CLINICAL PRACTICE

Exercises in Clinical Reasoning

Stressing Signal Versus Noise: An Exercise in Clinical Reasoning

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In this series, a clinician extemporaneously discusses the diagnostic approach (regular text) to sequentially presented clinical information (bold). Additional commentary on the diagnostic reasoning process (italics) is integrated throughout the discussion.

A 60-year-old blind man with a history of hypertension and chronic obstructive pulmonary disease presented to the emergency department with progressive dyspnea for 5 weeks.

Four weeks earlier, the patient was seen by his primary care doctor for dyspnea at rest and cough, and was treated empirically for community-acquired pneumonia with doxycycline followed by clarithromycin. His symptoms transiently improved. Subsequently, he reported increased purulent sputum production, fatigue, and diffuse abdominal discomfort for 2 weeks. He denied fevers, chills, night sweats, and weight loss. His medical history included retinitis pigmentosa with legal blindness and psoriasis. He smoked cigarettes daily and drank alcohol occasionally. He smoked marijuana but denied other illicit drug use.

Dyspnea is typically caused by a cardiac disorder (e.g., chronic heart failure), a pulmonary illness (e.g., chronic obstructive pulmonary disease), or anemia. A lingering COPD exacerbation following a viral upper respiratory infection could explain this presentation. The failure to resolve with two courses of antibiotics makes bacterial pneumonia less likely. Partially treated pneumonia could evolve into a lung abscess or empyema, but fever, sweats, and weight loss would be expected. If he takes immunosuppressive medications for his psoriasis, that would expand the spectrum of plausible pulmonary infections to include tuberculosis or endemic fungi. Heart failure can present with dyspnea and abdominal discomfort (from hepatic congestion). Dyspnea and abdominal pain can also arise from ascites, although sputum production would not be seen.

A problem representation (PR) is a one-sentence summary that defines a patient's condition in abstract terms. Sometimes clinicians state the PR, but often it can be inferred based on the features of the data set they choose to analyze and which data elements they disregard. The PR in this case is a middle-aged man and smoker with subacute productive cough, dyspnea, and abdominal pain. The dyspnea and cough elements collectively trigger illness scripts for various respiratory infections, but abdominal discomfort is not a characteristic of those conditions. At this early stage, the clinician does not know whether this isolated data point is part of the patient's underlying syndrome or is unrelated. Signal detection theory (SDT) describes how decision makers determine whether data in the environment is meaningful for solving a problem ("signal") or will have no bearing on the solution ("noise").[1]

The patient's temperature was 36.5 °C, pulse 92 beats per min, blood pressure 142/71 mmHg, respiratory rate 20 breaths per min, and oxygen saturation 96 % on ambient air. The patient was obese and jaundiced. He had scant crackles in his left upper lung field. There were no murmurs, rubs, or gallops. His neck veins were not distended. His abdomen was soft and protuberant without features of ascites. His legs had symmetric 3+ pitting edema. He had multiple erythematous plaques with overlying scale on the extensor surfaces of his elbows and knees. He had no stigmata of chronic liver disease. He was alert and oriented to person and place but not year. His discourse was tangential, but when redirected, he answered all questions appropriately. He had light perception only in his left eye. He was blind in his right eye except for a small preserved island of superotemporal vision. Cranial nerves III–XII were intact. He had normal strength, sensation, and reflexes. Asterixis was not present.

Jaundice in the company of persistent dyspnea, normal oxygen saturation, and a nearly normal lung exam could be explained by hemolytic anemia. However, hepatobiliary disease is more likely given the abdominal pain and distention, although he has no stigmata of chronic liver disease. His upper lobe crackles could reflect any focal pneumonitis arising from

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aspiration, bacteria, fungi, viruses, or tuberculosis. Focal parenchymal disease could also be edema, blood, tumor, or lobar collapse.

His marked lower extremity edema could arise from heart, liver, or kidney dysfunction, or venous insufficiency. Jaundice and abdominal distention without elevated neck veins implicates the liver.

