


Educational Case: Mantle Cell Lymphoma

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see <http://journals.sagepub.com/doi/10.1177/2374289517715040>.¹

Keywords

pathology competencies, organ system pathology, hematopathology, leukemia, lymphoma, morphology, classification, mantle cell lymphoma

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Primary Objective

Objective HWC3.1: Morphology of Acute Leukemia and Lymphoma. Describe the morphologic features that characterize typical cases of acute leukemia and lymphoma.

Competency 2: Organ System Pathology; Topic Hematopathology—White Cell Disorders (HWC); Learning Goal 3: Classification of Leukemia and Lymphomas.

Patient Presentation

A 58-year-old male presents to an otolaryngology clinic for current sinus pressure and pain with clear to yellow rhinorrhea lasting 2 weeks. He did not report any surgical interventions but reports his primary care physician recently prescribed him 2 weeks of amoxicillin-clavulanate (Augmentin) that he completed yesterday without resolution of his symptoms. He reports a limited past medical history of recurrent sinus infections lasting 1 to 2 weeks every 2 to 3 months over the past 2 years and “crushed sinuses” after a traumatic motor vehicle accident 30 years ago. On physical examination, there were no significant findings; most notably, there was no lymphadenopathy.

Diagnostic Findings, Part I

On rhinoscopy, normal mucosa of the anterior nose is seen and no polyps are visualized. These rhinoscopy findings were reported as normal.

Question/Discussion Points, Part I

What Is the First-Line Treatment for Acute Sinusitis?

The antibiotic of choice for acute sinusitis must cover *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*, the most common bacteria causing acute sinusitis. Antibiotics, such as amoxicillin or amoxicillin-clavulanate (Augmentin) for 2 weeks, has been the first-line treatment for

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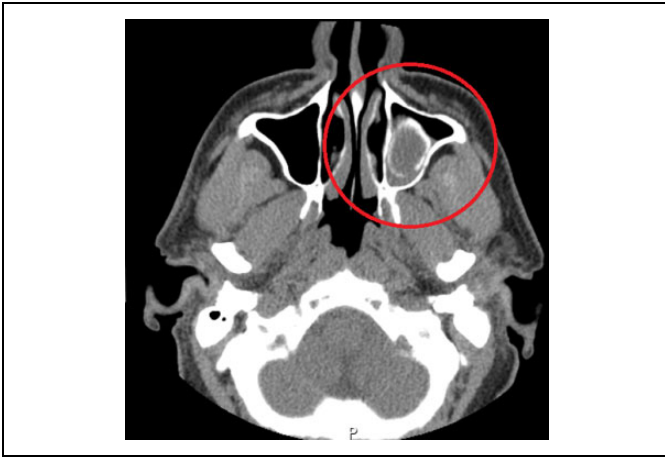


Figure 1. Computed tomography scan of his paranasal sinuses showing left nasal septal deviation, a left maxillary sinus polyp/cyst measuring 2.6 cm × 1.4 cm (circled in red), and mucosal thickening.

acute sinusitis. The addition of clavulanate, a β -lactamase inhibitor, provides better coverage for *H influenzae* and *M catarrhalis*. Other options for antibiotics include cephalosporins such as cefpodoxime and cefuroxime.

Given the Patient's Presentation, What Would Be Considered in the Differential Diagnosis?

A chief complaint of recurrent sinus infections and rhinorrhea can result in a broad number of differential diagnoses including chronic sinusitis, nasal polyp/polyposis, nasal papilloma, mucosal melanoma, and lymphoma. Given this patient's history and presentation, chronic sinusitis or a nasal polyp is highest on the list of differential diagnoses.

What Is an Appropriate Next Step in the Evaluation of This Patient?

Due to the broad range of possible diagnoses and insignificant physical examination, further evaluation and additional information is needed. Computed tomography (CT) imaging is the next diagnostic modality of choice.

Diagnostic Findings, Part 2

Please view Figure 1.

Question/Discussion Points, Part 2

What Are the Findings in the Imaging in Figure 1?

