FL5-A 2026: Gating Strategies for Plasma Cell Neoplasms

Introduction

Plasma cells are post-germinal center lymphocytes that arise from terminally differentiated B-cells. Neoplastic plasma cells secrete monoclonal immunoglobins (called M protein or paraproteins) and include a spectrum of related disorders, ranging from premalignant (monoclonal gammopathy of undetermined significance) to malignant (plasma cell myeloma).[1] The unique immunophenotype of plasma cells can be used by flow cytometry to identify plasma cell populations both in the diagnosis and post-treatment evaluation of plasma cell neoplasms.

Flow cytometry serves as a valuable diagnostic tool in the differentiation of neoplastic plasma cells exhibiting aberrant features, distinguishing them from normal/reactive plasma cell populations and, in general, from neoplastic plasma cells present in lymphomas with plasmacytic morphology.[2]

Additionally, flow cytometry can aid in quantifying plasma cells in bone marrow specimens as a way to monitor disease progression and evaluation of therapeutic effects (eg, anti-CD38 monoclonal therapy).[3] This educational activity reviews the normal versus abnormal phenotypic characteristics of plasma cells, common gating techniques used to assess plasma cell populations, and challenges that arise when evaluating for plasma cells in post-therapy settings.

Normal plasma cells

Plasma cells are characterized by very bright CD38 expression.[4] However, CD38 is not specific to plasma cells and is expressed across multiple hematolymphoid populations at varying levels. During B-cell ontogeny, CD38 expression is dynamic: it is relatively high in precursor B cells, decreases as cells mature into naïve B cells, and is subsequently upregulated in germinal center B cells. Germinal center B cells may then differentiate into plasma cells, which exhibit the highest level of CD38 expression among normal hematopoietic cells. Alternatively, germinal center B cells may give rise to memory B cells, in which CD38 expression is downregulated, with re-expression occurring upon terminal differentiation into plasma cells.[5] Despite this variability across B-cell subsets, the uniformly bright CD38 expression characteristic of plasma cells distinguishes them from other normal hematolymphoid populations and serves as a key feature for their identification.[6]

CD138 (syndecan-1) is another marker frequently employed to identify plasma cells and demonstrates relative specificity within the hematopoietic compartment. When used in combination with CD38, CD138 improves the discrimination and isolation of plasma cells from other hematolymphoid cells (see Figure 1).[7]

An additional marker for plasma cell identification is cytoskeleton-linking membrane protein of 63 kDa (CLIMP-63), an intracellular protein localized to the rough endoplasmic reticulum (RER) and detected by the monoclonal antibody VS38c (see Figure 1). CLIMP-63 is not lineage-specific; however, its diagnostic utility lies in expression intensity. Plasma cells, owing to their abundant RER required for immunoglobulin synthesis, demonstrate markedly higher CLIMP-63 expression than other hematopoietic cells, allowing for their distinction based on staining intensity. Detection of CLIMP-63 requires cellular permeabilization prior to analysis. In flow cytometry, markers are conventionally designated by the target antigen rather than the antibody clone used for detection. However, in the case of CLIMP-63, routine laboratory practice commonly refers to the antibody clone VS38c instead of the antigen itself. Although this represents a departure from standard nomenclature, the term VS38c will be used as a marker throughout this review to reflect common usage and facilitate practical interpretation. This approach is analogous to FMC-7, in which the antibody designation is used to describe a specific conformational epitope of the CD20 antigen. Finally, although the “c” in VS38c formally denotes a specific antibody subclone, it may also serve as a practical mnemonic to emphasize the cytoplasmic localization of CLIMP-63 and the associated requirement for permeabilization during intracellular staining.

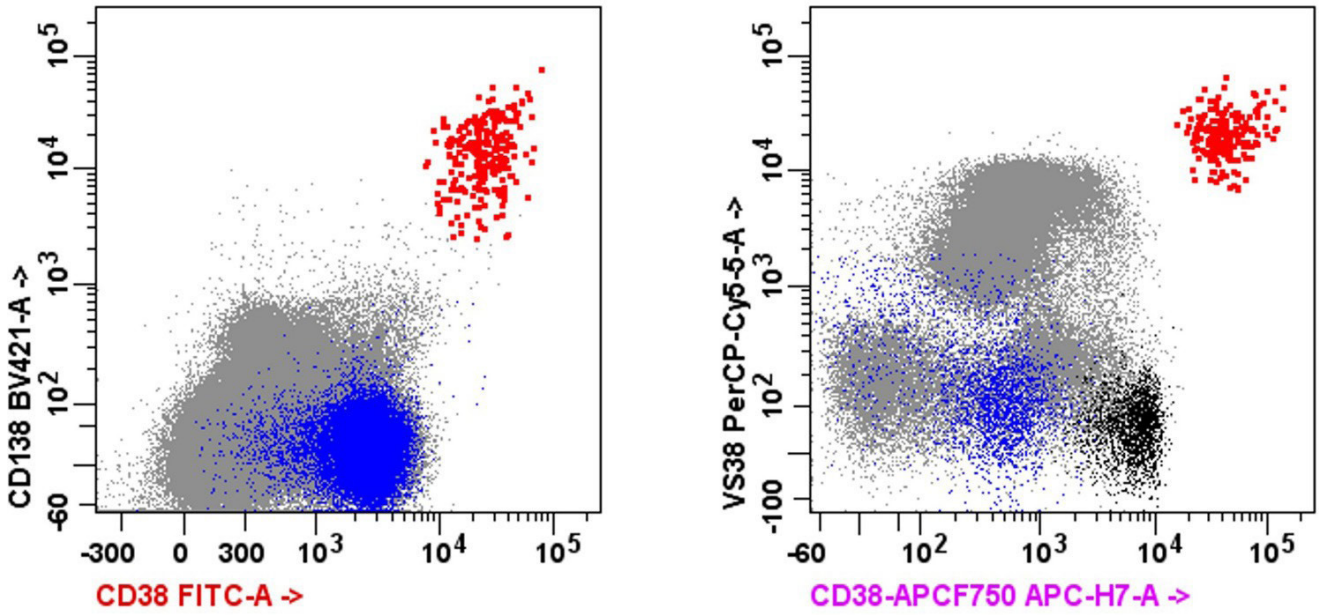

Figure 1: CD38, CD138, and VS38c Expression on Normal Plasma Cells

Normal plasma cells are depicted in red, normal mature B lymphocytes are shown in blue, and normal hematogones are represented in black. CD38 and CD138 are commonly used together as an initial step in gating to isolate plasma cells from other hematopoietic cells. Normal plasma cells exhibit bright expression of CD38 and positive expression of CD138. Similar to CD38, VS38c/CLIMP-63 is a nonlineage specific marker that helps identify plasma cells, as plasma cells exhibit the highest intensity of expression for each of these two markers compared to other cell types. CD38 is a surface glycoprotein, while VS38c is an antibody that targets the intracellular antigen CLIMP-63 associated with the rough endoplasmic reticulum requiring the cells to be permeabilized prior to staining.

