Mimicking Multiple Myeloma: the importance of the differential diagnosis

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Abstract

Here we describe the case of a caucasian man referred to our Center for a suspicion of Multiple Myeloma which comprehensive work-up ruled out the presence of plasma cells neoplasm and allowed us to perform a diagnosis of brown tumor (BT).

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Abstract Multiple Myeloma (MM) is a malignant plasma cells disorder that account for the 15% of hematologic malignancies. The clinical manifestation is defined by the presence of anemia, renal failure, hypercalcemia and osteolytic bone lesions called with the acronym CRAB. Here we describe the case of a caucasian man referred to our Center for a clinical suspicion of MM. A comprehensive work-up, including blood tests, radiological examinations and bone marrow biopsy ruled out the presence of plasma cells neoplasm Further investigations as CT guided-biopsy of a lytic lesion allowed us to perform a diagnosis of brown tumor (BT), a tumor-like lesion due to the bone remodeling process in prolonged hyperparathyroidism. This diagnosis was confirmed by endocrinological evaluations followed by a parotidectomy with resolution of the clinical manifestations. Our case outlines the importance of an accurate differential diagnosis in the suspicion of MM, because the concomitant occurrence of comorbidities and illnesses may confound the evaluation, In particular the combination of anemia, peripheral neuropathies and renal impairment could be associated to a number of other causes and it is mandatory a thorough anamnesis, clinical and instrumental examination and laboratory investigations to rule out other etiologies.

Introduction.

Multiple Myeloma (MM) is a neoplastic disorder due to the proliferation of clonal plasma cells that account for the 15% of the hematological 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 psitroalue of < 2 g/dl below the lowest limit of normal, or a hemoglobin value < 100 g/L), hypercalcemia (serum calcium >1 mg/dL higher than the upper limit of normal or > 11 mg/dL), renal failure (creatinine cleareance < 40 mL per min or serum creatinine > 2mg/dL) and bone lesions (one or more osteolytic lesions on skeletal radiography, Computer Tomography (CT), or Positron Emission Tomography-CT (PET-CT). This cohort of signs and symptoms is historically defined with the acronym of CRAB[3]. However, particularly in the elderly patients, these clinical manifestations are very frequent and could be caused by other diseases than MM. The concomitant presence of other pathologic conditions could led to a misdiagnosis with dramatic consequences for the patients. Here we present the case of an adult Italian patient with signs and symptoms coherent with suspicion of MM.

Case report.

Clinical history: He suffered from hypertension, well controlled with medical therapy

Case presentation: In the April 2020 a 57 years Caucasian old man was referred to our Hematologic Center by a nephrologist for anemia, renal failure, hypercalcemia and bone lesions with the suspicion of MM. The past medical history of patient reported fatigue, night swears and weight loss from January 2018. In the February 2018 it is documented a mild and progressive hypochromic-normocytic nemia (Hb 10,6 gr/dl) with hyperferritinemia, low iron blood levels and low count of reticulocytes. A colonoscopy showed two intestinal polyps with a high grade dysplasia. In the December 2019 it was performed a radiography of lumbar spine because of onset of pain with the finding of multiple lytic lesions. From January 2020 the patient was followed with blood tests with the documentation of a progressive anemia (Hgb 8,5 gr/dl), renal failure (serum creatinine 1,57 mg/dl, glomerular filtration 43 ml/min according to Modification of diet in renal disease (MDRD), glycosuria (with normal value of glycemia and glycated hemoglobin). He was referred to Nephrology Center for a comprehensive evaluation. It was confirmed the anemia and renal failure with a slight glomerular proteinuria (0,95 gr/24 hour). Blood tests showed hypercalcemia (serum calcium 12,9 mg/dl), normal serum albumin. A skeletal survey and total body CT confirmed the multiple bone lysis interesting the whole skeleton and particularly the pelvis, bilateral femurs, dorsal vertebrae with erosion of the bone cortical. Notably it was described a lesion of the left lobe of the thyroid gland.

Initial work-up: In the first hematological examination the patient complained fatigue and diffuse skeletal pain. There were not remarkable clinical signs. The blood test confirmed the mild normocytic-normochromic anemia, hypercalcemia, high levels of serum calcium and a mild renal failure. We performed investigation focused on definition of MM diagnosis . But, no monoclonal component was detected by serum and urine protein electrophoresis, serum and urine immunofixation. The levels of serum immunoglobulins and free light chains were normal according with renal function. Bone marrow biopsy and aspirate did not show a monoclonal plasma cell infiltrate. The patient underwent treatment with fluid hydration and Zoledronic acid to correct (with a reduction of dosage according with glomerular filtrate).

