Clinical Case Discussion

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CUSOM

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A 30-year-old woman with no regular medical care is brought to the emergency department via EMS with altered mental status.

Her family reports that the patient was in her usual state of health until about two weeks ago, when she complained of generalized fatigue and muscle aches. She also developed excessive urination.

One week ago, she went to a nearby urgent care center for evaluation. Her work up included negative screens for COVID, flu and RSV. In addition, a UA was negative for evidence of a UTI. She was diagnosed with a viral syndrome and instructed to rest, drink plenty of fluids and rest.

Her family reports that the patient did not feel like eating dinner and went to bed early last night. This morning, her family found the patient lethargic and moaning. The family immediately called EMS.

The patient's family reports her medical history as detailed next. In addition, the family cannot recall the patient complaining of fever, headache, chest pain, abdominal pain or difficulty breathing. In addition, the patient has had no sick contacts or recent travel.

PMH:

- G2P2, two uncomplicated vaginal deliveries at age 25 and 27
- Childhood asthma, no current treatment

Meds: None

PSurgHx: None

- Hospitalized x 2 for childbirth as outlined above
- No serious injuries
- Flu vaccine this year
- No recent COVID vaccine

NKDA

Social history: The patient is married and lives with her husband and two children. She does not work outside the home. She has never smoked. She drinks a glass of wine or beer on weekends. There is no history of drug use.

Family history:

- mother age 65, HTN, hypothyroidism
- father age 68, COPD
- 1 sister age 35, healthy
- 1 brother age 38, asthma
- 1 sister age 40, anxiety
- 1 son, age 3, healthy
- 1 daughter, age 5, healthy

Physical exam: The patient is a young woman who is unresponsive. She is agitated and moaning. She cannot cooperate for the exam
Vitals: bp: 95/70 p 116 RR 24 Temp 98.9F O2sat 93% on RA. FSBG 96 mg/dl

HEENT:	PERRL; eyes conjugate but with roving eye movements OP: dry mucous membranes; no exudate; tongue midline, dentition good
Neck:	full passive ROM; trachea midline; no adenopathy; no thyromegaly or thyroid masses
Car:	r/r/r, tachycardic, no murmur, rub or gallop
Lungs:	CTA B/L without wheezes, rales or rhonchi

Abdomen: nondistended, hypoactive bowel sounds, soft but the patient moans with palpation of all quadrants. No organomegaly.

Extremities: No edema, dp pulses 2+ B/L

Neuro:

CNs: Pupils as outlined above; face symmetric

Motor: withdraws to painful stimuli in all four extremities

Now what???

To correctly *diagnose* a patient, you must first correctly *summarize* a patient . . .

Synthesizing Clinical Data

- An example of one method:

"This is a case of (presenting symptoms and signs) in a (patient's age, gender) with a history significant for (relevant PMH/Soc hx/Fam hx).Physical examination is significant for (relevant positive and negative physical findings). Laboratory data are significant for (relevant positive and negative lab findings). EKG (when relevant) shows (relevant EKG findings). Imaging (when relevant) shows (relevant imaging studies and findings)."

Synthesizing Clinical Data

What we know so far . . .

This is a case of two weeks of worsening generalized fatigue, muscle aches and excessive urination, followed by 24 hours of worsening delirium in a 30-year-old woman, previously healthy, with family history of hypothyroidism Physical examination is significant for hypotension, tachycardia, mild tachypnea, no fever, unresponsiveness, roving eye movements, dry mucous membranes, no thyromegaly, regular rhythm, clear lungs, a soft abdomen with generalized tenderness, symmetric face, and equal withdrawal to pain in all four extremities.

An Approach to Differential Diagnosis: What broad categories apply to THIS patient?

V	Vascular
I	Infectious
N	Neoplastic
D	Drugs
I	Iatrogenic, Inflammatory
C	Collagen Vascular
A	Allergic, autoimmune
T	Trauma
E	Endocrine