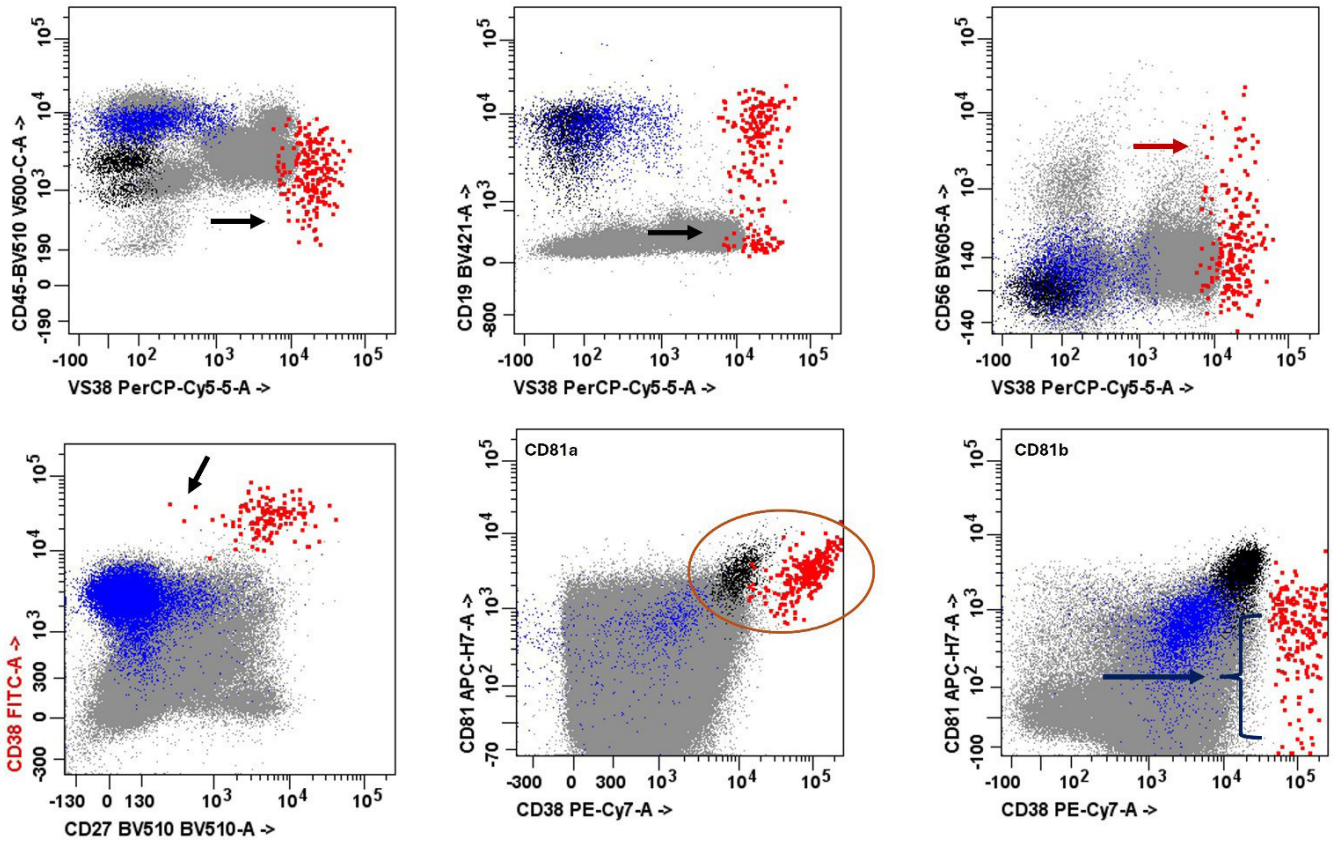

Figure 1a: CD45, CD19, CD56, CD27, and CD81 Expression on Normal Plasma Cells

Normal plasma cells are illustrated in red, normal mature B lymphocytes are shown in blue, and normal hematogones are represented in black. Most normal plasma cells show positive expression of CD45 and CD19; however, a small proportion of normal plasma cells may lack expression of CD45 and/or CD19 (see black arrows). Similarly, most normal plasma cells lack expression of CD56, but a small proportion of normal plasma cells can show positive CD56 expression (see red arrow). Normal plasma cells are also typically positive for CD27 showing bright expression compared to mature B lymphocytes, although small proportions of normal plasma cells may show decreased or negative expression. These features are important to recognize as lack of CD45 and/or CD19 and positive expression of CD56 are common features of neoplastic plasma cells in plasma cell neoplasms. Additionally, most normal plasma cells show bright expression CD81 near or at a level similar to hematogones (see plot labelled CD81a, orange oval); however, there will be cases where normal plasma cell populations show variable intensity with proportions of cells having dimmer to negative expression, as demonstrated in the plot labeled CD81b (see dark blue arrow and bracket).

Normal plasma cell populations exhibit additional immunophenotypic characteristics, including positive expression of CD19 and CD45, as well as CD27 and CD81. In contrast, normal plasma cells typically do not express CD20, CD22, CD28, CD56, CD200, and completely lack CD117 expression. It is important to recognize that certain markers may be expressed heterogeneously, whereby a minor subset of cells within the population may exhibit antigen expression patterns that deviate from the overall classification—specifically, demonstrating positivity for markers typically regarded as negative, or absence of expression for markers generally considered positive. (see Figure 1a).[8] While normal plasma cell populations usually display low to negative levels of surface immunoglobulin light chains, they express high levels of cytoplasmic immunoglobulin light chains in a polytypic manner (see Figure 2).[9]

