Contents lists available at ScienceDirect

Academic Pathology 11/2 (2024) 100117

Academic Pathology

journal homepage: www.journals.elsevier.com/academic-pathology

Educational Case

Educational Case: Multiple myeloma

Jerome P. Givi, MPH [a], Nathan Williams, MD [b,*,1], Rotem Hass, MD [b], Danyel H. Tacker, PhD [a], Aarti Goswami, MD [a], Cara Randall, MD [a]

[a] Department of Pathology, Anatomy, Laboratory Medicine, West Virginia University, Morgantown, WV, USA
[b] West Virginia University School of Medicine, USA

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 https://www.journals.elsevier.com/academic-pathology/pathology_competencies-for-medical-education-pcme.[1]

Keywords: Pathology competencies, Organ system pathology, Hematopathology, Hematologic malignancy, Multiple myeloma, Monoclonal gammopathy

Primary objective

Objective HWC3.7: Multiple Myeloma: Describe the clinicopathologic features of multiple myeloma in terms of clinical presentation, laboratory findings, radiologic findings, histologic features, and prognosis.

Competency 2: Organ System Pathology; Topic: Hematopathology – White Cell Disorders, Lymph Nodes, Spleen, and Thymus (HWC); Learning Goal 3: Classification of Leukemia and Lymphomas.

Patient presentation

A 71-year-old man presents to the clinic with his wife for an annual check-up. He reports a four-month history of fatigue and recurrent upper respiratory infections. His wife has noticed that he has become somewhat forgetful in the past year. The patient reports no episodes of fevers or nausea and no significant decrease in muscle strength. He does note he has had recent pain in the skull and neck. The patient has no history of trauma and is not taking any medications. The patient is a former smoker with a 12-pack-year history, has been retired for 6 years, and lives with his wife.

Diagnostic findings, Part 1

The patient is afebrile and appears tired. On physical exam, the patient's neck and skull are tender to palpation. The neurological exam is normal, and muscle strength is 5/5 in all groups. The patient weighs 15 pounds less than he did at his last check-up 12 months ago.

Questions/discussion points, Part 1

What is considered in the differential diagnosis? What basic set of tests should be ordered for this patient and why?

In a patient with weight loss, fatigue, recurrent infections, and bone pain, the differential is broad. One might consider a lymphoma, a chronic leukemia, or metabolic carcinoma to the bone in the setting of these symptoms. Chronic infections, autoimmune disorders, and endocrine abnormalities may also be included in the differential diagnosis for this patient.

In this patient, a complete blood count (CBC) with differential is a useful tool as it can help identify leukemias, anemia, chronic infections, and, in rare cases, lymphomas that may be causing this patient's symptoms. A basic metabolic panel (BMP) and urinalysis should also be ordered to help detect metabolic derangements that may be caused by various malignancies or endocrine abnormalities. A peripheral blood smear is also helpful to evaluate for leukemias, other marrow disorders, certain infections, or abnormalities in the red blood cells (RBCs) or platelets. An X-ray of the skull would also be helpful to investigate the etiology of the patient's atraumatic skull and neck pain.

* Corresponding author. Department of Pathology, University of Maryland Medical Center, Baltimore, MD, USA.
E-mail address: nathan.williams@umm.edu (N. Williams).
[1] Current address of N.W., Department of Pathology, University of Maryland Medical Center, Baltimore, MD, USA.

https://doi.org/10.1016/j.acpath.2024.100117
Received 6 May 2022; Received in revised form 4 February 2024; Accepted 19 February 2024; Available online xxxx
eISSN2374-2895/

Diagnostic findings, Part 2

The lab results, peripheral blood smear, and skull X-ray return.

Questions/discussion points, Part 2

Please evaluate the laboratory results shown in Table 1.

From the CBC, the patient has a normocytic, normochromic anemia. This finding has several potential etiologies, including but not limited to chronic infection and/or inflammation, bleeding, hemolysis, early stages of nutritional deficiency, dysfunction of the liver, kidney, bone marrow, or endocrine organs, and systemic disease. The BMP shows an elevated creatinine, and the urinalysis shows proteinuria and cloudy urine. Each of these findings suggests an ongoing problem with the kidney.