His confusion about the year and tangential speech must be presumed to represent acute changes in his cognition unless evidence to the contrary is provided by collateral history. Altered mental status is usually attributable to metabolic, infectious, structural, or toxic causes. Hepatic encephalopathy or spread of a pulmonary infection or malignancy to the brain is plausible.

The discussant is able to account for the jaundice, abdominal discomfort, and edema by hepatopathy, but this leaves the dyspnea and cough unexplained. Alternatively, the discussant can attribute jaundice and dyspnea to hemolytic anemia, but this neglects the abdominal discomfort and edema. At this point, it is unclear which data points are signal and which are noise. SDT predicts that a decision maker will provisionally treat data as signal when the cost of a false negative (incorrectly labeling a clinical finding as noise) is high. Therefore, the discussant keeps all of the major data points in his evolving problem representation.

The hemoglobin was 13.4 g/dL, the white blood count was 18,900 per cubic mL (85 % neutrophils, 7 % monocytes, 5 % lymphocytes, and 0 % eosinophils), and the platelet count was 136,000 per cubic mL. The serum sodium was 139 mmol/L, potassium 3.3 mmol/L, creatinine 0.7 mmol/L, aspartate aminotransferase (AST) 175 U/L (normal 5–35 U/L), alanine aminotransferase (ALT) 229 U/L (normal 7–56 U/L), bilirubin 5.6 mg/dL (normal 0.1–1.2 mg/dL), alkaline phosphatase 268 U/L (normal 40–125 U/L), and albumin 2.8 g/dL. The international normalized ratio (INR) was 1.1. Urinalysis was normal. Chest x-ray revealed a hazy left upper lobe opacity.

Leukocytosis usually signals infection (e.g., pneumonia or spontaneous bacterial peritonitis), but can also arise in the setting of autoimmunity or malignancy. His hypokalemia is trivial, but more substantial or persistent hypokalemia would warrant consideration of insufficient potassium intake, transient intracellular shift, or excess renal or gastrointestinal loss. The focal nature of the infiltrate favors infection or tumor over edema or hemorrhage, which tend to be more diffuse. Lung cancer is an important consideration with his smoking, although a sizable carcinoma would typically cause weight loss.

He has a mixed pattern of liver function test abnormalities, which invites consideration of nearly all liver diseases, because many cholestatic processes eventually cause hepatocellular injury, and many hepatitides cause cholestasis in their peak, resolving, or terminal phases. Antibiotics may have caused drug-induced hepatotoxicity, which might be superimposed upon fatty liver from his obesity or alcohol use. Biliary obstruction by stone, stricture, or tumor needs to be excluded by imaging.

The patient was admitted to the hospital. Ceftriaxone and doxycycline were administered for community-acquired pneumonia. Rapid influenza testing was negative, as were serology tests for viral hepatitis. Computerized tomography of the chest with contrast revealed a 5.7 × 5.4 cm left hilar mass with complete obstruction of the left upper lobe bronchus and left upper lobe collapse; the mass also encased the left pulmonary artery (Fig. 1). There was no evidence of pulmonary embolism. Subsequent positron emission tomorgraphy-computerized tomography (PET-CT) revealed a large left upper lobe mass, mediastinal lymphadenopathy, innumerable hepatic and bilateral adrenal lesions, and numerous bony lesions (Fig. 2).

A large mass that is FDG-avid, encases surrounding structures, and is associated with widespread lesions is likely cancer. The smoking history, size of the lung mass, and pattern of spread (e.g., to the adrenal glands) make a primary lung cancer far more likely than an extrapulmonary cancer that has spread to the lung.

Some infections, such as actinomycosis and histoplasmosis, are known mimics of lung cancer. The former invades adjacent structures more readily, while the latter characteristically involves the adrenal glands. Endocarditis with widespread septic emboli has not been excluded, although the CT scan has not characterized the primary lung lesion as an abscess.