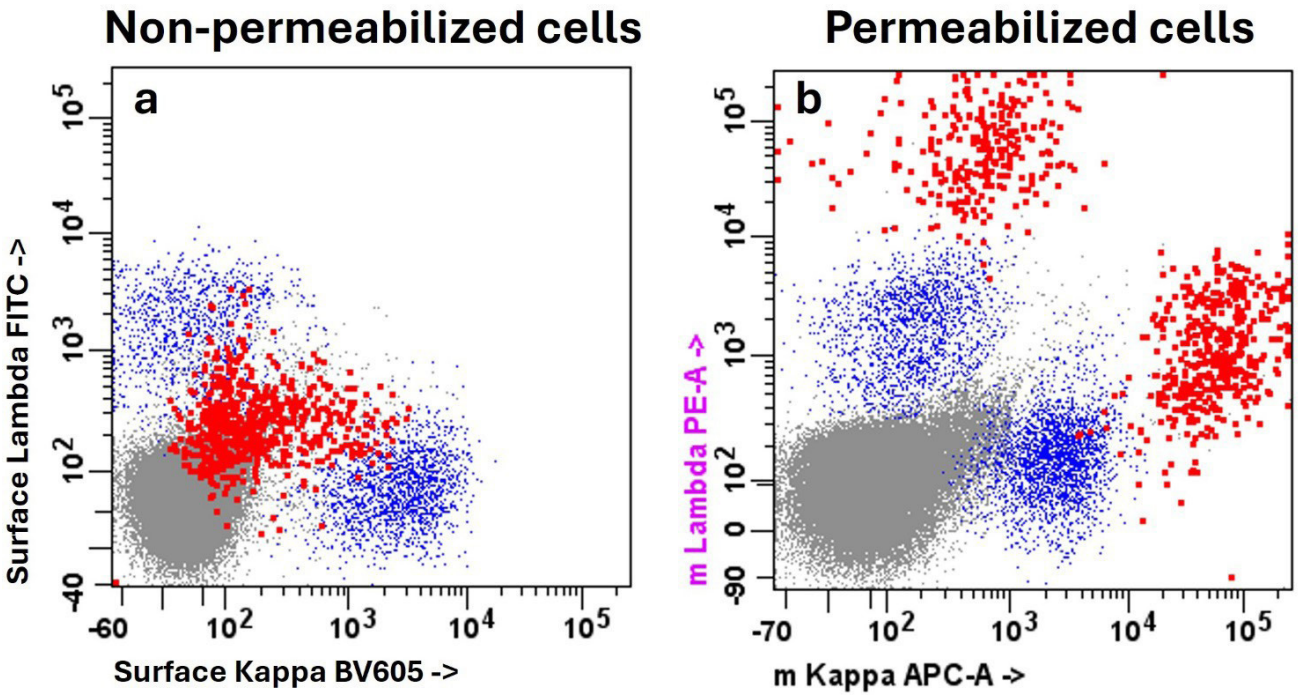

Figure 2. Immunoglobulin Light Chain Expression on Normal Plasma Cells

Normal plasma cells are illustrated in red, while normal mature B lymphocytes are depicted in blue. The first plot (labeled a) displays a typical surface staining pattern for immunoglobulin (Ig) light chains on nonpermeabilized cells. Plasma cells predominantly lack surface expression of Ig light chains, with only small proportions showing dim expression. The second plot (labeled b) reveals bright staining for immunoglobulin light chains in permeabilized plasma cells, indicating a high concentration of intracellular Ig light chains. In contrast, notice that the B-lymphocytes exhibit similar staining patterns in both permeabilized and nonpermeabilized cells. This is due to the minimal presence of intracellular Ig light chains in B lymphocytes, meaning that the positive staining primarily reflects surface expression on both plots.

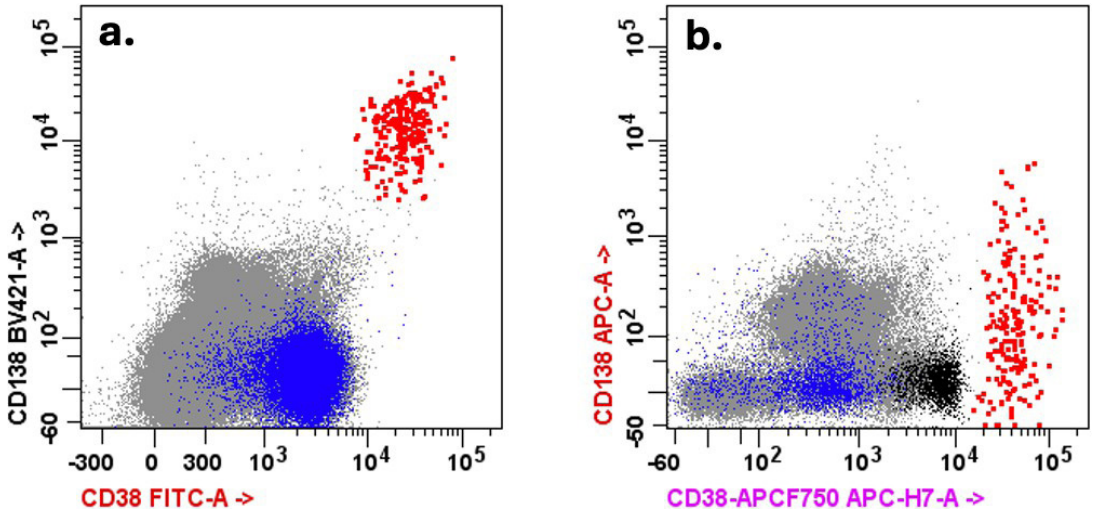

Figure 3. CD138 Expression on Normal Plasma Cells

Normal plasma cells are depicted in red, normal mature B lymphocytes are shown in blue, and normal hematogones are represented in black. CD138 (Syndecan-1) is a transmembrane heparan sulfate proteoglycan that serves as a highly specific surface marker for identifying plasma cells. However, it is important to remember that CD138 expression on plasma cells in flow cytometry can be sensitive to sample handling issues such as delays in processing, mechanical shear forces, and hypoxia. These factors can result in the degradation or internalization of CD138 from the plasma cell surface. In the first plot (labeled a), CD138 is analyzed in a sample that has just arrived at the flow cytometry laboratory, and the plasma cells exhibit the expected strong expression. In the second plot (labeled b), processing of the sample was delayed for more than 24 hours, leading to a noticeable loss of CD138 expression in the plasma cells.

Technical issues can occur during the collection and processing of samples for flow cytometry, which may impact the expression of markers on normal plasma cells. For instance, samples that are cryopreserved, more than 24 hours old, damaged by shear forces, or exposed to prolonged hypoxic conditions may show a decreased expression of CD138 (see Figure 3). Additionally, samples collected in tubes containing the anticoagulant heparin or processed using buffers with sodium azide can also exhibit reduced CD138 expression.[8,21]

Furthermore, normal plasma cell populations may exhibit immunophenotypic differences from typical plasma cells as a result of prior therapies, such as treatment with daratumumab. Therefore, it is crucial to interpret flow cytometry histograms in the context of the clinical picture and the processing protocol.

Neoplastic Plasma Cells

Neoplastic plasma cells are the primary cell type found in plasma cell neoplasms and represent one of the neoplastic cell subtypes in B-cell lymphomas with plasmacytic differentiation. The neoplastic plasma cells encountered in plasma cell neoplasms differ from those in B-cell lymphomas in terms of their immunophenotypic features. This review will focus on the neoplastic plasma cells observed in plasma cell neoplasms.

In plasma cell neoplasms, neoplastic plasma cells can be distinguished from normal plasma cells by specific immunophenotypic abnormalities that are commonly observed in nearly all cases. However, having one or even two aberrancies does not necessarily indicate a neoplastic plasma cell population, as subsets of normal plasma cell populations may also exhibit features that are typically considered aberrant for one or a few markers. Therefore, it is important to evaluate the population using multiple markers, including cytoplasmic immunoglobulin light chains.

Understanding the normal expression patterns of markers in normal plasma cells is crucial for identifying abnormal expression in neoplastic cells.

For instance, neoplastic plasma cells, like normal plasma cells, typically express CD38 and CD138. However, they often express these markers in a way that highlights their abnormal status, such as having a dimmer intensity of CD38 or a brighter intensity of CD138 compared to normal plasma cells.