The patient's CT scan of his paranasal sinuses showed a previous fracture with a left maxillary sinus polyp/cyst measuring 2.6 cm × 1.4 cm (Figure 1). He was diagnosed with a traumatic right frontal sinus deformity and a left maxillary cyst/polyp. The traumatic right frontal sinus deformity was consistent with his previous history of a motor vehicle accident. The patient's

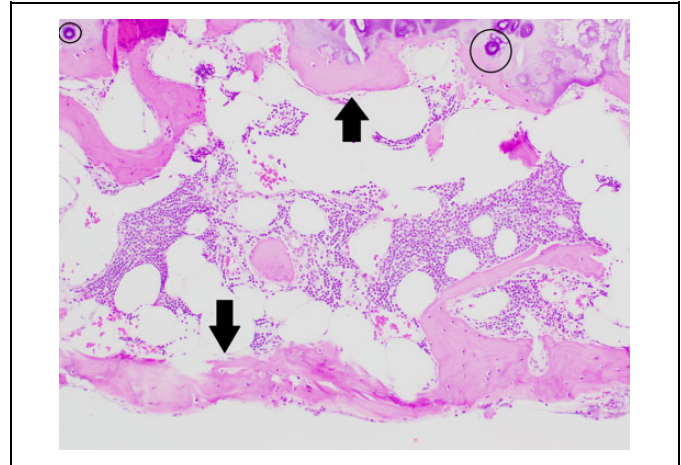


Figure 2. There are dense lymphoid aggregates between the bone (black arrow) and cartilaginous fragments (black circle) of the sino-nasal bone; these dense aggregates are atypically infiltrating and expanding the bone (hematoxylin and eosin, × 100).

recurrent sinus infections were attributed to the maxillary cyst/polyp secondary to nasal outflow blockage.

After the Imaging Studies, What Would be the Next Appropriate Steps?

Typically, on physical examination, large nasal polyps in the anterior nose can be visible with rhinoscopy, whereas smaller nasal polyps or polyps that are located deeper in the nasal cavity or in the sinus spaces require more extensive imaging or endoscopy. As this patient had a polyp or cyst located in the maxillary sinus space, it was not visible on rhinoscopy. Therefore, the patient was recommended to undergo nasal endoscopy for better visualization of the polyp, as well as polyp removal.

Diagnostic Findings, Part 3

An endoscopy of the left maxillary sinus is performed, and an excision of the polyp was performed by scraping the maxillary space. The tissue obtained was sent to the pathology department and is shown in Figures 2 and 3.

Question/Discussion Points, Part 3

Histologically, What Is Seen in Figures 2 and 3?

Pathohistological examination of the sinus contents showed multifocal small lymphoid aggregates and interstitial infiltrates within the medullary space, expanding the bony fragments; this is not a typical finding in a maxillary cyst/polyp (Figures 2 and 3). In addition, the soft tissue shown chronic inflammation without evidence of epithelial malignancies (ie, squamous cell carcinoma, adenocarcinoma).

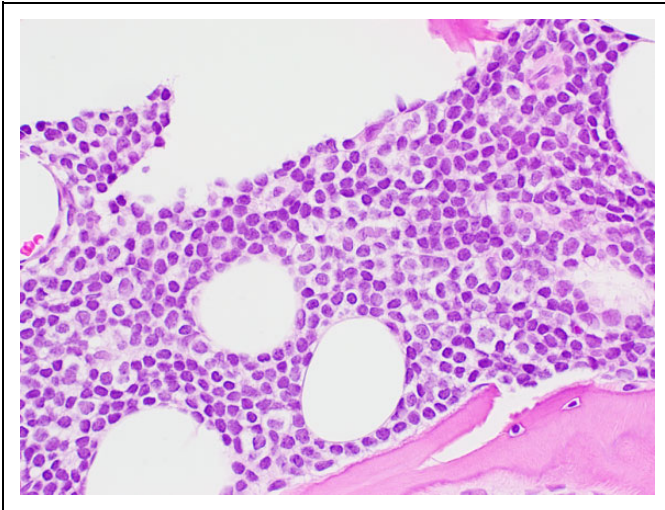


Figure 3. There are small monomorphic lymphocytes in the bony fragments. These lymphocytes have a high nuclear to cytoplasmic ratio, round nuclear contours, and no prominent nucleoli (hematoxylin and eosin, $\times 400$).

