CASE OF THE MONTH

CRAB Manifestations in a Middle-Aged Female: A Diagnostic Dilemma

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Abstract

A 56 year old lady, presented to our institute with six months history of low grade fever, generalized weakness, decreased food intake and fluctuating sensorium. Initial investigations revealed hypercalcemia, renal dysfunction and anemia. Initial working diagnosis of likely underlying hematological malignancy such as lymphoma or multiple myeloma (MM) was kept after hyperparathyroidism was ruled out. Her skeletal survey revealed lytic lesions in the skull, bone marrow aspirate showed 12% plasma cells and beta-two microglobulin level was markedly elevated. However, the criterion for MM was not fully satisfied. In view of persistent altered sensorium, MRI brain was done which suggested the diagnosis of disseminated tuberculosis and was further confirmed through MR spectroscopy, bone marrow biopsy (showing granulomas) and whole body PET. She was started on anti-tubercular therapy along with steroids with marked response within a week. We describe the details of this interesting case through a systematic approach to the various features.

Introduction

MMSmultiple myeloma is a disorder characterized by malignant proliferation of plasma cells. It accounts for 1% of all cancers. The diagnosis is suspected in light of certain clinical features such as hyperCalcemia, Renal dysfunction, unexplained Anemia and Bone lytic lesions on skeletal survey (CRAB). Malignancy and hyperparathyroidism account for most of the cases of hypercalcemia. However, chronic granulomatous diseases such as tuberculosis are also a rare cause. Also, there are very few cases of tuberculosis presenting with lytic lesions in the skull. Our case highlights the importance of systematic and thorough work up in order to avoid early and erroneous labelling of a particular diagnosis.

Case Description

A 56 year old female, presented to our hospital with one month history of mild to moderate grade fever associated with generalized weakness and decreased food intake. She was bedridden and unable to perform her routine daily activities for the past 20 days and had altered sensorium for the past 7 days. She had a history of multiple hospitalizations in the past six months at a private hospital with complaints of generalized weakness, fluctuating sensorium and decreased appetite. She was diagnosed as a case of chronic kidney disease (CKD) two months back on the basis of persistent deranged renal parameters. She was on oral hypoglycaemic agents and anti hypertensives in view of diabetes mellitus and hypertension respectively, for the past two years which well controlled. She had undergone two sessions of haemodialysis and also received two units of packed red blood cell (PRBC) transfusion two months back. She had no other significant past history. On examination, the patient was drowsy with a Glasgow Coma Score (GCS) of E3V3M6. Her vitals were stable. There was no peripheral lymphadenopathy or any organomegaly. Rest of the systemic and general physical examinations were unremarkable. On initial evaluation, the patient was found to have anaemia with a hemoglobin of 10.5 g/dL, deranged renal parameters with a creatinine level of 15.7 mg/dL.

Our patient was in a state of altered consciousness with no focal neurological signs on testing. This can be caused by many complex medical conditions including primary neurological disorders,

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Fig. 2: Plain radiograph of skull reveals ill-defined lytic lesions (arrow) in the parietal bone

Fig. 1: Chest radiograph AP view (Supine film) which appears grossly normal

Table 1: Causes of hypercalcemia

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
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<tbody>
<tr>
<td>Parathyroid-mediated</td>
<td>Primary hyperparathyroidism (sporadic)</td>
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<tr>
<td></td>
<td>Inherited variants</td>
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<tr>
<td></td>
<td>Multiple endocrine neoplasia (MEN) syndromes</td>
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<td></td>
<td>Familial isolated hyperparathyroidism</td>
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<td></td>
<td>Hyperparathyroidism-jaw tumor syndrome</td>
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<td></td>
<td>Familial hypocalciuric hypercalcemia</td>
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<tr>
<td></td>
<td>Tertiary hyperparathyroidism</td>
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<tr>
<td></td>
<td>Chronic renal failure, Vitamin D deficiency</td>
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<tr>
<td>Vitamin D related</td>
<td>Vitamin D intoxication</td>
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<tr>
<td></td>
<td>Usually 25-hydroxyvitamin D2 in over-the-counter supplements</td>
</tr>
<tr>
<td>Granulomatous disease</td>
<td>Sarcoïdosis, Berylliosis, Tuberculosis</td>
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<tr>
<td>Hodgkin’s lymphoma</td>
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<tr>
<td>Malignancy</td>
<td>Humoral hypercalcemia of malignancy</td>
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<td></td>
<td>Solid tumors, especially lung, head, and neck squamous cancers, renal cell tumors</td>
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<tr>
<td></td>
<td>Local osteolyis (mediated by cytokines)</td>
</tr>
<tr>
<td></td>
<td>Multiple myeloma, breast cancer</td>
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<tr>
<td>Medications</td>
<td>Thiazide diuretics</td>
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<td></td>
<td>Lithium</td>
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<td></td>
<td>Teriparatide</td>
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<td></td>
<td>Excessive vitamin A</td>
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<td>Theophylline toxicity</td>
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<tr>
<td>Miscellaneous</td>
<td>Hyperthyroidism</td>
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<td></td>
<td>Acromegaly</td>
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<td></td>
<td>Pheochromocytoma</td>
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<td></td>
<td>Adrenal insufficiency</td>
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<td>Immobilization</td>
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<td></td>
<td>Parenteral nutrition</td>
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<td>Milk-alkali syndrome</td>
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systemic conditions as well as extrinsic factors. In this patient, hypercalcemia was the evident cause. A wide range of disorders can produce hypercalcemia as mentioned in Table 1. Primary hyperparathyroidism and malignancy account for 80-90% of the cases. The normal range of serum calcium lies between 8.5 and 10.5 mg/dL (2.1-2.5 mmol/L). About 40-45% of the serum calcium is bound to albumin. When there is increased binding, elevation in the total calcium level can occur without an increase in the ionized calcium. Thus, during evaluation of hypercalcemia, elevation in the physiologically active unbound or ionized calcium needs to be confirmed first. Hypercalcemia can be classified as mild (Serum calcium < 12 mg/dL), moderate (12-14 mg/dL) or severe (> 14 mg/dL). The clinical manifestations of hypercalcemia are varied and depend upon the severity and rapidity of development.

