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Mimicking Multiple Myeloma: The Importance of the Differential Diagnosis

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Abstract

Multiple myeloma (MM) is a malignant disease of plasma cells that accounts for 15% of hematologic malignancies. Clinical manifestation is defined by the presence of anemia, renal failure, hypercalcemia, and osteolytic bone lesions, referred to by the acronym CRAB. Here, we describe the case of a Caucasian male who was referred to our center because of a clinical suspicion of MM. A comprehensive workup, including blood tests, radiologic studies, and a bone marrow biopsy, ruled out the presence of plasma cell neoplasia. Further investigations, such as the CT guided biopsy of a lytic lesion, allowed us to diagnose a brown tumor (BT), a tumor-like lesion resulting from the bone remodeling process associated with persistent hyperparathyroidism. This diagnosis was confirmed by endocrinological investigations, followed by parotidectomy, during which the clinical manifestations disappeared. Our case illustrates the importance of an accurate differential diagnosis when MM is suspected, as the simultaneous presence of comorbidities and diseases can confuse the evaluation. In particular, the combination of anemia, peripheral neuropathies, and renal dysfunction could be associated with a number of other causes, and it is imperative to perform a thorough history, clinical and instrumental examination, and laboratory tests to rule out other etiologies.

Introduction

Multiple myeloma (MM) is a neoplastic disease due to the proliferation of clonal plasma cells and accounts for 15% of hematologic neoplastic tumors [1,2]. The symptomatic phase of this neoplasm is characterized by the presence of one or more of the following signs and/or symptoms: anemia (hemoglobin psitro value of < 2 g/dL below the lower limit of normal or a hemoglobin value < 100 g/L), hypercalcemia (serum calcium > 1 mg/dL above the upper limit of normal or > 11 mg/dL), renal failure (creatinine clearance < 40 mL per minute or serum creatinine > 2 mg/dL), and bone lesions (one or more osteolytic lesions on skeletal radiography, computed tomography (CT), or positron emission tomography- CT (PET-CT). This cohort of signs and symptoms is historically defined by the acronym CRAB[3]. However, particularly in elderly patients, these clinical manifestations are very common and could be caused by diseases other than MM. The concomitant presence of other pathological conditions could lead to misdiagnosis with dramatic consequences for patients. Here we present the case of an adult Italian patient with signs and symptoms suggestive of MM.

Case Report

Clinical history: He suffered from hypertension, which was well controlled with drug therapy.

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Case presentation: In April 2020, a 57-year-old Caucasian man was referred to our hematology center by a nephrologist for anemia, renal failure, hypercalcemia, and bone lesions with a suspicion of MM. The patient's history included fatigue, night sweats, and weight loss starting in January 2018. In February 2018, a mild and progressive hypochromic-normocytic anemia (Hb 10.6 gr/dl) with hyperferritinemia, low iron blood level, and low reticulocyte count was documented. A colonoscopy revealed two intestinal polyps with high-grade dysplasia. In December 2019, a radiographic examination of the lumbar spine was performed because pain had occurred and multiple lytic lesions were noted. From January 2020, the patient underwent blood tests documenting progressive anemia (Hgb 8.5 gr/dl), renal failure (serum creatinine 1.57 mg/dl, glomerular filtration rate 43 ml/min according to Modification of diet in renal disease (MDRD), glycosuria (with normal values of blood glucose and glycated hemoglobin). He was referred to a nephrology center for a comprehensive evaluation. Anemia and renal insufficiency with mild glomerular proteinuria (0.95 gr/24 hour) were confirmed. Blood tests showed hypercalcemia (serum calcium 12.9 mg/dl), normal serum albumin. A skeletal examination and a whole body examination CT confirmed multiple bone lysis affecting the entire skeleton and in particular the pelvis, bilateral femurs and dorsal vertebrae with erosion of the bone cortex. Most importantly, a lesion of the left thyroid lobe of the thyroid gland.