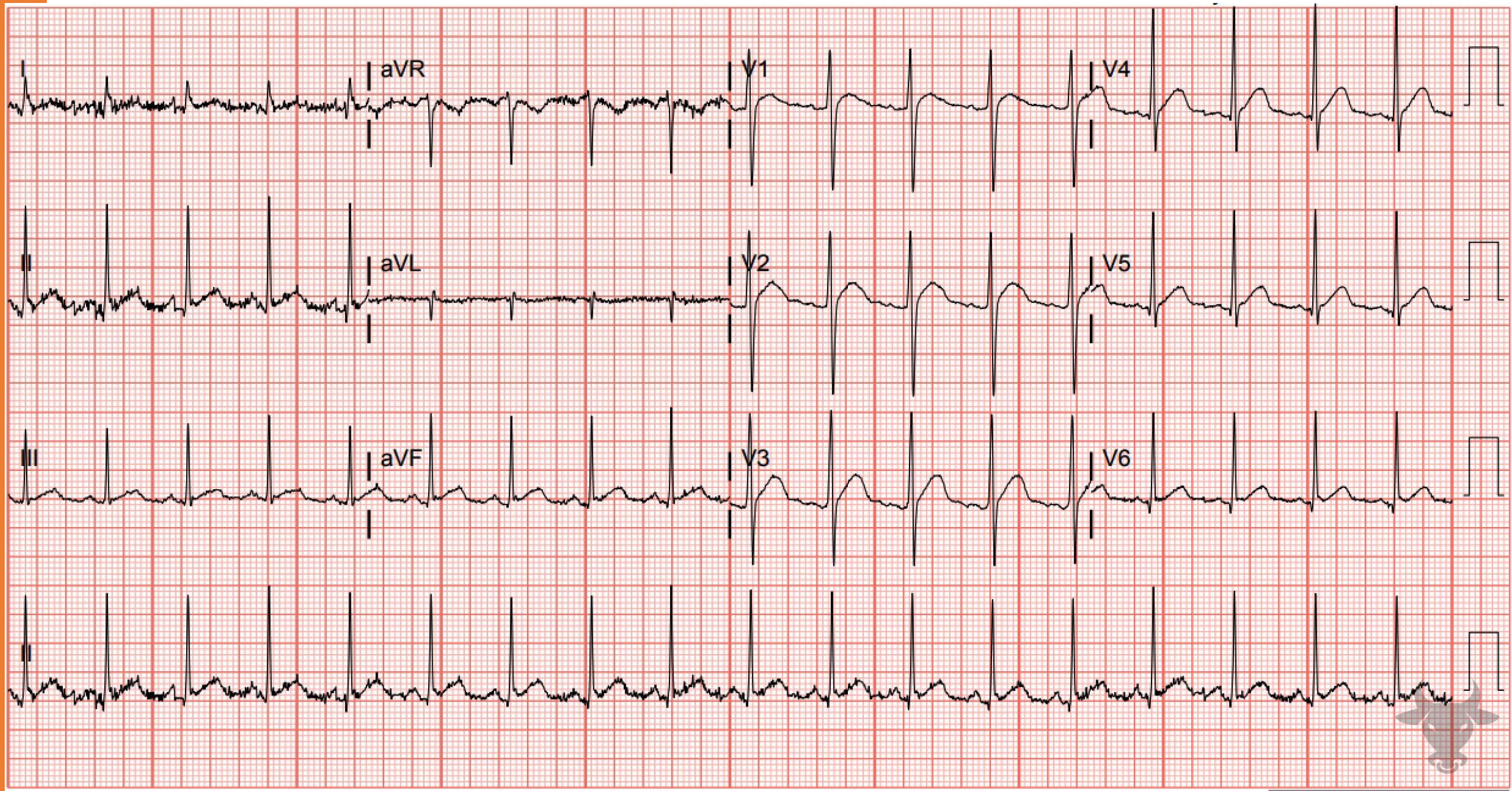
An Approach to Differential Diagnosis: Which specific diagnoses apply to THIS patinent?

V	Vascular	CVA, SAH, ACS
I	Infectious	Sepsis: CNS, Pneumonia, GU tract, intraabdominal
N	Neoplastic	Cancer: solid tumor, heme malignancy
D	Drugs	cocaine, amphetamines, opiates, other
C	Collagen Vascular	SLE
E	Endocrine	Thyrotoxicosis, myxedema, adrenal crisis, DKA, NKHS

