Atypical presentation of hypercalcemia in elderly

Ali SH1,2
1Geriatrics & Gerontology department, Faculty of Medicine, Ain Shams University, Cairo, Egypt.
2Ain Shams Ageing Research Center, Cairo, Egypt.

Background: Hypercalcemia is a common clinical problem with an estimated prevalence of 0.1% to 0.01% among hospitalized patients and this can be ten times more in elderly. The adage, “stones, groans, bones, and psychiatric overtones” is often used to describe the symptoms of hyperparathyroidism. However, 80% of elderly with primary hyperparathyroidism present with asymptomatic or atypical hypercalcemia. We are classically taught that two most common causes of hypercalcemia are malignancy and primary hyperparathyroidism (PHPT). Many case reports are published discussing the atypical presentation of hypercalcemia in elderly, meanwhile, the review article discussing hypercalcemia in elderly is since 1988 (1) which also is the gold standard upon which, symptoms of hypercalcemia in elderly are counted on and we can see that many cases are presented in a different way now. This mini review includes case reports of atypical presentation of hypercalcemia in elderly aiming to establish a new sight about presentation in this age group.

Atypical symptoms are classified upon underlying cause including:

I. Atypical presentation of hypercalcemia underlying malignancy
II. Atypical presentation of hypercalcemia underlying primary hyperparathyroidism
III. Atypical presentation of hypercalcemia underlying medications
IV. Atypical presentation of hypercalcemia underlying infections
V. Atypical presentation of hypercalcemia underlying other causes

Summary of the reported cases of different causes of hypercalcemia are illustrated in [table (1)]