Differential diagnosis: After excluding a monoclonal gammopathy our attempts were aimed to discover other neoplastic or endocrine diseases that could cause the clinical manifestations of our patient.

Further examination: A FDG PET-TC was performed to rule out further pathologic finding. This evaluation showed a diffuse hypercaptation of bone marrow and different bone sites, particularly the jaw, bilateral ribs, dorsal and lumbar vertebral vertebrae, pelvis and bilateral femurs. A CT-guided biopsy of the third dorsal vertebra was performed: the histologic examination was coherent with a "brown tumor" (fig.1a, 1b,1c).

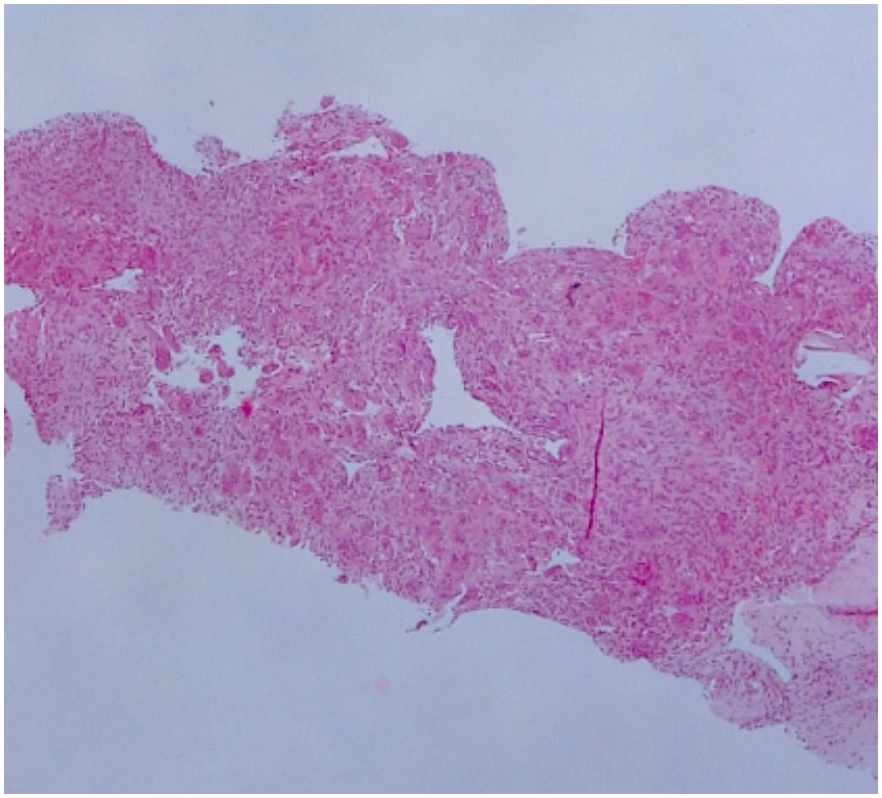

Fig.1a HE 10X and 1B HE 20X giant cell tumor uniformly distributed in the biopsy.