Initial examination: On initial hematological examination, the patient complained fatigue and diffuse skeletal pain. There were no abnormal clinical signs. Blood examination confirmed mild normocytic-normochromic anemia, hypercalcemia, high serum calcium levels, and mild renal insufficiency. We performed an investigation focused on defining the diagnosis MM. However, no monoclonal component was detected on serum and urine protein electrophoresis and serum and urine immunofixation. Serum immunoglobulin and free light chain levels were normal, consistent with renal function. Bone marrow biopsy and aspirate showed no monoclonal plasma cell infiltrate. The patient was treated with fluid supplementation and zoledronic acid (with dose reduction according to glomerular filtrate). Differential diagnosis: after ruling out monoclonal gammopathy, our attempts were aimed at detecting other neoplastic or endocrine diseases that could cause our patient's clinical manifestations. Further investigation: a FDG PET-TC was performed to exclude other pathological findings. This examination revealed diffuse hypercapsulation of the bone marrow and various bone sites, particularly the jaw, bilateral ribs, dorsal and lumbar vertebrae, pelvis, and bilateral femurs. A CT -guided biopsy of the third dorsal vertebra was performed: Histologic examination revealed a "brown tumor" (Figure 1a, 1b and 1c).

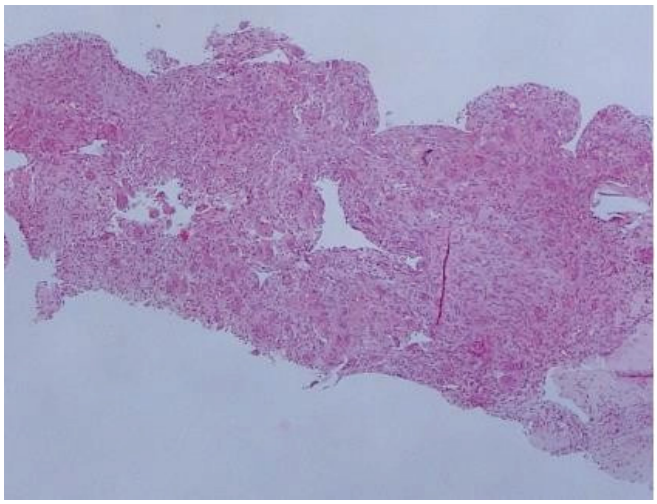

Figure 1a: HE 10X and 1B HE 20X giant cell tumor uniformly distributed in the biopsy.

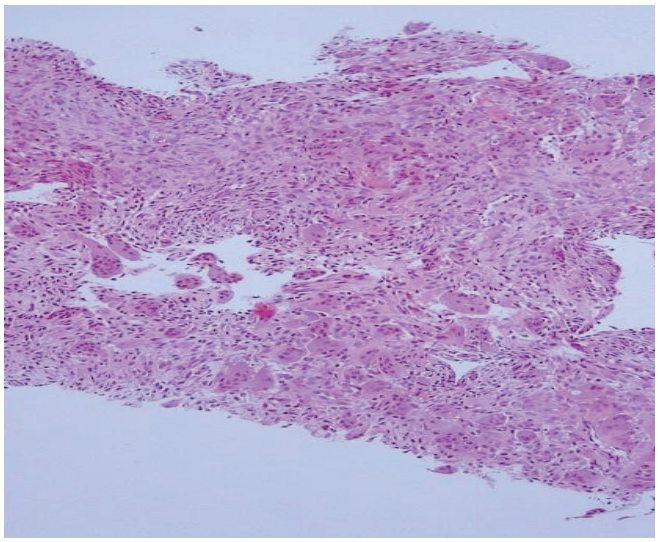

Figure 1b: HE 20X giant cell tumor uniformly distributed in the biopsy.

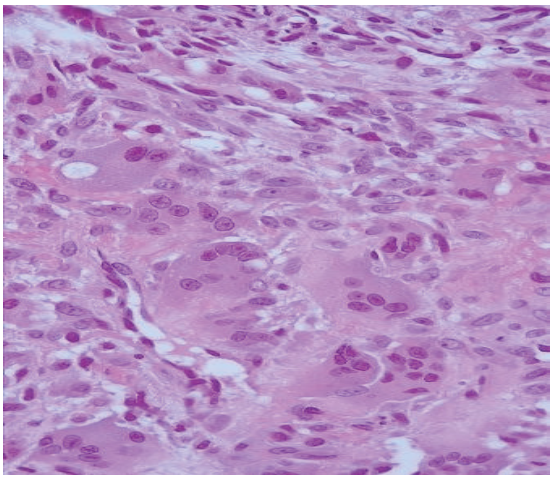

Figure 1c: HE 40X multinucleated giant cell embedded with mononuclear ovoid to spindled neoplastic cell.

