Paraneoplastic Syndromes

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Moderator: Dr Gyan Chand
Introduction

• ‘Paraneoplastic ‘ refers to features of disease considered to be due to **remote effects** of a cancer

• Cannot be attributed to a cancer’s direct invasive or metastatic properties

• Often considered to be due to aberrant hormonal or metabolic effects not observed in a cancer’s normal tissue equivalent
A number of criteria have been proposed for the diagnosis of paraneoplastic endocrine syndromes.

These include:
- Demonstration of elevated hormone concentrations in the blood
- Finding of normal or suppressed endogenous hormone production

Demonstration of:
- Hormone concentration gradients across the tumor and
- Biochemical or clinical resolution of the syndrome following surgery, radiotherapy, or chemo-therapy

Demonstration of hormone messenger RNA and the corresponding hormonal product provide direct lines of evidence for hormone production by the tumor.
Introduction...

• Paraneoplastic syndromes → are more common than is generally appreciated.

• Signs, symptoms, and metabolic alterations may be overlooked

• Atypical clinical manifestations in a patient with cancer → consider paraneoplastic syndrome.
History

• The first report dates back to 1890 when a French physician M. Auche, described the peripheral nervous system involvement in cancer patients.
• The earliest reports of endocrine syndromes in patients with non-endocrine cancers date back to the 1920s


• The concept of hormone production by malignant non-endocrine tumors was advanced by Dr. Fuller Albright in a Case Record from the Massachusetts General Hospital published in 1941
  – 51-yr-old man with a lytic lesion in the right ilium accompanied by marked hypercalcemia.
  – Biopsy of the bone lesion → metastatic renal cell carcinoma

## Nonspecific Paraneoplastic Syndromes

<table>
<thead>
<tr>
<th>Sl.</th>
<th>PNS</th>
<th>Associated tumors</th>
<th>Cause</th>
<th>Specific Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fever</td>
<td>Lymphomas, acute leukemias, sarcomas, *RCC, &amp; digestive malignancies</td>
<td>- Release of endogenous pyrogens, - Necrotic-inflammatory phenomenon of tumors - Altered liver functions leading to disorders of steroidogenesis</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Dysgeusia</td>
<td>Many malignancies</td>
<td>Alteration in body’s level of copper &amp; zinc or morphofunctional variation of tasting buds</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Anorexia &amp; cachexia</td>
<td>Many malignancies</td>
<td>Bioactive molecules produced by tumors (TNF alpha, peptides &amp; nucleotides)</td>
<td>-</td>
</tr>
</tbody>
</table>
## Rheumatologic Paraneoplastic Syndromes

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Paraneoplastic arthopathies</td>
<td>Myelomas, lymphomas, acute leukemias, malignant histiocytosis, tumors of colon, pancreas, prostate &amp; CNS</td>
<td>- ? autoimmunity</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Hypertrophic osteoarthopathy</td>
<td>Lung cancers, pleural mesotheliomas, phrenic neurilemmoma</td>
<td>- Idiopathic, - ? GH production by tumor, vagal hyperactivity</td>
<td>Resection of ipsilateral Vagus</td>
</tr>
<tr>
<td>3</td>
<td>Scleroderma</td>
<td>- Breast, uterus &amp; lung - Carcinoids &amp; lung tumors</td>
<td>Production of antinuclear antibody (ANA)</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Systemic lupus erythematosus</td>
<td>Lymphomas, breast, lungs, &amp; gonads</td>
<td>Production ANA</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Secondary amyloidosis of connective tissues</td>
<td>Myeloma, RCC, &amp; lymphoma</td>
<td>-</td>
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</tbody>
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## Gastrointestinal

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<tbody>
<tr>
<td>1</td>
<td>Watery diarrhoea</td>
<td>MTC, multiple myeloma</td>
<td>Prostaglandins PG E2 and F2</td>
<td>- PG inhibitors</td>
</tr>
<tr>
<td>2</td>
<td>Protein- losing enteropathy</td>
<td>Malignancies of digestive system</td>
<td>Tumor inflammation and exudation</td>
<td>-</td>
</tr>
</tbody>
</table>
## Renal

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<tbody>
<tr>
<td>1</td>
<td>Membranous nephropathy</td>
<td>Carcinomas of the lung, colon, &amp; stomach</td>
<td>Immune complexes deposition leading to complement activation</td>
<td>- Nephrotic syndrome may resolve with successful treatment of the underlying malignancy.</td>
</tr>
<tr>
<td>2</td>
<td>Hemolytic-uremic syndrome.</td>
<td>Giant hemangiomas &amp; hemangioendotheliomas, acute promyelocytic leukemia, prostate, gastric, &amp; pancreatic cancers</td>
<td>- Autoantibodies mediated</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Renal vasculitis</td>
<td>HCC* &amp; concomitant hepatitis C disease &amp; Lung cancer</td>
<td>- Secondary to cryoglobulinemia - Secondary to Henoch-Schönlein's purpura</td>
<td>-</td>
</tr>
</tbody>
</table>
# Hematologic

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</table>
| 1   | Erythrocytosis | RCC, hepatoma, Wilms tumor, hemangiomas, cerebellar hemangioblastoma, sarcomas, uterine fibroids, adrenal tumors, & PCC* | - Elevated serum erythropoietin (EPO) levels  
- ? Production of adrenal hormones & prostaglandins enhance the effect of EPO | - Control of the underlying neoplasm  
- Occasional phlebotomy required                                                                             |
| 2   | Anemia    | B-cell malignancies, mucin-producing adenocarcinomas.  
Rarely with solid tumors of GIT, lung, breast, RCC, thymoma heart, lung, & prostate | - Decrease EPO formation  
- Autoimmune hemolytic anemias  
- Microangiopathic hemolytic anemia | - Microangiopathic hemolytic anemia syndrome may respond to effective anticancer therapy                  |
| 3   | Granulocytosis | Lymphomas, & variety of solid tumors including gastric, lung, pancreatic, brain cancers & malignant melanoma | - Tumor production of growth factors.                                                               |                                                                                                         |
| 4   | Thrombocytosis | Lymphoma, & a variety of carcinomas & leukemias.                                     | - Tumor overproduction of thrombopoietin or interleukin 6.                                           | Treatment is not generally indicated                                                                  |
## Hematologic...

