscular lesion, and plasma cell neoplasm. Immunohistochemical studies showed that the spindle cell lesion was positive for CD138, CD79a, MUM1, and lambda (Fig. 2). Therefore, the final diagnosis for the lesion was plasma cell neoplasm with longitudinal crystal inclusion.

Case 3

A 65-year-old female patient presented with a thyroid lesion measuring 2.6 cm at its largest dimension. Microscopically, there were two distinct populations of atypical cells.

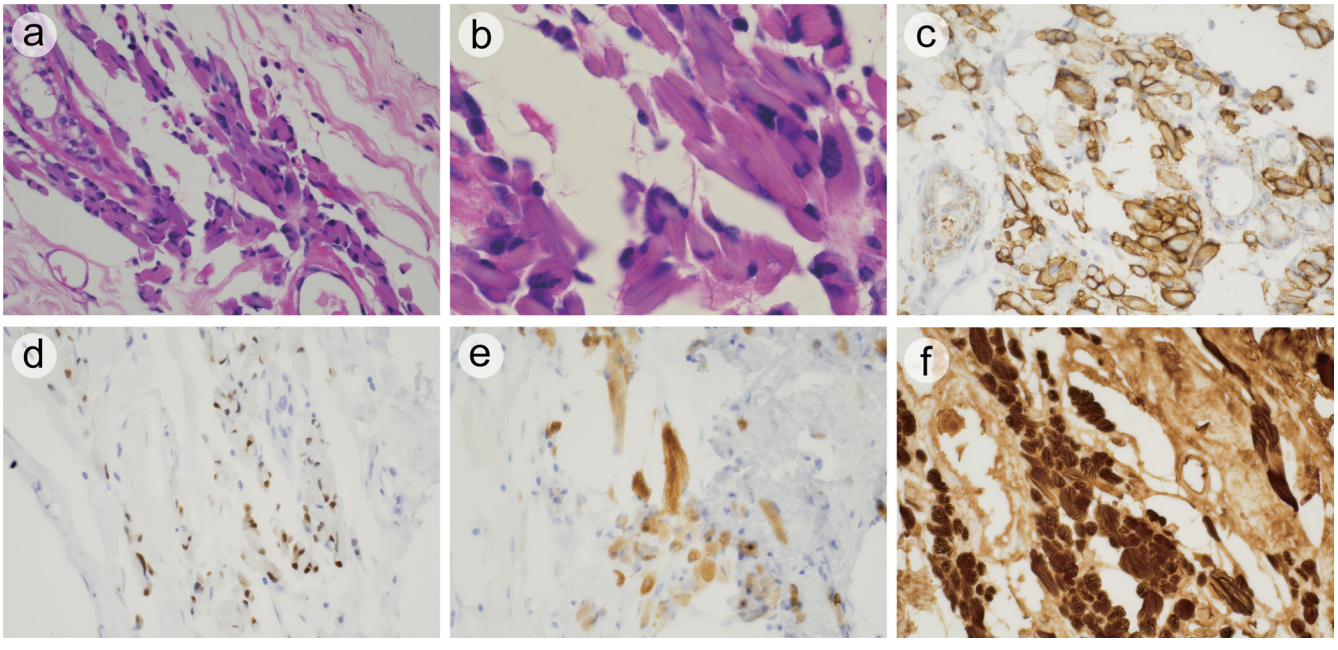

Fig. 2. Breast lumpectomy. (a) H&E 20×. (b) H&E, 60×, (c) CD138 40× (d) MUM1 10×. (e) CD79a 40×. (f) lambda 40×. CD79a, B-cell antigen receptor complex-associated protein alpha chain; CD138, syndecan-1; H&E, hematoxylin and eosin; lambda, light chain lambda; MUM1, multiple myeloma.

