29 y.o. Female with Increased Parathyroid Hormone Related Peptide (PTH-RP)
Patient Presentation

• 29 y.o. female with hypercalcemia and found to have mildly elevated PTH-RP. Endocrine team concerned for possible breast cancer.

• PMHx: Alcoholic cirrhosis, history of recurrent acute kidney injury requiring hemodialysis, hypertension
• PSHx: S/p liver transplant 9 months ago on tacrolimus for suppression
• FHx: No family history of cancer
Pertinent Labs

• Ca: 10.5 mg/dL (normal 8.6-10.2 mg/dL)
• Albumin: 4.9 g/dL
• PTH within normal limits (10–60 pg/mL)
• PTH-RP: 6.0 pmol/L (female over 18 normal 0.0-3.4 pmol/L)
• Tacrolimus trough: 7 ng/mL
• Creatinine: 1.17 mg/dL (normal 0.50-0.96 mg/mL)
• GFR: 54 mL/min/1.73m² (normal ≥ 60 mL/min/1.73m²)
Hypercalcemia & PTH-RP

• Hypercalcemia is when total serum calcium is greater than or equal to 10.5 mg/dL
  • Must be adjusted if albumin is low as 40% of serum calcium is bound to albumin
  • Differential includes PTH-dependent (hyperparathyroidism, FHH, lithium use) and PTH-independent (malignancy, Vitamin D intoxication, granulomatous disease, adrenal insufficiency, medication-associated)

• Parathyroid Hormone (PTH) is a part of the body’s calcium homeostasis and can be elevated in conditions such as chronic kidney disease (secondary hyperparathyroidism)
  • Renal Disease → low 1,25(OH)₂D production & decreased phosphate excretion → low calcium gut and renal reabsorption & high phosphate → increased PTH → increased serum Ca²⁺

• Elevated Parathyroid hormone-related peptide (PTH-RP) in the setting of hypercalcemia is seen in humoral hypercalcemia of malignancy, most commonly secreted in breast, lung, and kidney cancers
Other Imaging Workup

• Due to elevated PTH-RP, the patient underwent full imaging workup for primary malignancy

• Prior Imaging Workup: CT Chest/Abdomen/Pelvis, MRI Abdomen/Pelvis, and Neck US all negative for findings of malignancy.
What Additional Imaging Should We Order?
ACR Appropriateness Criteria

**Variant 2:** Breast cancer screening. Intermediate-risk women: women with personal history of breast cancer, lobular neoplasia, atypical ductal hyperplasia, or 15% to 20% lifetime risk of breast cancer.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Appropriateness Category</th>
<th>Relative Radiation Level</th>
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</thead>
<tbody>
<tr>
<td>Mammography screening</td>
<td>Usually Appropriate</td>
<td>☀️ ☀️</td>
</tr>
<tr>
<td>Digital breast tomosynthesis screening</td>
<td>Usually Appropriate</td>
<td>☀️ ☀️</td>
</tr>
<tr>
<td>MRI breast without and with IV contrast</td>
<td>May Be Appropriate</td>
<td>☀️</td>
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<tr>
<td>US breast</td>
<td>May Be Appropriate</td>
<td>☀️</td>
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<tr>
<td>FDG-PET breast dedicated</td>
<td>Usually Not Appropriate</td>
<td>☀️ ☀️ ☀️ ☀️</td>
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<tr>
<td>Sestamibi MBI</td>
<td>Usually Not Appropriate</td>
<td>☀️ ☀️ ☀️ ☀️</td>
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<td>MRI breast without IV contrast</td>
<td>Usually Not Appropriate</td>
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</tbody>
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This imaging modality was ordered by the Endocrine physician as the patient was undergoing complete malignancy workup due to elevated PTH-RP. While screening mammograms would not typically begin until 40, workup was warranted due to elevated PTH-RP.
Findings Unlabeled - MLO Images
Findings Labeled - MLO Images

Parallel linear calcifications identified within a tubular structure consistent with vascular calcifications.
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Final Dx:

Vascular Calcifications
BI-RADS 2, Heterogeneously Dense breasts with bilateral vascular calcifications. No evidence of primary malignancy in the breast.
Case Discussion - Vascular Calcifications

• **Vascular Calcifications** are defined by the BI-RADS atlas as parallel tracks or linear calcifications that are clearly associated with blood vessels.

• Due to calcific deposition in the media of arterioles, known as **Mönckeberg medial calcific sclerosis**.
  - Calcium deposition in the media without narrowing of the lumen

• Presence is considered an independent risk factor for coronary artery disease and is oftentimes seen in in older patients.

• Younger patients with extensive vascular calcifications may have associated diabetes mellitus and renal disease, as seen in this patient.

• In young patients with extensive vascular calcifications on mammography, it is important to consider the possibility of calciphylaxis, which is **systemic** medial calcific sclerosis and has features of skin necrosis, which this patient did not have. Calciphylaxis has an extremely poor prognosis.
Teaching Points

• Vascular calcifications on mammography may have many associations, including:
  • Coronary artery disease
  • Diabetes mellitus
  • Chronic kidney disease

• In younger patients, vascular calcifications are unexpected but may be due to:
  • Diabetes mellitus
  • Secondary hyperparathyroidism from severe renal disease
    • Vitamin D + PTH + Ca^{2+} + Phosphorous → increase in calcium phosphate precipitates
  • Calciphylaxis
Case Resolution

• Although PTH was normal, the extensive vascular calcifications on mammography were felt to be due to the patient’s known renal dysfunction and hypercalcemia.

• Tacrolimus, an immunosuppressive medication for liver transplant maintenance, dose was lowered to alleviate potential nephrotoxicity while maintaining appropriate immunosuppression.

• Calcium now down-trending to 10.2 mg/dL and GFR is increasing, now 60 mL/min/1.73m².

• The patient was sent for PET/CT to exclude malignancy because of the elevated PTH-RP, and so far no malignant cause of PTH-RP has been identified.

• Additional send-out workup is underway including intact PTH, N Terminal PTH-RP assay which is not affected by renal function, and ACTH/cortisol to evaluate for adrenal disease (which can sometimes elevate calcium).

  • C terminal PTH-RP has been reported to be falsely elevated in patients with renal dysfunction and hypercalcemia, so it is important to obtain N terminal PTH-RP from an outside laboratory if there is no obvious cancer
References:

1. Appropriateness Criteria [Internet]. [cited 2023 Sep 19]. Available from: https://acsearch.acr.org/list