

THE CERVICAL FRACTURE AS FIRST SYMPTOM OF MULTIPLE MYELOMA: A CASE REPORT

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ABSTRACT

Introduction: Multiple Myeloma (MM) is a clonal disorder characterized by proliferation and accumulation of malignant plasma cells in the bone marrow. Bone disease occurs in approximately 80% of patients with newly diagnosed MM. The cervical spine is the least common site of disease involvement.

Case presentation: A 60-year-old female patient was referred to the Department of Neurosurgery for bone pain. A magnetic resonance imaging (MRI) scan showed a pathological fracture of the sixth cervical vertebra (C6). The laboratory tests and the bone marrow examination led to a diagnosis of IgA κ MM (Durie Salmon stage IIIA). The patient underwent a cervical arthrodesis and started systemic Bortezomib-Thalidomide-Dexamethasone (VTD) combination chemotherapy. During chemiotherapeutic treatment the patient underwent a vertebroplasty of L4-L5. After 4 VTD cycles, the patient was dismissed showing a very good partial remission (VGPR). Later the patient subjected herself to hematopoietic stem cell transplantation (HSCT) obtaining a complete remission.

Discussion: We report a clinical case of MM in which the fracture of cervical spine represents the clinical onset. Indeed this clinical presentation is not common in this type of monoclonal gammopathy. This case underlines the importance of suspecting MM in all cases of compromised bone.

Key words: monoclonal gammopathy, bone lesion, osteolysis, bortezomib, cervical spine.

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Introduction

Multiple myeloma (MM) is characterized by a proliferation of malignant plasma cells and usually by the production of a monoclonal immunoglobulin derived from a single B-cell, most commonly either immunoglobulin G (IgG) or immunoglobulin A (IgA). MM accounts for 10% of all hematologic malignancies, the annual incidence is 6/100,000 in western countries and in Italy about 2,000 new cases a year are reported. The incidence increases with age, and the median age at diagnosis is 69

years^(1,2). Males are more commonly affected than female and incidence is higher in African-Americans than in Caucasians. The diagnosis of MM includes the observation of 10% or more clonal plasma cells on bone marrow examination and evidence of a clinical organ damage that can be attributed to the underlying plasma cell proliferative disorder. In absence of end-organ damage, the diagnosis requires 60% clonal bone marrow plasma cells⁽¹⁾. Bone disease, hypercalcemia, renal failure, anaemia and increased risk of infections are conditions associated with MM⁽³⁾.

The dysregulation of immune system could be considered the mechanism underlying the increased risk of infections⁽⁴⁻⁵⁾. The occurrence of bone pain should prompt physicians to evaluate different diagnostic hypotheses: MM, vitamin D deficiency, bone metastases. Examinations useful for the differential diagnosis include complete blood count, serum protein electrophoresis, radiographic examinations and dosage of vitamin D. Bone involvement takes place in 80% of cases with newly diagnosed MM, and in 70% of patients bone pain is the first symptom to be reported at disease onset⁽⁶⁾. Bone disease can impair patients' quality of life and is the main cause of morbidity. The spine is the most affected site. This observation could be explained by the presence of a large amount of hematopoietic bone marrow into the vertebral bodies⁽⁶⁾. Bone involvement can appear as generalized osteoporosis or as osteolysis located in vertebral bodies or, rarely, in transverse processes. The cervical spine is not involved as commonly as in the thoracic and lumbar spine⁽⁷⁾. The most commonly used therapies for treatment consisted of different types of chemotherapy, steroids, high-dose therapy and stem cell transplantation. Recently, however, new treatments have been introduced in the class of medications available: thalidomide, lenalidomide and bortezomib. Therapeutic efficacy of Bortezomib can be influenced by genetic factors, such as allelic variant of CYP3A4 gene, involved in the metabolism of several drugs⁽⁸⁻⁹⁾.

We present the case of a patient who suffered from a pathological cervical-spine fracture as the initial onset of MM.

Case presentation

A 60-year-old Caucasian woman was admitted to the Department of Neurosurgery of the University Hospital "P. Giaccone" in Palermo for neck pain, paresthesia and weakness of lower limbs. The most remarkable features of his medical history were high blood pressure, dyslipidemia, chronic obstructive pulmonary disease (COPD), Arnold Chiari Syndrome type II. Neurologic examination revealed no abnormalities. Spinal magnetic resonance imaging (MRI) showed pathological fracture of C6. Contextually, results of laboratory showed a mild anemia, low levels of IgG and IgM, high levels of IgA, hypercholesterolemia and hypertriglyceridemia. Capillary zone electrophoresis (CZE) and immunofixation electrophoresis