Describe the findings on the peripheral smear. What causes this phenomenon?

The abnormal finding that is seen in this peripheral smear (Fig. 1) is rouleaux formation or long chains of stacked RBCs. Rouleaux formation is caused by an increase in plasma proteins, such as fibrinogen and immunoglobulins.[2] These proteins negate the normally repelling negative charges on the RBC membranes and allow them to interact and stack on one another. Fibrinogen and other acute-phase reactants can be increased in several acute and chronic infections, as well as connective tissue diseases, chronic liver disease, and cancer. The primary and most concerning cause of increased immunoglobulins to a level sufficient to cause rouleaux is a plasma cell neoplasm, but increased plasma immunoglobulins can also be associated with chronic inflammatory disorders, autoimmune disorders, or some B-cell lymphomas. Rouleaux formation can also artificially appear on a peripheral smear when the slide is prepared poorly or when the slide is viewed in a thickened area (i.e., not in the monolayer, where peripheral smear analysis should be performed).[3]

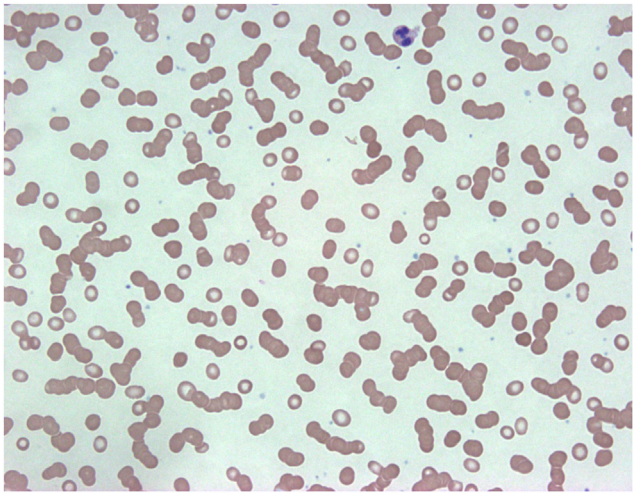

Fig. 1. The red blood cells in the peripheral blood smear show marked rouleaux formation (Wright Giemsa, 50x).

Table 1
Patient laboratory results.

Test	Result	Flag	Units	Reference interval
CBC with differential				
WBC	5.8		$x10^3$/uL	4.0–10.5
RBC	3.8	▼	$x10^6$/uL	4.1–5.6
Hemoglobin	9.6	▼	g/dL	12.5–17.0
Hematocrit	34.9	▼	%	36.0–50.0
MCV	88		fL	80–100
MCH	29.6		pg	27.0–34.0
MCHC	34.7		g/dL	32.0–36.0
RDW	13.5		%	11.7–15.0
Platelets	156		$x10^3$/uL	140–415
Neutrophils	62		%	40–74
Lymphocytes	28		%	14–46
Monocytes	6		%	4–13
Eosinophils	3		%	0–7
Basophils	1		%	0–3
Immature Granulocytes	0		%	0–1
Basic metabolic panel				
BUN	18		mg/dL	7–20
CO2	24		mmol/L	23–29
Creatinine	2.3	▲	mg/dL	0.7–1.3
Glucose	80		mg/dL	64–100
Chloride	101		mmol/L	96–106
Potassium	3.9		mEq/L	3.7–5.2
Sodium	140		mEq/L	136–144
Calcium	14.4	▲	mg/dL	8.5–10.2
Routine Urinalysis				
Appearance	Cloudy	!		Clear
Color	Yellow			Colorless, straw, yellow
Specific Gravity	1.012			1.005–1.030
Glucose	Not detected		mg/dL	Not detected
Blood	Not detected		mg/dL	Not detected
pH	5.5			5.0–8.0
Protein	20	▲	mg/dL	Not detected
Leukocytes	Not detected		WBC/uL	Not detected

▲ = elevated value. ▼ = low value. ! = abnormal.
Abbreviations: BUN = blood urea nitrogen; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = Mean corpuscular volume; RDW = red cell distribution width; WBC = white blood cell.

Describe the findings on the X-ray. What entities can cause this radiologic finding and how might this relate to the findings of the lab work?

