83-Year-Old Man With Nausea, Constipation, and Peripheral Neuropathy

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An 83-year-old man with chronic peripheral neuropathy was admitted to the hospital with a 1-month history of progressive nausea, worsening constipation, and a 6.75-kg weight loss. His nausea was intermittent, accompanied by dry heaves and occasional nonbloody emesis. He had no associated odynophagia or dysphagia. Food could both alleviate or aggravate his nausea. There were no other identifiable aggravating or alleviating factors. Esophagogastroduodenoscopy (EGD) 5 years previously revealed gastric polyps and a nonobstructive Schatzki ring. The gastric polyps were biopsied and were negative for malignancy. The patient was taking aspirin at a dose of 81 mg but did not take other nonsteroidal anti-inflammatory drugs. His chronic constipation had also worsened from a baseline of one stool every 4 days to approximately one stool every 10 days. There was no history of melena or hematochezia, and he reported no abdominal pain. His last colonoscopy, 5 years before the current presentation, had revealed pandiverticulosis.

His medical history was remarkable for peripheral neuropathy (believed to be hereditary), end-stage renal disease (thought to be secondary to nephrosclerosis) that had been treated with hemodialysis for the previous 2 years, hypertension, prostate cancer treated with radical prostatectomy, and peptic ulcer disease. In addition to aspirin, his current medications included calcium acetate, tramadol, paricalcitol, and omeprazole. The patient had never used tobacco and drank alcohol only occasionally. His family history was notable for peripheral neuropathy in a paternal uncle.

On examination, the patient appeared comfortable and was alert, oriented, and afebrile. His blood pressure was 140/72 mm Hg, heart rate was 81 beats/min, and respiratory rate was 15 breaths/min. His sclerae were anicteric. He had normal bowel sounds. His abdomen was mildly distended but nontender, and no organomegaly was present. Neurologic examination showed decreased sensation to light touch to just below the knees and to the mid level of his fingers. The rest of his examination yielded normal findings. A complete blood cell count revealed the following (reference ranges provided parenthetically): hemoglobin, 9.8 g/dL (13.5-17.5 g/dL); white blood cell count, 7.0 × 10^9/L (3.5-10.5 × 10^9/L); and platelet count, 204 × 10^9/L (150-450 × 10^9/L). The differential count was normal. Other laboratory results included the following: creatinine, 7.0 mg/dL (0.8-1.3 mg/dL); potassium, 5.6 mmol/L (3.6-5.2 mmol/L); bicarbonate, 21 mEq/L (22-29 mEq/L); phosphorus, 4.7 mg/dL (2.5-4.5 mg/dL); calcium, 10.3 mg/dL (8.9-10.1 mg/dL); and thyrotropin, 2.0 mIU/L (0.3-5.0 mIU/L).

1. On the basis of the information provided, which one of the following is the most appropriate next step?
   a. Treat with magnesium hydroxide
   b. Obtain a general surgery consultation
   c. Begin empirical treatment for Helicobacter pylori infection
   d. Upright abdominal radiography
   e. Emergent hemodialysis

Beginning treatment for constipation with magnesium hydroxide is premature at this point in the hospitalization because an obstruction has not been ruled out. In addition, it would be an especially poor choice in this patient because of his end-stage renal disease and the potential for magnesium accumulation and associated toxicities. Surgical consultation is not indicated because the patient does not have an acute abdomen and an etiology for his nausea and constipation that would require surgical intervention has not been established. Although the patient has a history of peptic ulcer disease, beginning empirical therapy for H pylori infection is premature at this time. Bismuth and certain antibiotics will interfere with H pylori test results, including stool antigen...
testing, endoscopic testing, and the urea breath test. Abdominal radiography is the most appropriate next step in this patient because it can identify a bowel obstruction or ileus, which is important to address at this point in the workup. Emergent hemodialysis is not indicated because the patient is not acidic and his electrolyte derangements are minimal. In addition, he does not have a cardiac rub or other signs of uremia, nor does he have evidence of hypervolemia.

Upright abdominal radiography showed a few scattered loops of air-filled nondilated small bowel and scattered air and stool within a normal-caliber colon. A gastroparetic diet consisting of low-fat foods and cooked vegetables was initiated, and the patient was told to eat small portions and to eat slowly. That evening, he was unable to eat most of his meal because of nausea, which was only partially relieved with ondansetron and prochlorperazine.