(IFE) revealed a significant increase of IgA with a peak in the β_2 zone and high levels of kappa light chains in serum (6.48 g/L). Bence-Jones Protein Urine test was negative. White cell count, platelet count, serum creatinine, calcaemia, natraemia, kalaemia, glycaemia, 25-hydroxyvitamin D [25(OH)D] were within normal ranges. Serum Free Light Chain (sFLC) assay showed following results: k sFLC 44.3 mg/L, λ sFLC 5.12 mg/L and k/ λ ratio 8.65 (Table 1, column A). White blood cell and platelet count were assessed within 3 h by flow cytometry (Beckman coulter, Pasadena, CA, USA)⁽¹⁰⁾. Total cholesterol and triglycerides were quantified by standard enzymatic-colorimetric methods^(11,12). Serum 25(OH) D levels were determined by high-performance liquid chromatography (HPLC)⁽¹³⁾. A C6 bone marrow biopsy showed a replacement with neoplastic plasma cells and 30% infiltration, monoclonality of plasma cells was confirmed by IgA and kappa light chains positivity (Figure 1).

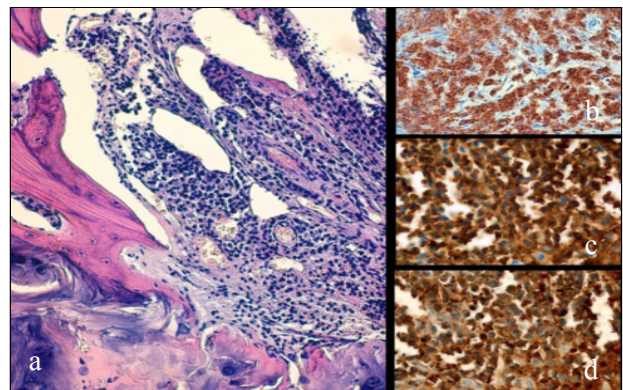


Fig. 1: Bone biopsy specimen (C6 vertebra):
 a - Bone marrow replacement with neoplastic plasma cells. The plasma cells exhibit mature features with abundant eosinophilic cytoplasm (inset). Hematoxylin and eosin stain, original magnification x200.
 b - On immunohistochemistry neoplastic plasma cells showed expression of CD138, a common plasma cell marker. Immunoperoxidase stain, original magnification x400.
 c, d- Monoclonality of plasma cells was confirmed by IgA and kappa light chains positivity. Immunoperoxidase stain, original magnification x400.

These findings were compatible with a diagnosis of IgA MM with kappa light chains. The patient underwent a cervical arthrodesis by means of anterior approach and C6 corpectomy, mesh insertion and C5-C7 anterior plating (Figure 2).

Started systemic Bortezomib-Thalidomide-Dexamethasone (VTD) combination chemotherapy.

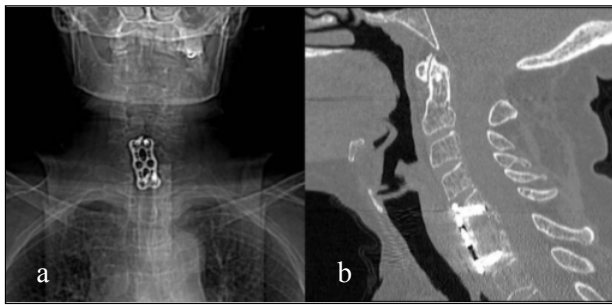


Fig. 2: Anteroposterior (a) and lateral (b) computed tomography (CT) of the cervical spine managed with C6 corpectomy, insertion of a titanium-mesh, and application of an anterior cervical plate from C5 to C7.

The patient completed 4 cycles of weekly VTD without complication obtaining a “Very Good Partial Remission” (VGPR). Laboratory data highlighted a clinical improvement: particularly by means of CZE hypogammaglobulinaemia was detected and sFLCs were within the normal range (k sFLC 9.11 mg/L, λ sFLC 6.14 mg/L, k/λ ratio 1.48) (Table 1, column B).