This X-ray demonstrates multiple well-circumscribed, round, lytic bone lesions in the skull and cervical spine (Fig. 2). Tumors and tumor-

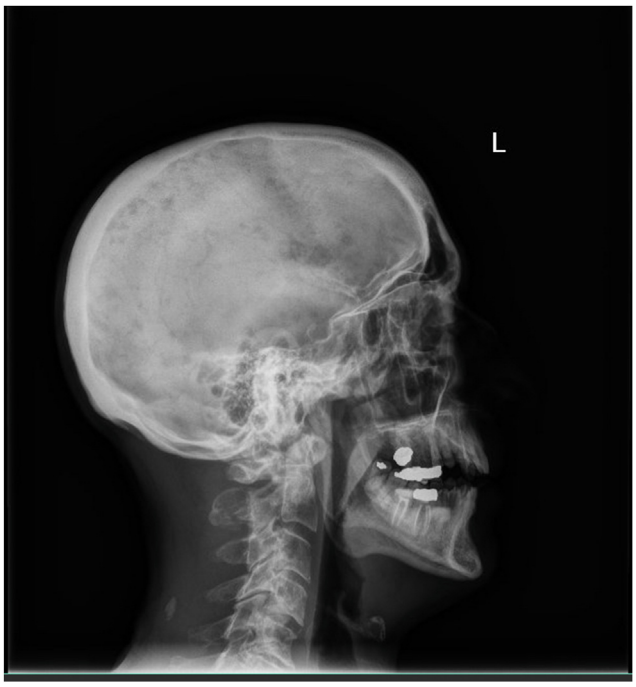

Fig. 2. X-ray image of the skull and cervical spine in the sagittal view, showing multiple lytic lesions.

like conditions can form osteolytic bone lesions. This includes metastatic cancer to bone, multiple myeloma (MM), Ewing sarcoma, osteosarcoma, osteoblastoma, chondroblastoma, enchondroma, giant cell tumors, fibrous dysplasia, bone cysts, osteomyelitis, bone infarcts, and more.[4] Regardless of the etiology, this finding indicates that there is an ongoing imbalance between bone formation and resorption, which may be the cause of this patient's hypercalcemia.

What is the current differential diagnosis? What minimally invasive tests could be ordered next? Please describe these tests

The most common malignant lesion of bone is metastasis from another site, so this should always be considered when discussing atraumatic bone lesions. Primary bone tumors also remain on the differential diagnosis. However, MM is currently the most likely diagnosis as this would explain the patient's symptoms, abnormal lab results, rouleaux formation, and lytic lesions seen on the X-ray.

Serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP) are non-invasive tests that can be done to identify disorders of serum or urine protein and could further support the suspicion of MM. In these tests, serum or urine is placed on a specific medium and a charge is applied; the net charge and size/shape of proteins allows for differentiation of the various serum/urine proteins. SPEP/UPEP can detect many patterns of protein abnormalities in the blood and urine. For example, abnormal SPEP studies can demonstrate changes in protein fractions that correlate with acute or chronic inflammation, protein loss or deficiency, and mixed disorders (e.g., acute inflammatory response superimposed on a renal loss pattern, as seen in acutely ill inpatients); UPEP studies can demonstrate patterns of proteinuria (e.g., glomerular versus tubular loss patterns).[5]

These tests could also detect the presence of an abnormal immunoglobulin called an M protein. The presence of a homogeneous M protein, indicated by an "M spike" on SPEP/UPEP, indicates a monoclonal gammopathy.[5] Monoclonal gammopathies are a group of malignant and potentially malignant disorders characterized by a proliferation of clonal plasma cells that produce large amounts of identical M protein. In the presence of an M spike, immunofixation electrophoresis (IFE) can be performed to identify the specific type of immunoglobulin creating the M spike. Following electrophoresis, this technique uses immunoglobulin antisera specific to each type of immunoglobulin found in the blood, including both heavy (IgG, IgA, IgM, etc.) and light chains (kappa and lambda), to detect abnormal levels of a specific type of immunoglobulin and further classify the serum or urine protein abnormality.

A free light-chain assay can also be performed to measure the amount of kappa and lambda light immunoglobulin chains that are unbound to heavy chains in the serum. Abnormal serum kappa to lambda free light-chain ratios indicate an excessive production of one of these proteins.