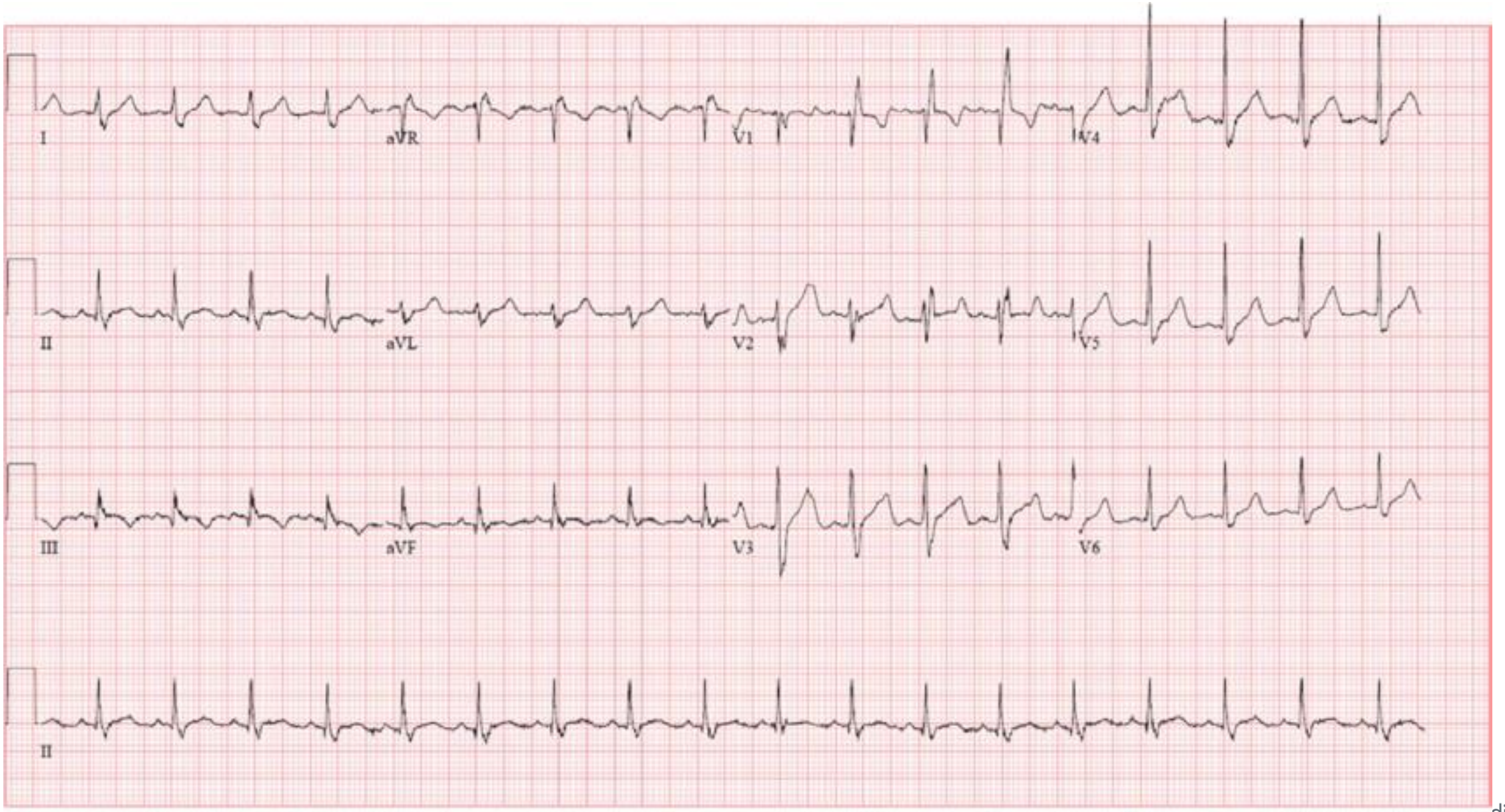
Now what???

She is tachycardic . . .

An EKG is performed . . .



Here is a normal EKG . . .



