THE CLINICAL PROBLEM SOLVERS BOOK

WARNING: MAY CAUSE USE DEPENDENCE

INTRODUCTION

Welcome, **Clinical Problem Solvers**! We are delighted to have you here, supporting the CPSolvers' new initiative.

This book was inspired by our virtual morning reports. It brings together outstanding case discussions and clinical reasoning pearls. In each chapter, you will navigate through a VMR session, learning from the discussion highlights - an excellent way to review key topics and enhance your clinical reasoning skills for practical use. Additionally, you can answer our quick questions about the chapters to ensure you have gained valuable insights.

The primary goal of this booklet is to establish a new and robust way of teaching within the CPS community, incorporating writing and reading alongside the already strong tradition of verbal discussions. Furthermore, we aim to share medical knowledge beyond the constraints of Wi-Fi. You can download it, so you won't need an internet connection to read it - feel free to read it anywhere: on flights, bus trips, and more. Our booklet is also entirely free and aligns with one of the pillars of CPS: knowledge democratization.

Come with us on this challenging but rewarding life journey of becoming a better clinician and educator every day. Continue incentivizing yourself daily; your personal and academic growth will be certain, and your patients will be thankful. If you want, grab a warm drink, find a cozy spot, and join us. But be aware, it may cause use dependence.

Sincerely,
The CPSolvers

ADDITIONAL RESOURCES

- Check out our recordings on the **CPSolvers virtual morning report (VMR)** YouTube channel https://www.youtube.com/@clinicalproblemsolvers1733
- Join us live on Zoom on our **VMRs.** To receive the zoom link subscribe here: https://clinicalproblemsolving.com/learn-live/
- Check out **CPSolvers website** at https://clinicalproblemsolving.com/
- **CPS on steroids**: Learn with Rabih and Prof. Reza at https://www.rlrcpsolvers.com/
- **CPSolvers schemas** in your pocket! https://clinicalproblemsolving.com/app/
- Listen to our **podcast** on Spotify: https://open.spotify.com/show/6KQCxbfRj2986mE1tj5TF8

GLOSSARY

DIFFERENTIATING NOISE AND SIGNAL: HEMATEMESIS MAY NOT ALWAYS BE THE CORE ISSUE

31-year-old male presents to the emergency department with two days of nausea and vomiting, accompanied by hematemesis and dizziness

When a patient presents with multiple symptoms, it is crucial to determine if these symptoms are related, part of a syndrome, or caused by different conditions. It can be challenging to establish this without further details about the patient. Nevertheless, we can attempt to consider potential causes:

Nausea and vomiting are symptoms that can be associated with various systems. The gastrointestinal (GI) tract is typically the first system that comes to mind, but these symptoms can also be caused by neurological conditions (such as intracranial hypertension), pulmonary impairment (e.g.cough), or extremity pain (due to fracture).

Here is a systematic approach to investigate nausea and vomiting:

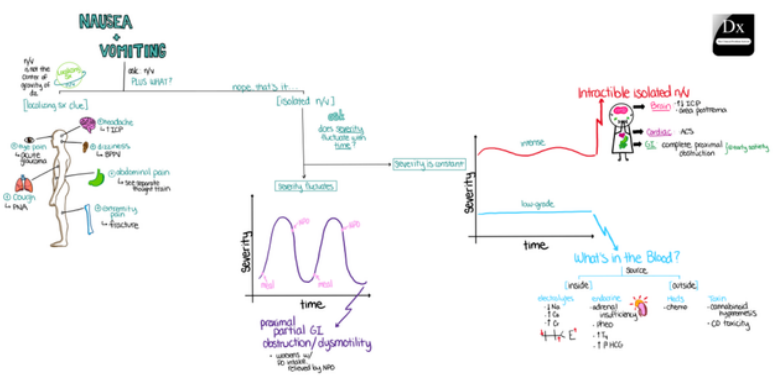


Fig. 1: CPS schema: nausea and vomit.

Hematemesis: This is an important symptom that requires further characterization. It is essential to know the number of episodes, whether the blood was frank or streaked, and if this is the first occurrence of this symptom. In most cases, hematemesis is caused

caused by gastric or duodenal ulcers, followed by esophageal varices.

Dizziness: There are three significant ways to consider this symptom:
1- Many patients describe their discomfort as dizziness, as a word used to convey not feeling good or healthy.
2- Dizziness can be caused by low blood pressure, or orthostatic hypotension -> hypovolemia.
3- Dizziness can also be described as vertigo (neurological symptom).

"*Every time your patient tells you about dizziness, within two minutes you must better characterize this symptom to better know what you are dealing with." - CPSolvers senior team member*

HPI: Two days ago, he celebrated his child's birthday and consumed more alcohol than usual. The day before admission, he experienced a headache and took over-the-counter aspirin, staying at home assuming it was a hangover. On the morning of admission, he had a sudden increase in headache in the bifrontal region and took Tylenol at home. Associated symptoms include dizziness, nausea, and vomiting. He has been vomiting for three days, with two episodes containing previously ingested food and the last episode consisting of frank blood.

With this new information, new hypotheses come to mind. Despite being a young patient, the history of alcohol consumption suggests the possibility of liver-related complications. Therefore, it is important to determine the quantity of alcohol consumed daily.