Diagnostic findings, Part 3

An SPEP was performed with results, as shown in Fig. 3B and immunosubtraction shown in Fig. 3C. A reference normal sample for comparison is shown in Fig. 3A.

Questions/discussion points, Part 3

Interpret the findings of the SPEP and immunosubtraction studies shown (Fig. 3B and C). In what conditions could this be seen?

Typically, an SPEP will demonstrate a polyclonal field of immunoglobulins in the gamma region (Fig. 3A), which composes approximately 10–20% of total protein density. This SPEP (Fig. 3B) shows a dense M protein where the typical polyclonal gamma region should be (arrow). M

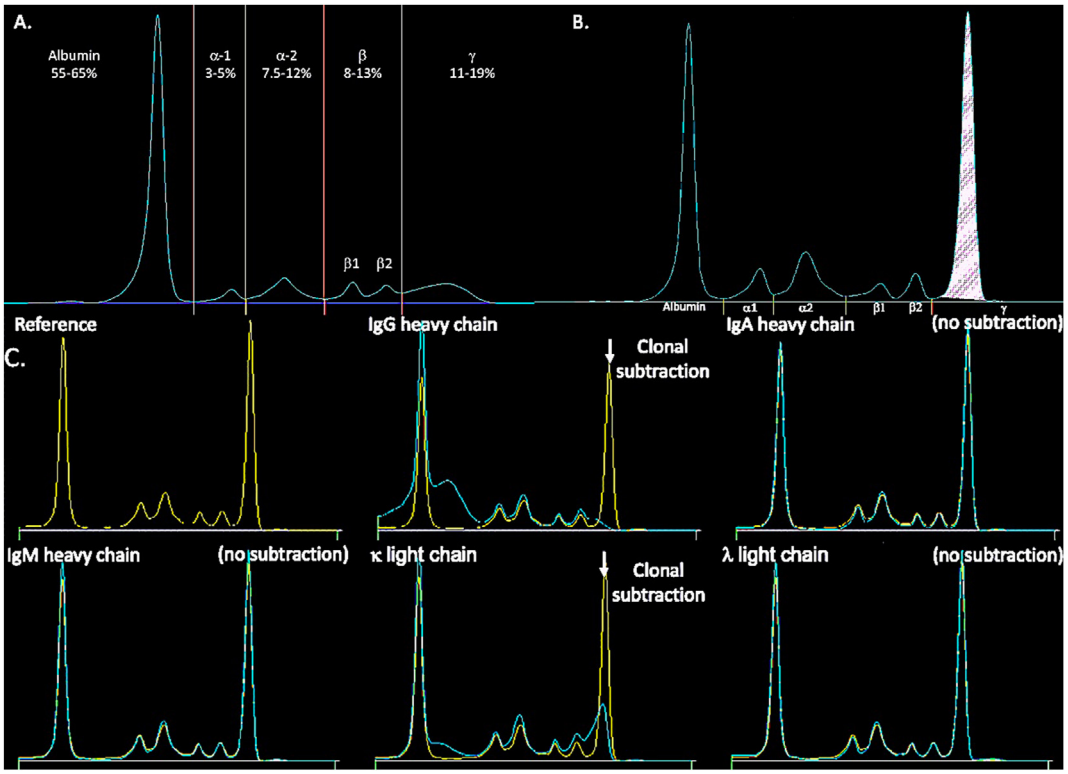

Fig. 3. Results of serum protein electrophoresis (SPEP) are portrayed above. A. Normal SPEP, with expected fraction concentrations and delimiters. B. Results of this patient, with the M spike protein highlighted. C. Immunosubtraction study done to type and confirm the M protein. Clockwise from top-left: Reference tracing (yellow) with no added antisera (this is overlaid in the other panes); IgG antisera–treated specimen (blue); IgA antisera–treated specimen (blue); lambda light-chain antisera–treated specimen (blue); kappa light-chain antisera–treated specimen (blue); and IgM antisera–treated specimen (blue).

proteins can be seen in different monoclonal gammopathies; these include monoclonal gammopathy of undetermined significance (MGUS), Waldenström macroglobulinemia, plasmacytoma, smoldering multiple myeloma (SMM), and MM.