Given the Pathologic Findings, What Lesions Would Be Considered in the Differential Diagnosis?

The differential diagnosis includes benign reactive lymphoid aggregates and small B-cell lymphomas. Small B-cell lymphomas comprise of but are not limited to mantle cell lymphoma (MCL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), hairy cell leukemia (HCL), follicular lymphoma (FL), and marginal zone lymphoma (MZL). It is difficult to determine the nature of these lymphoid aggregates without immunophenotyping; this can be done using flow cytometric analysis on fresh tissue and/or immunohistochemical staining on formalin-fixed tissue.

Diagnostic Findings, Part 4

Immunohistochemical stains with appropriate controls were performed on the tissue (Figure 4). The small monomorphic lymphoid aggregates were positive for B-cell markers including CD19, CD20, CD79a, and PAX5, as well as BCL2 (anti-apoptotic marker). T-cell markers such as CD3, CD4, and CD8 were negative. In addition, these cells had an aberrant expression of CD5, which is a normal T-cell marker.

Question/Discussion Points, Part 4

What Are Possible Differential Diagnoses After the Immunohistochemical Evaluation?

These features of morphology and immunophenotyping are consistent with a CD5-positive small B-cell lymphoma which is most commonly seen in CLL/SLL or an MCL. To differentiate between CLL/SLL and MCL, immunohistochemical staining for Cyclin D1 is a practical choice.

What Are Molecular Findings Associated With Mantle Cell Lymphoma and What Can It Tell Us About the Pathogenesis?

In addition to histological and flow cytometric evaluation, molecular studies are routinely performed for hematological malignancies. In 95% of MCLs, there is an associated encoded nuclear cyclin D1 (CCND1) and immunoglobulin heavy chain region (IgH) translocation on chromosome 11 and chromosome 14. Therefore, t(11;14) is pathognomonic for MCL.² These findings can be evaluated using cytogenetics or chromosomal karyotyping analysis for chromosomal translocations using fresh tissue or fluorescence in situ hybridization (FISH) analysis for the IgH-CyclinD1 protein using fresh or fixed tissue. Sequelae of this translocation results in deregulation and overexpression of Cyclin D1. This overexpression of Cyclin D1 leads to unregulated expression of cell progression through the cell cycle and increased proliferation.³

Diagnostic Findings, Part 5

Further immunohistochemical evaluation in this patient confirmed MCL with diffuse bright staining for Cyclin D1. The FISH analysis on his peripheral blood revealed a Cyclin-D1/IgH translocation on chromosomes 11 and 14 (Figure 5), which is a hallmark finding in MCL. This translocation was identified on FISH using the fusion probe. The presence of yellow indicates that there is a fusion/translocation present, whereas the red dot represents chromosome 14 and green dots represent chromosomes 11 and 18. In the absence of a translocation, 2 red dots (chr. 14) and 2 green dots (chr. 11 or chr 18) should be visualized. In the presence of a translocation, a yellow fusion dot (t(11;14)), a red dot (chr 11), and a green dot (chr 14) should be visualized. In addition, the proliferation index of lymphoma cells was evaluated using immunohistochemical stains by Ki-67; this revealed a low proliferation index of <10%.

Question/Discussion Points, Part 5

Now That the Patient Has a Formal Diagnosis of MCL, What Additional Data Would Be Important for Staging and Determining the Extent of His Disease?

As the next step for lymphoma staging, clinicians order a wide variety of studies including a complete blood count (CBC) with differential and a peripheral smear, kidney function panel (blood urea nitrogen, creatinine), liver function panel, lactate dehydrogenase, routine electrolytes, serum protein electrophoresis, HIV panel, hepatitis serology, β -2 microglobulin levels, bone marrow staging (aspiration and biopsy), positron emission tomography (PET) scan, and so on.