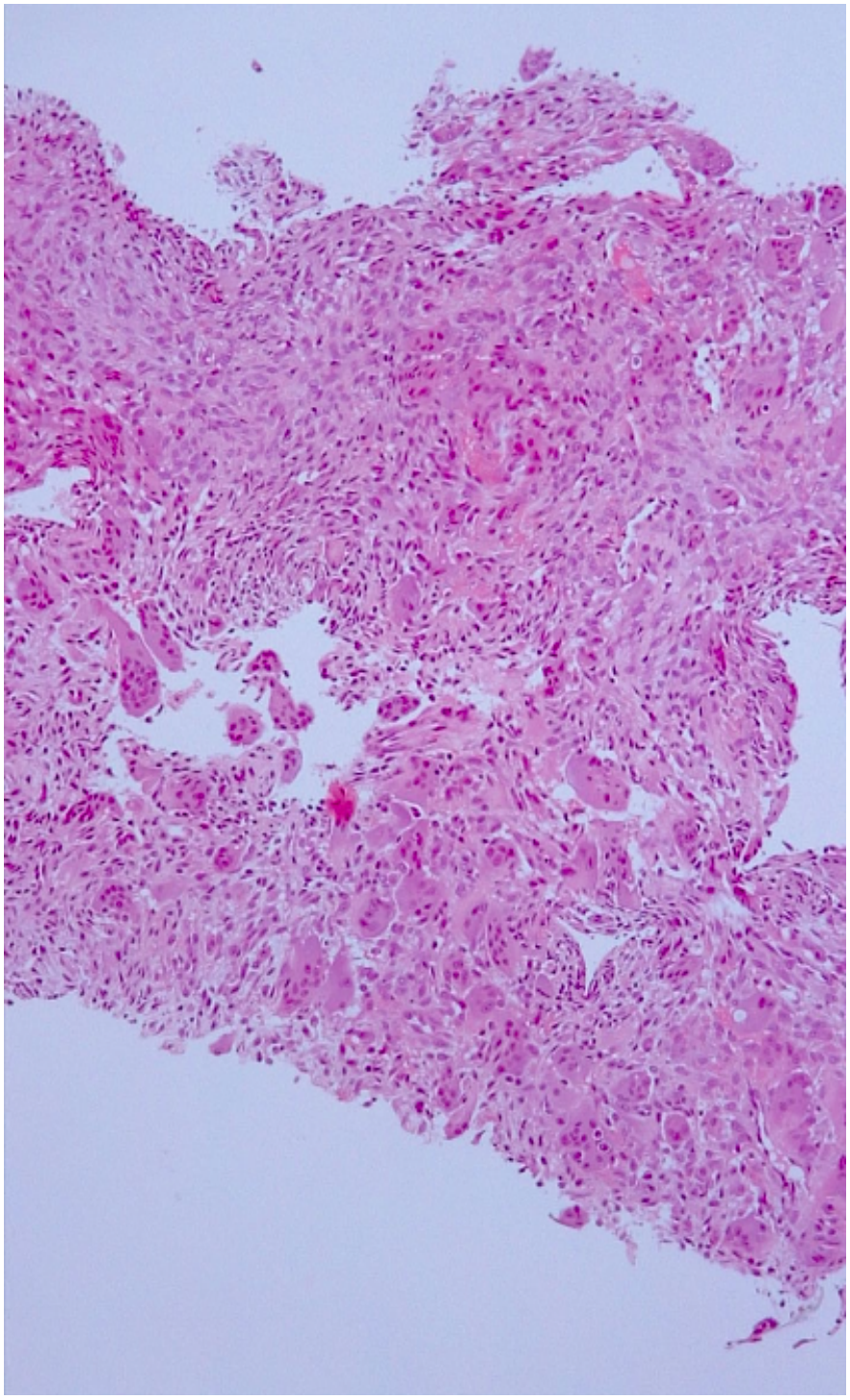

Fig.1b HE 20X giant cell tumor uniformly distributed in the biopsy.