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<tr>
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</table>
| 5     | Coagulopathies | Solid tumors (primarily adenocarcinomas). Plasm Cell dyscrasias, gastric, ACC, leukemias, lymphomas paraproteinemias, & lymphoproliferative disorders | - Acquired von Willebrand factor deficiency  
- Acquired hemophilia | - Supportive measures based on the degree of bleeding  
- IV immunoglobulin, plasmapheresis, corticosteroids, & immunosuppressive agents |
| 6     | Granulocytopenia | Hodgkin's lymphoma                                                                  | - Production of a factor that suppresses granulopoiesis by interfering with number of growth factors  
- Antibodies against granulocytes  
- Immune dysregulation of T cells | - Stimulation with growth factors, including granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor |
| 7     | Thromboembolism | Pancreatic cancer, gaynecologic malignancies                                        | - Hypercoagulable state  
- ↓ levels of Protein C, Protein S, & antithrombin  
- direct generation of thrombin; & thrombocytosis & activation of coagulation factors  
- ↑ secretion of plasminogen activators & ↓ in their inhibitors, activation of platelets, ↑ platelet aggregation | - Anticoagulation for an indefinite period.  
- Low molecular weight heparin preferred |
| 8     | Nonbacterial thrombotic endocarditis (Marantic endocarditis) | Adenocarcinomas of the lung & pancreas. | - Underlying coagulopathy  
- Microscopic edema, & degeneration of valvular collagen  
- ↑ local valvular effect of mucin-producing carcinomas | - Anticoagulation therapy |
Hematologic..

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| 9   | Eosinophilia & basophilia | - Hodgkin's lymphoma & mycosis fungoides  
- CML** & other myeloproliferative disorders | - Granulocyte-macrophage colony-stimulating factor, interleukin 3, or interleukin 5 |                                        |
| 10  | Thrombocytopenia | Lymphoid malignancies  
Rarely, solid tumors such as lung, breast, & GIT | - Autoantibodies                                                                | High-dose prednisone, &/ or splenectomy |
<p>| 11  | Gammopathies    | Lung cancers &amp; pleural mesotheliomas                                                | - Antigenic stimulus of the tumor on some immune clones                                 |                                        |</p>
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| 1   | Acanthosis nigricans: Gray –brown pigmentation usually accompanied by confluent papillomas, usually affects oral, umbilical, axillary and inguinal area. Tripe palms- Thickened palms with exaggerated hyperkeratotic ridges, a velvety texture, and brown hyperpigmentation usually associated with acanthosis nigricans. | - Typically with adenocarcinomas of the GI tract (gastric cancer). Also with other adenocarcinomas: lung, breast, ovarian, & hematologic malignancies  
- Lung & gastric cancers | - Overproduction of TGF | Acanthosis nigricans: Gray – brown pigmentation usually accompanied by confluent papillomas, usually affects oral, umbilical, axillary and inguinal area. Tripe palms- Thickened palms with exaggerated hyperkeratotic ridges, a velvety texture, and brown hyperpigmentation usually associated with acanthosis nigricans. |
| 2   | Acquired ichthyosis: characterized by generalized dry, crackling skin, hyperkeratosis & rhomboidal scales of the extensor surfaces | - Typically with Hodgkin's lymphoma. Also with other lymphomas, multiple myeloma, Kaposi's sarcoma, & other malignancies | - | Acquired ichthyosis: characterized by generalized dry, crackling skin, hyperkeratosis & rhomboidal scales of the extensor surfaces |
| 3   | Palmar hyperkeratosis  
  – Diffuse hyperkeratosis (tylosis)  
  - Punctuate hyperkeratosis: discreet hyperkeratotic papules on the palms | - Oesophageal (Howel-Evans syndrome), breast, & ovarian carcinoma  
- Cancers of the breast & uterus. | - | Palmar hyperkeratosis  
  – Diffuse hyperkeratosis (tylosis)  
  - Punctuate hyperkeratosis: discreet hyperkeratotic papules on the palms |
| 4   | Acrokeratosis paraneoplastica (Bazex's syndrome): characterized by symmetric psoriasiform acral hyperkeratosis | Squamous cell carcinoma of the esophagus, head & neck, or lungs. | - Cross-reaction between the basement membrane & tumor antigens  
- IGF-1 or TGF alpha | Acrokeratosis paraneoplastica (Bazex's syndrome): characterized by symmetric psoriasiform acral hyperkeratosis |
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<tr>
<td>5</td>
<td>Exfoliative dermatitis: progressive erythroderma with scaling</td>
<td>Lymphomas (not in the setting of cutaneous T-cell lymphoma) &amp; rarely solid tumors (lung, liver, prostate)</td>
<td>-</td>
<td>Exfoliative dermatitis: progressive erythroderma with scaling</td>
</tr>
<tr>
<td>6</td>
<td>Pachydermoperiostosis: subperiosteal new bone formation associated with acromegalic features</td>
<td>Bronchogenic carcinoma.</td>
<td>-</td>
<td>Pachydermoperiostosis: subperiosteal new bone formation associated with acromegalic features</td>
</tr>
<tr>
<td>8</td>
<td>Plane xanthomas: large yellow-orange patches &amp; plaques on the trunk</td>
<td>Commonest multiple myeloma. Also in many other leukemias &amp; lymphomas</td>
<td>-</td>
<td>Plane xanthomas: large yellow-orange patches &amp; plaques on the trunk</td>
</tr>
<tr>
<td>9</td>
<td>Vitiligo: white discoloration of the skin</td>
<td>Rarely with thyroid carcinoma &amp; melanoma.</td>
<td>-</td>
<td>Vitiligo: white discoloration of the skin</td>
</tr>
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<tr>
<td>10</td>
<td>Amyloid deposits: may manifest as macroglossia, superficial waxy yellow &amp; pink elevated nodules on the skin</td>
<td>Multiple myeloma or Waldenstroms’ macroglobulinemia</td>
<td>Amyloid deposits: may manifest as macroglossia, superficial waxy yellow &amp; pink elevated nodules on the skin</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Sweet's syndrome: acute onset of fever, neutrophilia, &amp; the appearance of erythematous painful raised cutaneous plaques on the face, neck, &amp; upper extremities.</td>
<td>Commonest with AML. Also with myelodysplastic syndromes, myeloproliferative &amp; lymphoproliferative disorders, &amp; carcinomas</td>
<td>- Hypersensitivity reaction</td>
<td>Sweet's syndrome: acute onset of fever, neutrophilia, &amp; the appearance of erythematous painful raised cutaneous plaques on the face, neck, &amp; upper extremities.</td>
</tr>
<tr>
<td>12</td>
<td>- Flushing: an episodic reddening of the face &amp; neck, lasting a few minutes. - Harlequin syndrome: is unilateral flushing &amp; sweating - Isolated palmar erythema</td>
<td>Typically with carcinoid syndrome. Also with leukemia, MTC**, RCC , PCC &amp; systemic mastocytosis - Liver failure secondary to hepatic malignancy</td>
<td>- Vasoactive peptides such as serotonin</td>
<td>- Flushing: an episodic reddening of the face &amp; neck, lasting a few minutes. - Harlequin syndrome: is unilateral flushing &amp; sweating - Isolated palmar erythema</td>
</tr>
<tr>
<td>13</td>
<td>Vasculitis</td>
<td>- Lung cell carcinoma, small cell carcinoma of the oesophagus, prostate, &amp; hematological malignancies</td>
<td>-</td>
<td>Vasculitis</td>
</tr>
<tr>
<td>14</td>
<td>Cutaneous ischemia</td>
<td>Neoplasms of solid organs &amp; blood</td>
<td>- Autoimmune phenomena (Raynaud's) - Leukostasis - Increased blood viscosity</td>
<td>Cutaneous ischemia</td>
</tr>
</tbody>
</table>