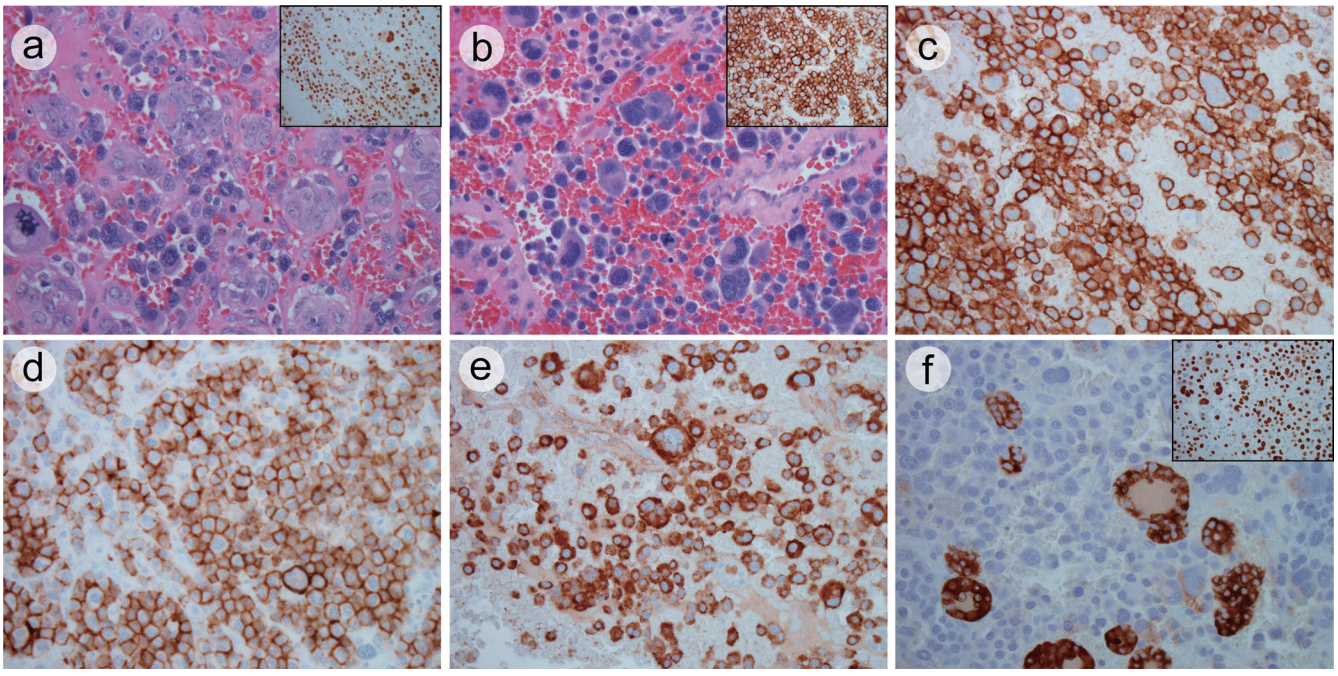

Fig. 3. Thyroid mass. (a) H&E 20×, two populations with distinct morphology, one arranged in a follicle, the other with pleomorphic cytology. Inset: MUM1 highlights the discohesive cells. (b) Pleomorphic cells showing mononuclear and multinucleated forms with pinkish cytoplasm, Inset CD56 strongly and diffusely positive, 40×. (c) CD138 40×. (d) CD43 40×. (e) lambda 40×. (f) Thyroglobulin 40×, highlight the follicles while the discohesive cells are negative, Inset P53, strongly positive in discohesive cells. CD43, leukosialin; CD56, neural cell adhesion molecule; CD138, syndecan-1; H&E, hematoxylin and eosin; lambda, light chain lambda; MUM1, multiple myeloma; MyoD1, myoblast determination protein 1; P53, tumor protein p53.

The first population was composed of poorly differentiated pleomorphic, discohesive cells, including cells with prominent nucleoli, irregular nuclear contours, some with multinucleation, and a small to moderate amount of cytoplasm admixed with more mature plasmacytoid cells. Such cells were dispersed in the nodule, infiltrating into the fibrous capsule (Fig. 3). The second population showed a microfollicular pattern with focal cytological features of enlarged clear nuclei, nuclear grooves, and occasional pseudo-inclusions. Based on the histomorphology of the two distinct populations, the differential diagnoses for the first population included anaplastic thyroid carcinoma, medullary thyroid carcinoma, melanoma, as well as hematopathological malignancies, including anaplastic large cell lymphoma, plasmablastic lymphoma, and plasmacytoma. Neoplastic cells were positive for CD138, leukosialin (CD43), MUM1, neural cell adhesion molecule (CD56), lambda, and tumor protein p53 (P53). Therefore, the final diagnosis was determined to be plasma cell neoplasm with anaplastic features for the first atypical population, whereas the second population showed features consistent with noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP).

Case 4

A 72-year-old male patient with a history of plasma cell myeloma status at post-chemotherapy and autologous stem cell transplant presented for routine follow-up. The bone marrow flow cytometry showed no clonal plasma cells. Microscopically, unusual multi-nucleated cells arranged in a pseudorosette or glandular pattern were identified. The differential diagnosis included metastatic neoplasms such as carcinoma and tumors of neural origin. The work-up immunophenotypes showed recurrent plasma cell neoplasms that were positive for CD138, MUM1, and kappa, as well as negative for lambda and cytokeratin AE1 / AE3 (AE1/AE3). Seemingly, the aberrant plasma cells did not survive the process of flow cytometry analysis (Fig. 4).

Case 5

A bone marrow sample was collected from a 72-year-old female with a history of plasma cell myeloma status at post-autologous stem cell transplant. The bone marrow biopsy showed variably cellular marrow with sheets of plasma cells with classic mature plasma cell cytomorphology (Fig. 5a, square box 1). However, a focal hypercellular area (Fig. 5a, square box 2) showed enlarged cells with pale nuclei, prominent nucleoli, and pinkish cytoplasm, suggesting secondary myeloid leukemia as a differential diagnosis. Further work-up by immunohistochemical stains showed that the two distinct populations were positive for CD138, but with a different intensity. The well-differentiated plasma cells had a strong CD138 stain, while the blast-like plasma cells had a weak stain. Cyclin D1 (BCL1) showed a similar staining pattern between the two populations. CD56 was strongly positive in the well-differentiated population but only focally dimly positive in the blast-like plasma cells (Fig. 5b-f). The case was diagnosed as a post-transplant lymphoproliferative disorder with plasmacytic differentiation, compatible with plasma cell myeloma/plasma cell leukemia.