The patient's marked lower extremity edema may be arising from liver dysfunction. The low albumin and low platelet

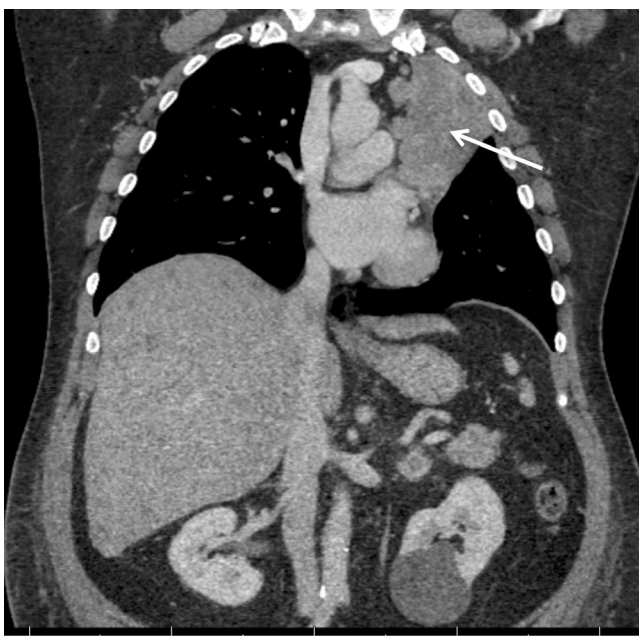

Figure 1 CT of the chest. Coronal view shows a 5.7 × 5.4 cm left hilar mass (*arrow*) with complete obstruction of the left upper lobe bronchus and left upper lobe collapse.

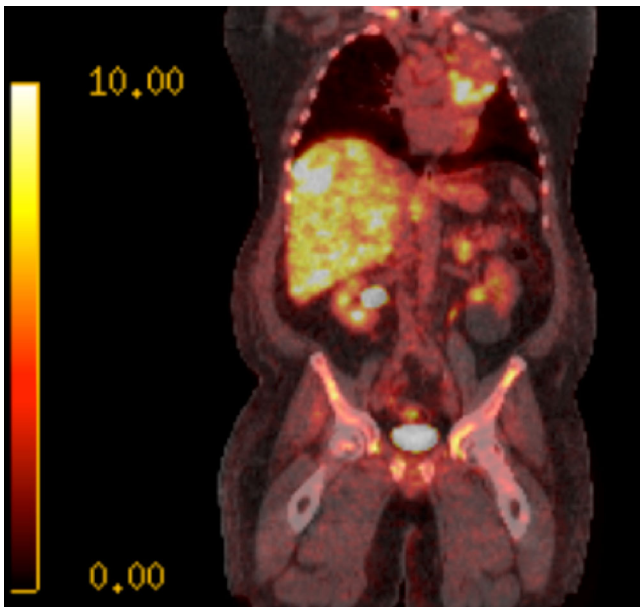

Figure 2 PET-CT of the body. Coronal view reveals a large left upper lobe mass, mediastinal lymphadenopathy, innumerable hepatic and bilateral adrenal lesions, and numerous bony lesions, all of which appear *yellow*.

count suggests liver failure, but the INR is normal and there is no cirrhosis on the abdominal images. Hypoalbuminemia alone does not cause edema, and there is no evidence of heart or kidney failure. Although his neurologic examination was normal, his baseline cognition remains uncertain. With such widespread disease, brain imaging is indicated.

As additional data emerge, the PR becomes increasingly long and complex, and starts to exceed the limits of working memory. The discussant reduces his cognitive load by replacing four elements—the lung mass, abdominal discomfort, liver function test abnormalities, and CT scan results—with one working diagnosis, "lung cancer with intra-abdominal metastases." However, the altered mental status, edema, and leukocytosis appear to be important (signal) but remain unattributed, and therefore must be carried on as independent data points. The discussant's updated PR (implied, not stated) is now a middle-aged man with metastatic lung cancer and altered mental status, lower extremity edema, and leukocytosis.