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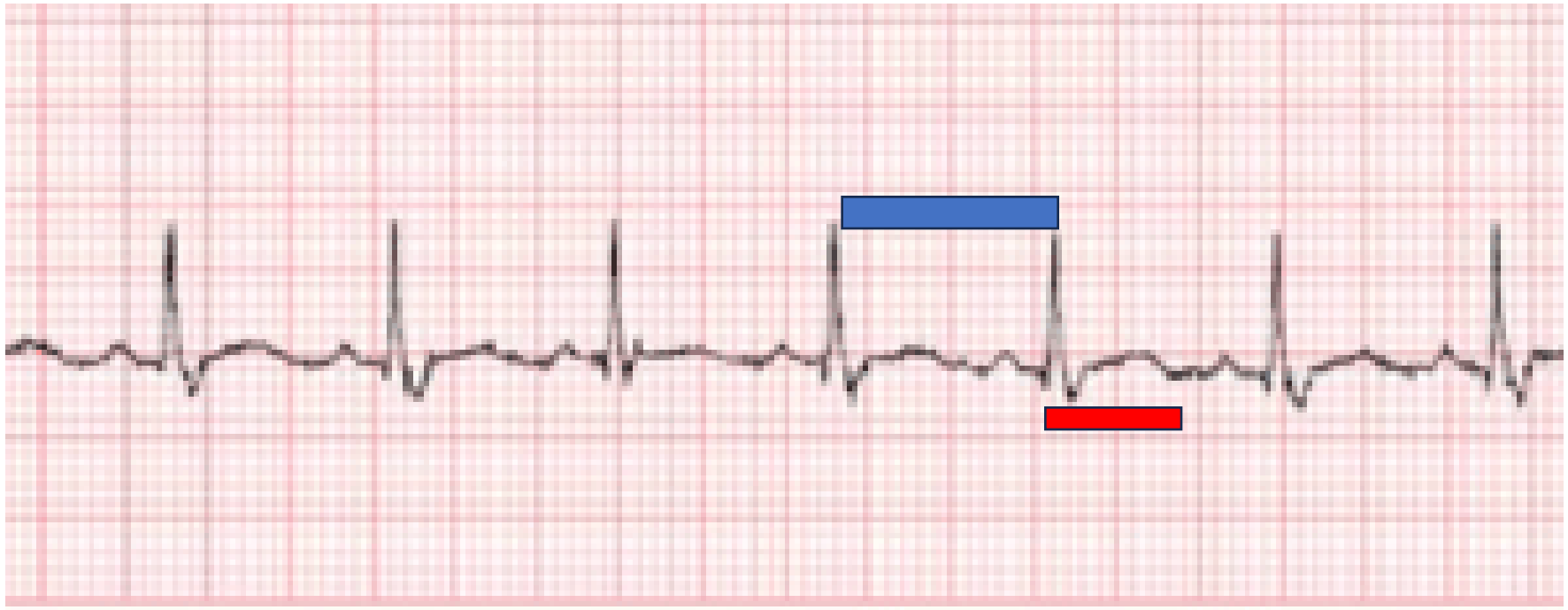
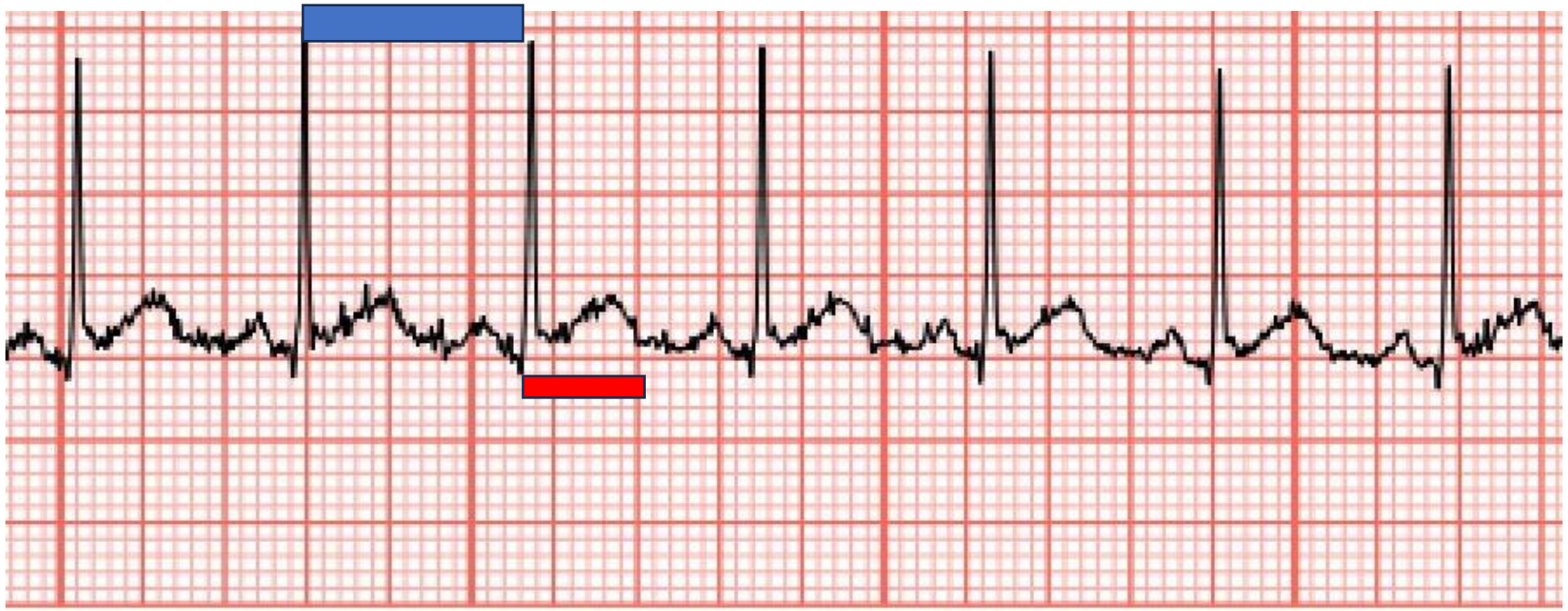
Normal QTc interval 360 to 460 msec in adult women



$$\text{QTc interval} = \frac{QT}{\sqrt{R\text{-}R}} = \frac{0.04 \times 8}{0.707} = 0.452 = 452 \text{ msec}$$

Our patient's QTc interval . . .



Short QTc interval

$$\text{QTc interval} = \frac{QT}{\sqrt{R\text{-}R}} = \frac{0.04 \times 6}{0.748} = 0.320 = 320 \text{ msec}$$

Now what???