Case 6

A 68-year-old female with a history of plasma cell myeloma status post-treatment, including, isatuximab—an anti-cluster of differentiation 38 (CD38) monoclonal antibody—and a stem cell transplant presented for a routine follow-up. Flow cytometry study showed no CD38+/CD138+ plasma cells (Fig. 6). Bone marrow core biopsy showed no obvious classic plasma cells, but an erythroid precursor-like population

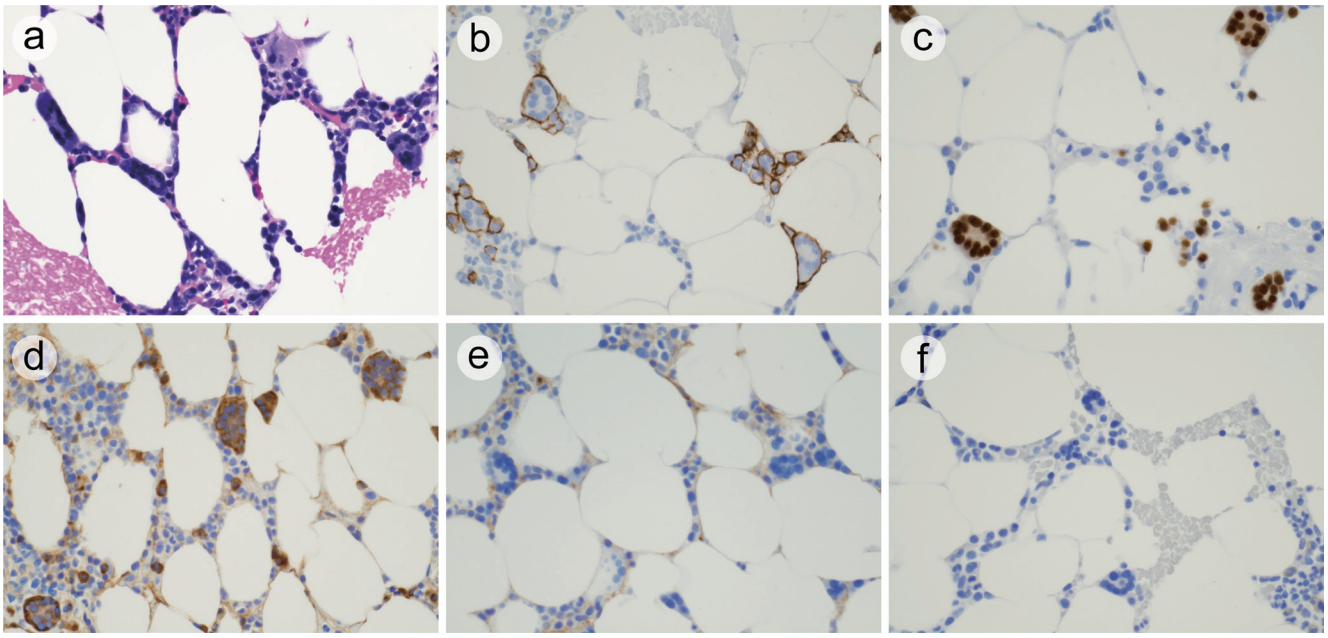

Fig. 4. Bone marrow biopsy. (a) H&E 20×. (b) CD138 20×, (c) MUM1 20×. (d) kappa 20×. (e) lambda 20×. (f) AE1/AE3, negative 20×. AE1/AE3; cytokeratin AE1 / AE3; CD138, syndecan-1; H&E, hematoxylin and eosin; lambda, light chain lambda; MUM1, multiple myeloma.

with a round nuclear contour was noted. CD138 stain showed positivity on the erythroid precursor-like cells, which were also positive for MUM-1. Flow cytometry analysis showed cytoplasmic kappa+, CD38-, CD138+, and clonal plasma cells. The particulars of the case, therefore, underscore the importance of correlation with clinical history, particularly when monoclonal antibody treatments were utilized.

Case 7

A bone marrow sample was collected from a 50-year-old male patient who had a lytic bone lesion on imaging studies. Flow cytometry analysis of the bone marrow aspirate showed