<table>
<thead>
<tr>
<th>Author</th>
<th>Age of the patient/gender</th>
<th>Presentation</th>
<th>Serum calcium mg/dl</th>
<th>PTH pg/dL (reference range, 15-65 pg/dL)</th>
<th>DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghazi et al, 20102</td>
<td>85 male</td>
<td>low grade fever, anorexia, abdominal discomfort and fullness in his left abdomen</td>
<td>13.3</td>
<td>15</td>
<td>high-grade malignant lymphoma</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25(OH)D 3 = 8.6 ( &lt;30 ng/ml)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25(OH)2D 3 = 12.7 (20-70 pg/ml)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PTHrP measurement was not available</td>
<td></td>
</tr>
<tr>
<td>Xynos et al, 20093</td>
<td>77 male</td>
<td>confusion. Other symptoms included general fatigue, anorexia, weight loss, nausea and occasional</td>
<td>12.6</td>
<td>1.55</td>
<td>Cholangiocarcinoma</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Author et al.</th>
<th>Gender</th>
<th>Age</th>
<th>Symptoms</th>
<th>BMD</th>
<th>B25D</th>
<th>B12</th>
<th>Other Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delgado-Guay et al, 2008</td>
<td>60 male</td>
<td>60</td>
<td>vomiting, confusion, with delusional thoughts and periods of visual hallucination then severe back pain</td>
<td>12.44</td>
<td>NA</td>
<td>normal or high</td>
<td>metastatic small cell prostate carcinoma</td>
</tr>
<tr>
<td>Abdalla et al, 2017</td>
<td>59 female</td>
<td>60</td>
<td>nausea and vomiting of one week and unintentional weight loss of 50 pounds in the last seven months</td>
<td>17.7</td>
<td>558</td>
<td>normal or high</td>
<td>primary hyperparathyroidism and multiple myeloma</td>
</tr>
<tr>
<td>Luceri and Haenel, 2013</td>
<td>79 female</td>
<td>79</td>
<td>nausea and worsening fatigue, along with constipation, poor appetite, and weight loss</td>
<td>15.8</td>
<td>96</td>
<td>normal or high</td>
<td>primary hyperparathyroidism and concomitant B-cell lymphoma</td>
</tr>
<tr>
<td>Lehmann, 2013</td>
<td>Among the 84 case reports of lithium-associated hyperparathyroidism, 34 individuals (40%) were over the age of 60. more common in women than men.</td>
<td>Variable (asymptomatic, mild fatigue (47%), constipation (20%), nephrolithiasis (13%), bone pain (13%) and abdominal pain (7%), severe (lethargy, drowsiness, paranoia, hallucinations and confusion)</td>
<td>normal or high</td>
<td>normal or high</td>
<td>lithium-associated hyperparathyroidism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASHIZAWA, 2003</td>
<td>78 male</td>
<td>78</td>
<td>Nausea AND lethargy and weakness, and on the day of admission he complained of severe chest pain which was not relieved by nitrate</td>
<td>16.2</td>
<td>10 pg/ml 1.25 (OH)2vitamin D, 37.6 pg/ml (20-60).</td>
<td>vitamin D intoxication,</td>
<td></td>
</tr>
<tr>
<td>Kaur and Winters 2015</td>
<td>60 male</td>
<td>60</td>
<td>altered mental status after a syncopal episode.</td>
<td>17.4</td>
<td>11 25-hydroxy vitamin D = 24 ng/ml (reference range 30–100), 1,25-dihydroxy-vitamin D = 13 pg/dl (reference range 18–72)</td>
<td>hypercalcemia associated with the use of a SLGT2 inhibitor (Canagliflozin,)</td>
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</tr>
<tr>
<td>Granieri et al, 2017</td>
<td>76 male</td>
<td>76</td>
<td>coma</td>
<td>16.8</td>
<td>NA</td>
<td>Hypercalcemia due to magnesium sulphate infusion</td>
<td></td>
</tr>
<tr>
<td>Spindel et al, 1995</td>
<td>According to site</td>
<td>NA</td>
<td>NA</td>
<td>Fungal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hanai et al, 2017</td>
<td>81 male</td>
<td>81</td>
<td>altered mental status. The patient did not have fever, cough, sputum or night sweat.</td>
<td>high</td>
<td>NA</td>
<td>active pulmonary tuberculosis</td>
<td></td>
</tr>
<tr>
<td>Edison et al, 2014</td>
<td>77 male</td>
<td>77</td>
<td>of fever, generalized weakness, and weight loss</td>
<td>NA</td>
<td>NA</td>
<td>Miliary TB</td>
<td></td>
</tr>
<tr>
<td>Arfeen et al, 2014</td>
<td>91 male</td>
<td>91</td>
<td>acute confusion and falls.</td>
<td>16.5</td>
<td>6.6</td>
<td>Sarcoïdosis</td>
<td></td>
</tr>
<tr>
<td>Lindquist, 2005</td>
<td>79 female</td>
<td>79</td>
<td>Acute mental status change and confusion</td>
<td>13.9</td>
<td>NA</td>
<td>Milk-alkali syndrome</td>
<td></td>
</tr>
<tr>
<td>Balasubramanian et al, 2017</td>
<td>65 female</td>
<td>65</td>
<td>headache, vomiting, weight</td>
<td>15.8</td>
<td>7.3 25-hydroxyvitamin</td>
<td>necrotizing sarcoid granuloma of the</td>
<td></td>
</tr>
</tbody>
</table>
loss, confusion and constipation. No fever, loss of appetite, cough, chest pain, visual disturbances or weakness. D 28 ng/ml (20–100 ng/ml), 1, 25-dihydroxyvitamin D (calcitriol) 119 pg/ml (20–62 pg/ml)

| Kikuchi et al, 2016 29 | 81 female | confusion and low-grade fever | 12.4 | 13 | hypercalcemia is attributable to the exacerbation of hyperthyroidism

| Khasawneh, 2013 28 | 65 male | constipation, polyuria, and unexplained weight loss of 54 lb. There was no fever or chills and no respiratory symptoms. | 12.4 | 6 | histoplasmosis

| Cheng et al, 2006 21 | 66 male | acute exacerbation of chronic renal failure | 14.1 | NA | Immobilization hypercalcemia