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Final Diagnosis: Severely elevated serum levels of parathyroid hormone (PTH) and urinary calcium and phosphorus confirmed the diagnosis of hyperparathyroidism. The patient underwent ultrasonography of the thyroid gland, which revealed an ovoid, highly vascularized mass in the left lobe. The patient was referred to an endocrinologist, who performed a parathyroidectomy for the presence of an adenoma, after which the pathologic manifestations resolved and the clinical course improved.

Diagnostic Report

The diagnosis of symptomatic MM is based on the detection of clonal plasma cells in the bone marrow ≥ 10% or biopsy-proven osseous or extramedullary plasmacytoma and one or more of the myeloma-defining events, such as anemia, hypercalcemia, lytic bone lesions, and renal failure [3]. These events are caused by direct plasma monoclonal cell activity (anemia, hypercalcemia, and bone lysis) or by paraproteins (renal failure). Anemia is usually normochromic-normocytic and is present in about 75% of patients at the time of diagnosis. The main causes are massive infiltration of the bone marrow by myeloma, induction of apoptosis of erythroblasts by myeloma cells, chronic anemia disorder (due to functional iron deficiency), erythropoietin deficiency in patients with renal failure, and paraprotein-induced hemodilution to increase plasma volume [4]. Bone lesions are detected at diagnosis in up to 80% and 100% in advanced stages. They can affect all bones, but in more than 60% the spine is involved. The most common clinical and radiological pictures are lithic lesions and diffuse osteoporosis, pathological fractures, spinal compression, bone pain and neoplastic hypercalcemia. Myeloma bone disease is characterized by significant deregulation of the physiological interaction between osteocytes, osteoblasts, immune cells, and the bone matrix, resulting in increased osteoclast activity and suppressed osteoblast function. Several aberrant molecular signaling pathways can lead to bone loss: RANK /RANKL and Notch signaling pathways are involved in osteoclast activation, while Wingless-type (Wnt) and beta-catenin signaling pathways regulate bone homeostasis and osteoblast differentiation [5,6]. Low-dose whole-body MRI CT is the current standard for diagnosis and evaluation of bone disease associated with multiple myeloma. PET-CT and whole-body MRI are also useful imaging modalities for the evaluation of bone disease associated with multiple myeloma. PET-CT is the gold standard for the follow-up of MM -related bone disease and the evaluation of metabolic response to therapy, including the detection of residual disease after treatment [7]. Hypercalcemia is the most common metabolic complication of MM, but its pathogenesis remains unclear. The primary cause of hypercalcemia is myeloma bone resorption, which leads to calcium efflux into the extracellular fluid. However, the pathobiology of hypercalcemia in this context is more complex: for example, this finding occurs most frequently in the myeloma patients who have the largest tumor volume, regardless of serum parathyroid hormone-related protein (PTHrP) status. The myeloma patients often have irreversible impairment of renal function with increased renal tubular calcium reabsorption. In this case, the kidneys' ability to excrete excess calcium from the bloodstream is overwhelmed, resulting in elevated serum calcium levels. Hypercalcemia associated with MM differs from the elevated calcium levels seen in patients with solid tumors, as the latter are due to excessive secretion of PTHrP. Myeloma hypercalcemia is almost always associated with renal failure and elevated serum phosphate, resulting in decreased glomerular filtration rate. In addition, unlike solid tumors, myeloma patients usually respond very rapidly to treatment to steroids because of rapid suppression of tumor plasma cell growth. Clinical findings depend on calcium levels: patients may be asymptomatic (≤ 12mg/dl) or they may present with symptoms such as dry mouth, anorexia and vomiting, polyuria, polydipsia, depression or confusion (12 to 16 mg/dl). In rare cases, patients may develop a life-threatening 'hypercalcemic crisis' (≥ 16 mg/dl) and a state of coma [8]. In the case of hypercalcemia, it is imperative to rule out other causes of elevated calcium levels: pseudo-hypercalcemia (increase in circulating proteins such as M protein), primary hyperparathyroidism (the first cause of hypercalcemia, especially in the elderly), paraneoplastic hypercalcemia (local production of OAF -like cytokines, systemic production of PTH-like peptide or calcitriol), hypervitaminosis D (pharmacological overdose, overproduction of neoplasms or granulomatous disease), medications (milk-alkaline syndrome, lithium, thiazides), tertiary hyperparathyroidism (renal failure), hypocalciuric familial hypercalcemia (rare autosomal dominant disorder with an alteration of the calcium receptor characterized by asymptomatic hypercalcemia since childhood and a family history of hypercalcemia). In newly diagnosed MM patients, 20% to 30% have an estimated glomerular filtration rate (GFR) < of 30 mL/min/1.73 m^2 at the time of diagnosis. Dialysis is required in up to 5% of patients. However, in these patients, GFR may decrease during the course of the disease, usually with relapse. The most common cause of decreased GFR in patients with multiple myeloma is light chain cast nephropathy. This clinicopathologic manifestation occurs when monoclonal free light chains (FLCs) from serum bind to and deposit on the Tamm-Horsfall protein in the distal nephron. The formation of the casts causes tubular obstruction (typically distal), which leads to an intense immune response resulting in a giant cell reaction around the casts and interstitial inflammation. Tubular obstruction causes rapid renal injury. Some medications commonly taken by these patients, such as nonsteroidal anti- inflammatory drugs for bone pain, can exacerbate or