The associated serum immunosubtraction study (Fig. 3C) confirms the M protein as an IgG kappa–specific monoclonal immunoglobulin, owing to the difference between the reference tracing and the antisera lanes (i.e., the subtraction obtained from antisera complexing with the involved heavy and light chains, respectively, which removes them from the viewing pane). Lacking subtraction in the uninvolved panes (IgA, IgM, lambda light chain) is consistent with suppression of polyclonal immunoglobulin production.

MM is a plasma-cell neoplasm diagnosed by the presence of clonal bone marrow plasma cell percentage of ≥10%, with at least one myeloma-defining event. Myeloma-defining events include end-organ damage attributable to plasma-cell proliferative disorder, manifesting as hypercalcemia, renal insufficiency, anemia, or bone lesions (the so-called CRAB symptoms). If CRAB symptoms are not present, the finding of at least one biomarker of malignancy can instead be used to reach the diagnosis of MM. These biomarkers include a clonal bone marrow plasma cell percentage of ≥60%, involved-to-uninvolved serum-free light-chain ratio of ≥100 (i.e., ratio of the amount of monoclonal light chain to the polyclonal light chain), or >1 focal bone lesion at least 5 mm in size on magnetic resonance imaging (MRI).[6]

MGUS is typically discovered unexpectedly during SPEP and is defined as the presence of M protein at a concentration of <30g/L, with less than 10% plasma cells in bone marrow biopsy and an absence of CRAB symptoms. MGUS affects 3–4% of individuals over age 50 and is considered an obligate precursor to MM; the risk of progression to MM is approximately 1% per year.[6]

SMM also shows an M protein on SPEP and is similar to MGUS in its lack of clinical manifestations but is more likely to progress to symptomatic myeloma; progression to MM is 10% per year for the first 5 years, 3% per year for the subsequent 5 years, and 2% per year for the 5 years following.[6] Diagnostic criteria for SMM are 10–59% clonal plasma cells in the bone marrow and/or M protein at myeloma levels, with an absence of myeloma-defining events.

Plasmacytomas, which are single localized tumors of monoclonal plasma cells, are also capable of producing an M spike.

Waldenström macroglobulinemia is a clinical syndrome associated with bone marrow involvement by lymphoplasmacytic lymphoma and an IgM monoclonal gammopathy of any concentration. The bone marrow infiltrate is composed of small lymphocytes mixed with variable numbers of plasma cells, plasmacytoid lymphocytes, and often with increased mast cells.[7]

Diagnostic findings, Part 4

Given the clinical, laboratory, and radiologic findings, a bone marrow biopsy is performed and is shown in Fig. 4.

Questions/discussion points, Part 4

Describe the findings of the bone marrow biopsy. What is the diagnosis? How does this relate to the CBC, urinalysis, and other lab findings?

The bone marrow aspirate in Fig. 4A shows a higher-than-expected prevalence of plasma cells. The bone marrow biopsy (Fig. 4B) also demonstrates an expanded plasma cell population making up ≥ 10% of total marrow cells. This is evidenced by both morphology and immunoreactivity to CD138, a plasma cell marker (Fig. 4C). This finding, along with the clinical presentation, is adequate to diagnose the patient with MM. Leukopenia, thrombocytopenia, and anemia are commonly seen in the CBCs of patients with MM. This is caused by the monoclonal plasma cell population crowding the bone marrow and hindering the production of other bone marrow precursors.[7] As MM stimulates osteoclasts to resorb bone, this diagnosis also explains the x-ray findings and the patient's hypercalcemia.

The excessive production of monoclonal immunoglobulin by this plasma cell population leads to free light-chain circulation in the serum. This excess free light-chain is eventually excreted in the urine as Bence Jones protein, named after the British pathologist who first described it, causing proteinuria in this patient. Deposition of this protein in the kidney tubules is toxic and can eventually cause renal failure, as indicated by the patient's increased creatinine levels.[8]

Describe the biology and epidemiology of MM. Are there any populations who are at increased risk of developing MM?