1. Atypical presentation of hypercalcemia underlying malignancy

Atypical case of lymphoma (Ghazi et al., 2008).² presented with splenic mass. While his chest and mediastinal CT scan was unremarkable and abdominal CT scan noted that the spleen was large and that it contained a definite mass occupying about two thirds of the splenic space. No abdominal or para-aortic lymph nodes were seen. Lymphoma diagnosis established only after surgical removal of the spleen and microscopic evaluation which revealed a high-grade malignant lymphoma with foci of necrosis. A bone marrow biopsy was performed and there was no bone marrow involvement. Based on the lack of lytic bone lesions, no bone marrow involvement, no plasmacytosis in bone marrow, and the lack of gammopathy in serum protein electrophoresis, other hematological malignancies, including multiple myeloma, were ruled out. There are collections of lymphoma cases presented as hypercalcemia and not mentioned here to avoid repetition.⁵,⁶

As regard Xynos et al, ³ case, computer tomography (CT) revealed a large multinodular mass in the right lobe of the liver consistent with neoplastic disease and smaller nodules in the right lung. Brain CT was normal. Bone scan with 99mTc-MDP showed no evidence of metastatic bone disease, and parathyroid scan with 99mTc-MIBI double phase was unremarkable. A liver surgical biopsy confirmed the diagnosis of cholangiocarcinoma.

Regarding prostate cancer case, Hypercalcemia is not a common finding in patients with prostate cancer, but when it is present, neuroendocrine tumors of the prostate are usually related to its development. Neuroendocrine carcinoma subtypes range from anaplastic small cell carcinomas to more differentiated carcinoid tumors. Patients with neuroendocrine tumors have a variable clinical course, but they typically present with early metastasis and involvement of unusual sites. Neuroendocrine carcinoma has been associated with endocrine paraneoplastic syndromes, such as ectopic corticotropin secretion.

In patients with advanced cancer, prospective data suggest a 28% to 42% prevalence of delirium on admission to a palliative care unit and rates as high as 88% before death. Most of the time, delirium is considered to be multifactorial, especially in patients with advanced cancer and elderly patients. In that patient, dehydration, advanced disease, and hypercalcemia played important roles in the development of delirium.

2. Atypical presentation of hypercalcemia underlying primary hyperparathyroidism

As regard Luceri and Haenel case ⁸, the patient was readmitted and Initial laboratory test results revealed a calcium level of 10.8 mg/dL, which trended up to 11.7 mg/dL during the next several days. Her concurrent intact PTH level was undetectable (<1 pg/dL), and a cause for hypercalcemia other than hyperparathyroidism was therefore considered. Occult malignancy was suspected, and a workup for cancer was initiated. Serum and urine protein electrophoresis results were negative the PTH-related protein (PThrP) level was 8 pg/mL (reference range, 14-27 pg/mL), the 25-hydroxyvitamin D level was low 19 ng/mL; (reference range, 30-100 ng/mL), and the 1,25 dihydroxyvitamin D level was elevated 131 pg/mL; (reference range, 18-72 pg/mL). Results of a full-body bone scan were unremarkable, but computed tomography of the abdomen and pelvis demonstrated a large (12.6-cm) retroperitoneal soft tissue mass surrounding the aorta. Fine-needle aspiration of the mass demonstrated a diffuse large B-cell lymphoma.
The prognosis was deemed to be very poor and was discussed with the patient and her family, who decided that she should receive hospice care; she died of her disease 2 days later.

Another case of double pathology is that of Abdall et al. case. Ultrasonography of the neck showed a complex cystic mass measuring 2.5 by 1.7 cm at the upper pole of the left lobe of the thyroid gland. The parathyroid scan showed hyperactive left upper parathyroid area. They stated “Despite the rarity of co-existence of primary hyperparathyroidism and multiple myeloma, bone marrow biopsy was obtained from our patient due to high suspicious features, i.e. weight loss, anemia, and thrombocytopenia even after confirming primary hyperparathyroidism. It revealed hypercellular marrow with decreased trilineage hematopoiesis and extensive involvement by plasma cells. Approximately there were 50% plasma cells in the aspirate smears and 80% in the core biopsy. Computed tomography of the abdomen showed mild splenomegaly and no lymphadenopathy. The bone survey didn’t show evidence of focal lytic lesions.