29/10/2013

Paraneoplastic syndromes
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</tr>
<tr>
<td>1</td>
<td>Myasthenia</td>
<td>Thymoma</td>
<td>Anti-ACHR antibodies at the postsynaptic level of the neuromuscular junction</td>
<td>- Surgery - Plasmapheresis - Corticosteroids - Immunosuppression</td>
</tr>
<tr>
<td>2</td>
<td>Lambert-Eaton myasthenic syndrome (LEMS)</td>
<td>Small cell lung cancer (SCLC)</td>
<td>- Anti calcium channels antibodies</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Opsoclonus-myoclonus syndrome</td>
<td>Neuroblastoma</td>
<td>Anti-Ri (ANNA-2)</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Subacute cerebellar degeneration</td>
<td>Hodgkin’s lymphoma, breast cancer, ovarian cancer, &amp; SCLC</td>
<td>Anti-Yo (APCA), Anti-tr, Anti-Ri (ANNA-2), Anti-Hu (ANNA-1)</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Subacute sensory neuronopathy</td>
<td>SCLC, RCC, breast, lymphoma</td>
<td>Anti-Hu (ANNA-1)</td>
<td>-</td>
</tr>
</tbody>
</table>
## Neuromuscular...

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</thead>
<tbody>
<tr>
<td>6</td>
<td>Encephalomyelitis</td>
<td>SCLC, sarcoma, neuroblastoma</td>
<td>Anti-Hu (ANNA-1), Antiamphiphysin</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Stiff-person syndrome</td>
<td>Breast, SCLC</td>
<td>Antiamphiphysin antibodies</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>Cancer-associated retinopathy</td>
<td>SCLC, melanoma</td>
<td>Anti-CAR</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>Limbic encephalitis</td>
<td>SCLC, Testicular tumors</td>
<td>Anti-Ta (Ma2)</td>
<td>-</td>
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</table>
## Endocrine