The pathogenesis of MM is complex and involves an interaction between inherited and acquired genetic changes and environmental factors, including the microenvironment of the bone marrow. Chromosomal translocations that occur during aberrant class-switch recombination and lead to oncogene overexpression are thought to be early events in the disease process, with additional mutations in different pathways that cause derangement of the plasma cells.[9] Most cases of MM have detectable genetic abnormalities; one commonly seen mutation is a translocation involving the *IGH* gene.[10,11]

MM is responsible for 1% of all malignant tumors, 10–15% of hematopoietic neoplasms, and 20% of deaths from hematopoietic malignancies; this equates to approximately 26,000 cases and over 11,000

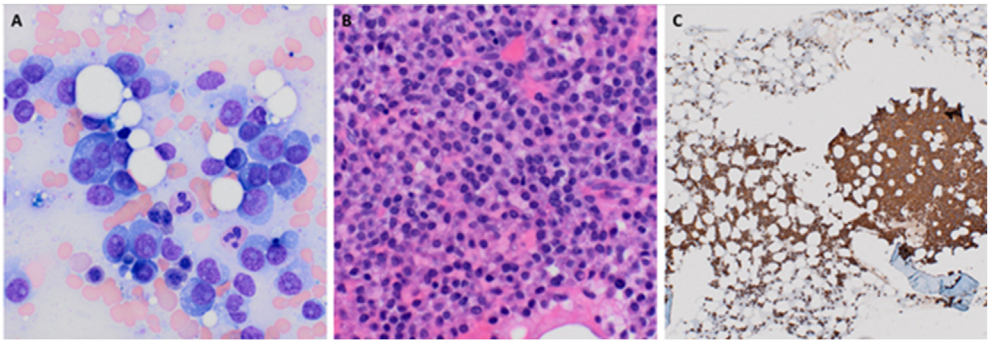

Fig. 4. Bone marrow examination findings are shown here. A. 50x image of aspirate w/Wright–Giemsa stain; B. 40x image of core biopsy of H&E stain; C. 4x image of CD138, an immunohistochemical stain for plasma cells.

deaths per year in the United States.[12] It has a slightly higher incidence in males and is nearly twice as frequent in individuals of African descent. The incidence also increases with age; >90% of cases occur in patients with ≥50 years of age, and the average age of diagnosis is 69 years.[6,13]

Why are patients with MM at an increased risk of infection?

These patients are immunocompromised on several levels. First, B-cell differentiation is suppressed, leading to hypogammaglobulinemia.[10] The immunoglobulins that are produced by the clonal plasma cell population are identical and have no immunological function. Dysfunction of T cells, dendritic cells, and NK cells can also occur. The cause of this dysfunction is unclear but is believed to be due in part to an immunologically hostile microenvironment in the bone marrow that is created by the myeloma cells through a variety of molecular cytokines.[14] Additionally, extensive marrow infiltration by the myeloma cells can overcrowd the marrow, causing neutropenia and lymphocytopenia. MM significantly hinders components of the adaptive and innate immune system, predisposing patients, who are generally older and have weaker immune systems at baseline, to infection. Finally, patients become even more immunosuppressed by chemotherapeutic treatments; the risk of infection is the highest in the first three months after diagnosis when chemotherapy is begun.

What other complications are seen in patients with MM?

The excess monoclonal immunoglobulin from MM can cause primary or light chain (AL) amyloidosis by depositing in a variety of organs including the liver, spleen, kidney, heart, blood vessels, and joints.[15] Amyloidosis can cause a variety of complications depending on the organ(s) affected. This includes hepatosplenomegaly and acute liver failure, splenic rupture, kidney failure, restrictive cardiomyopathy, arrhythmia, macroglossia, and more.[16–20] Amyloid protein deposition can be visualized on biopsy of the affected organ; histologically, the specimen will show apple-green birefringence of amyloid on Congo red staining under polarized light on histology.

An additional complication is hyperviscosity syndrome. The high levels of monoclonal protein in the blood cause it to thicken and prevent normal flow through small vessels.[21] Symptoms occur due to decreased organ perfusion; common symptoms include abnormal bleeding, chest pain, shortness of breath, headache, visual disturbances, and seizure. Hyperviscosity also raises one's risk of developing a thrombus, or blood clot, and patients are therefore prone to deep-vein thrombosis, pulmonary embolism, and stroke. Hyperviscosity syndrome is not restricted to MM; patients with profound increases in any circulating immunoglobulin may also exhibit signs and symptoms, and it is most common in Waldenstrom macroglobulinemia associated with an IgM monoclonal protein.