3. Atypical presentation of hypercalcemia underlying medications

In the Ashizawa et al. case, the serum concentration of total 1,25-(OH)2D was within the normal range. Several studies report normal or only marginally elevated total 1,25-(OH)2D levels among vitamin D intoxicity patients. In the increased free 1,25-(OH)2D levels might contribute to the pathogenesis of hypercalcemia related to vitamin D toxicity. Ina-OH-D3 is thought to suppress PTH either directly, or indirectly by increasing serum calcium. Although the value of HS-PTH, which is influenced by renal dysfunction, was above the normal range, the level of intact-PTH was at the lower limit of normal in this case, suggesting that the hypercalcemia was caused by a non-PTH-mediated mechanism, probably vitamin D intoxication.

In SGLT2 induced hypercalcemia case, a 60-year-old man with uncontrolled type 2 diabetes treated with insulin, glimepiride, metformin and canagliflozin, who was admitted with altered mental status after a syncopal episode. Laboratory work-up showed acute kidney injury, diabetic ketoacidosis (DKA), and parathyroid hormone-independent severe hypercalcemia of 17.4 mg/dl. DKA resolved with insulin treatment, and saline hydration led to improvement in hypercalcemia and renal function over 48 h, but was accompanied by a rapid increase in the serum sodium concentration from 129 to 162 mmol/l despite changing fluids to 0.45% saline. Urine studies were consistent with osmotic diuresis. Hypernatremia was slowly corrected with hypotonic fluids, with improvement in his mental status over the next 2 days. This was the first report of hypercalcemia associated with the use of a SLGT2 inhibitor. Although the exact mechanism is unknown, canagliflozin may predispose to hypercalcemia in patients ingesting excessive calcium because of dehydration from osmotic diuresis, with reduced calcium excretion and possible increased intestinal calcium absorption.

Saline therapy and osmotic diuresis may lead to hypernatremia from electrolyte-free water loss. Drugs that inhibit the sodium-glucose co-transporter-2 (SGLT2) are an exciting novel, insulin-independent treatment for diabetes that block glucose reabsorption from the proximal tubules of the kidney, leading to increased glucose excretion and lower blood glucose levels. Inhibition of SGLT2 activity also reduces sodium reabsorption, which together with glycosuria produces a mild diuretic effect with the potential for dehydration and hyperkalemia.

Another peculiar case of 76 years old man presented emergency room with marked asthenaemia, minimal effort dyspnea. Patient’s diagnosis was significant for cardiac disorders, presenting history of congestive heart failure (CHF) due to dilated, post-ischemic cardiomyopathy associated with serious reduction of the systolic function. Baseline calcium was not available.

Later, A telemetry revealed the presence of polymorphic ventricular tachycardia hence the following treatment was added to the above mentioned pharmacological therapy: intravenous infusion of magnesium sulphate (2 gr. in 10 minutes); amiodarone (one 200 mg tablet three times/day); continuous intravenous infusion (25 mL/h) of saline (500 mL of 0.9% sodium chloride) with the addition of potassium chloride (60 mEq) and magnesium sulphate (3 gr).

The morning after the patient was found comatose, with a Glasgow Coma Scale (GCS) score of 9 (E2 V2 M5). The patient was immediately submitted to the following investigations: head computerized tomography (CT) scan (negative for acute disease), ammoniemia (negative) and calcemia (abnormal: 16.8 mg/dL; RR 8.0 – 11.8 mg/dL). Despite a proper diuresis (about 6 L/t/day), calcium levels were still high (14.8 mg/dL) and associated with hypophosphoraemia (1.8 mg/dL; RR 2.5 - 4 mg/dL), low 25-hydroxy vitamin D3 (28.1 ng/mL; RR 30-80 ng/mL) and increased parathyroid hormone (PTH) levels (1.067 pg/ml; RR 11-67 pg/mL).