Considering a potential underdiagnosed cirrhosis, this patient may be presenting with bleeding esophageal or gastric varices, for example. Additionally, a decrease in clotting factor production or impaired platelet production could contribute to the bleeding, although both are unlikely in a patient without signs of liver failure.

Furthermore, the progression from vomiting food content to bleeding may indicate Mallory-Weiss syndrome, which occurs when forceful vomiting causes a tear in the esophageal mucosa, leading to bleeding. This is an important diagnosis that requires prompt management to prevent progression to Boerhaave Syndrome, a condition where the tear evolves into a complete dissection of the esophageal muscularis.

The patient also mentioned the use of aspirin, a non-steroidal anti-inflammatory drug (NSAID) that inhibits the production of COX-1 and COX-2, reducing the production of inflammatory cytokines. This medication also decreases the production of thromboxane-A2, which is responsible for clot formation. Overuse of aspirin and other NSAIDs is also associated with bleeding.

Finally, the patient added a new and crucial symptom to the case: headache. Headache, dizziness, nausea, and vomiting raise concerns about a possible neurological cause that needs to be promptly assessed. A thorough physical examination is essential to further evaluate this patient.

PMH: Rheumatic Heart Disease, Aortic Valve Replacement (AVR), Cardiomyopathy with preserved ejection fraction, Heart Failure, Hypertension.
Medications: warfarin (difficulty monitoring levels), aspirin, metoprolol, spironolactone, sacubitril/valsartan.
No previous family history.
Social History: Occasional drinker (1-2 beers on weekends). Non-smoker, no drugs.
No history of allergies.

This is an illustrative example highlighting the significance of a patient's past medical history in achieving a comprehensive understanding of their current situation. Considering the history of warfarin consumption with no monitoring levels, it is possible that this medication level exceeded the therapeutic range, potentially leading to GIT bleeding and hematemesis.

When confronted with a patient presenting bleeding attributed to elevated warfarin levels, the consideration of anticoagulation reversal becomes imperative. This can be achieved through the administration of Vitamin K (a gradual process) or blood factors (a more rapid procedure). However, the decision of whether to initiate reversal and the choice of reversal agent require careful reflection. To facilitate this decision-making process, the following factors should be taken into account:

1- Bleeding severity.
2- Risk of thrombosis: AVR holds an important risk of thrombosis. It is lower than the replacement of mitral valve, but it is still significant.

To make a decision, you may need more data about the case.

Physical Exam:
Tmax: 36.7|HR: 56|BP: 131 x 77|SpO2: 98% RA
Gen: comfortable, no pallor, equal pupils and reactive
CV: Bradycardic
Pulmonary: Clear lungs on auscultation
Neuro: oriented to time, person, place. Extraocular muscles intact, pupils reactive, no facial asymmetry, clear speech, intact finger-to-nose maneuver, no pronator drift, slight overshoot. Can't perform heel to shin, left unilateral nystagmus present.

After the physical examination, another organ dysfunction needs to be considered: brain injury. Since the inability to perform the heel to shin maneuver is a sign of cerebellar impairment, besides the nystagmus, which is a sign of vertigo. **Acute neurological syndrome is considered vascular until it is ruled out.** Considering the clinical scenario and patient's PMH, there are two main options:

1- Elevated warfarin Levels causing a hemorrhagic stroke.

2- Low Blood Concentration of the drug causing CNS thrombosis and resultant ischemic lesion.

The occurrence of headaches is atypical in ischemic stroke, though it might occur a few hours subsequent to the initial lesion, coinciding with the brain enlargement due to vasogenic edema.

Besides that, bradycardia associated with headaches can serve as an indicator of Intraparenchymal Hypertension (ICP), which necessitates immediate further workup.

WBC: 9.5|Hgb: 14|Plt: 165|HCT 38|MCV 85 Neutrophils 88.7
NA 144|K 4.4|Glucose: 143|INR 3.7
Brain CT: Acute parenchymal hematoma in the left cerebellar region measuring 2.1 by 2.5 with mild mass effect on the inferior aspect of the 4th ventricle.

What do you think the final diagnosis is?

DX: ACUTE INTRACRANIAL HEMORRHAGE

Management:

- Control the bleeding, and reverse the effect of warfarin with PCC (blood product - swift response in restoring coagulation).
- Maintain strict blood pressure control: it helps mitigate further bleeding and reduce intracranial pressure.
- Try to reduce the pressure in the brain with medications (mannitol), positioning, hyperventilation, and/or craniotomy.

Causes of intracranial bleeding:

- Epidural space: primarily attributed to traumatic events.
- Subdural space: often a result of trauma as well.
- Subarachnoid space: trauma and aneurysms.
- Intraparenchimal: hypertension (deep brain matter including cerebellum), cerebral amyloid angiopathy (CAA- cortex), anticoagulant related and underline mass.
- Intraventricular: may result from various underlying factors.

In this patient, the most probable cause was intracranial hemorrhage caused by exceeding the warfarin therapeutic range.

Takeaway messages:

- Past medical history adds great value to diagnosis.
- Physical exams can change diagnosis and save lives.

