Multiple myeloma

- Practice variations in indication, timing and outcome of Multiple Myeloma patients undergoing surgery for vertebral lesions - results from the European M2Spine study group
- Clinical Reasoning: A 64-Year-Old Man With Confusion, Nausea, Seizure, and Fever
- Non-Adjacent Bilateral Postherpetic Neuralgia in a Multiple Myeloma Patient: A Case Report
- Macrophage-derived pro-inflammatory cytokines augment the cytotoxicity of cytokine-induced killer cells by strengthening the NKG2D pathway in multiple myeloma
- Collision tumor of myeloma and infiltrative lipoma in the canine spine
- Teclistamab versus B-cell maturation antigen-targeting chimeric antigen receptor T-cell therapy in multiple myeloma: a comparative effectiveness analysis
- Individualized dynamic risk assessment and treatment selection for multiple myeloma
- Vorinostat attenuates UVB-induced skin senescence by modulating NF-κB and mTOR signaling pathways

Central nervous system involvement is a rare complication of multiple myeloma, and it can present as either an intraparenchymal or a leptomeningeal disease.

Intracerebral metastasis without the involvement of the cranium itself is rarer.

Metastases of multiple myeloma often occur in the cervical spine. These metastases may cause pain and associated spinal instability.

Classification

Multiple Myeloma (MM) is classified based on **immunoglobulin type, clinical presentation, risk stratification, and staging**.

1. Classification by Immunoglobulin Type

Myeloma is classified based on the **type of monoclonal immunoglobulin (M-protein)** produced:

Type	Prevalence	Description
IgG Myeloma	~50%	Most common subtype. Produces abnormal IgG monoclonal protein.
IgA Myeloma	~20%	Produces IgA monoclonal protein. Higher risk of renal and extramedullary disease.
IgM Myeloma	Rare (~0.5%)	More linked to Waldenström’s macroglobulinemia than MM.
IgD Myeloma	~2%	More aggressive, often diagnosed late.
IgE Myeloma	Extremely rare	Very aggressive.
Light Chain Myeloma (Bence Jones)	~20%	Produces only kappa or lambda light chains, leading to kidney failure.
Non-secretory Myeloma	~1%	No detectable M-protein in blood or urine, making diagnosis challenging.

2. Classification by Clinical Stages

A. Precursor Stages (Asymptomatic Myeloma)

- **Monoclonal Gammopathy of Undetermined Significance (MGUS)**:
    1. M-protein **<3 g/dL** and plasma cells **<10%**.
    2. No **CRAB symptoms**.
    3. **Risk of progression:** ~1% per year.
- **Smoldering (Asymptomatic) Myeloma (SMM)**:
    1. M-protein **≥3 g/dL** or plasma cells **10–60%**.
    2. No CRAB symptoms.
    3. **Risk of progression:** ~10% per year.

B. Active (Symptomatic) Multiple Myeloma

Defined by **CRAB criteria** (end-organ damage):

- **C**alcium elevation (**Hypercalcemia** >11 mg/dL).
- **R**enal insufficiency (**Creatinine** >2 mg/dL, eGFR <40 mL/min).
- **A**nemia (**Hemoglobin** <10 g/dL or >2 g/dL below normal).
- **B**one lesions (**Osteolytic lesions** on imaging).

3. Risk Stratification (Genetic Classification)

Genetic abnormalities detected by **fluorescence in situ hybridization (FISH)**.

A. Standard Risk

- **Hyperdiploidy** (extra copies of chromosomes 3, 5, 7, 9, 11, 15, 19, 21).
- **t(11;14) (CCND1/IGH)** → Seen in **IgG kappa myeloma**.
- **t(6;14) (CCND3/IGH)**.

B. High Risk

- **Deletion 17p (TP53 loss)** → Poor prognosis.
- **t(4;14) (IGH/FGFR3)** → Increased relapse risk.
- **t(14;16) (IGH/MAF)** → Poor prognosis.
- **Gain of 1q (1q21 amplification)** → Aggressive disease.

4. Staging Systems for Multiple Myeloma

A. International Staging System (ISS)

Based on **serum beta-2 microglobulin (β2M) and albumin**.

Stage	β2M (mg/L)	Albumin (g/dL)
I	<3.5	≥3.5
II	Intermediate levels	
III	≥5.5	Worst prognosis

B. Revised International Staging System (R-ISS)

Adds **genetic risk markers and LDH**.