What is the treatment and life expectancy of patients with multiple myeloma? What is the most common cause of death?

A number of different treatment options have been developed for patients with MM. This includes hematopoietic stem-cell transplant (HSCT), chemotherapy, immunomodulatory therapy, monoclonal antibodies, proteasome inhibitors, and chimeric antigen receptor T-cell therapy.[22]

To determine the treatment regimen and eligibility for HSCT, patients are stratified based on disease risk. Variables that guide stratification include host factors, tumor stage, presence or absence of certain prognostic cytogenetic abnormalities, and response to therapy. Patients who are at standard or intermediate risk are eligible for HSCT therapy once induction therapy is completed. Transplant-ineligible patients undergo additional cycles of chemotherapy.[19]

Unfortunately, even with HSCT, MM is considered incurable. The life expectancy for patients depends largely on the severity of symptoms and complications, with survival ranging from <6 months to >10 years after diagnosis.[23] Generally speaking, younger patients who have fewer comorbidities tend to have a favorable prognosis over older patients with concomitant diseases. Overall, the five-year survival rate is approximately 35%.[24]

Given the immunosuppression, the leading cause of death in MM is infection.[25,26] Pneumonia and urinary tract infections are the most common types of infection, and *Streptococcus pneumonia*, *Haemophilus influenzae*, and *Escherichia coli* are the most common infectious organisms in these patients.[18]

Teaching points

- MM is a systemic disease caused by a clonal bone marrow plasma cell population. It is diagnosed when a clonal plasma cell percentage of ≥10% in the bone marrow is seen in conjunction with CRAB symptoms, which include the following:
  - o C: Hypercalcemia
  - o R: Renal insufficiency
  - o A: Anemia
  - o B: Osteolytic bone lesions
- A variety of clinical tests are used in the diagnosis of MM, including urinalysis, CBC, peripheral blood smear evaluation, radiographic imaging, bone marrow biopsy, and electrophoresis (SPEP, IFE, and UPEP). Biopsies of other organs, including the kidney and heart, can reveal amyloidosis caused by the excessive immunoglobulins produced by the clonal plasma cell population.
- MGUS and SMM are premalignant conditions that can transform to MM. These conditions also display an M protein on SPEP but have a smaller monoclonal plasma cell population in the bone marrow and/or have no CRAB symptoms.
- The most common cause of death for patients with MM is an infection as MM severely compromises the immune system. Treatment depends on disease risk and commonly includes HSCT therapy and chemotherapy.

Funding

The article-processing fee for this article was funded by an Open Access Award given by the Society of '67, which supports the mission of the Association of Pathology Chairs to produce the next generation of outstanding investigators and educational scholars in the field of pathology. This award helps to promote the publication of high-quality original scholarship in *Academic Pathology* by authors at an early stage of academic development.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Nathan Williams reports financial support was provided by Society of '67. Nathan Williams reports a relationship with Society of '67 that includes: funding grants.

References

1. Knollmann-Ritschel BEC, Huppmann AR, Borowitz MJ, Conran R. Pathology competencies in medical education and educational cases: update 2023. *Acad Pathol*. 2023;10(3), 100086. doi:10.1016/j.acpath.2023.100086
2. Abramson N. Rouleaux formation. *Blood*. 2006;107(11):4205.
3. Adewoyin AS, Nwogoh B. Peripheral blood film - a review. *Ann Ib Postgrad Med*. 2014;12(2):71–79.
4. Subramanian S, Viswanathan VK. Lytic bone lesions. In: *StatPearls*. StatPearls Publishing; 2021. http://europepmc.org/books/NBK539837.
5. O'Connell TX, Horita TJ, Kasravi B. Understanding and interpreting serum protein electrophoresis. *Am Fam Physician*. 2005;71(1):105–112.
6. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127(20):2375–2390. doi:10.1182/blood-2016-01-643569