For more information about this case, watch the following episode on YouTube:

June 8, 2023 VMR with Rabih and CPS team - nausea, vomiting and hematemesis:https://www.youtube.com/watchv=TPQgMcsWelU&t=2405s

Case Presenter: John Claudio Romero, MD
Discussants: Rabih Geha, MD and Amanda Barreto, MS6
Text writer: Maryana Ribeiro, MD
Text reviewer: Rabih Geha, MD

QUESTIONS

1) Which of the following is the most important factor in deciding to empirically reverse anticoagulation in a patient with hemorrhage attributed to warfarin?

a. Severity of bleeding
b. Height of the INR
c. The patient is on vitamin supplements
d. Patient with pre-established iron deficiency anemia

2) A patient is presenting with a neurologic deficit. Which of the following etiologies must be ruled out first?

a. Inflammatory
b. Compressive
c. Vascular
d. Metabolic

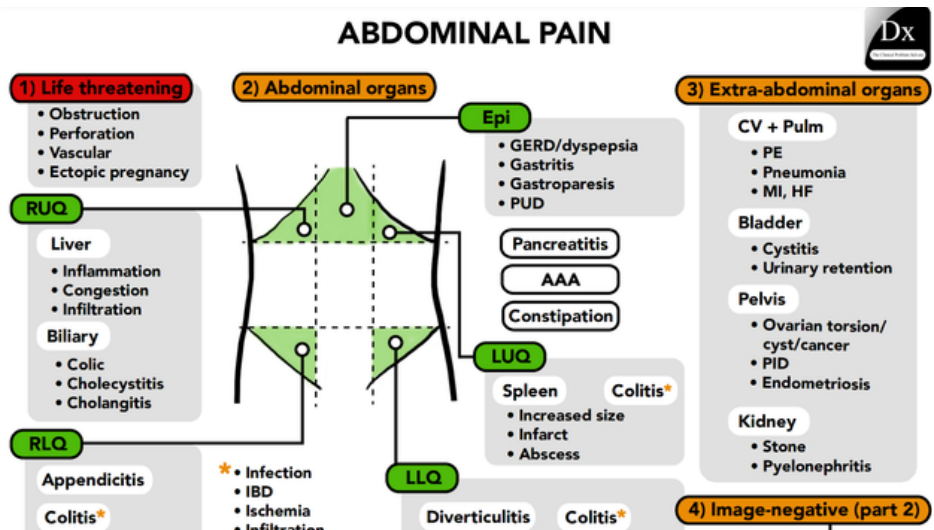
YOU CAN FIND THE ANSWER AT THE BOTTOM OF THE PAGE. IT IS UPSIDE DOWN TO AVOID SPOILERS.

1) A 2) C

A CURIOUS STORY ABOUT IMAGE-NEGATIVE ABDOMINAL PAIN

A 25-year-old female presents to the emergency department with abdominal pain and right flank pain

Pain localization could be an important clue when considering the disease process. This information helps us to understand the underlying anatomy involved and aids in generating a comprehensive list of potential differential diagnoses.



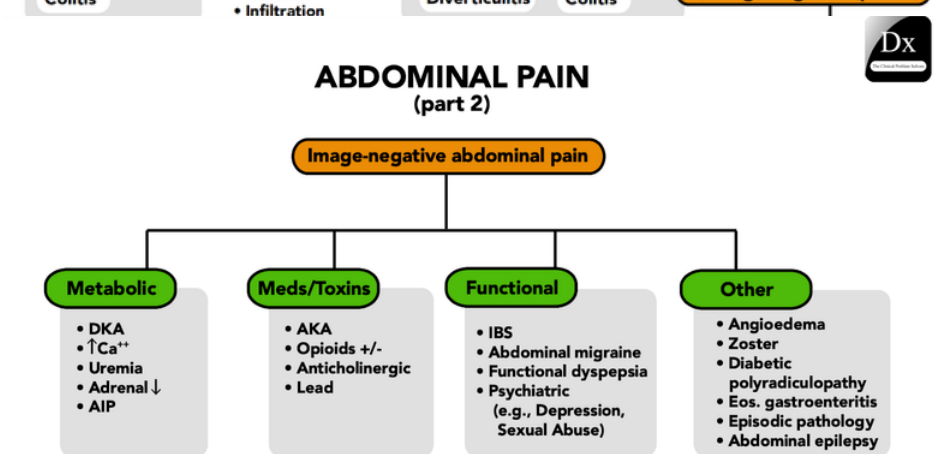


Fig. 2 and 3: CPS schemas: abdominal pain and image-negative abdominal pain.

HPI: The patient reports that the abdominal pain was accompanied by nausea and vomiting and started 4 hours ago. A CT was performed and no abnormality was seen. The patient was discharged with improvement, and pain control was prescribed. 1 day later the patient returned to the service with diffuse headache, fatigue, fever, malaise, nausea, vomiting, gum, and vaginal bleeding.

Patient returning to the hospital a few days after initial admission should raise a red flag. The most important thing is to start all over and be sure that, this time, nothing will be missed.

We have a patient again with abdominal pain, but now with associated headache, fatigue, fever, malaise, GI symptoms, and bleeding. All of these new complaints capture our attention, and raise suspicion for important and life-threatening conditions:

Headache, nausea, and vomiting: may indeed be indicative of acute neurological conditions, such as intracranial pressure changes, stroke, or severe sinus infection.

Fever and abdominal pain: may represent signs of infection, such as urinary tract infection (UTI), and gastroenteritis (viral, salmonella/shigella). It also could be associated with inflammatory conditions, such as appendicitis.