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<tr>
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</tr>
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<tbody>
<tr>
<td>1</td>
<td>Hypercalcemia:  Incidence 8% to 10% of all malignancies</td>
<td>Squamous carcinoma of the bronchus, carcinoma of the breast, &amp; multiple myeloma.</td>
<td>- PTHrp production  - Factors released by, or in response to, metastases in bone (activator of nuclear factor-κb lig&amp; [rankI], pthrp, TGF -α, TNF, interleukin-1 [il-1].)</td>
<td>- Hydration  - Anti-resorptive therapy: bisphosphonates &amp; calcitonin</td>
</tr>
<tr>
<td>2</td>
<td>Tumor-associated SIADH</td>
<td>SCLC, carcinoids, lung cancer, head &amp; neck cancer, genitourinary, gastrointestinal, &amp; ovarian cancers.</td>
<td>Activation of the vasopressin gene in tumors</td>
<td>- Fluid restrictio  - Salt tablets or saline  - Demeclocycline  - Conivaptan, (v2-receptor antagonist)  - Severe hyponatremia may require treatment with hypertonic (3%) or normal saline infusion</td>
</tr>
<tr>
<td>3</td>
<td>Ectopic Cushing's Syndrome: 10–20% of Cushing's syndrome</td>
<td>Bronchial carcinoids, SCLC, thymic &amp; other carcinoid, islet cell tumors, PCC &amp; MTC</td>
<td>- ↑ expression of the POMC gene leading to ACTH production  - CRH production  - Ectopic expression of various g protein–coupled receptors in the adrenal nodules eg; GIP</td>
<td>- Ketoconazole  - Metyrapone  - Mitotane  - Bilateral adrenalectomy</td>
</tr>
<tr>
<td>4</td>
<td>Tumor-Induced Hypoglycemia</td>
<td>Mesenchymal tumors, hemangiopericytomas, HCC, ACC*</td>
<td>Excess production of IGF-2 - bioavailability of IGF-2 is increased due to alterations in circulating binding proteins.</td>
<td>- Frequent meals &amp; iv glucose, especially during sleep or fasting,  - Glucagon, GH &amp; glucocorticoids</td>
</tr>
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<tr>
<td>5</td>
<td>Ectopic HCG production</td>
<td>Testicular embryonal tumors, germ cell tumors, extragonadal germinomas, lung cancer, hepatoma, &amp; pancreatic islet tumors.</td>
<td>Ectopic production of intact HCG</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Hypophosphatemic Oncogenic Osteomalacia or tumor-induced osteomalacia (TIO)</td>
<td>- Benign mesenchymal tumors, eg; hemangiopericytomas, fibromas, or giant cell tumors, often of the skeletal extremities or head - Rarely sarcomas prostate &amp; lung cancers</td>
<td>Phosphaturic factor: phosphatonin (FGF 23)</td>
<td>- Phosphate &amp; vitamin D supplementation - Octreotide</td>
</tr>
</tbody>
</table>
Endocrine Paraneoplastic Syndromes
Fig. 1. Spectrum of paraneoplastic endocrine syndrome. ACTH, adrenocorticotropic; ANP, atrial natriuretic peptide; CRH, corticotropin releasing hormone; FGF-23, fibroblast growth factor-23; GH, growth hormone; GHRH, growth hormone-releasing hormone; hCG, human chorionic gonadotropin; hPL, human placental lactogen; IGF-II, insulin-like growth factor; ILs, interleukins; LH, luteinizing hormone; PTH, parathyroid hormone; PTHrP, parathyroid hormone–related protein; TGF, transforming growth factor; vit D, vitamin D.
<table>
<thead>
<tr>
<th>Paraneoplastic Syndrome</th>
<th>Ectopic Hormone</th>
<th>Typical Tumor Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cushing's syndrome</td>
<td>Adrenocorticotropic hormone (ACTH)</td>
<td>Lung (small cell, bronchial carcinoid, adenocarcinoma, squamous), thymus, pancreatic islet, medullary thyroid carcinoma</td>
</tr>
<tr>
<td></td>
<td>Corticotropin-releasing hormone (CRH) (rare)</td>
<td>Pancreatic islet, carcinoid, lung, prostate</td>
</tr>
<tr>
<td></td>
<td>Ectopic expression of gastric inhibitory peptide (GIP), luteinizing hormone (LH)/human chorionic gonadotropin (hCG), other G protein–coupled receptors (rare)</td>
<td>Macronodular adrenal hyperplasia</td>
</tr>
</tbody>
</table>
## Less Common Paraneoplastic Syndromes

<table>
<thead>
<tr>
<th>Paraneoplastic Syndrome</th>
<th>Ectopic Hormone</th>
<th>Typical Tumor Types</th>
</tr>
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<tbody>
<tr>
<td>Non-islet cell hypoglycemia</td>
<td>Insulin-like growth factor (IGF-II)</td>
<td>Mesenchymal tumors, sarcomas, adrenal, hepatic, gastrointestinal, kidney, prostate</td>
</tr>
<tr>
<td></td>
<td>Insulin (rare)</td>
<td>Cervix (small cell carcinoma)</td>
</tr>
<tr>
<td>Male feminization</td>
<td>hCG&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Testis (embryonal, seminomas), germinomas, choriocarcinoma, lung, hepatic, pancreatic islet</td>
</tr>
<tr>
<td>Diarrhea or intestinal hypermotility</td>
<td>Calcitonin&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Lung, colon, breast, medullary thyroid carcinoma</td>
</tr>
<tr>
<td></td>
<td>Vasoactive intestinal peptide (VIP)</td>
<td>Pancreas, pheochromocytoma, esophagus</td>
</tr>
<tr>
<td>Paraneoplastic Syndrome</td>
<td>Ectopic Hormone</td>
<td>Typical Tumor Types</td>
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</tr>
<tr>
<td>Oncogenic osteomalacia</td>
<td>Phosphatonin [fibroblast growth factor 23 (FGF23)]</td>
<td>Hemangiopericytomas, osteoblastomas, fibromas, sarcomas, giant cell tumors, prostate, lung</td>
</tr>
<tr>
<td>Acromegaly</td>
<td>Growth hormone–releasing hormone (GHRH)</td>
<td>Pancreatic islet, bronchial and other carcinoids</td>
</tr>
<tr>
<td></td>
<td>Growth hormone (GH)</td>
<td>Lung, pancreatic islet</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Thyroid-stimulating hormone (TSH)</td>
<td>Hydatidiform mole, embryonal tumors, struma ovarii</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Renin</td>
<td>Juxtaglomerular tumors, kidney, lung, pancreas, ovary</td>
</tr>
</tbody>
</table>
Hypercalcemia of Malignancy
• 1941 - Albright first proposed the term *humoral hypercalcemia* in patients with cancer.

• Cancer-induced hypercalcemia occurs in 5% to 30% of patients with cancer during the course of their disease, depending on the type of tumor.


• Represents the most common paraneoplastic syndrome

• Incidence of 15 cases per 100,000 people per year.