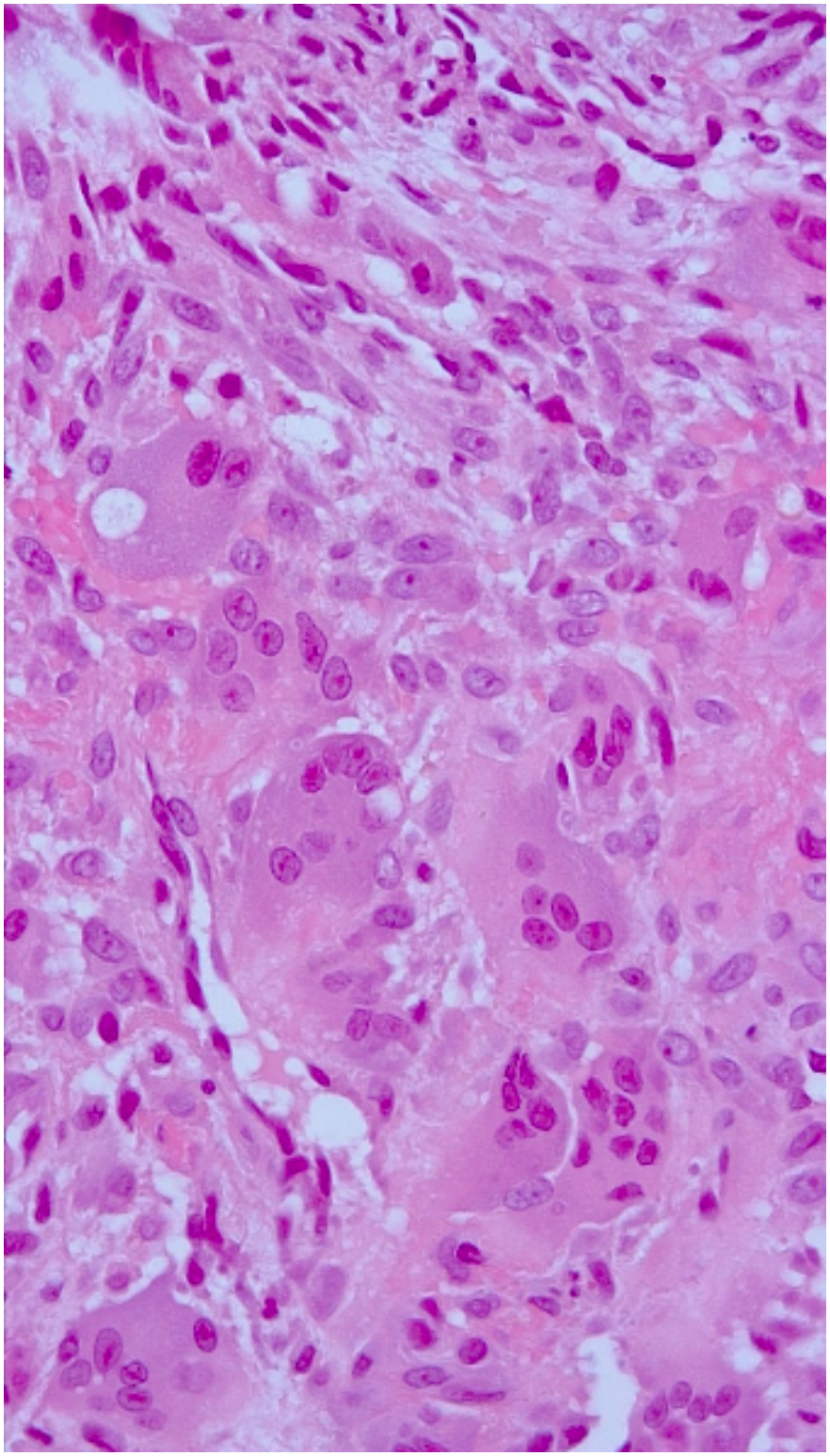

Fig 1c: HE 40X multinucleated giant cell embedded with mononuclear ovoid to spindled neoplastic cell.

Final diagnosis: High elevated levels of serum parathyroid hormone (PTH) and urine calcium and phosphorus, confirmed the diagnosis of hyperparathyroidism. The patient performed an ultrasound of the thyroid with the finding of a ovoidal mass, highly vascularized, in the left lobe. Referred to an endocrinologist it was performed an parathyroidectomy for the presence of adenoma with resolution of the pathologic manifestations and improving of the clinical outcome.