Our patient had anemia and renal dysfunction along with severe hypercalcemia [Serum calcium at presentation (15.7 mg/dL)] and constitutional symptoms for past six months. Evaluation of anemia revealed normocytic normochromic morphology of the RBCs with a decreased corrected reticulocyte count and no features of hemolysis. There was no pathology evident on chest x-ray (Figure 1) and the parathyroid hormone level was within the normal range. The kidney size was normal on ultrasound and the urine output was well preserved. The initial non-contrast computed tomography (NCCT) head was unremarkable. The total leukocyte count and the serum procalcitonin were also not suggestive of an infectious etiology. Thus, hematological malignancies such as lymphoma or multiple myeloma (MM) were considered a strong possibility and she was worked up for the same. She was started on saline diuresis and calcitonin in view of hypercalcemia. Further bisphosphonate (Pamidronate 90 mg, IV as single dose) was also added. She also received one session of hemodialysis in view of persistent hypercalcemia.

The diagnosis of multiple myeloma (MM) requires the presence of ≥ 10% clonal plasma cells in the bone marrow or biopsy-proven plasmacytoma along with evidence of end-organ damage. The definition of MM has recently been expanded by the international myeloma working group (IMWG) to include any one of the myeloma defining biomarkers even in the absence of end-organ damage (Table 2). The clonality of the plasma cells needs to be established by demonstration of kappa/lambda (κ/λ) light-chain restriction by immunohistochemistry or immunofluorescence, or by demonstration of phenotypic clonality by flow cytometry, or by immunoglobulin gene rearrangement studies.

Our patient’s skeletal survey showed two lytic lesions in the skull (Figure 2). There are a wide range of abnormalities which can result in calvarial lytic lesions as listed in Table 3. In light of the occurrence of the lytic lesions, along with the findings of hypercalcemia, renal dysfunction and anemia; the possibility of diagnosis of MM was further strengthened and we went ahead with the bone marrow examination. The bone marrow aspirate revealed 12% plasma cells (Figure 3). However,
Table 2: International Myeloma Working Group (IMWG) diagnostic criteria for multiple myeloma

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma and any one or more of the following CRAB features and myeloma-defining events (MDE):

- Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
  - HyperCalcemia: Serum calcium >0.25 mmol/L (>1mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11mg/dL)
  - Renal insufficiency: Creatinine clearance <40 mL per minute or serum creatinine >177 µmol/L (>2mg/dL)
  - Anemia: Hemoglobin value of >20g/L below the lowest limit of normal, or a hemoglobin value <100g/L
  - Bone lesions: One or more osteolytic lesion on skeletal radiography, CT, or PET/CT. (If bone marrow has <10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.)

*Any one or more of the following biomarkers of malignancy (MDEs):*

- 60% or greater clonal plasma cells on bone marrow examination
- Serum involved/uninvolved free light chain ratio of 100 or greater, provided the absolute level of the involved light chain is at least 100mg/L
- More than one focal lesion on MRI that is at least 5 mm or greater in size.

The clonality of these cells could not be established. No M-band was identified on the urine as well as the serum electrophoresis and immunofixation studies. The serum free light chain assay was also not suggestive of multiple myeloma. However beta 2 microglobulin which is a prognostic marker of multiple myeloma was markedly elevated. Thus, the diagnosis of multiple myeloma was in doubt. A magnetic resonance imaging (MRI) of the brain was ordered for the persistent altered sensorium even after correction of hypercalcemia.

