CAGPO 2012

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Metabolic Complications of Cancer: *Hypercalcemia and Hyponatremia*

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Medical Oncologist, Bioethicist
Conflicts of Interest

• None

• All of my conflicts are *internal*…..
Case: Mrs. HC

• **ID:** 75 year old female living alone with no significant past medical history

• **EC:** brought to ER by paramedics after neighbor called b/c she was found in her apartment unresponsive

• No collateral history
Examination

- Fluctuating level of consciousness
- Vitals normal, no fever
- Dehydrated
- Coarse upper airway sounds
- No other pertinent findings
Investigations

• CBC normal

• Mildly elevated BUN and Cr

• Normal LFTs

• Standard electrolytes normal
• Concern of pneumonia

• Chest x-ray ordered......
What do you see?

Multiple Pulmonary Metastasis: “Cannon Ball Lesions”

Calcium checked: 4.5
Objectives: Hypercalcemia of Malignancy

- Clinical Manifestations
- Diagnosis
- Etiology
- Treatment
Symptoms

- Usually nonspecific
- Many times patients present with very high calcium level
- Most research done in hyperparathyroidism
Gastrointestinal: GROANS

• Constipation is most common*
  – Exacerbated or confused with narcotic effects
  – Related to decreased smooth muscle tone/autonomic dysfunction

• Anorexia

• Vague abdominal pain

• Rarely can lead to pancreatitis

Renal Dysfunction: STONES

• Nephrolithiasis
  – More common in hyperparathyroidism

• Nephrogenic diabetes insipidus
  – Defect in concentrating ability
  – Polyuria and polydipsia

• Chronic renal failure
  – Longstanding high calcium
  • Calcification, degeneration, and necrosis of tubules
Neuropsychiatric: MOANS

- Anxiety
- Depression
- Cognitive dysfunction
  - Delerium
  - Psychosis
  - Hallucinations
  - Somnolence
  - Coma

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Cardiovascular

- Short QT interval*
- Supraventricular arrhythmias
- Ventricular arrhythmias

Physical Findings

- Usually not specific
- Dehydration secondary to diuresis caused by the hypercalcemia
- Corneal deposition of calcium
  - “band keratopathy” on slit lamp exam

*Findings related to the underlying malignancy*
Epidemiology

• Occurs in about 10 to 20% of patients with cancer

• Both solid and liquid tumors

• Most common
  – Breast
  – Lung
  – Multiple myeloma
Pathogenesis

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Three mechanisms

• Osteolytic bone metastases with local cytokine release

• Tumor secretion of parathyroid hormone-related protein (PTHrP)

• Tumor production of calcitriol
Osteolytic Metastases
• Most common
  – Breast cancer and Non-small cell lung cancer

• Cytokines released
  – Tumor necrosis factor
  – Interleukin-1
  – Stimulate osteoclast precursor differentiation into mature osteoclasts
    • Leading to more bone breakdown and release of calcium
PTH-Related Protein

- Most common in patients with non-metastatic tumors
- Called humoral hypercalcemia of malignancy
- Secretion of PTH itself is a rare event
- PTHrP binds to same receptor as PTH and stimulates adenylate cyclase activity
  - Increased bone resorption
  - Increases kidney calcium reabsorption and phosphate excretion
Calcitriol

• Promotes absorption of calcium in intestines and retention in kidneys

• Hodgkin’s disease (mechanism in majority)

• Non-Hodgkin’s (mechanism in 1/3)

• Usually responds to glucocorticoid therapy
Diagnosis: Hypercalcemia of Malignancy
• Clinical symptomology with
  – History of cancer
  – Risk factors for cancer
  – Suppressed PTH
• Some centers can test for PTHrP to confirm Dx of humoral hypercalcemia
• High PTHrP may predict response to pamidronate*
  – Less of a response

* Gurney, H, Grill, V, Martin, TJ. Parathyroid hormone related protein and response to pamidronate in tumour induced hypercalcemia. Lancet 1993; 341:1611.
• Malignancy must be ruled out in patients that present with a very high calcium and no other obvious cause
Aims of Treatment

• Lower serum calcium concentration

• Treat complications if present

• Treat underlying disease
Volume

• Large volume of normal saline administration

• Expands intravascular volume

• Increases calcium excretion
  – Inhibition of proximal tubule and loop reabsorption
  – Reduces passive reabsorption of calcium

• Follow fluid status b/c of danger of fluid overload

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Inhibition of Bone Resorption