The patient underwent biopsy of a liver lesion and was discharged home with oncology clinic follow-up. One week later, he presented to the emergency department with uncharacteristic conduct. He was accompanied by his wife, who reported that he had been "eccentric" for many years, but now noticed behavior changes including outbursts, loud singing, and walking around without clothing. He reported new large-volume, watery, non-bloody diarrhea and persistent mild dyspnea and cough.

His progressive mental status change requires consideration of new metabolic, infectious, structural, or toxic processes affecting the brain. Special attention should be given to causes of altered mental status in a patient with suspected cancer, including brain metastases, carcinomatous meningitis, paraneoplastic metabolic abnormalities such as hyponatremia, hypercalcemia, or hypercortisolism, and paraneoplastic neurodegeneration such as limbic encephalitis. Progressive liver failure with hepatic encephalopathy must be considered as well. A small cell carcinoma could produce ectopic adrenocorticotropic hormone (ACTH), leading to glucocorticoid-induced psychosis.

Diarrhea can be classified as acute or persistent and invasive (bloody/mucus) or noninvasive (watery). *Clostridium difficile* colitis following antibiotic treatment must be excluded. Diarrhea is often a non-specific response to illness, but occasionally can be linked to an underlying delirium or dementia. Acute hyperthyroidism can lead to confusion and hyperdefecation. Pellagra is characterized by delirium, diarrhea, and dermatitis. Whipple's disease causes dementia and malabsorptive diarrhea, but over a more protracted time course. A malignant carcinoid tumor, or a small cell tumor with a similar neuroendocrine profile, could secrete serotonin, leading to diarrhea.

Iatrogenesis can generate clinical phenomena that are unrelated to the original presentation. However, discerning iatrogenesis from a delayed manifestation of the underlying condition can be challenging. In this case, if the diarrhea is antibiotic-induced, it is "noise" (i.e., solving diarrhea will not help diagnose the patient's underlying condition). However, if the diarrhea can reasonably be attributed to a syndrome that is associated with cancer (or confusion), as in this case, it will be treated as "signal," which the discussant does here.

His vital signs were within normal limits. He was alert and oriented to person and place. He intermittently laughed inappropriately and interjected loud, nonsensical comments. Asterixis was present. His strength, reflexes, and sensation were intact. His potassium was 2.8 mmol/L, AST 150 U/L, ALT 197 U/L, bilirubin 11.9 mg/dL, white blood count 20,000 per cubic mL with 80 % neutrophils, and INR 1.5. Urinalysis, thyroid-stimulating hormone level, and serum calcium were normal. Stool assay for *Clostridium difficile* toxin was negative. Chest radiography revealed an unchanged left upper lobe opacity. Abdominal computerized tomography demonstrated progressive hepatic metastatic disease with no biliary dilation. Magnetic resonance imaging of the brain revealed subtly increased T2 enhancement in the mesial temporal lobes. The patient was treated empirically for sepsis with vancomycin and piperacillin-tazobactam. Cerebrospinal fluid (CSF) showed a white blood cell count of 1, red blood cell count of 6, glucose of 69 mg/dl, and protein of 29 mg/dl. Polymerase chain reaction (PCR) tests for herpes simplex virus (HSV) and varicella-zoster virus (VZV) were negative. IgG index and oligoclonal bands were normal.

The patient is disoriented and disinhibited. The rising bilirubin, coagulopathy, asterixis, and progressive liver lesions point to hepatic encephalopathy. The brain MRI excludes metastatic disease and does not suggest carcinomatous meningitis. Medial temporal lobe enhancement is compatible with paraneoplastic (or HSV) encephalitis, but this usually has some degree of

intrathecal inflammation on cerebrospinal fluid (CSF) studies. The subtlety of the MRI finding and the normal CSF makes infectious or immune encephalitis less likely.

His hypokalemia is now severe, but this is most likely due to his diarrhea. Should it prove to be refractory, then evaluation of urinary potassium and acid–base status would help to discriminate between renal and gastrointestinal loss of potassium. In the absence of diarrhea (or vomiting or diuresis), mineralocorticoid excess would be considered. New-onset hyperaldosteronism is unlikely, but mineralocorticoid effects from supraphysiologic glucocorticoids produced by ectopic ACTH will be an important consideration if small cell lung cancer is diagnosed.