Stage	Criteria
I	ISS Stage I + No high-risk cytogenetics + Normal LDH
II	Not Stage I or III
III	ISS Stage III + High-risk cytogenetics or Elevated LDH

5. Multiple Myeloma Variants

Certain variants of MM have distinct clinical characteristics.

Variant	Characteristics
Plasma Cell Leukemia (PCL)	Highly aggressive, >20% plasma cells in blood.
Extramedullary Myeloma	Tumor formation outside bone marrow.
Solitary Plasmacytoma	Single lesion, no systemic disease.
POEMS Syndrome	Polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes.

Summary

- **IgG Kappa Myeloma** is the most common subtype.
- **Classified by immunoglobulin type, clinical stage (MGUS, SMM, MM), genetic risk (FISH), and staging (ISS/R-ISS).**
- **Genetic markers (del17p, t(4;14)) influence prognosis.**
- **Variants like Plasma Cell Leukemia and POEMS Syndrome have distinct implications.**

Diagnosis

Anemia is common in multiple myeloma

In multiple myeloma, skeletal radiographs are still regarded as the reference imaging examination because they help to establish the stage of the disease according to the Durie-Salmon Staging

System. Whole-body MRI using T1 and STIR sequences increases the detection of myeloma lesions. MRI-measured diffusion has demonstrated high sensitivity in terms of detection in oncology.

MRI whole-body diffusion technique (called DWIBS)leads to an increase in the final Durie-Salmon stage. Although its place in the preoperative treatment of multiple myeloma still has to be assessed, a study suggests its potential interest [1)].

Pseudo hyponatremia: an artifact of indirect lab techniques. Unusually high levels of lipids (e.g., hypertriglyceridemia) or proteins (e.g., immunoglobulins as can occur in multiple myeloma) reduce the aqueous fraction of plasma and produce artifactually low sodium lab values. This error does not occur with direct measurement methods.

Complications

Carpal tunnel syndrome: (amyloid deposition in flexor retinaculum)

Treatment

Thromboprophylaxis is an important consideration in the management of patients with multiple myeloma, especially because these patients are at an increased risk of developing venous thromboembolism (VTE). This elevated risk is primarily due to the disease, certain myeloma treatments, and patient-related factors.

Key Factors Contributing to Thrombosis in Multiple Myeloma: Disease-Related Factors:

Multiple myeloma is associated with a hypercoagulable state, likely due to factors like increased levels of procoagulant proteins, endothelial damage, and reduced fibrinolysis. Treatment-Related Factors:

Immunomodulatory Drugs (IMiDs): Drugs like thalidomide, lenalidomide, and pomalidomide significantly increase the risk of VTE, especially when combined with dexamethasone or chemotherapy. Corticosteroids: High-dose corticosteroids, commonly used in myeloma therapy, also contribute to VTE risk. Other Chemotherapeutic Agents: Some chemotherapeutic regimens can further exacerbate the risk of thrombosis. Patient-Related Factors:

Age, obesity, a history of VTE, immobility, and other comorbidities (such as renal impairment or cardiovascular disease) can all increase the risk of thromboembolic events. Thromboprophylaxis Strategies: To mitigate the risk of VTE in multiple myeloma patients, thromboprophylaxis is recommended, especially for those receiving high-risk therapies such as IMiDs.

Risk Assessment:

A thorough assessment of the individual patient’s VTE risk should be conducted before initiating therapy. This includes evaluating both disease-specific and patient-specific risk factors. Pharmacologic Thromboprophylaxis:

Aspirin: Often recommended for patients at low to moderate risk of VTE. Low Molecular Weight Heparin (LMWH): Preferred for patients at higher risk. Direct Oral Anticoagulants (DOACs): An alternative to LMWH in some settings, though more data may be needed to fully establish their efficacy in this context. Warfarin: Occasionally used, though less commonly due to the need for regular monitoring and potential drug interactions. Duration of Prophylaxis:

Typically, prophylaxis is continued for at least the duration of high-risk therapy (e.g., the period during which the patient is receiving IMiDs), but it may be extended based on ongoing risk factors. Monitoring and Adjustments: Regular monitoring for signs of bleeding, as well as thrombotic events, is essential. Dose adjustments of anticoagulants may be necessary in patients with renal impairment or those at increased risk of bleeding. Conclusion: Thromboprophylaxis is a critical aspect of managing multiple myeloma patients, particularly those undergoing treatment with therapies known to increase VTE risk. The choice of thromboprophylactic agent and the duration of therapy should be tailored to the individual patient's risk profile, balancing the risk of thrombosis against the potential for bleeding complications.