• Three therapies
  – Calcitonin
  – *Bisphosphonates*
  – Gallium nitrate

• Historical therapy
  – Antitumor antibiotic plicamycin (mithramycin)
    • Multiple serious side effects
      – myelosuppresion
    • No longer manufactured
Calcitonin

- Salmon calcitonin
- Increases renal excretion of calcium
- Decreases bone reabsorption by interfering with osteoclast maturation
- Weak agent: less decrease in Ca$^{2+}$
- Works the fastest
  - I.M., SubQ, Intranasal spray (200 units)
Bisphosphonates

- Adsorb to the surface of bone hydroxyapatite
- Interfere with osteoclast activity
- Cytotoxic to osteoclasts
- Inhibit calcium release from bone
  - More potent than calcitonin
- Three commonly used
  - Pamidronate
  - Zoledronic acid
  - Etidronate (1st generation, weaker)
Prophylactic Bisphosphonates

• Pamidronate use in patients with known lytic lesions*
  – Less episodes of hypercalcemia
  – Less pathologic fractures
  – Less pain
  – Less spinal cord compression
  – Less need for radiation or surgery

* Hortobagyi, GN, Theriault, RL, Porter, L, et al for the Protocol 19
Aredia Breast Cancer Study Group. Efficacy of pamidronate in
reducing skeletal complications in patients with breast cancer and lytic
What tumor lytic lesions do we give bisphosphonates to as prophylaxis?

- Breast
- Prostate
- Multiple Myeloma
Bisphosphonates: What do you watch for in the long run?

- Renal toxicity
  - Nephrotic syndrome and Renal insufficiency
  - ASCO guidelines: check renal function before each dose

- Hypocalcemia
  - Zoledronic acid patients need Calcium and Vit D supplementation

- Osteonecrosis of the jaw
ONJ: Well known complication of long term bisphosphonate use*

- Usually presents as infection and necrosis of the jaw
- More common in mandible than maxilla
- Linked to long term bisphosphonate use
- Pathogenesis unknown
  - Possibly related to antiangiogenic activity of drug interfering with blood supply to jaw
- More education needed in recognition

DENOSUMAB

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• a fully humanized monoclonal antibody that binds to the RANK ligand, a key factor in the pathway for osteoclast formation and activation

Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study

Karim Fizazi, Michael Carducci, Matthew Smith, Ronaldo Damião, Janet Brown, Lawrence Karsh, Piotr Milecki, Neal Shore, Michael Rader, Huei Wang, Qi Jiang, Sylvia Tadros, Roger Dansey, Carsten Goessl

Summary
Background Bone metastases are a major burden in men with advanced prostate cancer. We compared denosumab, a human monoclonal antibody against RANKL, with zoledronic acid for prevention of skeletal-related events in men with bone metastases from castration-resistant prostate cancer.

Lancet 2011; 377: 813-22
Published Online
February 25, 2011
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Dialysis

- Last resort

- Dialysis fluid with little or no calcium is effective

- Useful when patients can’t tolerate large volume resuscitation

- If calcium needs to be corrected emergently
Hypercalcemia Recommendations

• Volume expansion
• Salmon calcitonin (if very symptomatic)
• IV zoledronic acid or pamidronate
  – Ongoing q monthly depending on malignancy
  – *Follow for complications*
• Close follow up of calcium level and symptoms
• *Treat underlying malignancy*
### Table 2. Pharmacologic Therapy for Hypercalcemia Associated with Cancer.*

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Dose</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydration or calciuresis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous saline</td>
<td>200–500 ml/hr, depending on the cardiovascular and renal status of the patient</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Furosemide</td>
<td>20–40 mg intravenously, after rehydration has been achieved</td>
<td>Dehydration, hypokalemia</td>
</tr>
<tr>
<td>Phosphate repletion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral phosphorus (if serum phosphorus ≤3.0 mg/dl)†</td>
<td>For example, 250 mg Neutraflous orally, four times daily until serum phosphorus level &gt;3.0 mg/dl or until serum creatinine level increases</td>
<td>Renal failure, hypocalcemia, seizures, abnormalities of cardiac conduction, diarrhea</td>
</tr>
<tr>
<td>First-line medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous bisphosphonates‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pamidronate</td>
<td>60–90 mg intravenously over a 2-hr period in a solution of 50–200 ml of saline or 5% dextrose in water§</td>
<td>Renal failure, transient flu-like syndrome with aches, chills, and fever</td>
</tr>
<tr>
<td>Zoledronate</td>
<td>4 mg intravenously over a 15-min period in a solution of 50 ml of saline or 5% dextrose in water</td>
<td>Renal failure, transient flu-like syndrome with aches, chills, and fever</td>
</tr>
<tr>
<td>Second-line medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucocorticoids¶</td>
<td>For example, prednisone, 60 mg orally daily for 10 days</td>
<td>Potential interference with chemotherapy, hypokalemia, hyperglycemia, hypertension, Cushing’s syndrome, immunosuppression</td>
</tr>
<tr>
<td>Mithramycin</td>
<td>A single dose of 25 µg/kg of body weight over a 4-to-6-hour period in saline</td>
<td>Thrombocytopenia, platelet-aggregation defect, anemia, leukopenia, hepatitis, renal failure‖</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>4–8 IU per kilogram subcutaneously or intramuscularly every 12 hr</td>
<td>Flushing, nausea</td>
</tr>
<tr>
<td>Gallium nitrate</td>
<td>100–200 mg/m² of body-surface area intravenously given continuously over a 24-hr period for five days</td>
<td>Renal failure</td>
</tr>
</tbody>
</table>