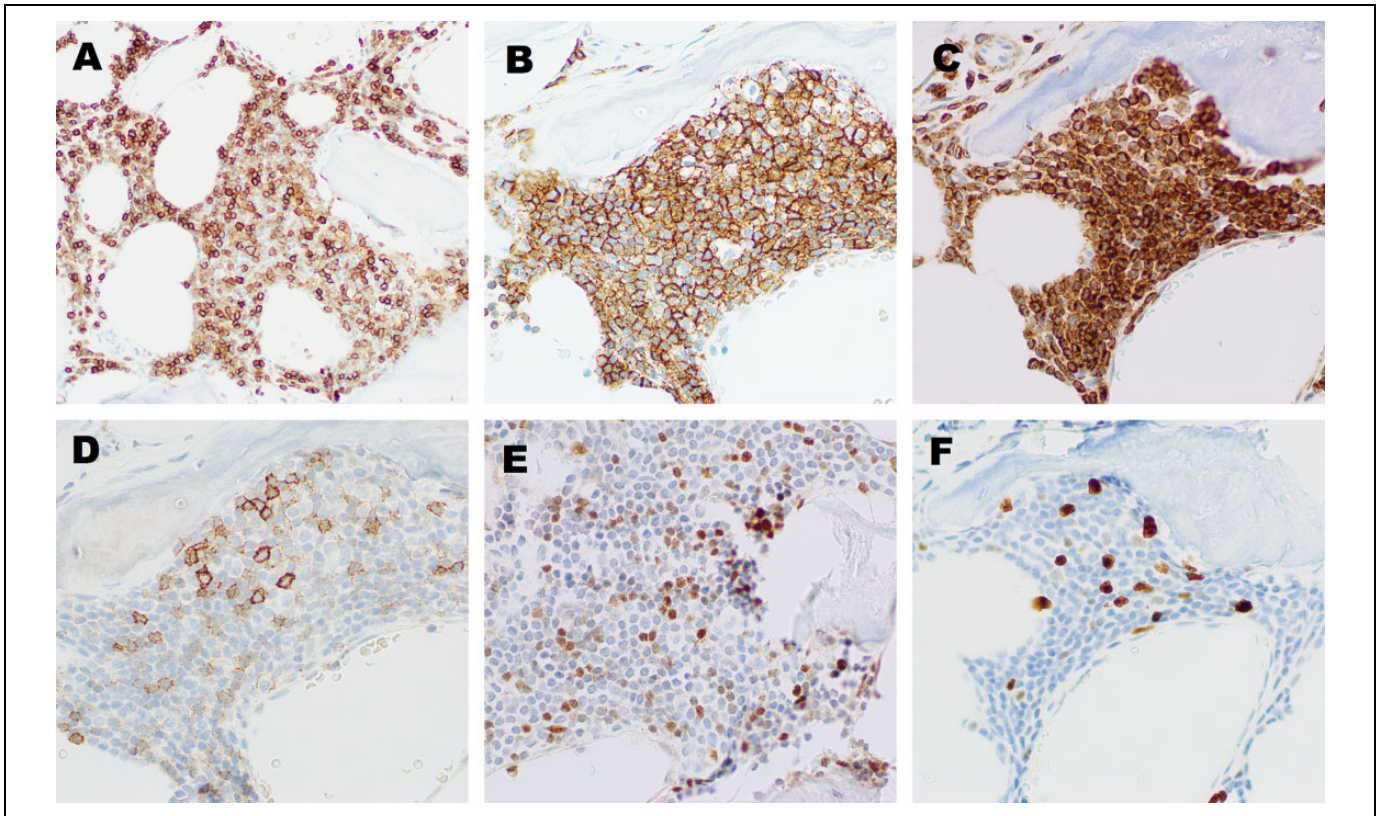


Figure 4. Immunohistochemical stains of CD5 with diffuse positive membranous staining (A), CD20 with diffuse positive membranous staining (B), BCL-2 with diffuse positive membranous staining (C), CD3 highlights scattered T cells (D), Cyclin D1 with positive nuclear staining (E), Ki-67 proliferation index of <10% (F; $\times 200$).