Vaginal bleeding: considering the associated abdominal pain and age of the patient, there are some differentials that should be ruled out here: miscarriage, ectopic pregnancy, and placenta abruption. Urinary B-HCG is indispensable here. However, when vaginal bleeding is assessed as associated with gum bleeding, other diagnoses become more probable, such as thrombocytopenia, and coagulopathy.

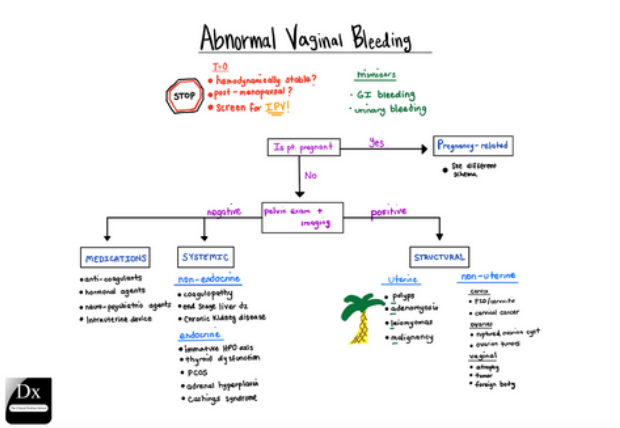


Fig. 4: Abnormal Vaginal Bleeding CPS schema.

PMH: Unremarkable
Meds: NSAIDs, Tramadol
Fam Hx: Unremarkable
Soc Hx: Unremarkable
Health-Related Behaviors: Social drinker. From Brazil.
Allergies: No

Sometimes the past medical history of the patient can be very helpful, but in this case, it may not yield new or substantial information that directly contributes to diagnosis. However, a piece of information here increases our list of differentials: where she comes from. Epidemiology plays an important role in diagnosis, mainly in infectious diseases. Considering this data, we should also think about arthropod-transmitted diseases, such as dengue, chikungunya, and zika, especially in a scenario of abdominal pain, headache, GI symptoms, and bleeding.

Physical Exam:
Tmax: 37.9C|HR: 102|BP:120x80|SpO2 98% RA
Gen: Mildly distressed, pale, and dehydrated
CV: Unremarkable
Pulm: Unremarkable
Abd: pain on percussion on Right flank
Extremities/skin: non-palpable petechiae all over the body, especially in the lower limbs.

The physical examination plays a pivotal role in uncovering valuable insights into the presence of the petechiae, non-blanching red to purple macules. They arise from bleeding into the skin from small capillaries that may signify the presence of hemorrhagic phenomena, thereby prompting consideration of potential vascular system issues. When conducting an assessment of abdominal pain upon percussion in the right flank, particularly in cases where imaging results appear negative, it's crucial to recognize that the severity of this symptom can indeed be directly linked to the seriousness of the underlying disease.

WBC: 2.000|Hgb: 11 (mild anemia)|Plt: 50k
Na: 136|K: 3.5
BUN: 10|Cr: 1.0
AST: 146|ALT: 123|Alk-P: 80|GGT: 446
T. Bili: 0.3 (direct 0.1)|INR: 1|aPTT: 31
Pregnancy test: negative
UA: Normal|CT: normal

Following the laboratory results, the evaluation of pancytopenia should encompass three primary categories: 1) marrow infiltration; 2) bone marrow failure; and 3) peripheral processes. However, it's worth noting that when a significant and disproportionate decrease in white blood cells (WBC) and platelets (PLT) is observed, it may strongly suggest the possibility of an arthropod-borne infection. This condition can indeed lead to a drop in WBC and PLT counts due to the body's immune response and the potential direct impact on the bone marrow. This suggests the importance of considering infectious causes in cases of pancytopenia when this pattern is evident, as it may lead to timely and specific interventions. Exploring the infectious etiology of alterations in liver enzyme levels can provide valuable insights, as the liver frequently plays a pivotal role in the context of infectious diseases, which could explain the elevated aminotransferase enzymes.

With this information in mind, what do you think the final diagnosis is?

Performed serology for Dengue+Chikungunya+Zika
IgM+IgG+ positive for Dengue

DX: DENGUE HEMORRHAGIC FEVER

Management:

- Hospitalization: Patients with dengue hemorrhagic fever often require hospitalization so that they can be closely monitored and receive appropriate care.
- Intravenous (IV) Fluids: Maintaining proper fluid balance is crucial in management. IV fluids are administered to help replace fluids lost due to fever, vomiting, and diarrhea and to prevent dehydration.

Takeaway messages:

- Epidemiology is crucial to diagnosis, especially for infectious disease
- A disease may evolve over hours or days, ultimately declaring itself with more clarity

For more information about this case, watch the following episode on YouTube:
May 11, 2023, VMR with Rabih and CPS team - Abdominal Pain: https://www.youtube.com/watch?v=QBOHeUnQV6Q&t=699s
Case Presenter: Amanda Barreto
Discussants: Rabih Geha and Youssef Saklawi
Text writer: Amanda Barreto
Text reviewer: Rabih Geha

QUESTIONS

1) What category of diseases should you have on your differential diagnosis when you see pancytopenia with a disproportionate decrease in WBC and PLTs?

a. Arthropod-borne infections
b. Bone marrow failure
c. Bone marrow infiltration
d. Peripheral destruction

2) What is a subtle lab abnormality that often accompanies arthropod-borne infections?

a. Mild elevation in LFTs
b. Mild elevation in creatinine and urea
c. Mild acidosis
d. Mild alkalosis

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A METALLIC QUERY

A 56-year-old woman is presenting with four weeks of lethargy, irritability, and bilateral numbness & tingling in the lower extremities.