MRI brain revealed multiple ring enhancing lesions diffusely scattered in the brain parenchyma along with meningeal enhancement (Figure 4). This corroborated lipid peak on MR spectroscopy (Figure 5). Whole body positron emission tomography - computed tomography (PET-CT) scan was also done to rule out malignancy as a source of hypercalcemia. It showed metabolically active granulomas in the brain and extensive miliary lesions in the lungs along with retroperitoneal nodes and involvement of vertebrae and para spinal soft tissues and cold abscess along the ribs (Figure 6). The bone marrow biopsy report was available by then, which also revealed granulomas (Figure 7). The fundus examination also revealed choroid tubercles bilaterally. With these, the diagnosis of disseminated tuberculosis was established and the patient was started on antituberculous therapy. Cerebrospinal fluid (CSF) examination was normal. However, the patient was started

![Bone marrow aspirate showing plasma cells (arrow)](image-url)
on corticosteroids (Dexamethasone 8mg TDS) in view of meningeal enhancement on MRI.

The differential diagnosis of multiple ring enhancing lesions is listed in Table 4.7 Neurocysticercosis followed by tuberculosis are the most common etiology of multiple ring enhancing lesions in our country.8 Magnetic Resonance Spectroscopy (MRS) is a superior technique to MRI and is useful in characterization of lesions, especially those inaccessible for biopsy. The specific metabolites in the microenvironment of the lesions produce certain changes which is detected by MRS. The type of microorganism can then be assumed based on the expected products for a particular microorganism as reflected in the metabolic signature. Tubercular lesions contain caseous material with mobile lipids in them and hence exhibit strong lipid resonances.9 Approach to ring enhancing lesions in the brain is explained in the form of a flow chart in Figure 8.10

During the hospital stay, our patient developed urinary tract infection (UTI) which resolved with broad spectrum antibiotic coverage of appropriate duration. She also developed leucocytopenia and significant thrombocytopenia. The leucocyte count had improved subsequently. However, thrombocytopenia was persistent. She received multiple platelet transfusions as she had severe bruising and bleeding gums. There was marked improvement in her sensorium within one week of starting antituberculous therapy. Her hypercalcemia responded to the treatment and her renal dysfunction also resolved. Work up for other causes of hypercalcemia such as hyper parathyroidism, vitamin D excess and sarcoidosis was negative. She was discharged one week after starting antituberculous treatment along with steroids.

Rarely, granulomatous diseases have been known to cause hypercalcemia.11 Among them tuberculosis and sarcoidosis are most common.12-15 The mechanism involves increased extra renal 1-alpha hydroxylase activity by the activated macrophages present in the granulomas. This leads to a non-parathormone (PTH) mediated increase in calcitriol levels.16-18 The diagnosis of tuberculosis was further established in our case by the MR spectroscopy and whole body PET imaging as well as by the remarkable clinical response to anti tuberculous therapy. Treatment of hypercalcemia in granulomatous diseases including tuberculosis consists of dietary and pharmacological measures along with the treatment of the underlying disease when possible. Dietary measures are aimed at minimizing the intestinal calcium absorption and calcitriol synthesis. These can be achieved by reducing calcium intake, elimination of dietary vitamin D supplements, and avoidance of sun exposure. Pharmacological measures include low dose glucocorticoids, bisphosphonates, and chloroquine.19-21

There have been case reports of tuberculosis presenting with lytic...
There have also been case reports of simultaneous occurrence of tuberculosis and multiple myeloma. This is probably the first case of disseminated tuberculosis in itself simulating full blown manifestations of multiple myeloma namely, hypercalcemia, renal dysfunction, anemia, lytic lesions in the skull as well as plasma cells in the bone marrow and elevated beta 2 microglobulin.

**Conclusion**

Hypercalcemia and lytic bone lesions including the skull. Elevated beta 2 microglobulin is used as a prognostic marker in several malignancies including multiple myeloma. Increased levels are also known to occur in infections such as tuberculosis.

Fig. 6: PET CT images revealing cold abscess along the right rib at T7 level (arrow) along with miliary mottling

Fig. 7: Bone marrow biopsy showed a well formed epithelioid cell granuloma (Arrow) with Langhans type of giant cell. AFB stain did not reveal any organism. CD-138 immunostain showed increase number of plasma cells in the marrow
lesions occurring together does not always mean malignancy. Granulomatous diseases such as tuberculosis can also present with similar presentation. Our case report highlights the importance of systematic and thorough work up in order to clinch the correct diagnosis. The diagnosis of multiple myeloma requires the presence of \( \geq 10\% \) clonal proliferation of plasma cells along with one of the CRAB criteria or elevation of any one of the myeloma defining biomarkers. Having a high index of suspicion and thorough work up is of paramount importance in such cases before embarking on treatment as the diagnosis is not always straight forward.

**References**

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