The persistent leukocytosis with no detected pathogens makes infection less likely, especially following antibiotic treatment. Lung cancer can cause leukocytosis through production of granulocyte-macrophage colony-stimulating factor (GM-CSF). Lymphoma and leukemia can be excluded by examination of a biopsy specimen, blood flow cytometry, and blood smear. Hypercortisolism usually causes neutrophilia with mature granulocytes.

The combination of edema, encephalopathy, leukocytosis, and hypokalemia in a patient with suspected metastatic lung cancer mandates evaluation of excess cortisol with assays of urinary cortisol and serum cortisol and ACTH. He does not have cutaneous findings of hypercortisolism, but striae, bruising, and fat redistribution are frequently absent with a fast-growing tumor. Myopathy and hyperglycemia can arise within this time frame, but they too are absent.

The discussant determines the subtle MRI findings to be "noise" in the absence of other findings supporting a diagnosis of paraneoplastic encephalitis. The hypokalemia, initially deemed mild and trivial, appears to be persistent and severe, and therefore becomes "signal" that may be integral to the PR.

The patient continued to have profuse diarrhea, dyspnea, and cough. His white blood cell count remained at 20,000 per cubic mL. Pathology from a liver biopsy specimen was consistent with small cell lung carcinoma (CD56+, synaptophysin+, chromogranin+, TTF-1+). Paraneoplastic antibodies from the cerebrospinal fluid (anti-Hu, anti-Yo, anti-Ri, LGI1, MaTa, Zic4, CV2, VGCC) were negative.

Diarrhea is not a typical feature of hypercortisolism, but small cell carcinoma is a neuroendocrine tumor (NET), so it may have the capacity to secrete peptides like serotonin, calcitonin, somatostatin, glucagon, gastrin, or vasoactive intestinal polypeptide that cause profuse diarrhea. It is possible that his diseased liver is unable to clear these peptides. Paraneoplastic ACTH, possibly with another paraneoplastic syndrome, is the leading diagnosis.

The serum cortisol was 95 ug/dL (normal 5–25 ug/dL); serum ACTH was 316 pg/ml (normal 6–50 pg/ml). After receiving 8 mg dexamethasone, the patient's morning cortisol was 97 ug/dL. The leukocytosis was attributed to his hypercortisolism. Antibiotics were discontinued, and cyclophosphamide was initiated for small cell lung cancer. Two days later, metyrapone was administered for hypercortisolism.

In the setting of hypercortisolism and associated immunosuppression, it is important to remain vigilant for infection, but to date there have been no localizing findings or suggestive test results.

The next day the patient became severely dyspneic and hypotensive. He was treated with broad-spectrum antibiotics and stress-dose steroids and was transferred to the intensive care unit and intubated. Serial chest x-rays showed no change in his left upper lobe opacity and did not reveal new infiltrates. Within hours, he developed refractory shock requiring three vasopressors. He was transitioned to comfort care and died the following day.

Blood cultures and sputum cultures subsequently grew *Klebsiella pneumoniae*. The source of his infection was unknown. Post-obstructive pneumonia was never demonstrated on CT imaging or serial radiographs. His diarrhea was unexplained but was ascribed to peptides that can be co-secreted with ACTH in lung cancer with paraneoplasia.[2,3]

DISCUSSION

In this case, a middle-aged smoker presented with shortness of breath, a lung mass, disorientation and disinhibition, hypokalemia, leukocytosis, edema, and diarrhea. When summarized in this way, the diagnosis of paraneoplastic hypercortisolism may appear nearly self-evident, but the road to that formulation—the problem representation—was challenging.

Problem representation (PR) is a key step and dynamic process in clinical reasoning.[4,5] However, there have been no studies on how clinicians choose which of the many data points in a case (symptoms, signs, or test results) to include and exclude in the problem representation. Insight into this issue is important when teachers are modeling, guiding, or analyzing problem representation for their learners.