Laboratory test	A	B	Reference interval
Red blood cell count	3.4 × 10 ⁶ /μL	3.98 × 10 ⁶ /μL	(3.8-5.0)
White blood cell count	5.15 × 10 ³ /μL	8.95 × 10 ³ /μL	(4.0-11.0)
Neutrophils	2.83 × 10 ³ /μL	6.05 × 10 ³ /μL	(2.0-8.0)
Lymphocytes	1.89 × 10 ³ /μL	2.02 × 10 ³ /μL	(1.0-5.0)
Monocytes	0.31 × 10 ³ /μL	0.71 × 10 ³ /μL	(0.16-1.0)
Eosinophils	0.11 × 10 ³ /μL	0.14 × 10 ³ /μL	(0.0-0.8)
Basophils	0.01 × 10 ³ /μL	0.03 × 10 ³ /μL	(0.0-0.2)
Platelets count	230 × 10 ³ /μL	358 × 10 ³ /μL	(150-450)
Haemoglobin	11.1 g/dL	12.5 g/dL	(12-16)
Hematocrit	31.8 %	37.5 %	(35-48)
Mean corpuscular volume	93.5 fL	94.2 fL	(80-99)
IgG	158 mg/dl	208 mg/dl	(700-1600)
IgA	4253 mg/dl	81 mg/dl	(70-400)
IgM	9 mg/dl	10 mg/dl	(40-230)
Kappa light chain (serum)	6.48 g/L	0.93 g/L	(1.38-3.75)
Lamba light chain (serum)	0.23 g/L	0.48 g/L	(0.93-2.42)
Kappa/Lamba (serum)	28.17	1.94	(1.17-2.93)
Capillary zone electrophoresis	Monoclonal gammopathy in beta-2	Hypogammaglobulinaemia	
κ sFLC	44.3 mg/L	9.11 mg/L	(3.30-19.40)
λ sFLC	5.12 mg/L	6.14 mg/L	(5.71-26.30)
κ/λ ratio	8.65	1.48	(0.26-01.65)
Beta-2- microglobulin	3.1 mg/L	1.7 mg/L	(0.8-2.2)
Sodium	141 mmol/L	139 mmol/L	(136-145)
Potassium	4.34 mmol/L	4.18 mmol/L	(3.3-5.1)
Total calcium	8.94 mg/dL	9.67 mg/dL	(8.4-10.2)
Total protein	9.7 g/dL	5.9 g/dL	(6.6-8.7)
Total cholesterol	338 mg/dL	243 mg/dL	(< 200)
Triglycerides	890 mg/dL	340 mg/dL	(< 175)
Glucose	83 mg/dL	84 mg/dL	(70-100)
Blood urea	34 mg/dL	48 mg/dL	(10-50)
Creatinine	0.55 mg/dL	0.46 mg/dL	(0.51-0.95)

Tab. 1: Laboratory test results at our patient’s initial assessment (column A) and after 4 VTD cycles showing VGPR (column B). sFLC: serum Free Light Chain; IgG: Immunoglobulin G; IgA: Immunoglobulin A; IgM: Immunoglobulin M.

During this period, the patient was admitted to Department of Neurosurgery of the University Hospital “P. Giaccone” in Palermo for weakness of lower limbs. Lumbosacral MRI showed lytic lesion of L4 (Figure 3).

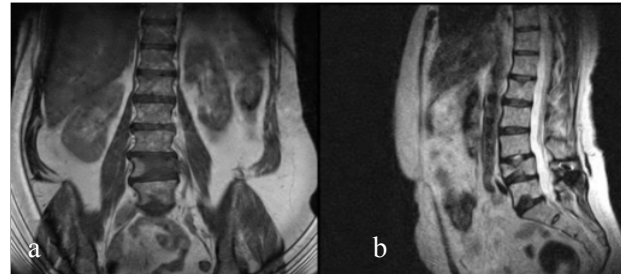


Fig. 3: MRI showing vertebral compression fracture of L4 hypointense in T1- weighted (T1W) coronal (a), and hyperintense in T2 - weighted (T2W) sagittal image (b).

Fracture was surgically treated by means of decompressive laminectomy and L4-L5 arthrodesis and monoportal vertebroplasty. Subsequently, the patient underwent autologous stem cells obtaining a “Complete Response” (CR).

Discussion

The most common clinical manifestations of symptomatic MM are anaemia, infections, osteopenic bone disease or pathological fracture and renal failure. Indeed MM is a disease with many faces and different diagnostic tools are needed. Clinical aspects, laboratory and radiological findings are useful to better assess MM clinical diagnosis and management.

Bone disease is observed in almost 80% of multiple myeloma patients, and spine is the most affected bone site to be involved in myeloma-induced osteoporosis, osteolysis, or compression fractures⁽⁶⁾. Bone lesions are frequently observed in MM patients and over 60% of them involve the spine. This could be due to the fact that vertebral bodies contain a high amount of hematopoietic bone marrow. Vertebral involvement in MM can appear as generalized osteoporosis or as osteolysis in vertebral bodies or, more rarely, in transverse processes. The shape of the lesion can vary depending on the site involved: vertebral collapses are found mainly in the dorsal region endplate lesions in the lumbar region, wedge lesions in the dorsal-lumbar transition, while cervical spine is rarely involved.

In addition to radiographic findings, Free Light Chain (FLC) assay is an important tool in the diagnosis, monitoring and management of MM; particularly, an abnormal ratio indicates a substantial risk of progression of disease^(14,15). Cervical spine lytic lesion can be the first clinical presentation of MM and it is a rare possibility of disease onset. We report a case of a female patient, presenting at the clinical onset with cervical spinal lesions. In the present case, diagnosis of MM occurred accidentally.

In conclusion a multidisciplinary approach is thus needed for the diagnosis and treatment of vertebral lesions in MM, in particular to properly manage the involvement of cervical region in this disease.

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Authors' contributions:

MC, BLS and LA designed and drafted the manuscript. EP and SM performed and participated in analysis of laboratory experiments data. AMF and AGG performed the histological and immunohistochemical assessment. CS, GB, DB and CB helped to draft the manuscript. All authors analyzed and interpreted data. All authors have contributed and approved the final manuscript.

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