Hyponatremia: SIADH

The Syndrome of Inappropriate Antidiuretic Hormone (ADH) Secretion
Hyponatremia

- Definition: a serum sodium concentration below 135 meq/L
- Huge differential diagnosis
- Two classification systems with low serum osmolality
  - Stratified based on levels of ADH
  - Stratified based on volume status
    - Hypovolemia
    - Euvolemia
    - Hypervolemia
SIADH Objectives

- Clinical Manifestations
- Pathophysiology
- Etiology/Diagnosis
- Treatment
Case

• 72 year old male with history of a recent fall is diagnosed with a new lung mass and mediastinal lymphadenopathy in your out patient practice

• Referred to Thoracic Surgeon

• Mediastinal node biopsy done…….
Small cell Lung Cancer

Na\(^+\): 124 meq/L
Clinical Manifestations

• Related to underlying disease and etiology

• Spectrum of CNS disturbances
  – Subtle changes in neurologic status
  – Lethargy, forgetfulness, confusion
  – Gait disturbance: *Increased risk of falls*
  – Delirium and psychosis
  – Seizures
Pathophysiology SIADH

- ADH: arginine vasopressin
- Secreted by the hypothalamus
- Normal triggers: serum osmolality, volume, and vascular pressure changes
- Increases the permeability of the collecting duct to water and urea
- Hyponatremia results from ADH-induced retention of ingested water
• Solute (eg. Na\(^+\)) handling of kidney intact

• No abnormality in volume regulating system related to the renin-angiotensin-aldosterone system or atrial natriuretic peptide
Pathogenesis

• Hyponatremia starts with ADH induced water retention

• Volume expansion = 2° natriuretic mechanisms that result in Na\(^+\) and water loss = restoration of near euvolemia (unless 2° issue with salt loss eg, vomiting, diarrhea)

• Hyponatremia, hypoosmolality, urine osmolality above 100 mosmol/kg, and urine [Na\(^+\)] > 40 meq/L, normal acid-base status
# Etiology of SIADH

## Table 1. Causes of the Syndrome of Inappropriate Antidiuresis (SIADH). *

<table>
<thead>
<tr>
<th>Malignant Diseases</th>
<th>Pulmonary Disorders</th>
<th>Disorders of the Central Nervous System</th>
<th>Other Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma</td>
<td>Infections</td>
<td>Infection</td>
<td>Hereditary</td>
</tr>
<tr>
<td>Lung</td>
<td>Bacterial pneumonia</td>
<td>Encephalitis</td>
<td>(gain-of-function mutations in the vaso-pressin V₂ receptor)</td>
</tr>
<tr>
<td>Small-cell</td>
<td>Viral pneumonia</td>
<td>Meningitis</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>Pulmonary abscess</td>
<td>Brain abscess</td>
<td>Transient</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>Tuberculosis</td>
<td>Rocky Mountain spotted fever</td>
<td>Endurance</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>Aspergillosis</td>
<td>AIDS</td>
<td>exercise</td>
</tr>
<tr>
<td>Stomach</td>
<td>Asthma</td>
<td>Bleeding and masses</td>
<td>General</td>
</tr>
<tr>
<td>Duodenum</td>
<td>Cystic fibrosis</td>
<td>Subdural hematoma</td>
<td>anesthesia</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Respiratory failure</td>
<td>Subarachnoid hemorrhage</td>
<td>Nausea</td>
</tr>
<tr>
<td>Genitourinary tract</td>
<td>associated with positive-</td>
<td>Cerebrovascular accident</td>
<td>Pain</td>
</tr>
<tr>
<td>Ureter</td>
<td>pressure breathing</td>
<td>Brain tumors</td>
<td>Stress</td>
</tr>
<tr>
<td>Bladder</td>
<td></td>
<td>Head trauma</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td></td>
<td>Hydrocephalus</td>
<td></td>
</tr>
<tr>
<td>Endometrium</td>
<td></td>
<td>Cavernous sinus thrombosis</td>
<td></td>
</tr>
<tr>
<td>Endocrine thymoma</td>
<td></td>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Lymphomas</td>
<td></td>
<td>Multiple sclerosis</td>
<td></td>
</tr>
<tr>
<td>Sarcomas</td>
<td></td>
<td>Guillian–Barré syndrome</td>
<td></td>
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<tr>
<td>Ewing’s sarcoma</td>
<td></td>
<td>Shy–Drager syndrome</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Delirium tremens</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute intermittent porphyria</td>
<td></td>
</tr>
</tbody>
</table>