Hypercalcemia of Malignancy..

• Most common in cancers of the
  – lung
  – head and neck
  – skin
  – esophagus
  – breast
  – genitourinary tract
  – multiple myeloma
  – Lymphomas
• Lung cancer, breast cancer and myeloma have the highest incidence - more than 50%
  

• Except in patients with multiple myeloma and breast cancer, prognosis is usually poor

• Mean survival - 2-3 months

• >30% of patients with multiple myeloma, 25% of those with squamous cell carcinoma and 20% of those with breast cancer may develop HHM

Hypercalcemia of Malignancy

• 10% of all patients with advanced cancer & conveys a poor prognosis

• 30 day mortality rate for cancer patients with hypercalcemia – 50%

• Four mechanisms of hypercalcemia of malignancy:
  1. Secretion of PTHrP by tumor cells – HHM-80% of cases – common with Squamous cell tumor
  2. Osteolytic activity at the site of skeletal metastasis– 20% of cases- breast cancer, multiple myeloma, lymphoma
  3. Tumor secretion of Vitamin D- Rare- certain lymphomas
  4. Ectopic tumor secretion of PTH
Mechanisms of hypercalcemia of malignancy

• Several humoral causes, most commonly overproduction of PTHrP
• bone metastases (e.g., breast, multiple myeloma) may produce PTHrP →
  – local osteolysis
  – hypercalcemia
PTHrP; Parathyroid Hormone related Protein

- Synthesized as 3 isoforms as a result of alternative splicing (139, 141, 173 aa)
- Can activate PTH receptor
- Physiological role in lactation - mobilization and/or transfer of calcium to the milk
- May be important in fetal development
PTHrP: Parathyroid Related Protein
**PTHrP**

- Structurally related to PTH
- Binds to PTH receptor → similar biochemical features of HHM and hyperparathyroidism
- Key role in skeletal development
- Regulates cellular proliferation and differentiation in other tissues including
  - skin
  - bone marrow
  - breast
  - hair follicles
- Mechanism of PTHrP induction in malignancy incompletely understood
PTHrP and PTH

**PTHrP**
- Distinct gene product with sequence homology to PTH only in a limited domain at the amino terminal end of the molecule
- Produces humoral hypercalcemia by increasing resorption of bone throughout the skeleton & renal resorption of Ca.
- **Stimulates only osteoclasts & low osteoblastic activity**

**PTH**
- Produces humoral hypercalcemia by increasing resorption of bone throughout the skeleton & renal resorption of Ca.
- **Stimulates bone resorption & formation**
Mechanisms of hypercalcemia of malignancy...

• Excess production of 1,25-dihydroxyvitamin D
  – Relatively common cause of HHM

• Lymphomas
  – can produce an enzyme that converts 25-hydroxy vit D to more active 1,25-dihydroxy vit D
  – enhanced gastrointestinal calcium absorption

• Other causes of HHM include tumor-mediated production of
  – osteolytic cytokines
  – inflammatory mediators
Clinical Manifestations hypercalcemia of malignancy...

• Typical presentation of HHM: patient with a known malignancy who is found to be hypercalcemic on routine laboratory tests

• Less often: hypercalcemia initial presenting feature of malignancy

• If Calcium levels markedly increased [>3.5 mmol/L (>14 mg/dL)]:
  – fatigue
  – mental status changes
  – dehydration
  – symptoms of nephrolithiasis
Diagnosis

- Features that favor hypercalcemia of malignancy as opposed to primary hyperparathyroidism
  - known malignancy
  - recent onset of hypercalcemia
  - very high serum calcium levels

- Like hyperparathyroidism, hypercalcemia caused by PTHrP is accompanied by
  - hypercalciuria
  - Hypophosphatemia
Diagnosis..

• Measurement of PTH is useful to exclude primary hyperparathyroidism:
  – PTH level should be suppressed in HHM

• An elevated PTHrP level confirms the diagnosis
  – increased in ~80% of hypercalcemic patients with cancer

• 1,25-Dihydroxyvitamin D levels may be increased in patients with lymphoma
Clinical features

- Nausea/vomiting
- Altered mental status
- Weakness
- Ataxia
- Hypertonia
- Lethargy
- Hypertension
- Bradycardia
- Renal failure
- Coma

Lab findings

- Hypercalcemia
  - Mild (10.5-11.9 mg/dl)
  - Moderate (12-13.9 mg/dl)
  - Severe (≥14.0 mg/dl)
- Low to normal PTH level (<20pg/ml)
- Elevated PTHrP levels (normal < 2.5 pmol/L)
Immunometric assays show complete separation of individuals with hypercalcemia of malignancy from those with hyperparathyroidism.
Differential diagnosis

• Hyperparathyroidism- primary, tertiary
• Malignancy- humoral, local
• Drug induced- Vit A,D intoxication, lithium, tamoxifen, thiazide
• Endocrine diseases- eg adrenal failure
• Others- sarcoidosis, immobilization, acute renal failure, familial hypocalciuric hypercalciuria, milk alkali syndrome
Approach to treatment

• Two different therapeutic approaches

Increase urinary excretion of calcium

Inhibit
• Osteoclastic bone resorption
• RANK Ligand
• Action of PTHrP
Treatment..

• First step → assess hydration state
• Saline infusion → depending upon severity of dehydration.
• Volume expansion alone ineffective in restoring normocalcemia → rehydration does not interfere with osteoclastic function
• Loop diuretics -enhance calcium excretion only after normovolemic reached
• Bisphoshonates
Treatment options

• Normal saline 200-500 ml/h
• Furosemide, 20-40 mg IV
• Pamidronate, 60-90 mg IV
• Zoledronate 4 mg IV
• Prednisolone 40-100 mg/d orally for lymphoma & myeloma
• Calcitonin 4-8 IU/kg SC or IM every 12 hrly
• Mithramycin 25 µg/kg IV requires multiple doses
• Gallium Nitrate 100-200mg/m²/d IV continuous infusion for 5 d
• Hemodialysis
Treatment options: Bisphosphonates

- Synthetic analogues of pyrophosphate
- Decrease serum calcium levels by inhibiting PTH-dependent osteoclast activation
- Potent inhibitors of osteoclast-mediated bone resorption
- Currently pamidronate, zoledronate and ibandronate drugs of choice
Bisphosphonates..