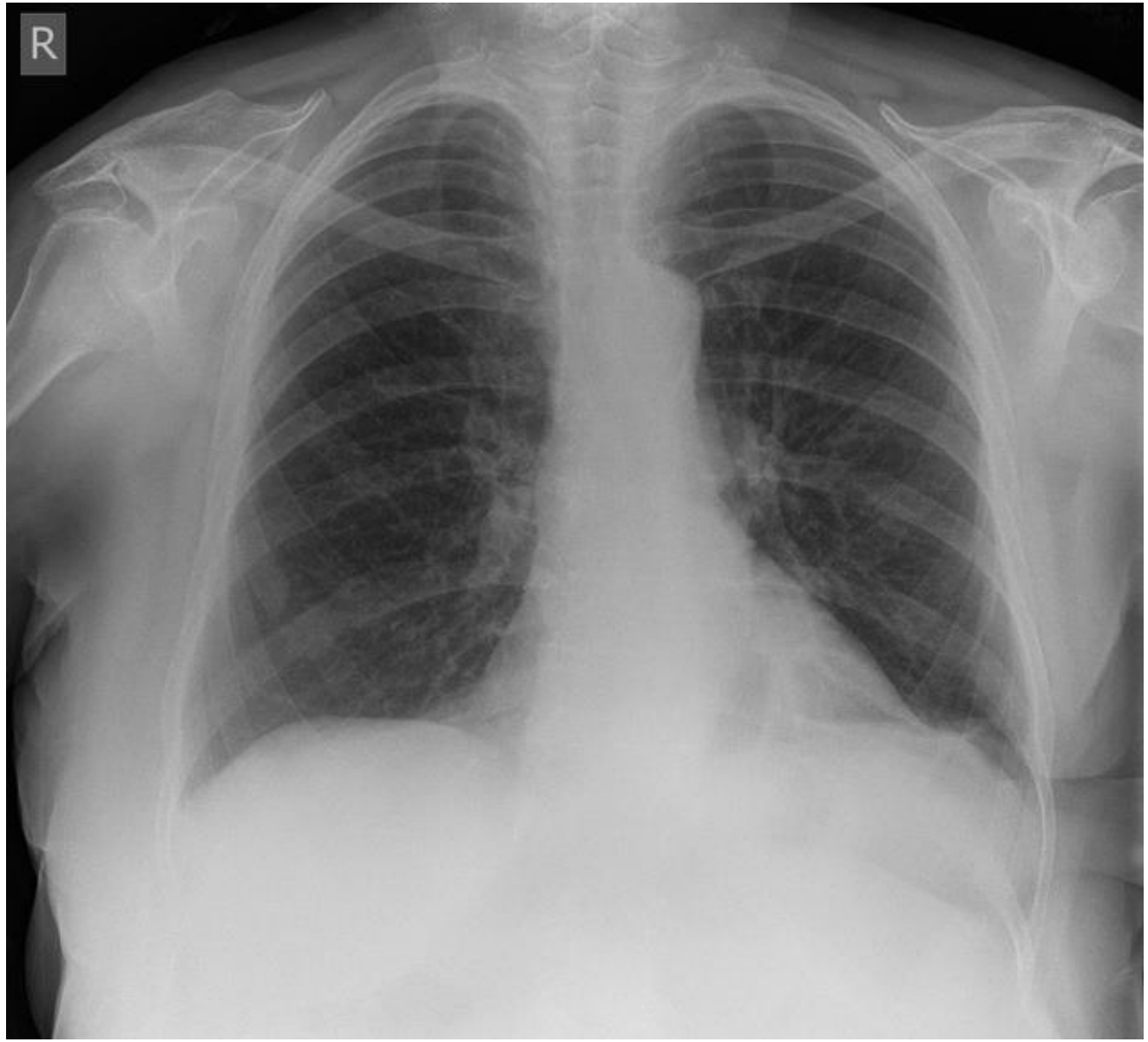
A Head CT is performed . . .

NORMAL.

Radiopaedia.com

A CXR is done . . .

- No infiltrate
- No edema
- No pleural effusion
- Normal heart size



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Now what???

Laboratory Data:

wbc	5.1
hgb	12
hct	36%
MCV	88
platelets	136,000

Na	134
K	4.2
CL	100
CO2	19
BUN	34
Cr	2.3
Glc	89
Ca	15.4

Laboratory Data:

wbc	5.1
hgb	12
hct	36%
MCV	88
platelets	136,000

Serum albumin 4.1, normal 3.5 to 5 g/dl

Na	134
K	4.2
CL	100
CO2	19
BUN	34
Cr	2.3
Glc	89
Ca	**15.4**

TSH 2.30 mIU/L (normal)

UA neg nitrites
neg leuk esterase
< 5 wbc
neg rbc
trace bacteria

Blood cultures pending

ESR 96 mm/hr (normal < 20 mm/hr)

Which processes cause an elevated ESR?

- Chronic infection
- Chronic inflammation
- Malignancy

Urine drug screen negative

Revise your summary with what we know now . . .

This is a case of two weeks of worsening generalized fatigue, muscle aches and excessive urination, followed by 24 hours of worsening delirium in a 30-year-old woman, previously healthy, with family history of hypothyroidism Physical examination is significant for hypotension, tachycardia, mild tachypnea, no fever, unresponsiveness, roving eye movements, dry mucous membranes, no thyromegaly, regular rhythm, clear lungs, a soft abdomen with generalized tenderness, symmetric face, and equal withdrawal to pain in all four extremities. Laboratory data are significant for normal CBC, elevated BUN/creatinine, severe hypercalcemia, normal albumin, negative UA, negative drug screen, normal TSH, elevated ESR. EKG shows a sinus tachycardia with a shortened QTc interval. CXR is negative for infiltrate, edema, pleural effusion or cardiomegaly. Head CT is normal.

Revise Your Differential Diagnosis In THIS Patient Based on What We Know:

V	Vascular	~~CVA, SAH, ACS~~
I	Infectious	Sepsis: CNS, ~~Pneumonia~~, ~~GU tract~~, intraabdominal
N	Neoplastic	Cancer: solid tumor, heme malignancy with hypercalcemia
D	Drugs	~~cocaine, amphetamines, opiates, other~~
C	Collagen Vascular	SLE
E	Endocrine	~~Thyrotoxicosis, myxedema, adrenal crisis, DKA, NKHS~~, hyperparathyroidism

Total calcium 15.4, normal 8.5 to 10.5 mg/dl. Serum albumin is normal, so no correction is needed.