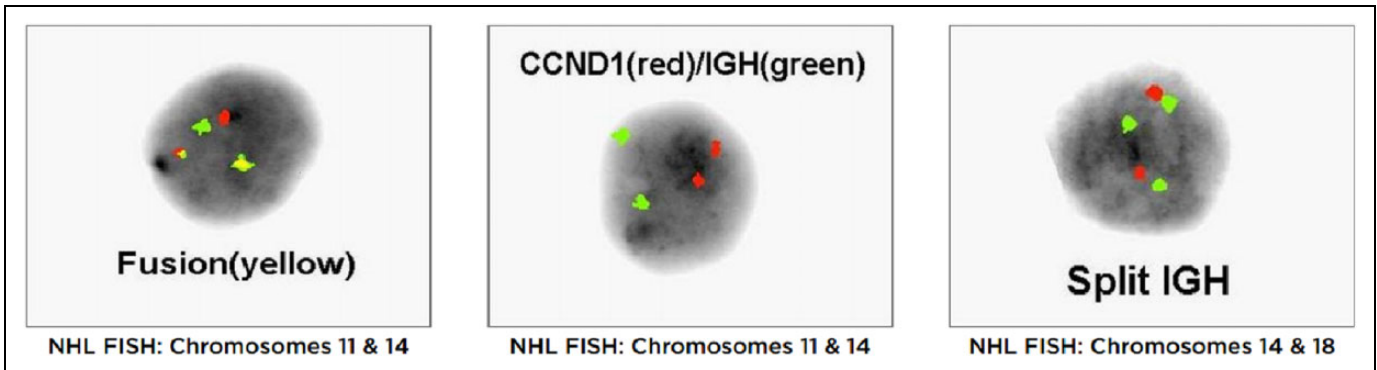


Figure 5. Fluorescence in situ hybridization (FISH) fusion probes indicating a positive fusion between CyclinD1 (CCND1) and IGH on chromosomes 11 and 14. The presence of yellow indicates that there is a fusion/translocation present, whereas the red dot represents chromosome 14 and green dots represent chromosomes 11 and 18. In the absence of a translocation, 2 red dots (chr. 14) and 2 green dots (chr. 11 or chr 18) should be visualized. In the presence of a translocation, a yellow fusion dot ($t(11;14)$), a red dot (chr 11), and a green dot (chr 14) should be visualized.

The examination of the peripheral smear is important to identify atypical lymphoid cells that may be associated with bone marrow involvement. The other laboratory biochemical tests not only contribute to staging but can also influence the type of chemotherapy that is selected for the patient. The PET scan is required to determine the extent of the disease.

Diagnostic Findings, Part 6

Subsequently, the patient was worked up further by the oncology team for staging. His CBC results were normal: white blood cell (WBC) count of 7300 cells/mcL, hemoglobin level of 13.6 g/dL, and a platelet count of 237 000 cells/mcL. However, on his peripheral blood smear, atypical lymphoid cells were identified. His peripheral blood was sent for flow