• Europe: Five bisphosphonates licensed: etidronate, clodronate, pamidronate, ibandronate, and zoledronate
• US: pamidronate and zoledronate licensed
• Efficacy of pamidronate in restoring normocalcemia: 40% -100%, depending on the dose and baseline serum calcium
• Some studies report that pamidronate inferior to zoledronate

Treatment options...

- Mithramycin, calcitonin, and gallium nitrate → mostly abandoned due to limited activity and side effects, especially renal
- New experimental approach → blockade of receptor activator of nuclear factor-kappa B ligand (RANKL)-osteoprotegerin, denosumab
- RANKL - key element in the differentiation, function, and survival of osteoclasts
  - removes Ca(++) from the bone in response to PTH stimulation
Figure 2. Interactions between osteoclasts and cancer-cells. PTHrP: parathyroid hormone-related protein, RANKL: receptor activator of nuclear factor-κ ligand, IGF: insulin-like growth factor, TGF-β: transforming growth factor-β, MAPK: mitogen-activated protein kinase.
SIADH
SIADH..

• SIADH is the second most common paraneoplastic endocrine syndrome
• ADH is also known as arginine vasopressin (AVP = ADH) because of its vasopressive activity, but its major effect is on the kidney in preventing water loss
Water content of the blood **LOW**

To much water drunk

Too much salt or sweating

Brain produces **More** ADH

High volume of water reabsorbed by kidney

Urine output **LOW**

(small volume of Concentrated urine)

Water content of the blood normal

Brain produces **Less** ADH

Low volume of water reabsorbed by kidney

Urine output **HIGH**

(large volume of dilute urine)
Cortex

Water leaves - ion concentration in filtrate increases

Chloride ions out (sodium follows) - ion concentration in filtrate decreases

Medulla

Filtrate reaches maximum concentration
• Several nephrons empty into one collecting duct.

• The collecting duct passes through the progressively more concentrated medulla, losing water by osmosis. This water is reabsorbed by the capillaries.

• This water is conserved, and a highly concentrated urine is produced.

Water reabsorbed into vasa recta, urine becomes more concentrated.
ADH: conserves body water and regulates tonicity of body fluids

- Regulated by osmotic and volume stimuli
- Water deprivation increases osmolality of plasma which activates hypothalamic osmoreceptors to stimulate ADH release
SIADH

• SIADH characterized by hypo-osmotic, euvoletic hyponatremia $\rightarrow$ 1% to 2% of all patients with cancer
• Small cell lung cancer: most of these cases $\rightarrow$ 10% to 45% of all patients
• Paraneoplastic SIADH arises from tumor cell production of

$$\text{ADH} \rightarrow \text{increases free-water reabsorption}$$

$$\text{ANP} \rightarrow \text{natriuretic and antidiuretic properties}$$

Atrial natriuretic peptide.
## Associated Cancers

<table>
<thead>
<tr>
<th>Small cell lung cancer</th>
<th>Oropharyngeal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesothelioma</td>
<td>Thymoma</td>
</tr>
<tr>
<td>Bladder</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Ureteral</td>
<td>Ewing sarcoma</td>
</tr>
<tr>
<td>Endometrial</td>
<td>Brain</td>
</tr>
<tr>
<td>Prostate</td>
<td>GI</td>
</tr>
<tr>
<td>Breast</td>
<td>Adrenal</td>
</tr>
</tbody>
</table>
Cancer patients with Urinary Na > 40mmol/L or Urine osmolality > 100mOsm/kg

<table>
<thead>
<tr>
<th>SIADH</th>
<th>Appropriate Secretion of ADH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euvolemic Hyponatremia</td>
<td>Hypovolemic Hyponatremia</td>
</tr>
<tr>
<td>Causes:</td>
<td></td>
</tr>
<tr>
<td>• Gastrointestinal losses</td>
<td>• Adrenal insufficiency</td>
</tr>
<tr>
<td>• Excessive diuresis</td>
<td>• Salt-wasting nephropathy</td>
</tr>
<tr>
<td>• Adrenal insufficiency</td>
<td>• Cerebral salt wasting</td>
</tr>
</tbody>
</table>
Clinical & Laboratory parameters

• Accurate assessment of volume status is critical for diagnosis & therapy
  – Euvolemic state
  – absence of orthostatic vital sign changes or edema
  – normal central venous pressure
  – serum uric acid concentration < 4 mg/dL
  – blood urea nitrogen level < 10 mg/dL
Diagnosis and Management of Hyponatremia in Cancer Patients

Jorge J. Castillo, Marc Vincent, Eric Justice

The Oncologist 2012;17:756–765

![Algorithm for the differential diagnosis of hyponatremia.](image)
Symptoms

Degree of hyponatremia

- MILD
  - Serum sodium levels < 125 mEq/L within 48 hrs

- SEVERE
  - Altered mental status
  - Seizures
  - Coma
  - Respiratory collapse, Death.