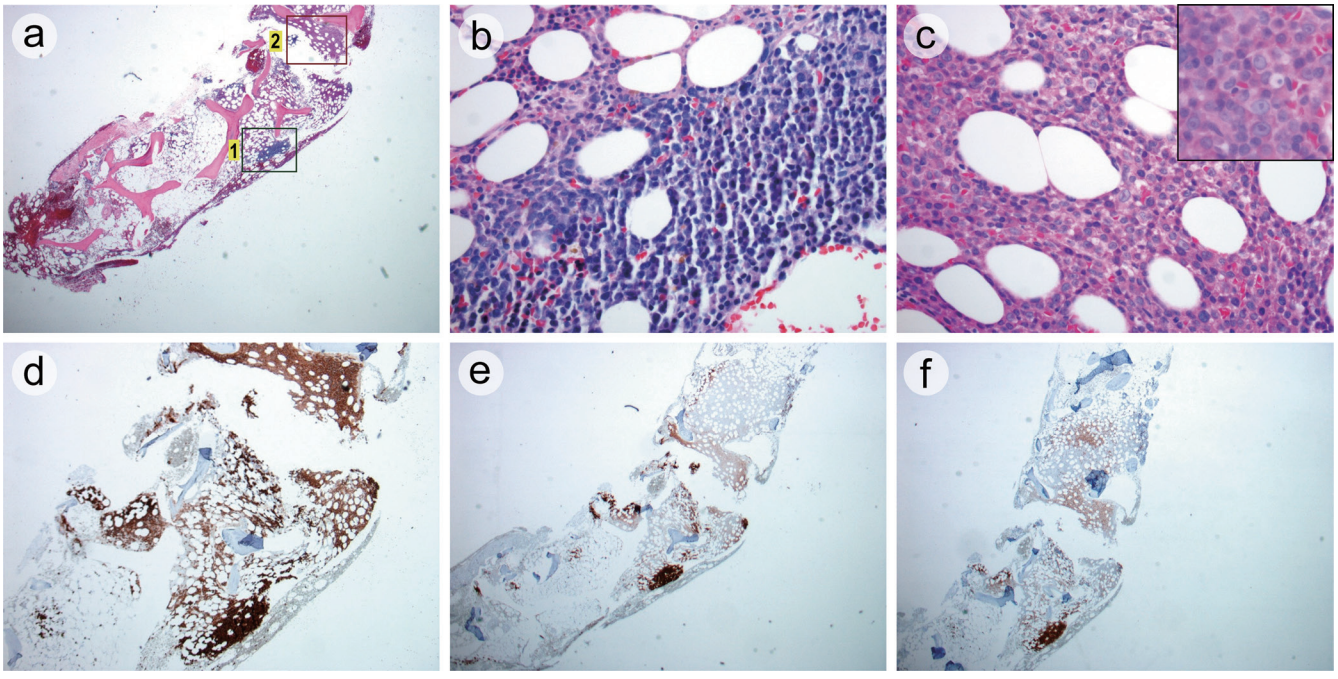

Fig. 5. Bone marrow biopsy. (a) H&E, 4×, revealing two areas marked as 1 and 2 (b) H&E 20× from 1(c) H&E 20× and 2, inset 40× showing cells with prominent nucleoli, and pinkish cytoplasm. (d) CD138 stain 10x, area 1 with strong CD138 stain, area 2 with reduced CD138 stain. (e) CD56 stain 10x, area 1 with strong CD56 stain, area 2 with reduced CD56 stain. (f) BCL1 stain 10× with the same staining pattern as seen in CD56 and CD138, area 1 strong stain, area 2 with reduced BCL1 stain. BCL1, Cyclin D1; CD56, neural cell adhesion molecule; CD138, syndecan-1; H&E, hematoxylin and eosin.