What is the next step???

Parathyroid hormone level = < 5 ng/L

Normal parathyroid hormone level = 10 to 65 ng/L

Parathyroid level with concurrent hypercalcemia	Differential Diagnosis
Normal or high	~~Primary hyperparathyroidism~~
Low	Hypercalcemia of malignancy ~~Vitamin D toxicity~~

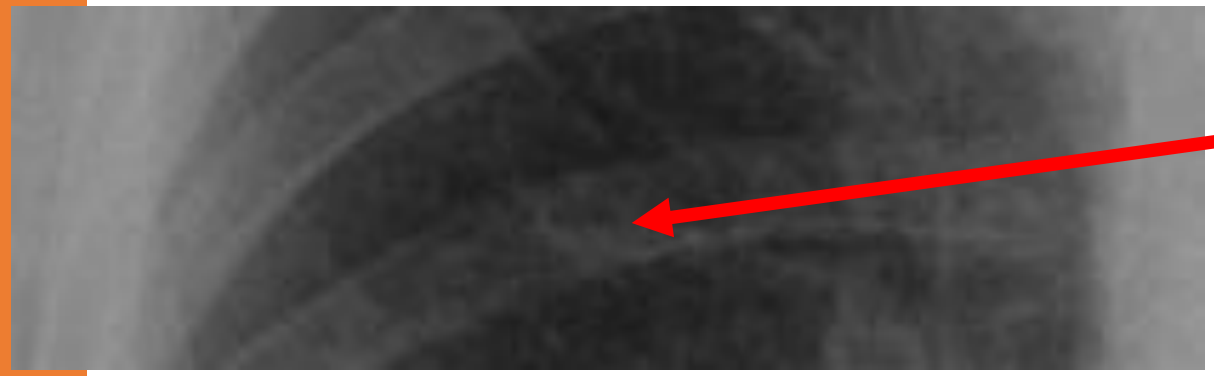
Cancers Associated with Hypercalcemia

- Prostate
- Breast
- Kidney
- Thyroid
- Multiple myeloma
- Lung
- Lymphoma
- Squamous cell carcinoma