### Drugs
- Drugs that stimulate release of AVP or enhance its action
  - Chlorpropane
  - SSRI
  - Tricyclic antidepressants
  - Clofibrate (Atromid-S, Wyeth–Ayerst)
  - Carbamazepine (Epitol, Lemmon, Tegretol, Ciba–Geigy)
  - Vincristine ( Oncovin, Lilly, Vincasar, Pharmacia and Upjohn)

### Other Causes
- Hereditary (gain-of-function mutations in the vaso-pressin V₂ receptor)
- Idiopathic
- Transient
- Endurance exercise
- General anesthesia
- Nausea
- Pain
- Stress

---

* AIDS denotes the acquired immunodeficiency syndrome, AVP arginine vasopressin, SSRI selective serotonin-reuptake inhibitor, and MDMA 3,4-methylenedioxyamphetamine.

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Treatment of the Hyponatremia in SIADH

- *Treat the underlying disease*
  
  - **Our Case:** Ectopic secretion of ADH by a Stage 3 Small Cell Lung Cancer (SCLC)
  - Treatment: cisplatin/etoposide with concurrent radiotherapy
  - Stop cancer, Stop excess ADH
- Initial therapy to raise the serum sodium
- Maintenance therapy in patients with persistent SIADH
Rate of correction: KEY

• Maximum rate of correction of chronic hyponatremia should be LESS than 10 meq/L in 24 hours and less than 18 meq/L 48 hours.

• Risk of osmotic demyelination (usually irreversible) with about 6 day latency.

• Initial correction rate in an emergent situation (eg, seizures) can be 2 to 4 meq/L in the first 2-4 hours.
Happy Brain Coral

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Brain Edema from water shift into the brain 2° to the hyponatremia

“It hurts! My Pons hurts!!! Get those osmolytes out!”

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“Hey, I am a brain. I can adapt. This hyponatremia is not so bad. Look all of my fish friends are back!!! ”
“See that CRACKED area. That is where my Pons used to be….off to ICU for me…..and good luck losers… “

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Ode to my many days and nights as an internal medicine resident on call .......

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**Formulaic correction of Na⁺**

Table 4. Formulas for Calculating Initial Saline Infusion Rates.*

<table>
<thead>
<tr>
<th>Source</th>
<th>Step 1</th>
<th>Step 2</th>
<th>Example of Rate (ml/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional</td>
<td>Na required = TBW × ([Na]₂ - [Na]₁)</td>
<td>Volume (liter) = ( \frac{Na \text{ required (mmol)}}{513 \text{ mmol/liter}} )</td>
<td>82</td>
</tr>
<tr>
<td>Adrogue and Madias¹</td>
<td>( \Delta[Na]<em>s ) (with 1 liter) = ( \frac{[Na]</em>{\text{inf}} - [Na]_s}{TBW + 1} )</td>
<td>Volume (liter) = ( \frac{\text{Desired } \Delta[Na]_s}{\Delta[Na]_s \text{ (with 1 liter)}} )</td>
<td>107</td>
</tr>
<tr>
<td>Barsoum and Levine³</td>
<td>( \Delta[Na]<em>s = \frac{(V</em>{\text{inf}})[Na]<em>{\text{inf}} - (V_u)[E]</em>{\text{urine}} - (\Delta V)[Na]_s}{TBW + \Delta V} )</td>
<td>Volume (liter) = ( \frac{\text{Desired } \Delta[Na]_s}{\Delta[Na]_s \text{ (with 1 liter)}} )</td>
<td>107</td>
</tr>
<tr>
<td>Nguyen and Kurtz⁵</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Janicic and Verbalis⁹</td>
<td>Rate (ml/hr) is the goal rate of [Na]ₙ rise (mmol/liter/hr) per kg of body weight</td>
<td></td>
<td>70</td>
</tr>
</tbody>
</table>