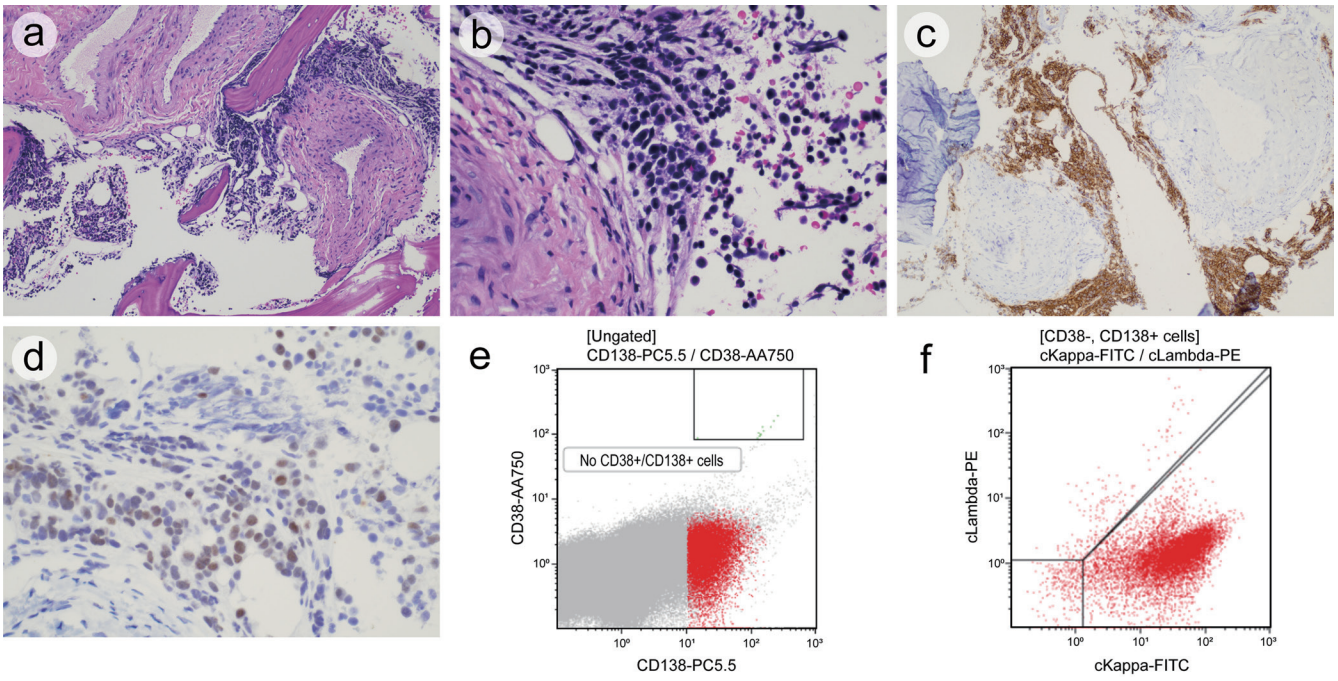

Fig. 6. Bone marrow core biopsy. (a) H&E 10× showing vasculatures and scant marrow elements. (b) H&E 20× showing some neoplastic cells with round nucleolus mimicking erythroid precursors, (c) CD138, 20×. (d) MUM1 stain 20×. (e) Dot plot, CD38 vs CD138, no CD38+/CD138+ cells in the upper left corner box. (f) Dot plot: cytoplasmic lambda vs kappa on CD138+ cells (in red) showing cytoplasmic kappa restricted atypical plasma cells. CD38, cluster of differentiation 38; CD138, syndecan-1; H&E, hematoxylin and eosin; kappa, light chain kappa; lambda, light chain lambda; MUM1, multiple myeloma.

a siglec-3 (CD33)+, protein tyrosine phosphatase, receptor type, C (CD45)+, and proto-oncogene c-KIT (CD117)+ population, mimicking aberrant acute myeloid precursors, which was also the challenging part of the diagnosis. Additional positive markers included CD38, CD138, and cytoplasmic kappa. Morphologically, they were typical plasma

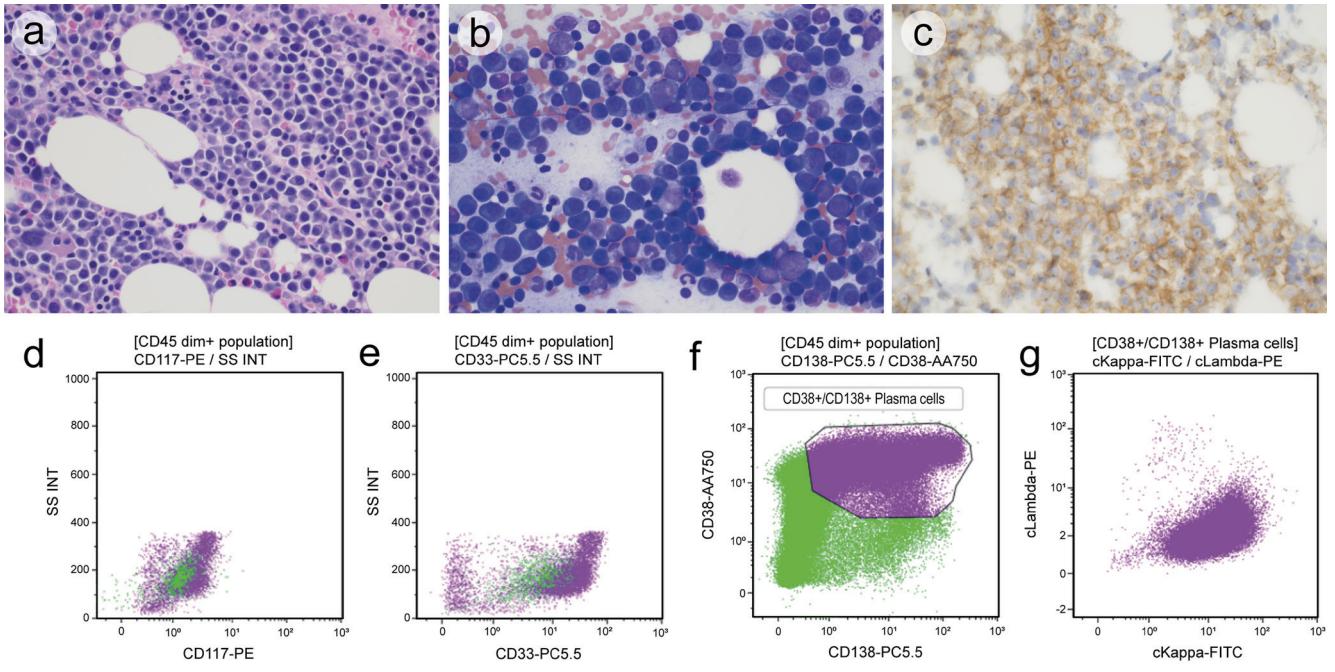

Fig. 7. Bone marrow biopsy. (a) H&E 40×, (b) bone marrow aspirate smear 100×, (c) CD33 was diffusely and weakly positive. (d) Dot plot, side scatter vs CD117 from CD45 dim+ cells from blast gate. (e) side scatter vs CD33 from CD45 dim+ cells from blast gate. (f) CD38 vs CD138 from CD45 dim+ cells. G. cytoplasmic lambda vs kappa from CD38+/CD138+ population, the plasma cells with cytoplasmic kappa restriction. CD33, siglec-3; CD38, cluster of differentiation 38; CD45, protein tyrosine phosphatase, receptor type, C; CD117, proto-oncogene c-KIT; CD138, syndecan-1; H&E, hematoxylin and eosin.

cells with eccentric nuclei and clock-faced chromatin, and no immature blast morphology was noted (Fig. 7). Neoplastic plasma cells are usually negative for CD45 and may be positive for CD117.[8] However, the combination of CD33, CD45, and CD117 positivity made the case challenging.