When faced with a presentation of multiple complaints, one must select the highest-yield complaint that may identify a patient's underlying disease. Three of this patient's symptoms; namely their lethargy, irritability, and brain frog; are non-specific and could be attributed to a multitude of diseases, neurologic or else. Yet their peripheral neuropathy, described as numbness and tingling, provides a clear framework to approach a specific diagnosis.

Fig. 5: Peripheral Neuropathy CPS schema.

When approaching neuropathy, think of the three categories under which neuropathies fall: mononeuropathy, mononeuritis multiplex, and polyneuropathy. Memorizing their differential diagnoses may help (*Fig.5)*, but understanding their focal points of origin ensures long-term retention.

Mononeuropathy describes neuropathy of a single nerve and is

ioften due to radiculopathy or other sites vulnerable to compression - e.g, carpal tunnel.

Mononeuritis multiplex describes MULTIPLE asymmetric nerve involvement. Because of the multiple nerve involvement, the differential diagnosis in mononeuritis multiplex is mainly attributed to systemic diseases, including inflammatory conditions, infections, hematological malignancies, and inherited diseases (see above).

Polyneuropathy describes symmetric, and often time-dependent, involvement of peripheral nerves that may be secondary to myelopathy. In approaching polyneuropathy, one must ask themselves "for how long has it been going?" Establishing the tempo of one's presentation allows for quick evaluation for pretest probability, and thus ordering high-yield diagnostics.

1. In acute presentations, remember your TAG mnemonic: Toxins (thallium and arsenic), AIP (acute intermittent porphyria), and GBS (Guillain-Barre Syndrome).
2. In chronic presentations, the differential diagnosis follows a similar framework to mononeuritis multiplex: inflammatory conditions, infections, hematological malignancies, and inherited diseases. Herein, it may be useful to memorize the underlying etiologies under each subset to differentiate.

HPI:A 56-year-old woman with hypothyroidism on levothyroxine and recent hip arthroplasty is presenting with four weeks of bilateral numbness & tingling in the lower extremities. Six weeks ago, the patient noticed anorexia and progressive fatigue. And upon investigation, the TSH was noted to be low. Thus, the thyroxine dose was increased. Four weeks ago, she noticed lethargy, irritability, brain fog & bilateral numbness & tingling in the lower extremities.

Systemic review is positive for severe headache, tinnitus, worsening of clouding of thoughts, short-term memory loss impairing activities of daily living, anxiety, sense of paranoia, palpitations, and ataxia 2 weeks before presenting.

She has a history of depression and anxiety is on fluoxetine and had undergone a splenectomy following a road traffic accident. Four months ago, she underwent Cobalt arthroplasty of her left hip without any noted postoperative complications. She smokes 5 cigs/day and is a social drinker.

On physical examination, she had reduced sensation distally up to the mid forearms in the upper extremities and bilateral numbness and tingling up to the mid shins in the lower extremities. The patient was also noted to have sensory ataxia and reduced strength in all extremities (⁴⁄₅).

Upon hearing this patient's HPI, it is important to address the acuity of this patient's presentation. A severe headache is a major red flag in almost all patients. One must address the tempo, location, and severity immediately as it will paint a roadmap for further investigations. This patient did not undergo either as their headache was found to be of non-concerning features for emergent evaluation.

Anchoring bias must be dealt with carefully. While hypothyroidism is known to cause bilateral symmetric neuropathy, notice how this patient's thyroid dose adjustment did not improve their symptoms.. Thus, it remains of utmost priority to take all other symptoms into account. This patient's systemic review puts forth a clear picture of an underlying neurologic cause. After characterizing their neuropathy as polyneuropathy, toxic causes must be ruled out, primarily because this patient's symptoms had only started two months following their arthroplasty (temporal relationship).

Just like any other medical intervention, arthroplasties carry a risk of post-operative complications. Risks include those associated

with any major procedures (e.g. atelectasis, urinary tract infections, deep venous thrombosis, wound infection, etc.) but also specific complications. An important specific complication is implant loosening and cobalt toxicity [1]. This is one particular concern in patients with metal-on-metal implants. As these implants erode, their components are released into the bloodstream, mounting an immune response that leads to osteolysis and implant failure.

While this patient's neuropathy is not of acute onset, it is neither chronic. This is because it is not slowly progressive. We call such a subacute neuropathy an atypical neuropathy. Other atypical features include motor predominance, acute onset, and/or the presence of autonomic features [2]. All atypical neuropathies must be consulted by a neurologist. Atypical neuropathies are typically approached via the ABCD mnemonic.

A: AIDP (most common variant of GBS)
B: B vitamin deficiencies
C: Cauda equina syndrome
D: Drugs and toxins

Patients with cobalt toxicity will present systemically (i.e. not limited to neuropathy/neurologic symptoms!). Manifestations may be related to cardiomyopathy, neuropathy, endocrinopathy (recall that our patient had worsening hypothyroidism of unknown etiology), and polycythemia)[3]. Patients with high suspicion may be evaluated for serum and urine levels of cobalt and chromium (chromium is added onto these implants, alongside cobalt, to increase the durability of the alloy) before pursuing other investigations.