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even accelerate kidney damage. Other medications that may be associated with light chain cast nephropathy include angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Intravenous contrast agents may pose an associated risk for cast nephropathy, although recent studies have found the association to be less significant. Monoclonal immunoglobulin deposition disease (MIDD), amyloidosis, and rarely renal infiltration by myeloma cells or acquired Fanconi syndrome in adults represent other renal pathologies in patients with MM. The diagnostic workup when MM is suspected must exclude other causes of these symptoms and signs [9,10]. Indeed, all of these events are nonspecific and could be associated with other diseases. In particular, MM is a disease strongly related to age: about 70% of newly diagnosed myeloma patients are older than 65 years and 40% are older than 75 years. Diagnosis in this patient population can be challenging, as comorbidities and diseases can complicate the evaluation. For example, anemia, peripheral neuropathies, and renal insufficiency may be associated with a number of other causes. Therefore, a thorough history, examination, and laboratory differential diagnosis is essential to rule out other etiologies (Table 1).

Table 1: Differential diagnosis of signs and symptoms of Multiple Myeloma.

Clinical features of myeloma	Alternate diagnoses that can mimic myeloma
Hypercalcemia (13% at diagnosis) Increased osteoclastic bone resorption Increased renal tubular calcium resorption	Hypercalcemia Primary hyperparathyroidism Tertiary hyperparathyroidism (CKD, vitamin D deficiency) Malignancy (e.g. bone metastases) Drugs (e.g. thiazides, lithium, vitamin D, vitamin A) Endocrine conditions (e.g. thyrotoxicosis, Addison's disease) Granulomatous conditions (e.g. sarcoidosis, tuberculosis) Other (e.g. prolonged immobilization, milk-alkali syndrome)
Renal failure (19% at diagnosis) Light chain cast nephropathy Hypercalcemia Monoclonal immunoglobulin deposition disease Plasma cell infiltration of the kidneys Concurrent amyloidosis Drug-induced (NSAIDs, bisphosphonate)	Renal failure AKI (acute kidney injury) Prerenal causes (e.g. dehydration, sepsis) Renal causes (e.g drug-induced, infections) Postrenal causes (e.g. acute urinary retention) CKD (chronic kidney disease) (60% of >80 year old) Age-related decrease in eGFR Hypertension Diabetic nephropathy Drug- induced (eg diuretic, NSAIDs) Obstructive uropathy (e.g. due to BPH) Glomerulonephrities
Anemia (35% at diagnosis) Bone marrow infiltration by plasma cells Cytokine-mediated suppressive effect on erythropoiesis Renal failure (decreased erythropoietin production)	Anemia (25% of >80 year old) Anemia of chronic disease Iron deficiency (dietary and/or blood loss) Vitamin B12 or Folate deficiency Chronic kidney disease Myelodysplasia Others (e.g. hemolytic anemia, thalassemia)
Bone pain (58% at diagnosis) Increased osteoclast activity causing lytic bone lesions, osteoporosis, pathological fractures Plasmocytomas affecting the bone	Bone Pain Nonmalignant causes Osteoporosis Osteomalacia Osteomyelitis Paget's disease Injury (e.g. fractures) Malignant causes Primary bone cancer Bony metastases (e.g breast, prostate, lung, thyroid, kidney, testicular, ovarian)