In patients with multiple myeloma (MM) there is a high risk of vertebral compression fracture. In the majority of cases, the method of treatment is percutaneous vertebroplasty (PV) or kyphoplasty (PK). The number of studies verifying their efficacy in MM is still relatively small.

Case series

Newly diagnosed patients with MM with computed tomography (CT) scans of the spine within three months of diagnosis were identified through an electronic patient database. Clinical baseline data were manually extracted from the patient charts. Fractured levels were graded on CT scans following the Genant grading system, and spinal instability was assessed through the Spinal Instability Neoplastic Score (SINS).

Results: A total of 385 patients with 6289 eligible vertebrae were eligible for inclusion. The mean age at diagnosis was 67 years, and 60% were male. At least one VCF was present in 180 patients (47%). A quarter of fractures were classified as severe. The incidence of fractures increased with more advanced disease stages, and men were more likely to have a fracture than women.

Conclusions: Our data show that 47% of MM patients present with one or more VCFs at the onset of their disease, of which 20% were classified as unstable, meaning a surgical consultation is recommended [2)].

2015

There was a prospective group of 34 MM cases in which a total of 131 vertebral bodies were augmented by means of PV. It was possible to follow up 22 patients who agreed to take part in the assessment. Their level of daily activity and the level of pain were assessed using the Oswestry Back Pain scale and a visual analogue scale (VAS) before PV and at a later date (medium-term follow up was a mean of 10 months after the last operation). Five out of eight cases in which 4.5-5 years had elapsed since the first PV were tested again (long-term follow-up).

Relief of pain and improvement of QL, assessed a mean of 10 months after PV, proved to be statistically significant. On the average, pain decreased by 4.7 points as measured on the VAS scale and the average improvement in the QL measured on the Oswestry scale was 27.7%. There were no neurological or general complications. After 4.5-5 years, there has not been any significant change in the level of pain relief or the improvement in the QL in the 5 cases in which long-term assessment was possible.

In MM cases, PV is a simple, effective and safe method for the treatment of vertebral infiltration and compression fractures, giving permanent long-term pain relief and concomitant improvement in the QL [3].

2006

A retrospective chart review of patients with multiple myeloma metastases to the cervical spine was undertaken. Between 1993 and 2005, 35 patients were treated with external-beam radiation and/or surgical stabilization at the University of Texas M. D. Anderson Cancer Center in Houston, Texas. Nineteen of 20 patients with sufficient follow-up data experienced resolution of their pain when treated with radiation without surgical intervention. Twenty-three patients had evidence of spinal instability on radiographic images; 15 of these were treated with radiation alone. Of these, 10 had sufficient follow-up data, and none showed any clinical progression of instability. Radiographic follow-up images demonstrated an arrest of further progression of instability and, in some cases, healing of pathological fractures by means of radiation alone.

The results of this series suggest that, in selected cases, external-beam radiation for multiple myeloma metastases to the cervical spine is an effective palliative treatment, even in cases involving clinical or radiographically documented instability [4].

Case reports

Multiple myeloma case reports.

1)
Narquin S, Ingrand P, Azais I, Delwail V, Vialle R, Boucecbi S, Tasu JP. Comparison of whole-body diffusion MRI and conventional radiological assessment in the staging of myeloma. Diagn Interv Imaging. 2013 Jun;94(6):629-36. doi: 10.1016/j.diii.2013.01.005. Epub 2013 May 15. PubMed PMID: 23683788.
2)
Zijlstra H, Wolterbeek N, Ponds NHM, Koene HR, Terpstra WE, Delawi D, Kempen DHR. The incidence of vertebral compression fractures and spinal instability in newly diagnosed multiple myeloma patients. J Orthop. 2023 Mar 21;38:62-67. doi: 10.1016/j.jor.2023.03.008. PMID: 36974337; PMCID: PMC10038922.
3)
Jurczyszyn A, Czepko R, Banach M, Godlewski B, Czepko RA, Masłowski P, Skotnicki AB. Percutaneous Vertebroplasty for Pathological Vertebral Compression Fractures Secondary to Multiple Myeloma - Medium-Term and Long-Term Assessment of Pain Relief and Quality of Life. Adv Clin Exp Med. 2015 Jul-Aug;24(4):651-656. doi: 10.17219/acem/38556. PubMed PMID: 26469110.
4)
Rao G, Ha CS, Chakrabarti I, Feiz-Erfan I, Mendel E, Rhines LD. Multiple myeloma of the cervical spine: treatment strategies for pain and spinal instability. J Neurosurg Spine. 2006 Aug;5(2):140-5. PubMed

PMID: 16925080.