* The examples assume a body weight of 70 kg, current serum sodium ([Na]₁) level of 110 mmol per liter, desired [Na]₂ level of 120 mmol per liter, total body water (TBW) of 42 liters, time of 10 hours, urinary volume of 1 liter, urinary sodium level of 80 mmol per liter, urinary potassium level of 40 mmol per liter, and treatment fluid (infusion) of 513 mmol per liter, where [Na]ₙ is the current [Na]ₙ and [Na]₂ represents the [Na]ₙ level desired after treatment, \( \Delta[Na]_s = [Na]_s - [Na]_s \); [E] is [Na] + [K]. If the actual rate of correction is different from that predicted, it may be useful to calculate the electrolyte-free water clearance, to help guide treatment. The electrolyte-free water clearance is calculated as

\[
C_{H₂O}^e = V \left( 1 - \frac{U_{Na} + U_K}{P_{Na}} \right),
\]

where \( C_{H₂O}^e \) denotes electrolyte-free water clearance, \( U_{Na} \) urinary sodium, \( U_K \) urinary potassium, and \( P_{Na} \) plasma sodium. If the clearance value is greater than 0, then ongoing losses of free water are contributing to the rise in [Na]₂. In all cases, the formulas are used only to estimate the initial infusion rate; the rate must be adjusted on the basis of the measured rate of the rise in serum sodium. Inf denotes infused fluid.

Emergent Situation

- 100 mL IV bolus of 3% saline (513 meq each of Na\(^+\) and Cl\(^-\))
- Will raise serum Na\(^+\) by 1.5 meq/L in men and 2.0 meq/L in women
- Rise in serum Na\(^+\) will pull water out of the brain and decrease cerebral edema
- Bolus can be repeated a second time
- Rapid increase of Na\(^+\) of 2 - 6 meq/L can reverse severe symptoms
Fluid Restriction

• Mainstay of therapy
• Goal intake of less than 800 mL/day
• Negative water balance will raise Na+ toward normal and with maintenance should keep it stable
• Can lead to volume depletion due to an actual existing “salt deficit”
• Compliance can be an issue
Oral Salt Tablets

• 3 grams tid (154 meq of Na\textsuperscript{+} and Cl\textsuperscript{-})

• All 308 meq will be excreted and water will follow

• Same NEJM formulas apply

• Less compliance issues
Salt plus a loop diuretic

• Effect of given Na\(^+\) can be increased
• A loop diuretic interferes with countercurrent concentration in the kidney and decreases NaCl reabsorption in the medullary aspect of the loop of Henle = increases water excretion and lowers urine osmolality
• Effective if urine 2X serum osmolality (urine above 500 mosmol/kg)
Salt plus a loop diuretic

• Potassium levels must be followed and some patients may need supplementation or the use of K+ - sparing diuretic (eg, amiloride)

• Dose: Furosemide 20 mg po bid
Vasopressin receptor antagonists: aquareisis

- Oral: tovaptan, satavaptan, lixivaptan
  - Selective for V2 receptor
- IV: conivaptan
  - Blocks V2 and V1a receptor
- Data supporting efficacy: “SALT trails”
- Limitations:
  - Thirst
  - Possible over correction
  - COST (single tolvaptan tablet: $300)
Demeclocycline or Lithium

• Act on collecting tubule cell to lessen responsiveness to ADH = increased water excretion

• Demeclocycline more predictable but can cause nephrotoxicity nausea, vomiting, and photosensitivity (difficult to acquire tablets now)

• Fallen out of favor

• Goal of 130 meq/L or higher can be achieved in almost all patients with fluid restriction, salt tabs +/- loop diuretic WITHOUT these drugs
Our case

- Patient has mild hyponatremia but still symptomatic (lethargy, forgetfullness, a fall)

- Treatment plan:
  - treat cancer
  - In interim: fluid restriction, salt tabs, and close monitoring
  - Can discontinue after cancer treatment done and patient felt to be disease free
Maintenance therapy

• 5 months later the patient’s SCLC recurs and it is resistant to chemotherapy
• Usual sequence still used…
• Fluid restriction
• Oral salt
• Reduce urine osmolality by increasing water excretion with a loop diuretic
Thank you. Questions?
PLEASE
DON'T THROW
YOUR CIGARETTE ENDS
ON THE FLOOR
THE COCKROACHES
ARE GETTING CANCER

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