<table>
<thead>
<tr>
<th>MILD</th>
<th>SEVERE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>Altered mental status</td>
</tr>
<tr>
<td>Weakness, Fatigue, Muscle cramps</td>
<td>Seizures</td>
</tr>
<tr>
<td>Memory difficulties.</td>
<td>Coma</td>
</tr>
<tr>
<td></td>
<td>Respiratory collapse, Death.</td>
</tr>
</tbody>
</table>

When hyponatremia develops over a longer period, neurologic complications may not occur.
Lab findings

• Hyponatremia
  – Mild (130-134 mEq/L)
  – Moderate (125-129 mEq/L)
  – Severe (<125 mEq/L)

• Increased urine osmolality
  – >100 mOsm/kg in the context of euvolemic hyponatremia)
## TREATMENT

<table>
<thead>
<tr>
<th>Symptomatic hyponatremia developing within 48 hours</th>
<th>Chronic hyponatremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goal: ↑ S. Na 1-2 mmol/L per hr ≤ 8-10 mmol/L in 1st 24 hrs</td>
<td>Goal: 0.5-1 mmol/L per hr</td>
</tr>
<tr>
<td>If Rapidly corrected</td>
<td></td>
</tr>
<tr>
<td>↓ water egress</td>
<td></td>
</tr>
<tr>
<td>↓ brain dehydration</td>
<td></td>
</tr>
<tr>
<td>↓ central pontine and extrapontine myelinolysis,</td>
<td></td>
</tr>
<tr>
<td>C/F : Lethargy, Dysarthria, Spastic quadriparesis, Pseudobulbar palsy</td>
<td></td>
</tr>
</tbody>
</table>

29/10/2013 Paraneoplastic syndromes
TREATMENT

• Optimal therapy ➔ treatment of the underlying tumor

• Short term ➔ fluid restriction (usually <1L/day, depending on
  – S. Na
  – urinary excretion
TREATMENT

IV fluids
1. Normal (0.9%) saline - osmolality of 308 mOsm/kg.
   ↓
   If the urine osmolality > 308 mOsm/kg
   ↓
   Retention of free water
   ↓
   ↓ ↓ serum sodium level

2. Hypertonic (3%) saline - osmolality of 1026 mOsm/kg
   <1-2 mL/kg/h
   Problems:  Central venous access
              Risk of overly rapid correction.

Diet- Adequate protein and sodium intake
TREATMENT

DRUG TREATMENT

1. **Demeclocycline** 300-600 mg orally twice daily
   - Mechanism of action: Interferes with the renal response to ADH

   • Adverse effects
     - Nausea
     - Anorexia
     - Diarrhea
     - Renal toxicity (especially in the presence of baseline renal impairment).
     - Diabetes insipidus (on prolonged use)
     - Superinfection (on prolonged use)
2. **Vasopressin receptor antagonists**
   - After fluid restriction fails
   - Hospital setting
   - Frequent monitoring of S. Na

**Mechanism of action:**

- **Vasopressin or ADH has three receptors**
  - V1a & V1b (vasoconstriction & ACTH release).
  - V2 (Antidiuretic response)

- **Vasopressin receptor antagonists** ➔ *selective water diuresis without interfering with sodium and potassium excretion*
• Vasopressin receptor antagonists -potential benefits:
  – patients can undergo chemotherapy with platinum-based regimens without concerns for further hyponatremia
  – in patients who will not be treated with chemotherapy, these agents may reduce the risks and mitigate the symptoms associated with hyponatremia.
• Three vasopressin antagonists (conivaptan, tolvaptan, mozavaptan) introduced into clinical practice and others (e.g., lixivaptan, satavaptan) have undergone clinical testing
## TREATMENT

<table>
<thead>
<tr>
<th>Conivaptan</th>
<th>Tolvaptan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasopressin V1A- and V2-receptor antagonist</td>
<td>Oral vasopressin V2-receptor antagonist</td>
</tr>
<tr>
<td>euvolemic or hypervolemic hyponatremia</td>
<td></td>
</tr>
<tr>
<td>Dose: 20-40 mg/d IV</td>
<td>Dose: 10-60 mg/d orally</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Adverse effects</td>
</tr>
<tr>
<td>Infusion site reactions</td>
<td>Dry mouth</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>Thirst</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Constipation</td>
</tr>
</tbody>
</table>

29/10/2013

Paraneoplastic syndromes
Cushing's Syndrome Caused by Ectopic ACTH Production

Cushing syndrome $\rightarrow$ 5% to 10% paraneoplastic.

(hypercortisolism) $\downarrow$

50% to 60% neuroendocrine lung tumors (small cell lung Ca & bronchial carcinoids)

• Often present with symptoms of paraneoplastic Cushing syndrome before diagnosis of cancer.
• Relapse of paraneoplastic Cushing syndrome $\rightarrow$ tumor recurrence
## Associated cancers

<table>
<thead>
<tr>
<th>Small cell lung cancer,</th>
<th>Bronchial carcinoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thymoma</td>
<td>Medullary thyroid cancer</td>
</tr>
<tr>
<td>GI</td>
<td>Pancreatic</td>
</tr>
<tr>
<td>Adrenal</td>
<td>Ovarian</td>
</tr>
</tbody>
</table>
Pathophysiology

ACTH

CRH

ADRENAL ➔ Cortisol ↑
<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Lab Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Weight gain with centripetal fat distribution less common in paraneoplastic Cushing syndrome</td>
<td>• Baseline S. cortisol &gt; 29 μg/dL</td>
</tr>
<tr>
<td>• Hypertension</td>
<td>• Urinary free cortisol &gt; 47 μg/24 h</td>
</tr>
<tr>
<td>• Hypokalemia</td>
<td>• Midnight S. ACTH &gt; 100 ng/L</td>
</tr>
<tr>
<td>• Muscle weakness</td>
<td>• Hypokalemia &lt; 3.0 mmol/L</td>
</tr>
<tr>
<td>• Generalized edema</td>
<td>• High-dose dexamethasone</td>
</tr>
<tr>
<td></td>
<td>➢ not suppressed (Vs suppressed for pituitary source)</td>
</tr>
<tr>
<td></td>
<td>➢ urine 17-hydroxycorticosteroid (suppressed &lt; 50%)</td>
</tr>
<tr>
<td></td>
<td>• Imaging studies to locate the primary tumor</td>
</tr>
<tr>
<td></td>
<td>➢ CT</td>
</tr>
<tr>
<td></td>
<td>➢ magnetic resonance imaging</td>
</tr>
<tr>
<td></td>
<td>➢ somatostatin receptor scintigraphy (ie, octreotide scan)</td>
</tr>
</tbody>
</table>