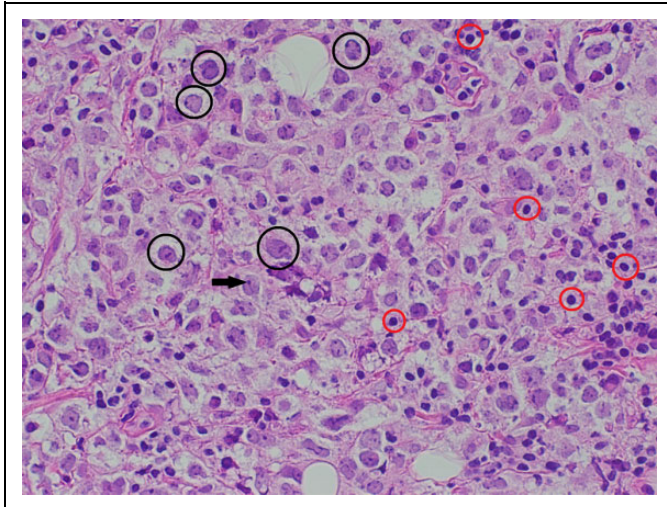


Figure 6. There are large pleomorphic lymphocytes (black circles) admixed with smaller lymphocytes (red circles). These larger lymphocytes have a high nuclear to cytoplasmic ratio, irregular nuclear contours, and prominent nucleoli (black arrow; hematoxylin and eosin, $\times 400$).

cytometry, which revealed a small monoclonal B-cell population, approximately 15% of the total lymphocytes, that was again positive for B-cell markers (CD19, CD20, CD22, FMC7) with aberrant expression of CD5. In addition, the cells showed surface immunoglobulin kappa light chain restriction, indicating clonality. The immunophenotype by flow cytometry from the peripheral blood confirmed that it was the same abnormal clonal population as in the sinus bone marrow. A PET scan with F-18 fluorodeoxyglucose was performed for staging, revealing no hypermetabolic lymphadenopathy. Along with the low proliferation index, these findings were suggestive of an indolent nature and a diagnosis of non-nodal leukemic MCL was made. The oncology team deemed that he did not require chemotherapeutic treatment at the moment and scheduled follow-ups every 6 months to monitor for disease progression.

Question/Discussion Points, Part 6

What Is the Prevalence of Mantle Cell Lymphoma?

Mantle cell lymphoma constitutes approximately 6% of all cases of non-Hodgkin lymphomas (NHL) and is typically found in the lymph nodes.⁴ Extranodal manifestations of MCL include locations such as the gastrointestinal tract, the tonsils, and the respiratory tract.⁵ Mantle cell lymphoma is typically diagnosed in middle-aged adults with a median age of 60 at initial presentation; there is a predilection for males.⁶

Primary nasopharyngeal lymphomas are rare in the Western population, as many cases reported are more typically seen in the Asian population.⁷ This particular case is unique in that it arises in the sinonasal lamellar bone. Lymphomas arising in the sinonasal tract are uncommon and comprise approximately 3% to 5% of all total NHLs, with the most common histological type of primary lymphoma seen in the nasopharynx being a

diffuse large B-cell lymphoma (DLBCL).⁸ Histologically, it is easy to differentiate a classic MCL from a DLBCL due to the size of the lymphoma cells (Figure 6) and positivity of Cyclin D1. The malignant cells in a DLBCL are 3 to 6 times larger than the typical cells found in classic MCL. Cyclin D1 is also negative in DLBCL.

What Is the Typical Presentation of Mantle Cell Lymphoma?

The clinical presentation of leukemia and lymphomas can vary drastically depending on the type of leukemia or lymphoma. Generally, patients can experience fatigue due to the anemia, bleeding and/or bruising due to the thrombocytopenia, fever, night chills, and infection from the lack of functioning WBCs, and lymphadenopathy and/or hepatosplenomegaly secondary to the infiltration of leukemic or lymphoma cells. In some cases, particularly indolent leukemias and lymphomas, patients can be completely asymptomatic.

Classical MCL typically presents with lymphadenopathy and hepatosplenomegaly with advanced extranodal, bone marrow, and peripheral blood involvement.⁹ On the contrary, a specific subtype of MCL, leukemic non-nodal MCL, is diagnosed when the patient presents with peripheral blood, bone marrow, or splenic involvement in the absence of lymphadenopathy on physical examination and on CT scan. Similar to MCL, DLBCL can present with advanced presentation with a rapidly enlarging mass with associated B-symptoms (fever, weight loss, fatigue, night sweats, chills).⁴ Therefore, presenting symptoms are not useful in the differentiation of lymphoma subtypes.

What Morphological Features Aid in the Diagnosis of Mantle Cell Lymphoma?