Discussion

Morphologically, plasma cells can display multiple faces. As reported in recent literature, they can appear as a signet ring, spindle, anaplastic, megakaryocyte-like, multi-nucleated or pseudorosette, as well as, myeloid blast or erythroid blast, monocytoid, and flower-like cells.[9–11] Hussein et al, have described six categories of morphologic and phenotypic types of plasma cell myeloma: small cell, cleaved cell, monocytoid, pronormoblast-like, megakaryocytoid, and blastoid.[3] Other non-plasmacytic neoplasms can also be a 'wolf in sheep's clothing' mimicking plasma cell neoplasms, such as carcinoid neoplasm or carcinoma, and sarcoma. Another pitfall in diagnosing such cases is the small cell variant of plasma cells, in which the plasma cells are small, resembling lymphocytes. Diagnosis can be missed if there is no previous history and plasma cell markers are not included in the initial work-up along with the T and B-cell markers. The small cell type is usually positive for B-lymphocyte antigen CD20 (CD20) and BCL1, which can easily be mistaken for Mantle cell lymphoma.[12] Knowing such mimics helps to reach a correct diagnosis and avoid delays in patient care. The authors have previously reported a case in an 85-year-old male presenting with multiple lytic bone lesions and showing small lymphoplasmacytic cells in a biopsy, which was initially misleading but positivity for CD38, CD138, kappa, CD20, and BCL1, and supported a diagnosis of the small cell variant over the initial assumption of Mantle cell lymphoma given the morphology, as well as, CD20 and BCL1 positivity.[5]

Histologically, plasma cell neoplasms show several varieties. To date, several histological patterns have been described namely, the follicular pattern, trabecular pattern, pseudo alveolar variant, lobular carcinoma-like variant, and intra-sinusoidal pattern of infiltration or those containing immunoglobulin inclusions, like nuclear inclusion known as Dutcher body and cytoplasmic inclusion known as Russell body.[3,13] Sometimes unusual shaped inclusions are observed, such as those mimicking striated skeletal muscles as shown in Case 2 and which have been previously described in research.[14–18]

Phenotypically, the classic plasma cell neoplasms usually express CD38, CD138, MUM1, and cytoplasmic kappa or lambda.[19] However, high-grade or anaplastic plasma cell neoplasms can show improper expression of other myeloid markers, such as CD33 as observed in Case 7, and even B-lymphoid markers, such as CD20, as well as, T-cell antigens like clusters of differentiation 4 (CD4) and keratins.[20] Besides aberrantly gaining other lineage markers, plasma cell neoplasms can show abnormal loss of markers, such as CD38, CD138, and cytoplasmic light chain(s) such as Case 1, which makes diagnosis more challenging.[3,21] The authors have previously reported a case of anaplastic myeloma which presented as an atrial mass in the heart, cluster of differentiation 3 (CD3), CD20, and CD138 were negative in an initial immunohistochemical work-up. However, these anaplastic cells were positive for MUM1, as well as lambda restricted and in addition, flow cytometry also showed a small clonal, CD38 positive and CD138 negative population.[6]

CD138 is a cell adhesion marker, which is a transmembrane heparan sulfate proteoglycan.[22,23] As indicated by its name, the neoplastic plasma cells once mobilized to peripheral blood, can lose CD138, and enter blood circulation causing plasmacytic leukemia, subsequently regaining the CD138 in some cases.[24] Therefore, when reviewing the peripheral blood flow cytometry for aberrant plasma cell involvement, it is important to pay attention to CD138 negative cells. The authors encountered a case of a 9-year-old male, a post-heart transplant with Barth syndrome (rare X-linked disorder), who presented with hyperviscosity symptoms and serum protein electrophoresis that showed a monoclonal population. The peripheral blood showed leukocytosis with plasmacytoid cells, positive for MUM1, kappa, and P53, as well as negative for CD138. The case was diagnosed as plasma cell leukemia due to the high percentage of plasma cells in the peripheral blood.[7] Depending on CD138 for diagnosis of plasma cell neoplasm can also raise some other challenges, such as differential diagnosis of Plasmablastic lymphoma. The latter are usually positive for CD138, negative for both CD3 and CD20, in addition to being associated with EBV infection.[25] Plasmablastic lymphoma can rarely be negative for CD138.[26] Non-hematological malignancies can also be positive for CD138, especially in carcinomas, such as plasmacytoid urothelial carcinoma.[27] Therefore, the morphology and additional plasma cell markers such as CD38, MUM1, and CD79a are needed to reach the final diagnosis, especially when it is a poorly differentiated or high-grade plasma cell neoplasm.

Currently, many immunotherapeutic agents, like monoclonal antibodies, are used in the treatment of lymphomas and myeloma. Knowing a patient's targeted antibodies is key to making a diagnosis. In Case 6, the patient received anti-CD38 (isatuximab) treatment, thus leading to the loss of CD38 in the relapsed plasma cell population.[28] Without knowing the clinical medication, the plasma cells are gated according to the population with double positivity for both CD38 and CD138, which leads to an error. Not all patients who receive anti-CD38 treatment lose CD38 expression.