2. Which one of the following is the best evaluation option at this time?

a. EGD
b. Gastric emptying study
c. Computed tomography of the abdomen
d. Magnetic resonance imaging (MRI) of the abdomen
e. Observation and symptomatic treatment adding intravenous lorazepam to the antiemetic regimen

The best step at this time is EGD to exclude mechanical obstruction and assess for mucosal abnormalities such as gastritis or peptic ulcer disease. Although a gastric emptying study may eventually be indicated and can be useful in patients with unexplained nausea and vomiting, it is more important at this point in the workup to exclude mechanical obstruction or mucosal disease, especially given the patient’s history of peptic ulcer disease. Imaging with computed tomography or MRI would not assess for peptic ulcer disease, which is fairly high on the differential diagnosis at this point. In addition, iodinated contrast dye cannot be removed via hemodialysis, and performing an MRI would place the patient at unacceptable risk for nephrogenic systemic fibrosis. Simple observation and symptomatic treatment may be appropriate in some patients with acute nausea with or without an identifiable cause. However, our patient had experienced an associated 6.75-kg weight loss and had issues with oral intake, both of which are quite concerning. In addition, benzodiazepines should be avoided in elderly patients because of the increased risk of adverse reactions such as excessive sedation or respiratory depression in this population.

On hospital day 2, the patient continued to be nauseated. The EGD showed a nonobstructive Schatzki ring, gastropathy, multiple antral erosions, and severe duodenitis with superficial ulcers. Biopsies were obtained for *H pylori* testing and Congo red staining. Omeprazole was then increased from 20 mg/d to 40 mg/d. Over the next 24 hours, the patient’s nausea and constipation improved. He was scheduled for an outpatient follow-up appointment and discharged. The following day, the patient’s biopsy studies were reported as negative for *H pylori* and positive for amyloid deposition on the basis of Congo red staining.

3. In view of the biopsy findings, which one of the following should be performed next?

a. Chemotherapy for AL (formerly called primary) amyloidosis
b. Liquid chromatography—tandem mass spectrometry (LC-MS/MS) on biopsy samples
c. Repeated EGD with biopsies in 3 months
d. Immunofluorescence staining on biopsy samples
e. Bone marrow biopsy

Chemotherapy is an option for AL amyloidosis. However, the amyloid subtype has not been established, so chemotherapy would be premature and indeed harmful if the diagnosis is not AL amyloidosis. The test of choice to differentiate the amyloid subtypes and guide therapy is LC-MS/MS. AL amyloidosis is a progressive disease, so waiting 3 months to repeat EGD would simply be delaying needed therapy because the amyloid depositions would not resolve without treatment. Immunofluorescence has been used to identify amyloid subtypes. However, this technique has very low sensitivity (especially when compared with mass spectrometry) because of numerous issues.
related to the fixation of the sample and protein sequence variations in amyloidosis. A bone marrow biopsy is premature but may be warranted if a monoclonal protein is detected on serum protein electrophoresis (SPEP) or urinary protein electrophoresis (UPEP).

The following studies were ordered: LC-MS/MS evaluation of the biopsy specimen; transthyretin (TTR) genetic testing on peripheral blood; and SPEP, UPEP, and immunofixation studies, which were negative for a monoclonal protein.

4. Given this patient’s clinical presentation, which one of the following is the most likely amyloid subtype?
   a. AL amyloidosis
   b. AA (previously called secondary) amyloidosis
   c. β2-Microglobulin amyloidosis
   d. Hereditary amyloidosis
   e. Wild-type TTR amyloidosis

AL amyloidosis is unlikely. The patient had negative results of SPEP, UPEP, and immunofixation studies; therefore, suspicion for AL amyloidosis related to a plasma cell disorder is low. If the patient has a known plasma cell dyscrasia such as Waldenström macroglobulinemia or multiple myeloma, AL amyloidosis should be suspected. Additionally, our patient’s peripheral neuropathy has been present for 30 years, and a slow course of amyloidosis would be unusual. AA amyloidosis occurs in the setting of chronic inflammatory disorders or infection. The patient does not have any of the commonly associated conditions, such rheumatoid arthritis or inflammatory bowel disease, making AA amyloidosis unlikely. β2-Microglobulin amyloidosis is associated with hemodialysis. However, it typically occurs in patients who have undergone hemodialysis longer than 2 years that our patient had been undergoing treatment. Additionally, current dialysis technology provides increased clearance of β2-Microglobulin. Although the patient’s paternal uncle had peripheral neuropathy, there is no known family history of amyloidosis, so a hereditary process is unlikely. Given his age, gender, and lack of risk factors for the other subtypes, the most likely subtype is age-related, or senile, amyloidosis caused by deposition of normal wild-type TTR.

Liquid chromatography—tandem mass spectrometry detected wild-type TTR amyloid deposition in our patient. Peripheral blood testing did not reveal genetic sequence variation.

5. Which one of the following is the best therapeutic option for this patient?
   a. Chemotherapy with melphalan and dexamethasone
   b. Symptomatic care
   c. Colchicine
   d. Genetic counseling
   e. Liver transplant

Chemotherapy is appropriate in the setting of AL amyloidosis. In our patient, symptomatic care with propylene glycol for constipation and antiemetics for nausea is the best therapeutic option because he has wild-type TTR amyloidosis, for which there is no specific treatment. Colchicine has been used in some variants of AA amyloidosis, particularly in the context of familial Mediterranean fever, but does not have a role in the treatment of wild-type TTR amyloidosis. Genetic counseling would be appropriate if there had been a sequence variation in the TTR gene, but our patient had wild-type TTR. Liver transplant can be used for some hereditary forms of amyloidosis; however, it would not be appropriate in our patient.