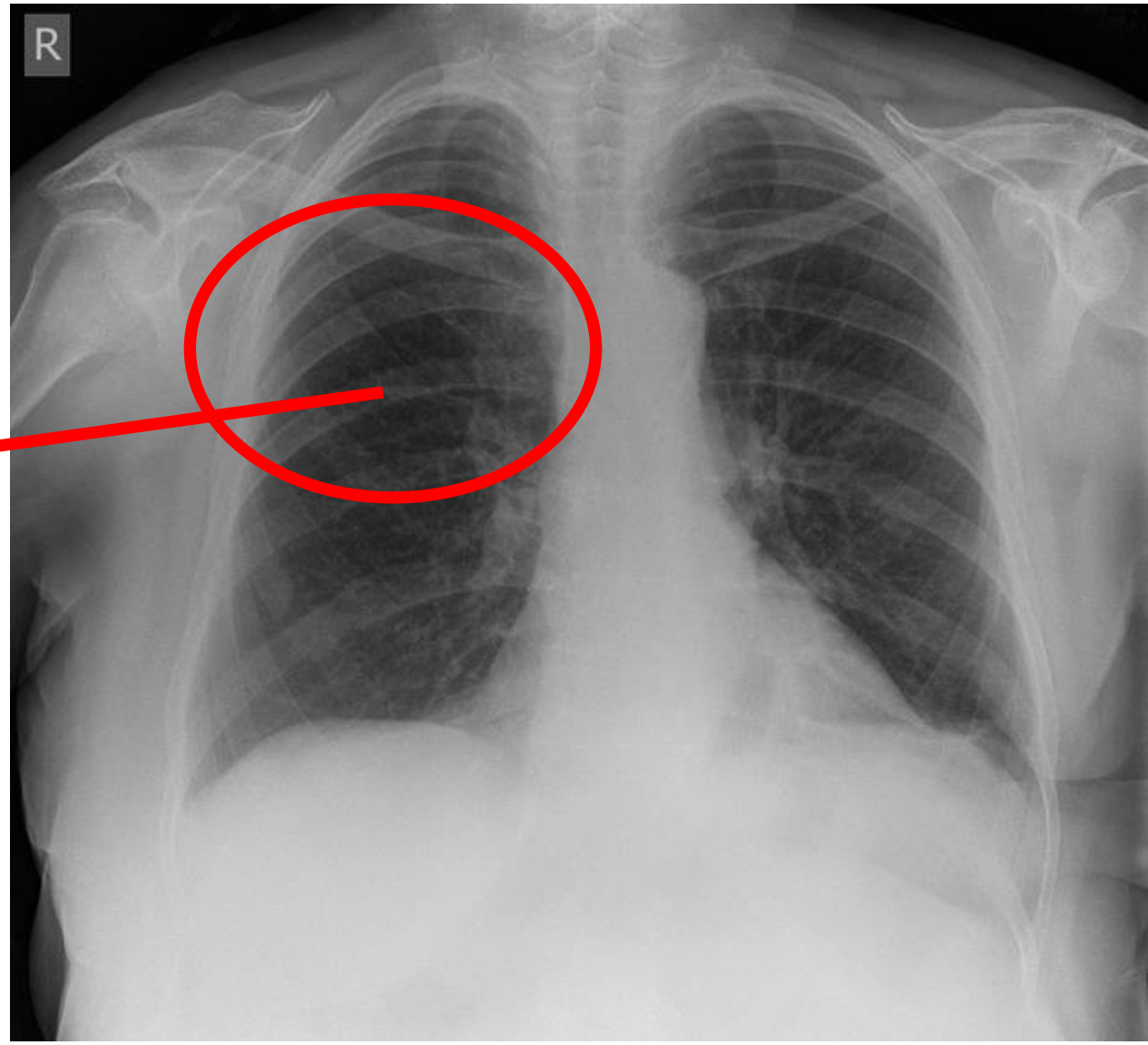
Horwitz, M, Up to Date 2024

Further examination of the patient reveals a 2 x 3 cm hard mass in the upper outer quadrant of the R breast. There is also a R axillary lymph node palpable which is mobile and measures 1 cm with firm consistency.

A CXR is officially read . . .



Osteolytic lesion anterior R 5th Rib



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Diagnosis: Delirium due to hypercalcemia of malignancy, suspected secondary to metastatic breast cancer.

She is admitted to the ICU for close monitoring.

She receives 2 liters of normal saline and a Foley catheter is placed.

Repeat vital signs: bp 102/76 p 90 RR 20 temp 98.6F O2 sat 94% on 2 L NC. She remains unresponsive but she is breathing comfortably with no respiratory distress.

She continues normal saline at 200 ml/hr and her UOP is about 100 ml/hr for the next six hours. . .

She receives calcitonin 4 mg/kg SQ q12 hours (70 kg weight) = 280 mg SQ q 12 hrs

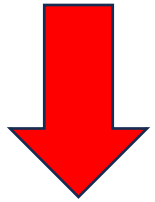
A 25-hydroxy vitamin D level is checked and is 30 (normal 25 to 65 pg/ml)

She also receives Zoledronic acid 4mg IV x 1 . . .

Repeat labs six hours later . . .

She continues to receive calcitonin 280 mg SQ q 12hrs x 4 doses total (ie. 48 hour course)

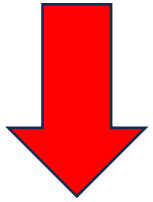
Na	138
K	3.7
CL	100
CO2	24
BUN	23
Cr	1.7
Glc	89
Ca	**14.6**



She continues NS at 150 ml/hr and monitoring in the ICU for the next three days. . .

On hospital day 4, she is more alert and can answer yes/no questions. Vitals remain stable.

Na	139
K	3.8
CL	99
CO2	24
BUN	18
Cr	1.3
Glc	89
Ca	**13.8**

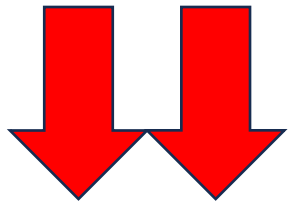


On hospital day 4, she is more alert and conversant. She is now tolerating a diet. Vital signs are stable. She is transferred to the floor and begins to work with PT.

On hospital day 7, she is feeling close to baseline. Her care team discusses her diagnosis with her and the suspicion for metastatic breast cancer and a treatment plan including inpatient consultation with hematology/oncology. Her care team also recommends a total body bone scan.

Labs done on hospital day 7 . . .