29/10/2013
Paraneoplastic syndromes
TREATMENT

• Underlying cause

• Drugs:

  1. Steroid production inhibitors

     - Ketoconazole (600-1200 mg/d orally) - best tolerated
     - Adverse effects: nausea and hepatotoxicity
     - Mitotane (0.5-8 g/d orally)
     - Metyrapone (~1.0 g/d orally)
     - Aminoglucotethimide (0.5-2 g/d orally)

  2. Antihypertensive agents and diuretics

     - Monitor S. K⁺
3. Other drugs (Less common)

- Octreotide (600-1500 μg/d SC) - blocks ACTH release
- Etomidate (0.3 mg/kg/h IV) — inhibits steroid synthesis
- Mifepristone (10-20 mg/kg/d orally) - binds competitively to the glucocorticoid receptor
  - Off label use

4. B/L Adrenalectomy - when medical management fails
Hypoglycemia

IGF-II
Hypoglycemia

Tumour associated hypoglycemia

Islet cell

Non Islet cell

Recurrent/ constant hypoglycemia

Elderly, Advanced cancer

Blood glucose as low as 20 mg/dl

Occasionally hypoglycemia precedes underlying tumour

29/10/2013
Pathophysiology (Non Islet cell tumour)

Tumour production of

IGF 2 — Insulin

<table>
<thead>
<tr>
<th>Diagnosis</th>
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</tr>
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<tbody>
<tr>
<td>↓ Blood glucose</td>
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</tr>
<tr>
<td>↓ Insulin (&lt;1.44-3.6 μIU/mL)</td>
<td>↑ Insulin</td>
</tr>
<tr>
<td>↓ C peptide (&lt;0.3 ng/mL)</td>
<td>↑ C peptide</td>
</tr>
<tr>
<td>↑ IGF2: IGF1 ratio (&gt;10.1)</td>
<td>Normal IGF2: IGF1 ratio</td>
</tr>
</tbody>
</table>
### ASSOCIATED CANCERS

- Mesothelioma
- Sarcomas
- Lung
- GI

### CLINICAL FEATURES

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Paraneoplastic Syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweating</td>
<td>Tremors</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Palpitations</td>
</tr>
<tr>
<td>Hunger</td>
<td>Weakness</td>
</tr>
<tr>
<td>Seizures</td>
<td>Confusion</td>
</tr>
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<td>Coma</td>
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Pathophysiology (Non Islet cell tumour)

Tumour production of

IGF 2 \rightarrow Insulin

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<tr>
<td>Normal IGF2: IGF1 ratio</td>
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</tbody>
</table>
TREATMENT

 Treat underlying tumour, resect if possible

 Not possible

 Maintain blood glucose level

 Acute ↓ Bld Glc

 Recurrent/ Chronic

 1 amp IV 50% dextrose (25g dextrose/50ml)-immediate effect

 Oral glucose- effect in 15-30 mins

 Corticosteroids
 - Dexamethasone (4 mg 2 or 3 times daily)
 - Prednisone (10-15 mg/d)

 Growth hormone (2 U/d SC often with corticosteroids)

 Diazoxide (3-8 mg/kg/d orally divided in 2-3 doses)
 - inhibits insulin secretion
 - used in islet cell tumour hypoglycemia
 - Hypoglycemia - hyperinsulinism due to extrapancreatic malignancy

 Octreotide (~50-1500 µg/d SC)
 - sometimes worsening of hypoglycemia - give a test dose

 Glucagon infusion (0.06-0.3 mg/h IV)
 - requires adequate hepatic glycogen stores- test with 1 mg IV glucagon challenge

 29/10/2013

 Paraneoplastic syndromes
Human Chorionic Gonadotropin

- Associated with
  - Testicular embryonal tumors
  - Germ cell tumors
  - Extragonadal germinomas
  - Lung cancer
  - Hepatoma
  - Pancreatic islet tumors
Pathophysiology

Males - ↑hCG
   ↓ Testicular Leydig cells
   ↓ Steroidogenesis &
   ↓ aromatase activity
   ↓ ↑ estrogen
   ↓ Gynecomastia

Females - asymptomatic
Investigations

- Serum hCG - (normal 0-5 mU/ml in male/non pregnant)
TREATMENT

• Treat underlying malignancy
ONCOGENIC OSTEOMALACIA

Associated with

• Benign mesenchymal tumors
  - Hemangiopericytomas
  - Fibromas
  - Giant cell tumors

• Sarcomas
• Prostate cancer
• Lung cancer
Pathophysiology

• Fibroblast growth factor 23 (FGF23) (phosphaturic factor)

• ↓ renal tubular reabsorption of phosphate

• renal conversion of 25-OH vit D $\rightarrow$ 1,25-dihydroxyvitamin D

• ↓ S.Pi

• Renal phosphate wasting

• Muscle weakness

• Bone pain

• Osteomalacia

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FGF23
LABORATORY FINDINGS

- Normal S. Ca, PTH
- ↓ 1,25 dihydroxyvit D

Imaging – Octreotide scan

TREATMENT

- Removal of tumour
- Phosphate & Vit D supplementation
- Octreotide- useful in tumors expressing somatostatin receptor subtype 2.
Thank You