Two of the most reliable distinguishing features of neoplastic plasma cell populations are their patterns of CD19 and CD45 expression. Normal plasma cell populations predominantly express both CD19 and CD45, with only a small number of cells lacking one or both markers. In contrast, neoplastic plasma cell populations typically demonstrate a complete absence or a significant reduction of CD19 and/or CD45 expression.[10,11]

Another key characteristic of neoplastic plasma cells is their restricted pattern of either κ or λ immunoglobulin light chain expression, in contrast to the polytypic expression seen in normal plasma cell populations. In a typical population of normal plasma cells, a small percentage may show positive expression of CD56 and/or CD28. However, neoplastic plasma cell populations generally exhibit stronger and more uniform positive expression of CD56 and/or CD28.[12]

Additional aberrancies that may be observed include decreased or negative CD27, positive CD117, positive CD33, and positive CD200 (Table 1).[8,22]

Table 1. Phenotypic Differences between Benign and Malignant Plasma Cells[4,11,13,14]

Marker	Benign Plasma Cells	Malignant Plasma Cells
Cytoplasmic κ and λ	Polytypic Expression	Monotypic Expression
CD10	-	-/+
CD19	+	-/+ (dim)
CD20	-	-/+
CD27	+ (bright)	-/+ (dim)
CD28	-	+
CD33	-	-/+
CD38	+ (bright)	+
CD45	+	-/+ (dim)
CD56	-	+
CD81	+ (bright)	-/+ (dim)
CD138	+	+/+ (bright)
CD117	-	-/+
CD200	-/+	+/-
VS38c	+	+

Identifying these features, particularly immunoglobulin light chain restriction, is especially useful for detecting small populations of neoplastic plasma cells amid polytypic plasma cells, such as in cases of monoclonal gammopathy of undetermined significance or persistent disease following therapy.[3,8]

An initial selection of antibodies for plasma cell analysis should include both cytoplasmic and surface markers to identify normal B cells and plasma cells, as well as aberrant B cells and plasma cells. Common markers used in plasma cell screening typically include CD45, CD19, CD5, CD34, CD38, CD138, VS38c, CD22, CD56, and both surface and permeabilized κ and λ light chains.

A combination of VS38cCD38, and/or CD138, along with orthogonal or side scatter (SSC) or CD45, can effectively identify both normal and neoplastic plasma cells in the majority of cases. Other gating strategies can also be utilized, depending on the specific case and situation, incorporating various plasma cell-associated markers. Additionally, cytoplasmic immunoglobulin light chains can be part of a sequential gating strategy, as plasma cells uniquely exhibit bright expression of these markers. A common gating strategy for isolating plasma cells and identifying aberrancy is shown in Figures 4a - 4e; however, this is only one example of the many possibilities.

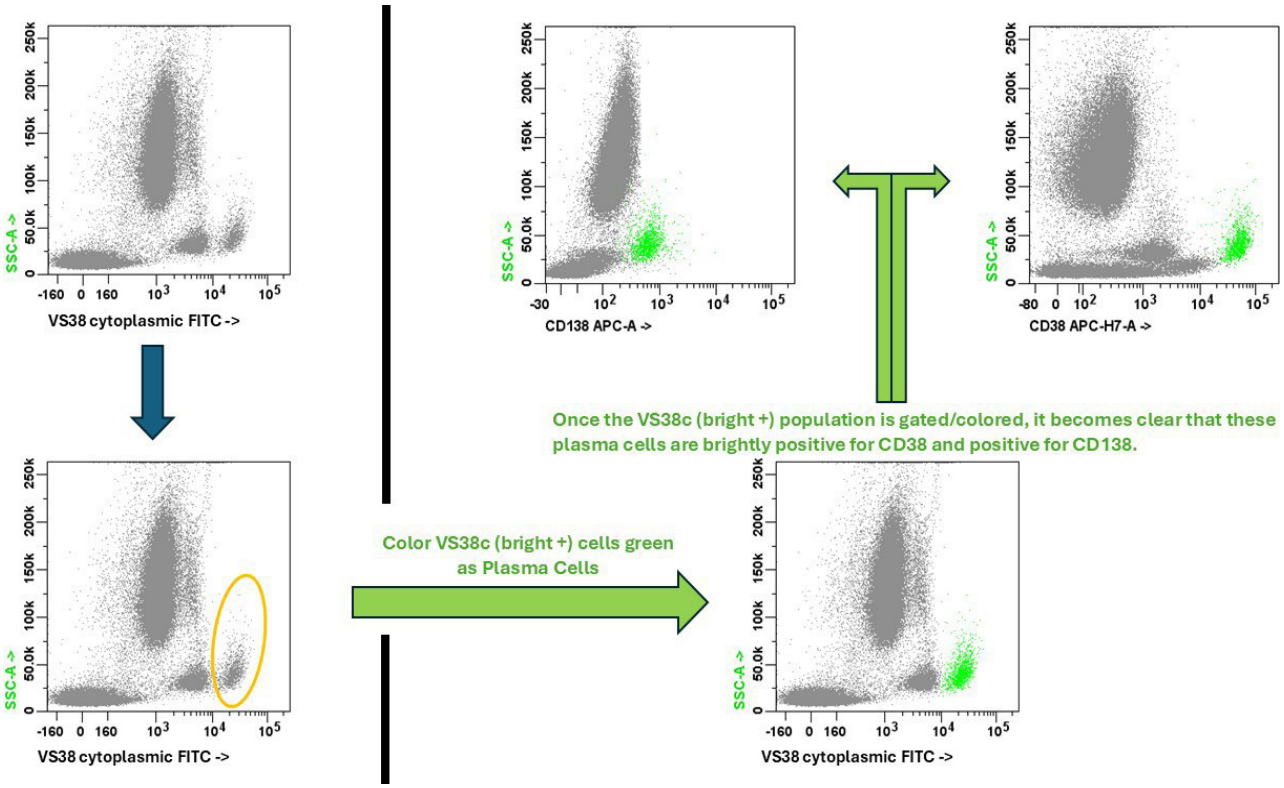

Figure 4a. Flow Cytometry Histograms of a Malignant Plasma Cell Population

In this example, VS38c/SSC is used to initially gate plasma cells, which show brightest expression of CLIMP-63 (recognized by VS38c) versus other hematolymphoid cells.