Diagnostic report. The diagnosis of symptomatic MM is based on the demonstration of clonal bone marrow plasma cells [?] 10% or biopsy-proven bony or extramedullary plasmacytoma and any one or more of the myeloma defining events as anemia, hypercalcemia, bone lytic lesions and renal failure[3]. These events are caused by a direct activity of the monoclonal plasma cells (anemia, hypercalcemia and bone lysis) or the paraprotein (renal failure). Anemia is usually normochromic-normocytic and is present in roughly the 75% of patients at diagnosis. The main causes are massive bone marrow myeloma infiltration, induction of apoptosis of erythroblast by myeloma cells, chronic anemia disorder (due to a functional iron deficiency), erythropoietin deficiency in patients with renal failure, paraprotein-induced hemodilution for increasing of plasma volume[4]. The bone lesions are detected in up to 80% at diagnosis and 100% in advanced stage. They can affect all bones but more of 60% involve the spine. The most frequent clinical and radiological pictures are represented by lithic lesions and diffuse osteoporosis, pathological fractures, cord spinal compression, bone pain and neoplastic hypercalcemia. Myeloma bone disease is characterized by significant deregulation of the physiological interaction among osteocytes, osteoblast, immune cells and the bone matrix with a consequent increasing of osteoclast activity and suppressed osteoblast function. Different aberrant molecular pathway can lead to the bone loss: the RANK/RANKL and Notch signaling pathwayss are involved in the osteoclast activation and the Wingless-type (Wnt) and beta-catenin pathway as regulator of bone homeostasis and osteoblast differentiation[5,6]. The whole-body low-dose CT constitutes the current standard for the diagnosis and assessment of multiple myeloma-related bone disease. PET-CT and whole-body MRI are also useful imaging modalities for multiple myeloma-related bone disease evaluation and PET-CT is the gold standard for the follow-up of MM-related bone disease and assessment of metabolic response to therapy, including 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 the hypercalcemia is myeloma bone resorption that leads to efflux of calcium into the extracellular fluid. However the pathobiology of hypercalcemia is more complex in this setting: for example this finding is most common in those myeloma patients who have the greatest tumor volume, irrespective of serum parathyroid hormone-related protein (PTHrP) status. The myeloma patients have frequently irreversible impairment in renal function with increased renal tubular calcium reabsorption. In this case the capacity of the kidneys to clear excess calcium load from the circulation effectively is overwhelmed, resulting in elevated serum calcium levels. The hypercalcemia related to MM differs from the elevated calcium levels in patients with solid tumors because the latest one is due to excessive secretion of PTHrP. The myeloma hypercalcemia is almost always associated with renal failure and increased serum phosphate that lead to a decreased glomerular filtration rate. Moreover, unlike the solid tumors, the Myeloma patients usually respond very rapidly to steroids because of the quick suppression of tumor plasma cells growth. The clinical findings are dependent on the calcium level: 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). Rarely, patients may develop a life-threatening 'hypercalcemic crisis' ([?] 16 mg/dl) and a state of coma[8]. In case of hypercalcemia is mandatory to rule out other causes of elevated levels of calcium: pseudo-hypercalcemia (increase in circulating proteins like M-protein), primary hyperparathyroidism (the first cause of hypercalcemia, especially in elderly people), paraneoplastic hypercalcemia (local production of OAF-type cytokines, systemic production of PTH-like peptide or calcitriol), hypervitaminosis D (pharmacological overdose, overproduction of neoplasms or granulomatous diseases), drugs (milk-alkalin syndrome, lithium, thiazides), tertiary hyperparathyroidism (renal failure), hypocalciuric familial hypercalcemia (rare autosomal dominant disease with calcium-sensing receptor alteration characterized by asymptomatic hypercalcemia since childhood and family history of hypercalcemia). In newly diagnosed MM patients, 20% to 30% will present with estimated glomerular filtration rates (GFRs) < 30 mL/min/1.73 m^2 at the time of diagnosis. Dialysis is required in up to 5% of patients. However these patients may develop decreased GFRs during the disease course, usually in

case of relapse. The most common cause of decreased GFR in patients with multiple myeloma is light chain cast nephropathy. This clinical-pathology manifestation occurs when serum monoclonal free light chains (FLCs) bind and precipitate with Tamm-Horsfall protein in the distal nephron. The formation of the casts causes tubular obstruction (typically distal) that leads to intense immune response, resulting in a giant cell reaction around the casts and interstitial inflammation. The tubular obstruction causes a rapid kidney injury. Some medications frequently taken by these patients, as nonsteroidal anti-inflammatory drugs for bone pain, may aggravate or even precipitate the kidney injury. Other drugs that may be associated with light chain cast nephropathy include angiotensin- converting enzyme inhibitors and angiotensin receptor blockers. Intravenous contrast can represent a associated risk for cast nephropathy, although recent studies found the association to be less significant. Monoclonal immunoglobulin deposition disease (MIDD), amyloidosis, and rarely, kidney infiltration by myeloma cells or acquired adult Fanconi syndrome represent other renal pathologies in patients with MM. The diagnostic work-up in case of suspicion of MM needs to rule out other causes for these symptoms and signs[9,10]. In fact all of these events are non-specific and could be associated with other diseases. Particularly MM represents a disease strongly related to age: roughly the 70% of newly diagnosed Myeloma patients are older than 65 years and 40% older than 75 year. The establishment of the diagnosis in this setting of patients can be challenging because comorbidities and illnesses may confound the valuation. For example anemia, peripheral neuropathies and renal impairment could be associated to a number of other causes and it is mandatory a thorough anamnesis, examination and laboratory differential diagnosis to rule out other etiologies (**Tab.1**)