BPH: benign prostatic hypertrophy, NSAIDs: nonsteroidal anti-inflammatory drugs; eGRF: estimated glomerular filtration rate

This case demonstrates the importance of differential diagnosis, as the events described above are associated with a case of hyperparathyroidism that mimics the signs and symptoms associated with a suspicion of MM. In particular, the diagnostic journey for this patient led to the detection of a brown tumor (BT), a pathological expression of "osteitis fibrosa cystica" associated with uncontrolled hyperparathyroidism. This skeletal manifestation was first described by Recklinghausen in 1891 and is the result of overproduction of PTH in primary or secondary hyperparathyroidism: osteoblasts increase expression of RANKL, which binds to the corresponding RANK receptor on osteoclasts and promotes osteoclast activity. PTH also lowers osteoprotegerin levels (PG), preventing interactions between RANKL and RANK and thus inhibiting bone resorption. Due to this process, this tumor-like lesion represents the final stage of the bone remodeling process with an overall incidence of 2-3% [11]. BT can affect any part of the skeleton, but they are most commonly found in the jaw, ribs, clavicles, extremities, and pelvic girdle, and although they have no malignant potential, they can be invasive. Clinical manifestations include swelling, pathologic fractures, diffuse skeletal pain, and in the case of multiple bones, these lesions may mimic metastatic disease. Pathologic features are characterized by non-neoplastic reactive tissue associated with extensive osteoclastic bone resorption and osteoclast-like multinucleated giant cells, bony microfractures and hemorrhage, and hemosiderin deposition. The term brown tumor refers to an accumulation of hemosiderin pigment, and radiologic examination reveals osteolytic lesions with well-defined borders. The differential diagnosis primarily includes bone metastases, multiple myelomas, amyloid cysts, chondromas, aneurysmal bone cysts, osteosarcomas, and giant cell tumors [12]. Hyperparathyroidism (HPT) is the third most common endocrine disorder after diabetes and thyroid disease. HPT can be primary, secondary, or tertiary. Primary HPT occurs when ≥1 parathyroid gland produces too much PTH; the main causes of this clinical condition are solitary adenoma in 80-85% of patients, multiple adenomas in 5%, parathyroid hyperplasia in 10-15%, and carcinoma in less than 1-5%. Secondary HPT is when the increased PTH secretion is due to an organic cause (e.g., renal, hepatic, or intestinal disease causing hypocalcemia and subsequent increase in PTH secretion). Tertiary HPT is the result of

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persistent parathyroid stimulation (e.g., long- standing secondary hyperparathyroidism) leading to autonomic (unregulated) PTH function.

In this clinical case, the overlap of symptoms makes the diagnosis very difficult, because not only were the signs and symptoms highly suspicious for MM, but the blood test and radiological findings were also typical for plasma cell disease. In particular, the whole-body examinations CT and PET-CT were reminiscent of myeloma bone disease. The refractoriness to zoledronic acid therapy, the absence of monoclonal proteins and pathologic plasma cells in the bone marrow, and the presence of PTH prompted us to consider an alternative cause for the clinical manifestations, and only histopathologic examination helped us to reach a diagnosis. Immediate endocrinologic evaluation and surgical therapy were essential to resolve the patient's symptoms and improve his quality of life.

Conclusions

Our case reminds clinicians that they should always consider multiple differential diagnoses when confronted with a cohort of signs or symptoms related to a suspicion of MM that cannot be confirmed by investigations, as the CRAB could be nonspecific and related to various non-neoplastic diseases, especially in elderly patients.

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Competing interests: The authors have declared that no competing interests exist.

Consent: Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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