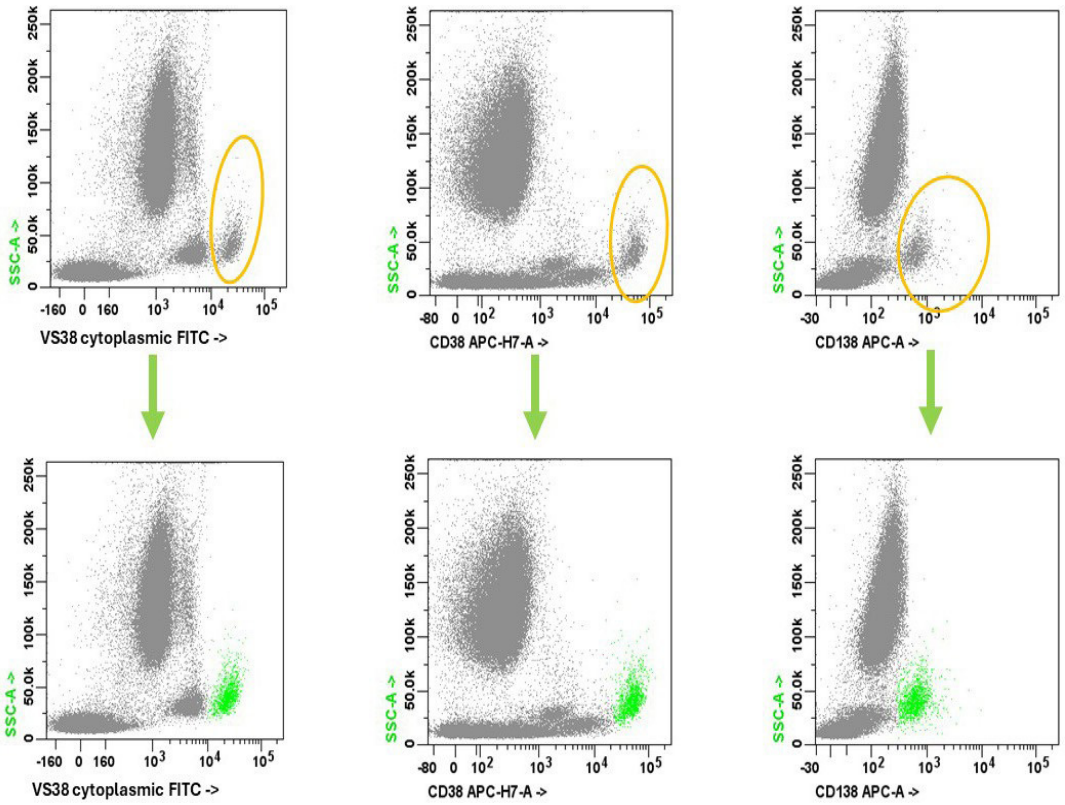

Figure 4b. Flow Cytometry Histograms of a Malignant Plasma Cell Population

CD38 and/or CD138 could also have been used for the initial gating in this case. Both of which appropriately gate for the plasma cell population.

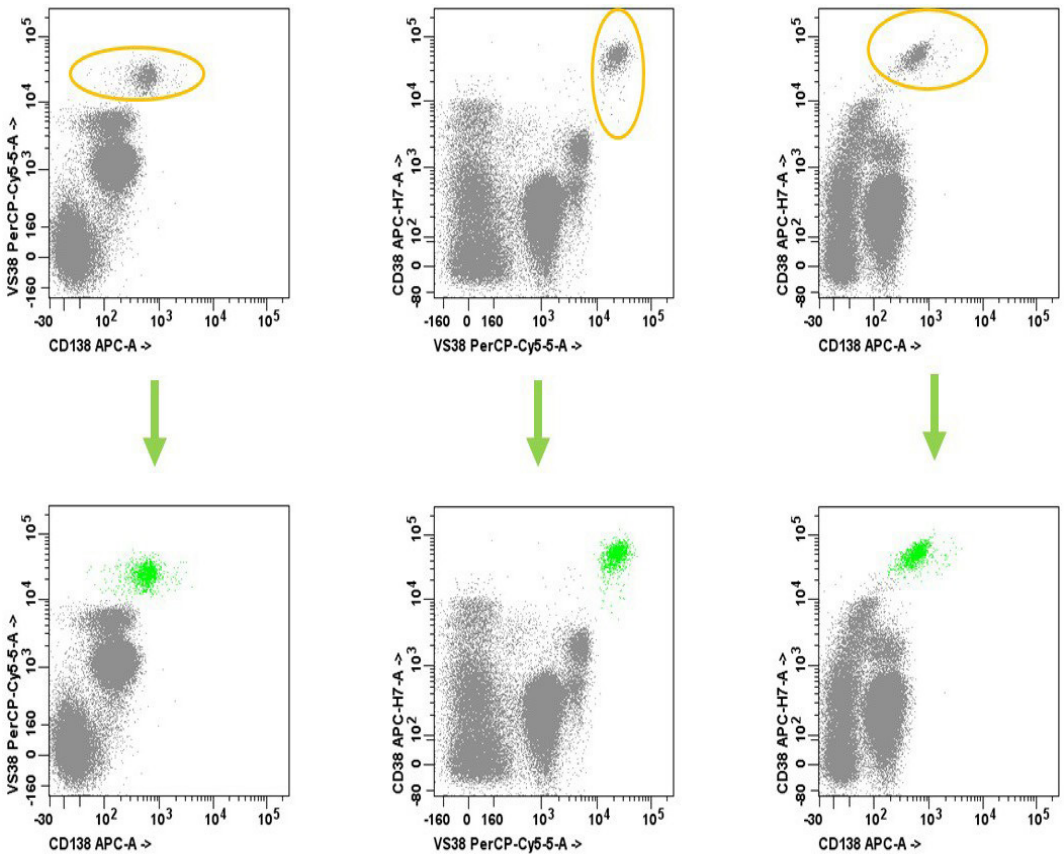

Figure 4c. Flow Cytometry Histograms of a Malignant Plasma Cell Population

In some instances, one of these plasma cell markers may exhibit aberrantly low expression intensity. In such cases, it may be beneficial to utilize a plot with two plasma cell defining markers for initial gating, such as VS38c/CD138, CD38/VS38c, or CD38/CD138.

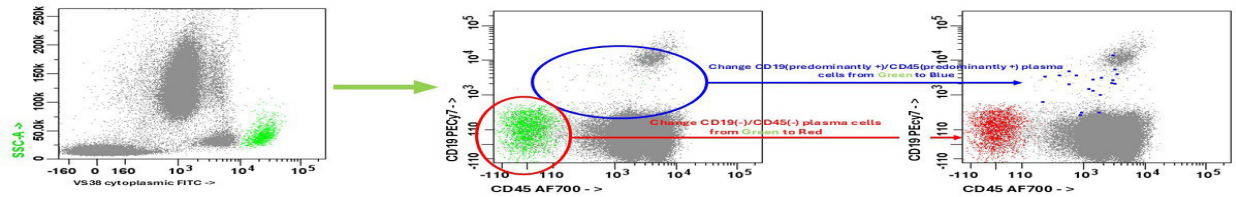

Figure 4d. Flow Cytometry Histograms of a Malignant Plasma Cell Population

Once the plasma cells are isolated, we can investigate for any aberrancies. Here, there is a large subset of plasma cells that aberrantly lack both CD19 and CD45 expression, while a smaller subset exhibits predominantly positive expression for both CD19 and CD45. We can distinguish these two populations by using different colors—red for aberrant and blue for normal. Subsequently, we can compare these populations across all the markers measured. The aberrant plasma cell population demonstrates increased forward and side scatter compared to the normal population. This group shows positivity for CD38 and CD138, although at slightly lower intensity for both markers. Additionally, the aberrant population exhibits positive expression of CD56 and a restricted expression pattern for cytoplasmic κ immunoglobulin light chains, in contrast to the polytypic κ and λ light chain expression observed in normal plasma cells.