WBC:12.7 (high neutrophils)|Hgb: 18.8|MCV: nl|HCT 67%|Plt: nl
Na: 134|K: 2.4|Ca: 10.6|Mag: 0.9|Cl:nl
BUN: nl|Cr: nl|Glucose: 377 |HbA1c: 7.9
Troponin: 202-> 216, aspirin & statin were administered
TSH: improving|AST, ALT, Alk-P, & Albumin: nl
Lyme & EBV serology: neg

What do you think the final diagnosis is?

EKG: Sinus tachycardia / Echo: 65% LVEF, normal valves
Serum toxicology: Cobalt 592 (normal <10), Chromium 62.4 (normal <0.16)
X-ray hip: normal. Thus, pt. was taken to OR, where joint erosion was noted.

DX: COBALT-CHROMIUM TOXICITY

Management:

- Eroded implant removed.

Patients with cobalt/chromium toxicity secondary to their implants can be managed with implant removal [4], which usually improves their symptoms. Evaluation of the arthroplasty pre-removal can be carried out with conventional radiography. If radiography is unequivocal, digital subtraction arthrography can be pursued next. This patient received thiamine and n-acetylcysteine alongside implant removal, which has rapidly improved their symptoms, including their polycythemia. This patient had also undergone an echocardiography, partly because of the association of non-ischemic cardiomyopathy secondary to cobalt. Luckily, this patient had no imaging suggestive of cardiomyopathy. However, she is scheduled to undergo further echocardiography on follow-up as cardiomyopathy may manifest later down the road.

Takeaway messages:

- A deep dive into a patient's history can profoundly influence your analysis of c case
- When a patient presents with 'peripheral neuropathy,' your first step must be to characterize the neuropathy as above.

References:

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4.Dahms K, Sharkova Y, Heitland P, Pankuweit S, Schaefer JR. Cobalt intoxication was diagnosed with the help of Dr House. The Lancet. 2014 Feb 8;383(9916):574.

For more information about this case, watch the following episode on YouTube:
October 12, 2023 VMR with Rabih & CPS Team- lethargy, irritability and neuropathy: https://www.youtube.com/watch?v=bbM6flh_HHo

Case presenter: Jasdeep Bajwa, DO
Case Discussants: Rabih Geha, MD and Alex, MD
Text writer: Ibrahim Omer, MS3
Text reviewer: Rabih Geha , MD

QUESTIONS

1) What is a red flag in polyneuropathy?

a. Sensory predominant
b. Slowly progressive
c. Symmetric
d. Acute in onset

2) Match the pattern with the definition and the ddx:

1: Mononeuropathy
2: Mononeuritis multiplex
3: Polyneuropathy

A: Multiple asymmetric nerve involvement.
B: Symmetric peripheral nerve involvement.
C: Single nerve involvement.

a. 1A 2B 3C
b. 1B 2A 3C
c. 1C 2B 3A
d. 1C 2A 3B

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1) D 2) D

A QUESTION OF FRAMING: WHAT DOES THE INFORMATION REALLY MEAN?

62 year old male presenting with two days of generalized weakness and lower extremity numbness, associated with one month of polydipsia and polyuria.

Breaking this problem down, we have two dimensions.

1- Generalized weakness with lower extremity numbness:
The most common causes of lower extremity numbness are peripheral neuropathies, like diabetic neuropathy. The typical polyneuropathy follows the rule of 3 Ss: symmetric, sensory, and slowly progressive. This patient has a symmetric and sensory-predominant presentation, however, the acuity makes us worried.

2- Polydipsia and polyuria:
This often represents diabetes, either mellitus or insipidus, though mellitus is far more common. Primary polydipsia is also possible.

The patient had no healthcare encounter since the age of 20 years old. It was difficult to obtain further history given the confusion. Past medical history, current medications, and family history are unknown. The patient is retired and lives with his brother. Health-related behaviors are also not known.

Physical Exam: T: afebrile HR: nl BP: nl RR: 5L nasal cannula
CV: normal
Pulm: crackle right lower lobes
Neuro: diffuse myoclonus, carpopedal spasm while measuring BP, not oriented to time and place
Extremities/skin: 4/5 strength diffuse, mild hyporeflexia on patellar tendon bilaterally, no edema.
POCUS CV: globally reduced wall motility POC glucose: 496

Many things jump out in this aliquot. Let's break it down.

Acute hypoxic respiratory failure (AHRF) with pulmonary compromise (crackles):
Pulmonary edema from heart failure? No other criteria for this diagnosis: no JVD, abdominal-jugular reflux, dyspnea, lower extremity edema, etc.
Pneumonia? Although we have some respiratory symptoms, we are lacking the typical history (cough, shortness of breath for a few days), and we also lack an inflammatory signature.

Generalized weakness, myoclonus, carpopedal spasm, hyporeflexia:
Interesting to note here that the problem is not only in the peripheral nervous system anymore - we also have altered mental status. The disease is also having a central effect.
This carpopedal spasm upon inflating the cuff is called Trousseau's sign. It is very sensitive and specific for hypocalcemia. This electrolyte imbalance can explain the neurologic findings very nicely.