Histologically, lymphoid cells in classical MCL are monotonous, small to medium in size with dispersed chromatin, inconspicuous nuclei, with abnormal nuclear contours.¹⁰ The immunophenotype of these cells are positive for pan-B cell markers (CD19, CD20, CD79a, PAX5), BCL-2, Cyclin D1, and aberrant expression of CD5 (a T-cell marker). It is negative for CD10, CD23, and BCL-6.¹¹

What Is the Differential Diagnosis for a Small B-Cell Lymphoma?

Differential diagnoses to consider are other “small B-cell lymphomas” such as CLL/SLL, HCL, FL, and MZL. The best way to distinguish is by immunophenotyping, either by flow cytometry or immunohistochemistry (summarized by Table 1). Chronic lymphocytic leukemia/SLL is characterized by positivity for CD5, CD23, and CD200, whereas HCL will be positive for CD11c, CD25, CD123, and CD200. Follicular lymphoma has an immunophenotype that is typically positive for CD10, BCL2, and BCL6; further molecular testing usually shows a t(14;18). Marginal zone lymphoma has no specific

Table 1. Comparison of Flow Cytometry Profiles.

	This case	Mantle cell lymphoma	Chronic lymphocytic leukemia/small lymphocytic lymphoma	Hairy cell leukemia	Follicular lymphoma	Marginal zone lymphoma	Diffuse large B-cell lymphoma
CD5	+	+	+	–	–	–	–
CD10	–	–	–	–	+	–	Variable
CD19	+	+	+	+	+	+	+
CD23	–	–	+	–	–	–	–
CD25	–	–	–	+	–	–	–
CD43	–	–	+	–	–	–	–
CD123	–	–	–	+	–	–	–

markers and should only be considered as a diagnosis when all other entities listed previously are ruled out.

What Are the Different Prognoses for the Different Variants of Mantle Cell Lymphoma?

According to the most current World Health Organization classification of hematopoietic and lymphoid tumors, there are 3 subtypes of MCL: classical MCL, leukemic non-nodal MCL, and in situ mantle cell neoplasia. Within the classical MCL, there are 4 variants: blastoid, pleomorphic, small cell, and marginal zone-like. With the exception of leukemic non-nodal MCL and in situ mantle cell neoplasia, mantle cell lymphoma is aggressive and unresponsive to treatment.¹² Even with treatment, the mean survival period is only 3 to 5 years for classical MCL.¹³ Among the MCL variants, the blastoid and pleomorphic variants have a poorer prognosis, whereas the marginal zone-like and small cell variants tend to have a better prognosis. Leukemic non-nodal MCL and in situ mantle cell neoplasia tend to have a more indolent nature with a lower mitotic activity, a lower proliferation index, and a better prognosis.¹⁴ The reported mean survival period for leukemic non-nodal MCL is around 6 to 7 years.¹⁵

Teaching Points

- The clinical presentation of leukemia and lymphomas can vary drastically depending on the type of leukemia or lymphoma. Generally, patients can experience “B symptoms,” bleeding and/or bruising, infection, lymphadenopathy, and/or hepatosplenomegaly. In some cases, particularly indolent leukemias and lymphomas, patients can be completely asymptomatic.
- For small B-cell lymphomas, differential diagnoses to consider include CLL/SLL, HCL, MCL, FL, and MZL. The best way to distinguish is by immunophenotyping, either by flow cytometry or immunohistochemistry.
- The MCL subtype is rare and constitutes approximately 6% of all cases of NHLs; it is typically found in the lymph nodes.
- The MCL typically presents with advanced extranodal, bone marrow, peripheral blood, splenic, and/or gastrointestinal involvement.

- Histologically, lymphoid cells in MCL are small in size with dispersed chromatin, inconspicuous nuclei, and abnormal nuclear contours.
- Most cases of MCL are associated with cyclin D1 (CCND1) and immunoglobulin heavy chain region (IgH) translocation on chromosome 11 and chromosome 14 resulting in t(11;14).
- The MCL has a poor prognosis, even with treatment. The mean survival period is only 3 to 5 years.


Declaration of Conflicting Interests

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