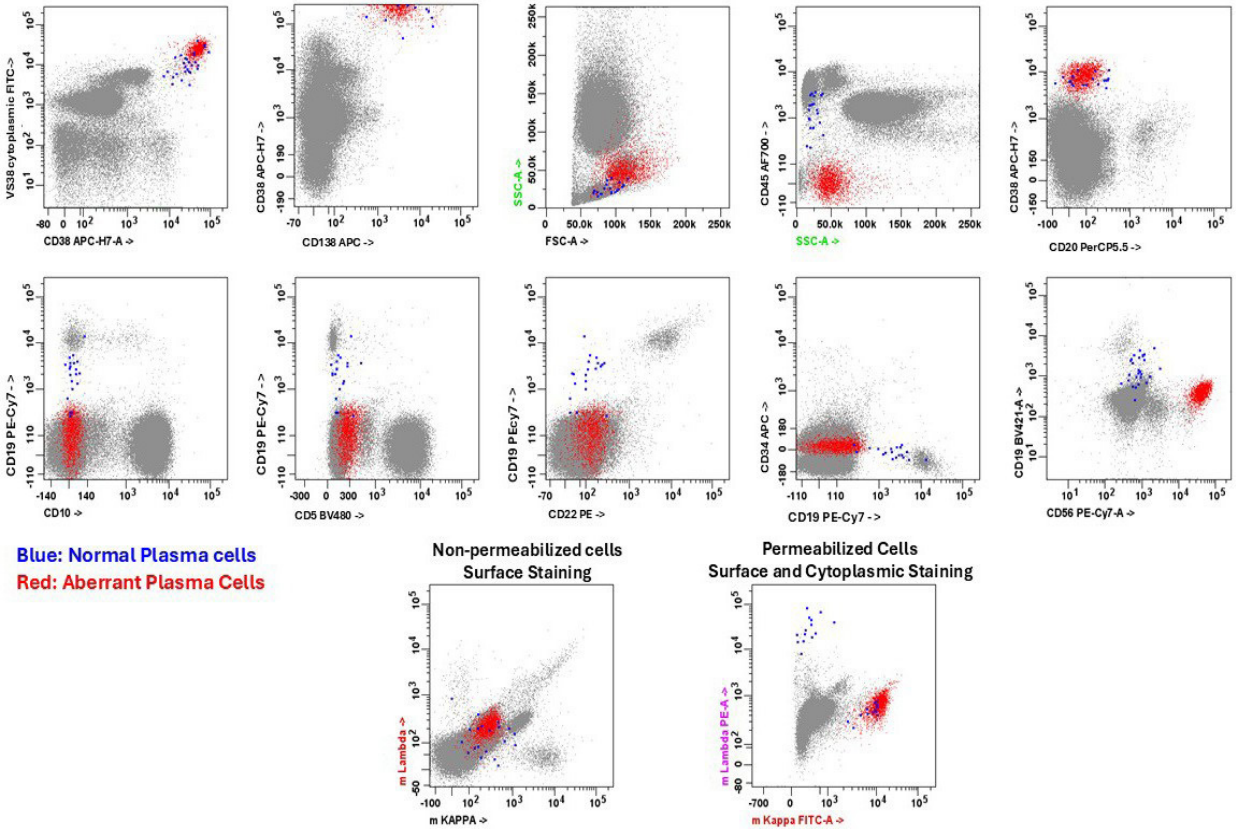

Figure 4e. Flow Cytometry Histograms of a Malignant Plasma Cell Population

In this example, the malignant plasma cells (red) show increased forward and side scatter compared to normal plasma cells (blue). They exhibit negative CD45 and CD19 expression, show CD38 and CD138 positivity at nearly the same brightness of normal plasma cells, and are aberrantly positive for CD56. They also show restricted monotypic expression of cytoplasmic κ light chains (compared to polytypic κ and λ light chain expression of normal plasma cells).

Immunophenotypic variants of Plasma cell neoplasms

Plasma cell neoplasms, like normal plasma cell populations, typically do not express CD20. However, there are occasional cases where CD20 expression is observed (see Figure 5). These instances often involve smaller plasma cells and are associated with the t(11;14) chromosomal translocation. This can lead to confusion when differentiating between plasma cell neoplasms and mantle cell lymphoma. Nevertheless, flow cytometry can effectively distinguish the characteristics of a neoplastic plasma cell population from those of a mature B-cell lymphoma. Key indicators include a plasma cell population often with typical features of aberrant plasma cells such as CD45 negativity, CD56 positivity, and cytoplasmic immunoglobulin light chain restriction.[15]

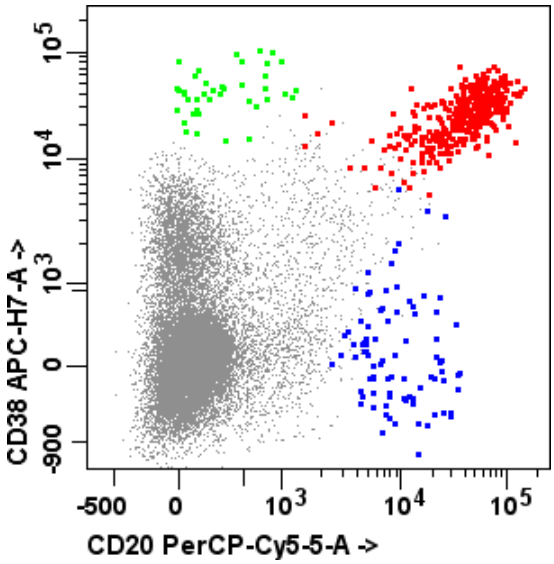

Figure 5. Plasma Cell Neoplasm with t(11:14)

Normal plasma cells are depicted in green, while normal mature B lymphocytes are represented in blue. Neoplastic plasma cells are shown in red. Typically, normal plasma cells and most plasma cell neoplasms do not express CD20. However, in this case, the neoplastic plasma cell population (in red) shows positive expression of CD20, which is often associated with plasma cell neoplasms that contain a t(11;14) translocation. Additionally, while the neoplastic plasma cells exhibit relatively bright expression of CD38, their intensity of expression is slightly lower than that of the normal plasma cell population. This observation is a common finding among most plasma cell neoplasms, regardless of their genetic associations.

Some plasma cell neoplasms show aberrant expression of stem cell and/or myeloid associated markers such as CD117 and CD33 (see Figure 6).