Na	136
K	3.7
CL	98
CO2	24
BUN	15
Cr	0.9
Glc	78
Ca	**12.2**

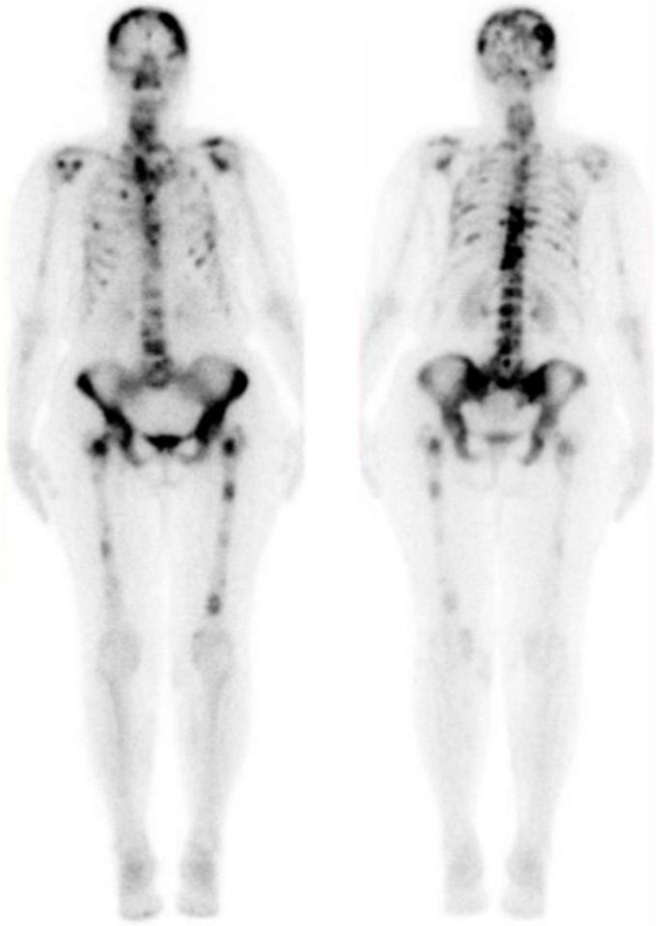


A total body bone scan is performed . . .

Normal Bone Scan

AFP, Volume 41, Issue 9, September 2012

Bone scan with osseous metastatic disease



Appl. Sci. **2020**, *10*(3), 997

What is a normal serum calcium???

- Normal total serum calcium = 9 to 10.5 mg/dl
- Normal ionized calcium = 4.65 to 5.25 mg/dl

Shane E, UpToDate 2024

Confirming Hypercalcemia

- Repeat total serum calcium
- About 40% of calcium is bound to albumin in serum
- Therefore, serum calcium will change according to changes in albumin
- If serum albumin is *low* then calcium must be *corrected*.
- Corrected calcium = serum calcium + 0.8 x (Normal albumin – Patient albumin), where normal albumin is 4 mg/dl
- Alternatively, ionized calcium may be measured directly

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Clinical Manifestations of Mild hypercalcemia (10.5 to < 12 mg/dl)

- Often asymptomatic
- Often found incidentally on routine blood chemistries

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Clinical Manifesations of Moderate Hypercalcemia (12 to 14 mg/dl)

- Polyuria
- Polydipsia
- Dehydration
- Anorexia
- Nausea
- Muscle weakness
- Delirium

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Clinical Manifesations of Severe Hypercalcemia (>14 mg/dl)—worsening of moderate symptoms

- Polyuria
- Polydipsia
- Dehydration
- Anorexia
- Nausea
- Muscle weakness
- **Delirium**

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Differential diagnosis of hypercalcemia

- *Generally, but not universally*:
  - Calcium < 11 mg/dl = primary hyperparathyroidism
  - Calcium > 13 mg/dl = hypercalcemia of malignancy

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Cancers Associated with Hypercalcemia

- Prostate
- Breast
- Kidney
- Thyroid
- Multiple myeloma
- Lung
- Lymphoma
- Squamous cell carcinoma

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Etiology of Hypercalcemia of Malignancy

- Tumor secretion of parathyroid hormone-related protein (PTH-r)
- Osteolytic metastases with cytokine release
- Tumor production of 1,25-dihydroxy- vitamin-D

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Work up of hypercalcemia

- Simultaneously measure corrected serum calcium and parathyroid (PTH):
  - PTH at mid level or upper level of normal or elevated = primary hyperparathyroidism
  - PTH low = hypercalcemia of malignancy
- If diagnosis remains unclear
  - SPEP
  - UPEP
  - TSH
  - Vitamin A
  - Skeletal imaging

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Management of Mild hypercalcemia (10.5 to < 12 mg/dl)

- No immediate treatment required
- Six to eight glasses of water per day
- Avoid:
  - Thiazide diuretics
  - Lithium
  - Volume depletion
  - Prolonged immobility
  - Daily calcium intake > 1000 mg
  - Calcium supplements
  - Daily Vitamin D > 800 IU

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Management of Moderate hypercalcemia (12 to 14 mg/dl)

- No immediate treatment required

- See recommendations for mild hypercalcemia

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Management of Severe hypercalcemia (>14 mg/dl)

- Isotonic saline 200 to 300 ml/hr then adjust to maintain urine output of 100 to 150 ml/hr
- If patient is at risk of fluid overload, add a loop diuretic

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Management of Severe hypercalcemia (>14 mg/dl): Use of Calcitonin

- Increases renal excretion of calcium and interferes with osteoclast function which decreases bone resporption.
- Initial dose: 4 units/kg IM or SQ
- Repeat calcium in six hours and if improved, repeat calcitonin every 12 hours for a total duration of 24 to 48 hours
- If calcium NOT improved, increase calcitonin 8 units/kg every six to 12 hours for total duration of 24 to 48 hours
- Effect lasts only 48 hours

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Management of Severe hypercalcemia (>14 mg/dl): Use of Bisphosphonate

- Required for long-term control of hypercalcemia or malignancy.
- Before bisphosphonate treatment, check 25-hydroxy vitamin D level: if < 20 ng/dl then start vitamin D 400 to 800 IU po daily
- Zoledronic acid:
  - Bisphosphonate of choice for long term control of hypercalcemia of malignancy
  - 4 mg IV x 1 over 15 minutes
  - Starts to work in about seven days
  - If hypercalcemia persists, may repeat the dose at seven days
  - For maintenance, dose is repeated yearly

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Questions?

Thank you!