7. Kaur P, Shah BS, Baja P. Multiple myeloma: a clinical and pathological profile. *Gulf J Oncolog.* 2014;1(16):14–20.
8. Hogan JJ, Alexander MP, Leung N. Dysproteinemia and the kidney: core curriculum 2019. *Am J Kidney Dis.* 2019;74(6):822–836. doi:10.1053/j.ajkd.2019.04.029
9. Morgan GJ, Walker BA, Davies FE. The genetic architecture of multiple myeloma. *Nat Rev Cancer.* 2012;12(5):335–348. doi:10.1038/nrc3257
10. Rawstron AC, Davies FE, Owen RG, et al. B-lymphocyte suppression in multiple myeloma is a reversible phenomenon specific to normal B-cell progenitors and plasma cell precursors. *Br J Haematol.* 1998;100(1):176–183. doi:10.1046/j.1365-2141.1998.00525.x
11. González D, van der Burg M, García-Sanz R, et al. Immunoglobulin gene rearrangements and the pathogenesis of multiple myeloma. *Blood.* 2007;110(9):3112–3121. doi:10.1182/blood-2007-02-069625
12. Michels TC, Petersen KE. Multiple myeloma: diagnosis and treatment. *Am Fam Physician.* 2017;95(6):373–383.
13. Padala SA, Barsouk A, Barsouk A, et al. Epidemiology, staging, and management of multiple myeloma. *Med Sci.* 2021;9(1):3. doi:10.3390/medsci9010003
14. Pratt G, Goodyear O, Moss P. Immunodeficiency and immunotherapy in multiple myeloma. *Br J Haematol.* 2007;138(5):563–579. doi:10.1111/j.1365-2141.2007.06705.x
15. Bustamante JG, Zaidi SRH. Amyloidosis. In: *StatPearls. StatPearls Publishing*; August 9, 2022. https://www.ncbi.nlm.nih.gov/books/NBK470285/.
16. Cross TJ, Wendon JA, Quaglia A, Salisbury JR, Heneghan MA, Harrison PM. Myeloma associated amyloidosis presenting as subacute liver failure. *Postgrad Med.* 2006;82(969):e13. doi:10.1136/pgmj.2006.044883
17. Buzalewski J, Fisher M, Rambaran R, Lopez R. Splenic rupture secondary to amyloid light-chain (AL) amyloidosis associated with multiple myeloma. *J Surg Case Rep.* 2019;3. doi:10.1093/jscr/rjz021
18. Vakiti A, Padala SA, Mewawalla P. Myeloma kidney. In: *StatPearls*. StatPearls Publishing; 2022. http://www.ncbi.nlm.nih.gov/books/NBK499952/.
19. Albagoush SA, Shumway C, Azevedo AM. Multiple myeloma. In: *StatPearls. StatPearls Publishing*; February 24, 2022. https://www.ncbi.nlm.nih.gov/books/NBK534764/.
20. Parrilla F, Calderon RE, Figueroa R, Gurrea C. Cardiac amyloidosis secondary to multiple myeloma. *Bol Asoc Med P R.* 2013;105(2):39–42.
21. Gertz MA. Acute hyperviscosity: syndromes and management. *Blood.* 2018;132(13):1379–1385. doi:10.1182/blood-2018-06-846816
22. Martino M, Canale FA, Alati C, et al. CART-cell therapy: recent advances and new evidence in multiple myeloma. *Cancers.* 2021;13(11):2639. doi:10.3390/cancers13112639
23. San Miguel JF, García-Sanz R. Prognostic features of multiple myeloma. *Best Pract Res Clin Haematol.* 2005;18(4):569–583. doi:10.1016/j.beha.2005.01.012
24. Smith D, Yong K. Advances in understanding prognosis in myeloma. *Br J Haematol.* 2016;175(3):367–380. doi:10.1111/bjh.14304
25. Li L, Wang L. Multiple myeloma: what do we do about immunodeficiency? *J Cancer.* 2019;10(7):1675–1684. doi:10.7150/jca.29993
26. Nucci M, Anaissie E. Infections in patients with multiple myeloma in the era of high-dose therapy and novel agents. *Clin Infect Dis.* 2009;49(8):1211–1225. doi:10.1086/605664