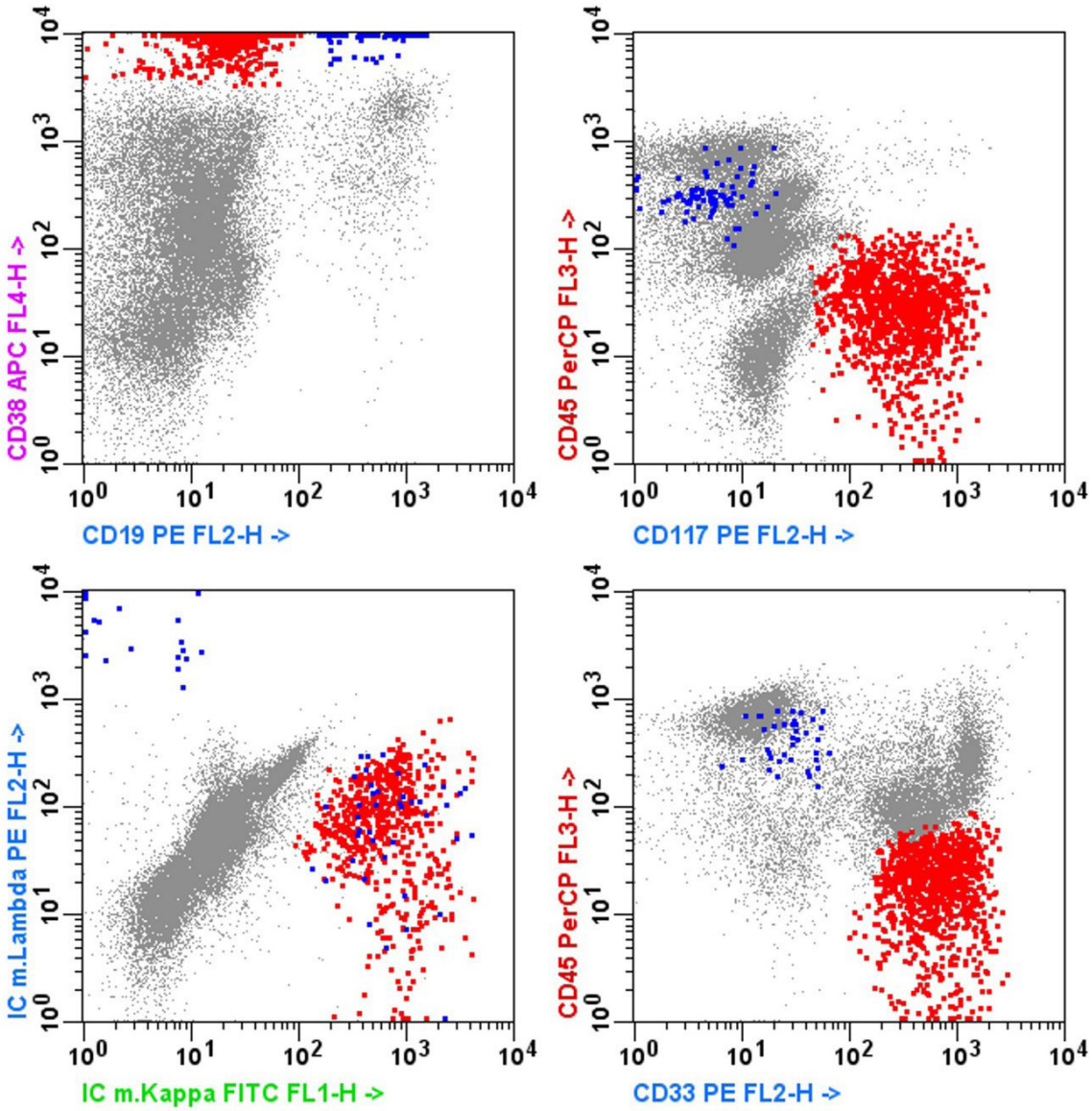

Figure 6. Aberrant CD117 and CD33 Expression on Neoplastic Plasma Cells

Normal plasma cells are depicted in blue, while neoplastic plasma cells are shown in red. Normal plasma cells do not express the stem cell marker CD117 or the myeloid marker CD33. In some instances, as illustrated here, neoplastic plasma cells may aberrantly express CD117 and/or CD33.

A key characteristic of plasma cell neoplasms is the restricted pattern of staining for cytoplasmic immunoglobulin light chains. However, in rare cases, a plasma cell neoplasm may present with two distinct clones that exhibit opposite immunoglobulin light chain restrictions (see Figure 7). Identifying this can be challenging because the abnormal plasma cells may cluster together, making them appear polytypic when assessed for light chain expression. The key to identifying this neoplasm lies in its distinctive immunophenotype, which may present as CD19(-), CD56(+), and CD45(-). A comprehensive evaluation of all markers often reveals variations in the expression of specific markers between the two separate clones (see Figure 7). In some cases, there may be no identifiable immunophenotypic differences between the two populations, except for the contrasting restrictions of κ and λ light chains. In these instances, even if the intracellular κ-to-λ ratio appears normal, the abnormal immunophenotype should raise suspicion for the presence of a neoplasm.

In such situations, serum protein electrophoresis can be particularly helpful, as it may demonstrate two M-components: one for κ and one for λ.

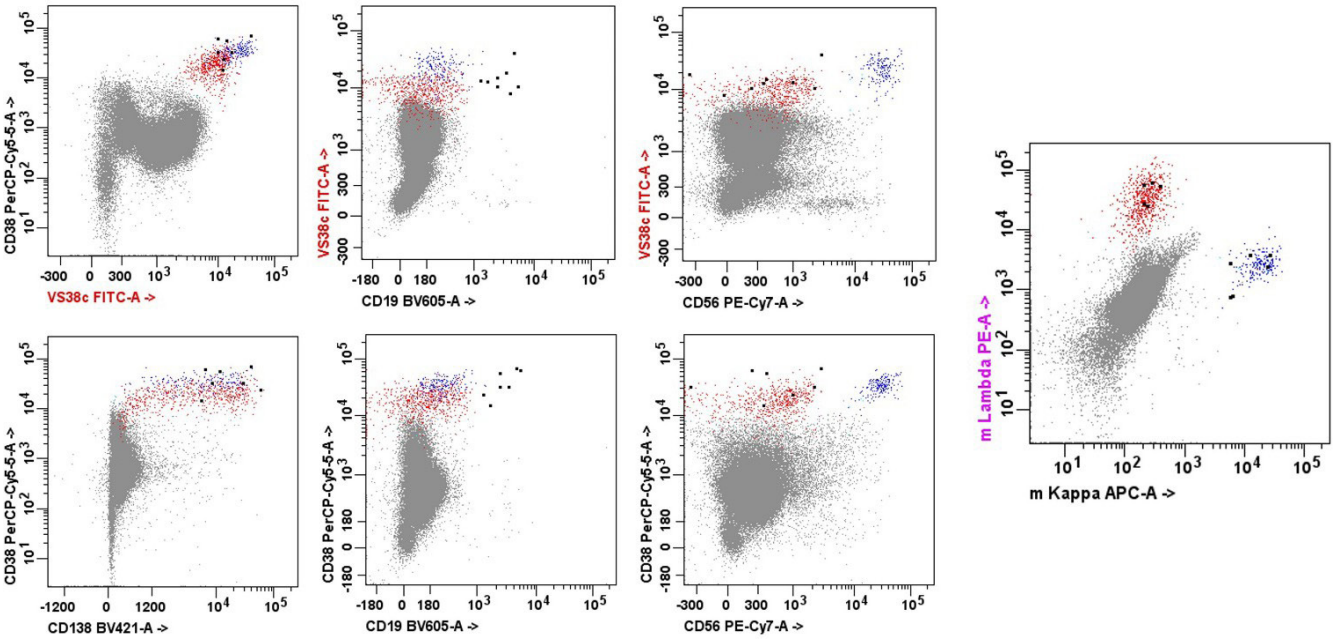

Figure 7. Biclonal Plasma Cell Neoplasm

Normal plasma cells are represented in black. Neoplastic plasma cell population No. 1 is indicated in red, while neoplastic plasma cell population No. 2 is shown in blue. The first neoplastic plasma cell population, depicted in red, exhibits abnormal underexpression of CD19 and slightly diminished expression of CD38 and VS38c. In contrast, the second neoplastic plasma cell population, shown in blue, displays abnormal underexpression of CD19 and abnormal overexpression of CD56. A concurrent serum electrophoresis with immunofixation confirmed these biclonal results by revealing two distinct M components: one κ and one λ.