Polydipsia, polyuria, hyperglycemia:
Now with the hyperglycemia, we can confidently say that this patient has diabetes mellitus.

Globally reduced heart wall motility
If hypocalcemia is confirmed, it can explain those findings - after all the heart is just a special muscle.
It's definitely challenging to see how those problems connect with one another. We should investigate those issues separately for now, and try to connect later, just to make sure we are not missing anything.

WBC: 15.7k (predominantly neutrophilia) | Hgb: 15.7| Plt: 357k
Na: 131 | K: 5.4 | Cl: 96 | BUN: 45 | Cr: 1.86
Ca: 7.5 | Mag: 2 | Phos 5.2
AST: 90 | ALT: 42 | Alk-P: 67 | T. Bilirubin 0.7
Total Protein: 7.5 | Albumin: 3.5 |HbA1c 9%
CK 1941|UA normal|BNP 35
Urinary toxicology & serum ethanol negative

Now we can make some progress on our problems!

For the AHRF, we had two hypotheses.
Pulmonary edema from heart failure seems less likely, now that we have a normal BNP. However, remember that this test can be falsely negative in patients with higher BMIs.

The second hypothesis was community acquired pneumonia.
We have AHRF, leukocytosis, and a pulmonary infiltrate. So we have a pulmonary inflammatory syndrome that is consolidating in a pulmonary infiltrate, most likely pneumonia. Treatment is definitely warranted. Keep in mind that pneumonia likely will not explain all his problems.

For the metabolic derangements, we have:
- Hyponatremia
- Hyperkalemia
- Acute kidney injury
- Hypocalcemia
- Hyperphosphatemia
- Normal magnesium
- Transaminitis
- CK elevation
- Confirmation of diabetes mellitus

One possible way to progress is to pick the one that has the narrowest differential diagnosis, the most unusual. In this case, hypocalcemia. It also seems to be driving most of his symptoms (generalized weakness and lower extremity numbness).

If we choose other electrolyte derangements, we can easily get sidetracked. For instance, we could explain hyponatremia and hyperkalemia in multiple ways. This patient may have adrenal insufficiency. This patient may be dehydrated and have an acute kidney injury complicated by electrolyte abnormalities.

Now, for the hypocalcemia:

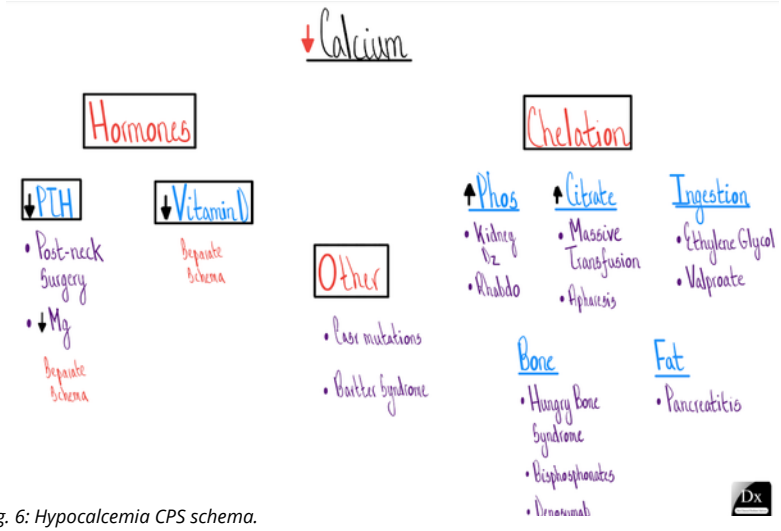

Fig. 6: Hypocalcemia CPS schema.

Since we do not have PTH and vitamin D levels right now, let's look at chelation and think. This patient has no exposure to citrate, no altered anion gap to think of ethylene glycol, and no hallmarks of pancreatitis or bone diseases.

What he does have is hyperphosphatemia. If this patient had chronic kidney disease, he would not be able to excrete phosphate. The excess phosphate would bind calcium and would result in hypocalcemia. The hypocalcemia in turn would drive PTH production up. So if we ordered PTH levels, we would expect it to be elevated. This is secondary hyperparathyroidism. His kidney function right now is not so good, but it is unclear if it is an acute or chronic change. **High PTH levels would support the hypothesis of chronic kidney disease complicated by secondary hyperparathyroidism.**

What about rhabdomyolysis? It is a compelling hypothesis. The CK is only mildly elevated now, but he could have had levels much higher in the days prior to the presentation. Let's entertain this hypothesis for a minute. There are many conditions that can cause non-traumatic exertional muscle injury. The most common are medications, electrolyte disturbances (hypokalemia and hypophosphatemia), and toxins (most commonly alcohol). We don't have the current medication list for this patient. He doesn't

have the usual electrolyte imbalances in the levels that could cause rhabdomyolysis. But what we do have is a clinical picture of a patient with pneumonia, mild AST and ALT elevations, and muscle injury. This could be all caused by alcohol use. **This patient could have alcohol induced rhabdomyolysis, mild transaminitis from alcohol, and aspiration pneumonia.** It is key to investigate further his alcohol use. Remember that alcohol levels are useful only for current intoxication. Patients may not divulge alcohol use easily because of fear of bias and prejudice.