Some non-hematopoietic neoplasms, such as carcinoma and melanoma, can mimic plasma cell myeloma. Being aware of such mimics, especially during examining frozen sections can help in guiding tissue triage, or considering the additional ancillary studies which will be needed. MUM1 or interferon regulatory factor 4 (IRF4) is a transcription regulatory factor involved in the development of both B and T cell immunity. It can be expressed in many types of cells and neoplasms, such as plasma cell neoplasms, post germinal center or activated B cell lymphoma including plasmablastic lymphoma, aberrant mature T cell lymphoma, classic Hodgkin lymphoma, and non-hematopoietic neoplasms, like PEComas.[29] For patients with a history of plasma cell neoplasm, status post-treatment with routine bone marrow follow-up biopsy sample, the authors strongly recommend adding additional plasma cell markers such as MUM1, PRDM1, CD79a or aberrant markers such as CD56, OX-2 membrane glycoprotein (CD200), cluster of differentiation 28 (CD28), CD117, CD20, and CD52. Immunoglobulin light or heavy chains can also be helpful. The relapsed plasma cell neoplasm can be patchy, and a flow cytometry sample may not contain the neoplastic cells, or similar to Case 4, the neoplastic cells may be scattered, or not be well-preserved enough to survive the process of flow cytometry analysis. Therefore, additional plasmacytic markers performed on the bone marrow or tissue core are necessary to identify residual or early relapsed plasma cell neoplasm.

Conclusion

The authors have described here a spectrum of plasma cell

neoplasm encountered in our institute. Awareness of the spectrum of morphological and immunophenotypic variability in plasma cell neoplasms is key to avoiding misdiagnosing variants and delaying clinical workup. Due to the rarity of most variants described in this study, the authors find themselves short of providing an accurate incidence rate and the prognostic impact of these variants. Correlation with clinical and laboratory findings and evaluation by immunostaining to confirm plasma cell origin is necessary to reach a correct diagnosis.

Acknowledgments

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None.

Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

YW, YS, AA, and JC collected patient information, prepared the manuscript and images, YS, AA, JC, and RM prepared the manuscript draft, YW, YS, AA, JC, RM, OI, QW, XT, and YF previewed the manuscript and edited the manuscript. All authors have made a significant contribution to this study and have approved the final manuscript.

Ethical statement

This study was carried out in accordance with the recommendations of 45 CFR 46.110 and 21 CFR 56.110 as Category 5, Albert Einstein College of Medicine Institutional Review Board (FWA# 00023382). The protocol was approved by the Albert Einstein College of Medicine Institutional Review Board (FWA# 00023382). The individual consent for this retrospective analysis was waived. (Retrospective study).