In rare instances, neoplastic plasma cells may lack detectable expression of light chains, a condition referred to as a nonproducing plasma cell neoplasm (see Figure 8). In these cases, there is typically a significant number of neoplastic plasma cells; however, due to a defect in immunoglobulin synthesis, no light chains can be identified. Serum protein electrophoresis and urine protein electrophoresis are not helpful in these situations, as they typically show no M spike. While serum free light chain assays are often employed to identify nonsecretory plasma cell neoplasms, they may still yield negative results in truly nonproducing cases.[16] This abnormal lack of light chain expression can lead to misdiagnosis.

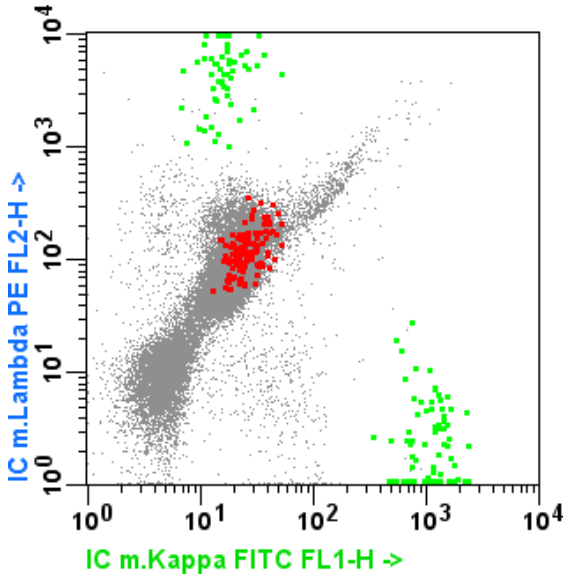

Figure 8. NonProducing Plasma Cell Population

The cells have been permeabilized for analysis. The normal plasma cell population is represented in green and can be divided into two subsets: one that expresses κ light chains and another that expresses λ light chains. This characteristic is referred to as a polytypic population. In contrast, abnormal plasma cells are shown in red and do not express cytoplasmic immunoglobulin light chains, as indicated by their placement on the diagonal of the plot.

Impact of Targeted Therapy on Flow Cytometric Analysis

Immunotherapeutic agents can influence the expression of surface antigens on plasma cells, making it challenging to evaluate malignant plasma cell populations in the post-therapy setting. Therapeutic monoclonal antibodies targeting CD38, such as daratumumab, bind to the same epitope on CD38 as the conventional antibody reagents used to identify CD38 expression. This interaction leads to the masking of CD38, resulting in an inability to effectively detect CD38 expression on cells through flow cytometry. This masking effect can persist for up to six months after therapy.[17,18] As a result, alternative markers are necessary for plasma cell gating.

One effective strategy is to use a multiepitope CD38 antibody reagent, which contains antibodies that recognize multiple different epitopes on the CD38 molecule. This approach allows for the detection of CD38 expression even in the presence of anti-CD38 therapy (see Figure 9).[19] Additionally, other strategies for analyzing plasma cells after daratumumab therapy include using alternative surface markers such as CD54, CD229, and CD319, as well as the cytoplasmic marker VS38c.[20]

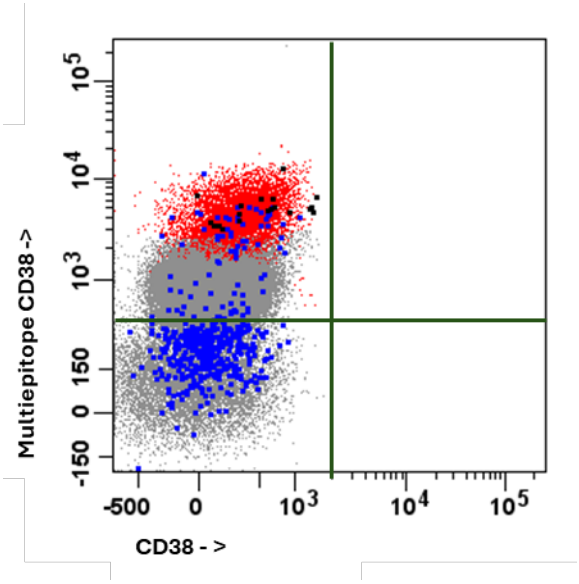

Figure 9. Multiepitope CD38 in Patient Treated with Daratumumab

Neoplastic plasma cells are illustrated in red, while normal mature B lymphocytes are shown in blue, and normal plasma cells are represented in black. Daratumumab is a therapeutic monoclonal antibody that targets CD38 and is commonly used to treat plasma cell neoplasms. In patients receiving daratumumab, plasma cells often show reduced or absent staining with conventional CD38 reagents due to epitope masking. This masking occurs because daratumumab binds to the same epitope as these conventional reagents, making it challenging to identify plasma cells using flow cytometry. In contrast, the multiepitope CD38 reagent recognizes multiple, non-competing epitopes on the CD38 molecule, allowing it to bind effectively even in the presence of daratumumab. In the plot, all hematolymphoid cells fail to stain positively with the conventional CD38 antibody, but appropriate staining is observed in cells expressing CD38 with the multiepitope CD38 reagent.

Summary

This continuing education activity reviewed the normal immunophenotypic pattern of plasma cells and presented scenarios where the typical pattern of expression on normal plasma cells deviates. Strategies for gating plasma cell population were reviewed. A panel that includes typical cytoplasmic and surface markers expressed on normal B cells and plasma cells in addition to aberrant B cells and aberrant plasma cells will help characterize for the majority of atypical plasma cell populations. Identifying the patterns of expression, expression of light chain immunoglobulins, and expression of aberrant markers in the context of the clinical picture and sample processing are key to delineating aberrant versus normal plasma cell populations. Additional gating techniques can be utilized in the event of unusual plasma cell immunophenotypes, such as plasma cells with morphologic overlap between B-cell neoplasms and plasma cell populations without expression of light chains. Finally, additional markers and techniques can be used to identify plasma cell population post-therapy, such as multiepitope CD38 and cytoplasmic expression of CLIMP-63/VS38c.

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