Tab.1 : differential diagnosis of signs and symptoms of

Multiple Myeloma

Clinical features of myeloma
Hypercalcemia (13% at diagnosis) Increased osteoclastic bone resorption Increased renal tubular calcium resorption
Renal failure (19% at diagnosis) Light chain cast nephropathy Hypercalcemia Monoclonal immunoglobulin deposition diseas
Anemia (35% at diagnosis) Bone marrow infiltration by plasma cells Cytokine-mediated suppressive effect on erythropoiesis
Bone pain (58% at diagnosis) Increased osteoclast activity causing lytic bone lesions, osteoporosis, pathological fractures Pl

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

This case demonstrates the importance of the differential diagnosis because the events described above are associated to a case of hyperparathyroidism mimicking the signs and symptoms coherent with a suspicion of MM. Particularly, the diagnostic journey for this patient led to a evidence of a brown tumor (BT), a pathologic expression of "osteitis fibrosa cystica" associated to an uncontrolled hyperparathyroidism. This skeletal manifestation was first described by Recklinghausen in 1891 and is the result of the overproduction of PTH in primary or secondary hyperparathyroidism: osteoblasts will increase RANKL expression, which binds to its corresponding RANK receptor on osteoclasts and promotes osteoclast activity. PTH also reduces osteoprotegerin (PG) levels, preventing RANKL and RANK interactions and thus inhibiting bone resorption. Based on this process, this tumor-like lesion represents the terminal stage of the bone remodeling process with an overall incidence of 2–3%[11]. BT can involve in any part of the skeleton, but most frequently they are found in the jaws, ribs, clavicles, extremities, and pelvic girdle and although the lack of malignant potential, it may be invasive. Clinical manifestations include swelling, pathological fracture diffuse skeletal pain and in case of multiple bones these lesions can mimic metastatic disease. The pathology features are characterized by non-neoplastic reactive tissue associated to an extensive osteoclastic bone resorption and osteoclast-like multinucleated giant cells, osseous microfractures, and hemorrhage as well as hemosiderin depositions The term brown tumor refers to an accumulation of hemosiderin pigment, giving the lesion its macroscopically brown appearance The radiological examination shows osteolytic lesions with well-defined borders and differential diagnosis includes primarily bone metastasis, Multiple Myeloma, amyloid cysts, chondroma, aneurysmal bone cyst, osteosarcoma, and giant cell tumor[12]. Hyperparathyroidism (HPT) is

the third most common endocrine disease after diabetes and thyroid disorders. HPT can be can be primary, secondary, or tertiary. Primary HPT occurs when [?]1 parathyroid glands produce too much PTH; the main causes of this clinical condition are a 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 occurs when the increased PTH secretion is due to an organic cause (such as kidney, liver, or bowel disease causing hypocalcemia and a subsequent increase in PTH secretion). Tertiary HPT is a consequence of persistent parathyroid stimulation (such as long-standing secondary hyperparathyroidism), which results in autonomous (unregulated) PTH function.

In this clinical case the overlap of symptoms makes the diagnosis very challenging because not only the signs and symptoms were very suspicious for MM but also the blood test and the radiological findings were typical for the plasma cells disease. Particularly the whole-body CT and PET-CT mimicked the myeloma bone disease. The refractoriness to the therapy with Zoledronic Acid, the absence of monoclonal protein and pathologic bone marrow plasma cells and the arising of PTH led us to consider an alternative cause of the clinic manifestations and only the histopathologic examination helped us to achieve a diagnosis. A prompt endocrinology evaluation and surgery therapy were essential to resolve the patient's symptoms with an improvement of his outcome and quality-of-life.

Conclusions. Our case reminds clinicians they should always consider multiple differential diagnosis when face a cohort of signs or symptoms coherent with a suspicion of MM not confirmed by investigations because, particularly in elderly patients, the CRAB could be non-specific and associated with different non-neoplastic diseases.

Authorship and Disclosures . DD and MP reviewed the literature and wrote the paper. CC, TD, DP, SN and AML followed the patient and wrote the paper. GLS supervised the work.

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