The infusion of magnesium sulphate was then discontinued and, within 24 hours, patient’s neurological conditions clearly improved, calcemia gradually decreased in parallel with the occurrence of hypomagnesemia (1.2 mg/ dL; RR 1.7 - 2.2 mg/dL). Fourteen days later, the general clinical picture was stabilized and the patient was discharged with mild hypercalcemia (13 mg/dL) and hypomagnesemia (1.6
mg/dL). He was diagnosed as hyperparathyroidism. In the reported case, the administration of magnesium sulphate for the treatment of polymorphic ventricular tachycardia in a patient most likely suffering from unacknowledged hypercalcemia and hypomagnesemia resulted in a dramatic worsening of the hypercalcemic crisis: the correction of magnesium levels in fact, might have induced the physiologic effects of PTH further exacerbating hypercalcemia.

4. Atypical presentation of hypercalcemia underlying infections

In fungal infections presented with hypercalcemia (Spindel et al, 1995), one mechanism for this hypercalcemia in infections is via the excess production of 1,25-di-hydroxyvitamin D from extra-renal sources. The authors describe an AIDS patient infected with Cryptococcus neoformans who had suggestive evidence of vitamin D-mediated hypercalcemia. He had an elevated serum 1,25-dihydroxyvitamin D value, a normal 25-hydroxyvitamin D value, and low values for parathyroid hormone and parathyroid hormone-related peptide. Most previously reported cases of hypercalcemia associated with fungal infections did not include sufficient evidence to implicate a role for excess 1,25-dihydroxyvitamin D production, except for two case reports involving patients with hypercalcemia with infections due to Pneumocystis carinii and Candida albicans.

The tuberculous case presented as delirium (Hanai et al, 2017) was a nursing home resident aged 81 years. He was admitted because of altered mental status. The patient did not have fever, cough, sputum or night sweat. Hypercalcemia was identified as a cause of the consciousness disturbance. Chest radiograph showed no acute process. Laboratory workups revealed elevated serum levels of 1,25-(OH)2 vitamin D3 and positive T-spot test. Microscopic examination of the suctioned sputum identified acid-fast bacilli, which was confirmed as Mycobacterium tuberculosis.

Another 77 years old man presented with hypertension, diabetes mellitus type 2, and nephrolithiasis (status-post left nephrectomy), presenting with a one-month history of fever, generalized weakness, and weight loss. Laboratory data was significant for anemia, hypercalcemia, and acute kidney injury. Chest radiograph showed ground glass opacities and interstitial infiltrates. Empiric antibiotics for community acquired pneumonia were initiated, however, fever persisted. Extensive workup was performed to evaluate fever and hypercalcemia. Malignancy, hormonal, and septic workup were all unremarkable.

PPD skin test was negative. Sputum, pleural fluid, bronchoalveolar lavage, and cerebrospinal fluid were AFB smear negative. Remarkably, urine AFB smear was positive. Anti-tuberculosis therapy was initiated which lead to clinical improvement. However, his hospital course was complicated by small bowel obstruction and respiratory failure. He subsequently developed loss of cardiac electrical activity and expired. Postmortem autopsy confirmed the presence of tuberculosis in multiple organs including his remaining kidney. This is unusual case of miliary tuberculosis. Miliary tuberculosis should always be one of the differential diagnoses of fever of unknown origin with hypercalcemia. Moreover, workup for renal tuberculosis with urine AFB should be done in high-risk patients with a history of kidney stones.

5. Atypical presentation of hypercalcemia underlying other causes

In the sarcoidosis case, although this patient has not undergone bronchoscopy to make a gold-standard histological diagnosis, an empirical diagnosis of sarcoidosis explains the hypercalcemia (and its response to steroids), the hilar lymphadenopathy, the recurrent cranial nerve lesions, and the elevated serum ACE levels.

In milk alkali syndrome case, the patient has baseline dementia with superimposed delirium. Notably, her lab showed elevated levels of bicarbonate, calcium and Creatinine. They also found half bottle of calcium carbonate antacid which was added to her calcium supplementation which led to excess calcium intake. The triad of hypercalcemia, elevated bicarbonate, elevated Creatinine is called Milk-alkali syndrome.