Signal detection theory (SDT) was originally used to describe the ability of radar operators to discriminate friend from foe, but it is now widely used to describe how decision makers determine whether information is meaningful for solving a problem ("signal") or will have no bearing on the solution ("noise").[6] SDT highlights not only the task of recognizing information in the environment, but also the greater challenge of how to classify it.

It is likely that clinicians initially categorize data points as "signal," and therefore include them in their PR, when the data (1) match features held in relevant illness scripts (e.g., unilateral lower extremity edema readily maps onto deep venous thrombosis), (2) discriminate among illness scripts (e.g., fever in the case of monoarthritis favors septic joint over osteoarthritis), (3) are foreseeable as part of the solution in the

evolving context (e.g., back pain in a patient with lower extremity paresthesia but not back pain in a patient with diffuse pruritus), or (4) are significantly abnormal (e.g., sodium of 121 mg/dL but not sodium of 134 mg/dL).

Pruning of the data is essential for managing cognitive load in complex cases, but this editing process carries the risk of excluding relevant information.[7] Decision makers set their threshold for signal versus noise based on the benefits and costs of those classifications.[6] A conservative stance in threshold setting is to temporarily classify uncertain data as signal that remains in the PR, because prematurely calling them noise could be diagnostically catastrophic. A liberal stance is to relinquish data that does not meet predefined criteria early on in the PR process. SDT emphasizes that this tendency (or bias) is not a feature of the data point, but rather of the individual clinician, based on their individual tolerance of signal false-positive (which unnecessarily adds to cognitive load) versus signal false-negative (which forfeits a potential clue) classifications. It is likely that experience with myriad data points across many patients—and the lessons learned when such data points were included or omitted—is required to calibrate these judgements and tendencies.[8]

Two findings in this case underscore the challenges in determining signal versus noise. The patient initially presented with hypokalemia, which was at first mild and therefore disregarded as "noise." Later it was attributed to diarrhea, and was thus considered an epiphenomenon. Only when it persisted and was severe was it viewed as a key feature that was characteristic of and referable to the final diagnosis of paraneoplastic Cushing's syndrome. Conversely, the brain MRI disclosed "subtly increased T2 enhancement in the mesial temporal lobes," which was given early attribution (by the patient's treating clinicians) as "signal." Given the need to explain the behavior change, and the compatibility of this finding with the working hypothesis of paraneoplastic encephalitis, there was a strong inclination to include this finding in an early problem representation. But as the discussant's analysis revealed, this turned out to be inconsequential ("noise").

This case illustrates the important clinical reasoning skill of recognizing when a data point is signal, when it is noise, and the many times it can be both.

CLINICAL TEACHING POINTS

1. Approximately 5–10 % of cases of Cushing's syndrome are paraneoplastic. Up to 12 % of cases of small cell lung cancer will produce Cushing's syndrome.[9]
2. Paraneoplastic Cushing's syndrome presents with hypertension, hypokalemia, psychosis, glucose intolerance, myopathy, hyperpigmentation, and generalized edema. Other typical cushingoid features such as moon facies, buffalo hump, and striae are usually absent in paraneoplastic Cushing's syndrome, which progresses too quickly for these soft tissue changes to develop.[9,10]
3. Ectopic ACTH production is diagnosed by high levels of serum cortisol, serum ACTH, and urinary cortisol, and the failure of serum cortisol to decrease following the administration of high-dose dexamethasone.[11]
4. The primary therapy for paraneoplastic Cushing's disease is treatment of the underlying malignancy. Temporizing pharmacologic treatments which inhibit steroid production include ketoconazole, mitotane, metyrapone, and aminoglutethimide.[11]
5. Immunosuppression from overproduction of cortisol in ectopic Cushing's syndrome increases the risk of early death from infection.[12]

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Compliance with Ethical Standards:

Conflict of Interest: *The authors of this manuscript, Neha Gupta, Kenneth Feingold, and Gurpreet Dhaliwal, declare that they have no conflict of interest.*

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