References

[1] Lorsbach RB, Hsi ED, Dogan A, Fend F. Plasma cell myeloma and related neoplasms. Am J Clin Pathol 2011;136(2):168–182. doi:10.1309/AJCPENJ68FFBRIYB, PMID:21757591.
[2] Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Araujo IBO, Berti E, *et al*. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia 2022;36(7):1720–1748. doi:10.1038/s41375-022-01620-2, PMID:35732829.
[3] El Hussein S, Medeiros LJ, Hu S, Lin P, Wang W. The many faces of plasma cell neoplasms: morphological and immunophenotypical variants of the great imitator. Pathology 2022;54(1):32–42. doi:10.1016/j.pathol.2021.09.011, PMID:34887091.
[4] Cree IA. The WHO Classification of Haematolymphoid Tumours. Leukemia 2022;36(7):1701–1702. doi:10.1038/s41375-022-01625-x, PMID:35732830.
[5] Wheat J, Wang Y. Atypical Presentation of a Small-Cell Subtype Multiple Myeloma with High Expression of CD20 and BCL1. Available from: https://imagebank.hematology.org/image/63810/atypical-presentation-of-a-smallcell-subtype-multiplemyeloma-with-high-expression-of-cd20-and-bcl1. Accessed October 19, 2021.
[6] Choudhuri J, Janmey V, Ding J, Dailey D, Shi Y, Wang Y. Cardiovascular Involvement of a CD138-Negative Anaplastic Myeloma: A Diagnostic Dilemma. Hematol Rep 2023;15(1):66–72. doi:10.3390/hematolrep15010007, PMID:36810550.
[7] Li Y, Offenbacher R, Corral NH, Bansal N, Ding J, Gennarini L, *et al*. A 9-year-old male with Barth syndrome and cardiac transplant presenting with hyperviscosity syndrome caused by EBV-negative plasmacytoid posttransplant lymphoproliferative disorder. Pediatr Blood Cancer 2021;68(12):e29264. doi:10.1002/pbc.29264, PMID:34339100.
[8] Kumar S, Kimlinger T, Morice W. Immunophenotyping in multiple myeloma and related plasma cell disorders. Best Pract Res Clin Haematol 2010;23(3):433–451. doi:10.1016/j.beha.2010.09.002, PMID:21112041.
[9] Giudice V, De Novellis D, Guariglia R, Fumo R, Ciancia G, Serio B, *et al*. Giant plasma cells with multiple immature nuclei in a young woman with newly diagnosed multiple myeloma. J Clin Lab Anal 2022;36(12):e24782. doi:10.1002/jcla.24782, PMID:36397299.
[10] Yolcu A, Aydogdu I. Signet-Ring Plasma Cells. N Engl J Med 2020;383(3):e13. doi:10.1056/NEJMicm1917237, PMID:32668117.
[11] Sall A, Seck M, Samb D, Faye B, Gadji M, Diop S, *et al*. Flower-Like Plasma Cell Nuclei in Multiple Myeloma. Turk J Haematol 2021;38(2):153–154. doi:10.4274/tjh.galenos.2020.2020.0471, PMID:33006548.
[12] Heerema-McKenney A, Waldron J, Hughes S, Zhan F, Sawyer J, Barlogie B, *et al*. Clinical, immunophenotypic, and genetic characterization of small lymphocyte-like plasma cell myeloma: a potential mimic of mature B-cell lymphoma. Am J Clin Pathol 2010;133(2):265–270. doi:10.1309/AJCPUS3PRRT5ZXVS, PMID:20093236.
[13] Lara-Torres CO, Ortiz-Hidalgo C. Well-differentiated (Marschalko-type) plasmacytoma resembling thyroid follicular structures. J Hematop 2008;1(2):127–129. doi:10.1007/s12308-008-0015-7, PMID:19669211.
[14] Fang H, Chiu A, Reichard KK. Crystal-Storing Histiocytosis in Bone Marrow: A Clinicopathologic Study of Eight Cases and Review of the Literature. Am J Clin Pathol 2018;149(2):148–163. doi:10.1093/ajcp/aqx150, PMID:29385417.
[15] Gruszecki AC, Reddy VV. Plasma cell crystalline inclusions. Arch Pathol Lab Med 2002;126(6):755. doi:10.5858/2002-126-0755-PCCI, PMID:12087975.
[16] Matoso A, Rizack T, Treaba DO. Intracellular and extracellular rhomboid shaped crystalline inclusions in a case of IgG lambda restricted plasma cell myeloma: a case report and review of the literature. Diagn Pathol 2010;5:6. doi:10.1186/1746-1596-5-6, PMID:20205792.
[17] Stewart CJ, Spagnolo DV. Crystalline plasma cell inclusions in helicobacter-associated gastritis. J Clin Pathol 2006;59(8):851–854. doi:10.1136/jcp.2005.033233, PMID:16537672.
[18] Patriarca C, Giunta P, Di Pasquale M, Comandè M. Images in pathology. Crystalline inclusions in plasma cell myeloma. Int J Surg Pathol 2007;15(3):301. doi:10.1177/1066896907302360, PMID:17652543.
[19] Wang HW, Lin P. Flow Cytometric Immunophenotypic Analysis in the Diagnosis and Prognostication of Plasma Cell Neoplasms. Cytometry B Clin Cytom 2019;96(5):338–350. doi:10.1002/cyto.b.21844, PMID:31566910.
[20] Fang H, Xu J. Blastoid plasma cell leukemia mimicking acute leukemia. Blood 2020;136(8):1012. doi:10.1182/blood.2020006666, PMID:32818251.
[21] Kawano Y, Fujiwara S, Wada N, Izaki M, Yuki H, Okuno Y, *et al*. Multiple myeloma cells expressing low levels of CD138 have an immature phenotype and reduced sensitivity to lenalidomide. Int J Oncol 2012;41(3):876–884. doi:10.3892/ijo.2012.1545, PMID:22766978.
[22] O'Connell FP, Pinkus JL, Pinkus GS. CD138 (syndecan-1), a plasma cell marker immunohistochemical profile in hematopoietic and non-hematopoietic neoplasms. Am J Clin Pathol 2004;121(2):254–263. doi:10.1309/617D-WB5G-NFWX-HW4L, PMID:14983940.
[23] Liebersbach BF, Sanderson RD. Expression of syndecan-1 inhibits cell invasion into type I collagen. J Biol Chem 1994;269(31):20013–20019. PMID:8051085.
[24] Ridley RC, Xiao H, Hata H, Woodliff J, Epstein J, Sanderson RD. Expression of syndecan regulates human myeloma plasma cell adhesion to type I collagen. Blood 1993;81(3):767–774. PMID:8427968.
[25] Seegmiller AC, Xu Y, McKenna RW, Karandikar NJ. Immunophenotypic differentiation between neoplastic plasma cells in mature B-cell lymphoma vs plasma cell myeloma. Am J Clin Pathol 2007;127(2):176–181. doi:10.1309/5EL22BH45PHUPM8P, PMID:17210522.
[26] Choudhuri J, Pan Z, Yuan J, Chen M, Wu X, Zheng G, *et al*. CD138- Plasmablastic Lymphoma: A Multi-institutional Study and Review of the Literature. Arch Pathol Lab Med 2023;147(6):643–654. doi:10.5858/arpa.2021-0462-OA, PMID:36161544.
[27] Sood S, Paner GP. Plasmacytoid Urothelial Carcinoma: An Unusual Variant That Warrants Aggressive Management and Critical Distinction on Transurethral Resections. Arch Pathol Lab Med 2019;143(12):1562–1567. doi:10.5858/arpa.2018-0139-RS, PMID:30865491.
[28] Frampton JE. Correction to: Isatuximab: A Review of Its Use in Multiple Myeloma. Target Oncol 2021;16(6):867. doi:10.1007/s11523-021-00846-x, PMID:34623573.
[29] Ferenczi K, Lastra RR, Farkas T, Elenitsas R, Xu X, Roberts S, *et al*. MUM-1 expression differentiates tumors in the PEComa family from clear cell sarcoma and melanoma. Int J Surg Pathol 2012;20(1):29–36. doi:10.1177/1066896911418204, PMID:21903680.