Necrotizing sarcoid granulomatosis (NSG) is a rare variant of sarcoidosis with pathologic features of necrosis and vasculitis that overlap with rheumatologic and infectious diseases. Hypercalcemia is occasionally the presenting feature of classical sarcoidosis occurring in 10–20% of patients, most commonly in association with pulmonary involvement. However hypercalcemia in NSG is less common and has not been previously described when NSG primarily affects the liver. 65-year-old Caucasian female who presented with hypercalcemia and NSG of the liver without pulmonary involvement. Conclusion: Hypercalcemia was mediated by 1, 25-vitamin D which was most likely produced by hepatic granulomas and it resolved rapidly with prednisone. An interesting case of 81 years old woman with Graves’ disease and osteoporosis was referred to the hospital because of anorexia over one month and impaired consciousness. She also presented with low-grade fever and emaciation. Laboratory tests revealed marked hypercalcemia (corrected serum calcium level of 12.4 mg/dL), which was initially suspected to result from vitamin D toxicity, because she had been taking...
vitamin D3 (alphacalcidol of 0.5 µg/day) for the treatment of osteoporosis. However, discontinuation of vitamin D3 and fluid infusion did not ameliorate hypercalcemia one week later. After excluding hyperparathyroidism and malignancy-related hypercalcemia, hypercalcemia was considered to be attributable to the exacerbation of hyperthyroidism (free T4 of 6.69 ng/dL, free T3 of 13.27 pg/mL and thyroid stimulating hormone (TSH)).

Concerning histoplasmosis case, a case of a 65-year-old diabetic male who presented with unexplained weight loss and hypercalcemia. Multiple brain space-occupying lesions and bilateral adrenal enlargement were evident on imaging studies. Biopsies showed caseating granulomas with budding yeast, consistent with histoplasmosis. The patient’s symptoms resolved after liposomal amphotericin B and itraconazole therapy.

Immobilization hypercalcemia mainly results from rapid bone turnover and may be seen after spinal cord injury or long bone fracture in children and adolescents. In the elderly population, immobilization hypercalcemia is usually a sequela of cerebrovascular accident and is easily misdiagnosed due to several pitfalls related to poor nutritional and inflammatory status with low serum albumin and 25(OH)D3 levels. Disturbed consciousness in a recent stroke patient may be easily attributed to intracranial events, such as a new infarction, hemorrhage, or infection. Our patient had recurrent hypercalcemia and acute exacerbation of chronic renal failure during hospitalization. His high urine FECa excluded reabsorptive hypercalciuria; while his low serum iPTH and 1,25-(OH)2D3 excluded parathyroidal hypercalcemia and endogenous or exogenous vitamin D-related hypercalcemia. A detailed review of his medications ruled out the possibility of milk-alkali syndrome and vitamin D analogue overdose. Further studies, including serum cortisol, ACTH, Gallium scan, CT scan of whole abdomen, and whole body bone scan failed to conclude either adrenal insufficiency or occult malignancy. Because of cautious exclusion of other causes and an excellent response to passive mobility on paralyzed limbs, immobilization was confirmed as the final cause of hypercalcemia.

Conclusion:
The symptoms of hypercalcemia among elder people are variable and nonspecific. The underlying mechanisms and causes of hypercalcemia should be identified and properly treated. Among elderly, the most common causes of hypercalcemia are primary hyperparathyroidism and malignancy.

Corresponding Author: Safaa Hussien Ali: fersanarabia@gmail.com

References:
5. Ha JM, MD1 Eun Kim, MD1 Woo Joo Lee, MD1 Ji-Won Hwang, MD1 Sehyo Yune, MD1 Young Hyeh Ko, MD,PHD2 Jooy Young Choi, MD,PhD3 Sek Jin Kim, MD, PhD1 Won Seog Kim, MD, Cancer Res Treat. 2014;46(3):307-311
15. Edison So, Dennis TB. Hypercalcemia: atypical presentation of miliary tuberculosis. BMJ Case Reports 2014;