Patient underwent fluid resuscitation, with the improvement of hyperkalemia and acute kidney injury.
Treatment for CAP with antibiotics was also started.
Vitamin D normal, PTH low
CT head: negative
MRI brain: chronic ischemia
RUQ US: hepatomegaly with 1.9 cm left liver lesion.
TTE: normal LV wall thickness, moderately reduced EF, no regional wall motion abnormalities.
Nuclear stress test: EF 36%, no evidence of ischemia.

Going back to our hypotheses:

- The hypocalcemia can be explained by the low PTH levels. This is the pathophysiology of hypoparathyroidism.
- Some of the other problems were caused by dehydration (since labs got better after fluid resuscitation).

Let's talk about the results in the context of this patient, by revisiting and updating the problem representation.

60 year old male with no known PMHx presenting with:

- Generalized weakness and lower extremity numbness, found to have myoclonus and carpopedal spasm, found to have hypocalcemia with low PTH.
- Polydipsia and polyuria, found to have hyperglycemia and elevated HbA1c.
- Heart with globally reduced motility, found to have reduced EF.
- Hepatomegaly with mild transaminitis.

60 years old male with no known PMHx presenting with:

- Hypoparathyroidism
- Diabetes mellitus
- Heart failure with reduced ejection fraction
- Hepatomegaly with mild transaminitis

We definitely have a disseminated disease process. We have to *balance Occam's razor (one unifying diagnosis) with Hickam's dictum (the patient can have as many diseases as they damn well please)*. The biggest factor that sways us to look for a unifying diagnosis is how unusual non-iatrogenic hypoparathyroidism is. It is often a part of a larger systemic syndrome.

Let's see the schema for this ddx:

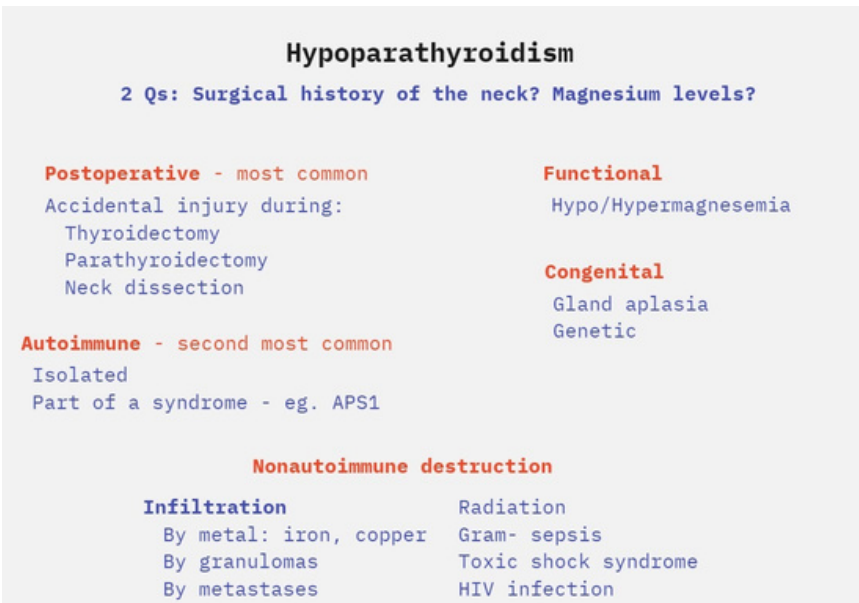

Fig. 7: Author's Hypoparathyroidism schema.

When we have a patient with multiple endocrinopathies, one way to approach it is to think of a few causes first: pituitary adenoma with compression, POEMS, and one other particular condition. Leave rare diseases like autoimmune polyendocrine syndromes for later, unless the case is very compelling.

What can cause hypoparathyroidism, DM, HF, and hepatomegaly?

What do you think the final diagnosis is?

Let's find out the answer to this diagnostic mystery!

TSH normal | HIV, RPR, Hep negative | B9, B12 normal | SPEP no paraprotein
Transferrin saturation elevated, ferritin elevated
MRI liver: Increase uptake liver & spleen without cirrhosis, Hepatic haemangioma on left side without HCC features
Genetic study: Homozygous for Hereditary Hemochromatosis mutation C282Y

DX: HEREDITARY HEMOCHROMATOSIS

This was a challenging case because of it had many data points to keep track of.

Takeaway messages:

- Revisit the problem representation often.
- Pull on an objective but unusual finding, in this case hypocalcemia that led us to hypoparathyroidism.

For more information about this case, watch the following episode on YouTube:
September 21, 2023 VMR with Rabih & CPS Team - generalized weakness and lower extremity numbness: https://www.youtube.com/watch?v=amTOlEaPDqU&t=2s
Case presenter: Mark Heslin, MD
Case Discussants: Rabih, MD & David, MD
Text writer: Noah, MS6
Text reviewer: Rabih Geha, MD

QUESTIONS

1.When faced with a hemodynamically stable patient suspected of multiple endocrinopathies, which of the following etiologies must be ruled out first?

a. Pituitary
b. Adrenal
c. Hypothalamic

2.Which of the following is the most specific sign of hypocalcemia?

a. Chvostek's sign
b. Trousseau's sign
c. CPSolvers sign
d. Kehr sign

YOU CAN FIND THE ANSWER AT THE BOTTOM OF THE PAGE. IT IS UPSIDE DOWN TO AVOID SPOILERS.

1) A 2) B