The patient was instructed to take propylene glycol, 17 g/d, and to use a bisacodyl suppository on nondialysis days. After 4 weeks of therapy, the patient had improvement in his constipation and less nausea. A follow-up visit was scheduled.

DISCUSSION

Our patient presented with a 6.75-kg weight loss, impaired gastric motility, and a history of peripheral neuropathy. Duodenal biopsy confirmed perivascular deposition of amyloid, concerning for amyloidosis. Serum and urinary protein electrophoresis with immunofixation were negative for a monoclonal protein, and LC-MS/MS detected a peptide profile consistent with wild-type TTR amyloid deposition. Peripheral blood testing did not reveal TTR sequence variation. Consequently, the patient required no additional therapy other than symptomatic treatment. This case highlights the importance of identifying amyloidosis.
medical education

subtype to ensure appropriate treatment and avoid interventions that may not be indicated and may even be harmful.

Amyloidosis refers to a group of disorders that share the common feature of abnormal protein accumulation and deposition. The amyloid protein is an extracellular substance that has a standard physical structure when deposited in the body. Nonbranching fibrils are arranged in a characteristic β-pleated sheet, which allows for the characteristic Congo red staining and birefringence of amyloid proteins often used in pathologic identification. The clinical presentation of amyloidosis is classified into systemic and localized categories, depending on the extent of amyloid deposition. The major systemic amyloidosis subtypes include AL amyloidosis, AA amyloidosis, hereditary amyloidosis, senile (wild-type TTR) amyloidosis, and dialysis-related amyloidosis.

AL amyloidosis manifests as protein deposition from an overproduced immunoglobulin light chain, and the diagnosis requires demonstration of a plasma cell dyscrasia. AL amyloidosis is strongly associated with plasma cell dyscrasias, most notably multiple myeloma and Waldenström macroglobulinemia. AA amyloidosis results from overproduction of a serum protein secondary to chronic inflammatory conditions. Chronic inflammation and the resultant cytokine release increase the production of AA protein, which is produced in the liver. The conditions associated with AA amyloidosis include rheumatologic disease, inflammatory bowel disease, subcutaneous drug use, and nonimmunoglobulin-producing malignancy. Chronic infections, such as Mycobacterium tuberculosis and osteomyelitis, and familial Mediterranean fever are also associated with AA amyloidosis.

Age-related (senile) amyloidosis is caused by deposition of normal (wild-type) TTR. There is often myocardial deposition, and carpal tunnel syndrome may also be seen. Renal involvement is less common. Hereditary amyloidosis is characterized by deposition of protein in both peripheral and autonomic nerves. The protein most commonly involved is a mutated TTR. More than 100 TTR mutations have been described. The presentation of these diseases is variable, depending on the specific mutation present. In addition to TTR, numerous other mutations that have been described in other genes can lead to amyloid deposition. These include Alzheimer amyloid precursor protein, prion protein, gelsolin, and apolipoprotein A-I and A-II.

Dialysis-related amyloidosis is considered a late complication of end-stage renal disease and results from accumulation of β2-microglobulin due to decreased clearance of the protein and its deposition in osteoarticular structures. Carpal tunnel syndrome, destructive arthropathy, and bone cysts and fractures may develop, usually after several years of dialysis. Because clearance of β2-microglobulin from blood is dependent on dialyzer membrane pore size, the prevalence and severity of dialysis amyloidosis is lower with use of current high-flux dialyzer membranes.

Tissue is required for the diagnosis of amyloidosis. Fat pad aspiration may be performed. Alternative biopsy sites include the liver, kidney, and rectum. Although the sensitivity of biopsy from these sites may be higher, they are more invasive and associated with higher rates of complications, particularly bleeding. Therefore, abdominal fat pad aspiration is recommended as the first biopsy, with subsequent biopsies if initial test results are negative and clinical suspicion remains high. In cases with organ involvement, biopsy specimens should be obtained from the involved organs. Once Congo red staining has identified amyloidosis, subtype analysis should be performed. Subtype analysis is a critical step, even in the setting of a known plasma cell dyscrasia. Although AL amyloidosis may be suspected, it is not uncommon for a patient to have a plasma cell disorder and a non-AL amyloidosis. This is a critical distinction that has major therapeutic implications.

Tissue immunofluorescence has been used to subtype amyloidosis. However, the sensitivity of this test is low. This limitation was demonstrated in a retrospective study from the United Kingdom. Of 375 patients who had been diagnosed with AL amyloidosis based on the available clinical and laboratory data, 10% were found to have a hereditary form of the disease. Mass spectroscopy is a technique that has yielded extremely high sensitivities and specificities (95%-100%) for identification of amyloidosis subtypes AL (both Ig-k and Ig-l), AA, and TTR.

In cases in which TTR amyloidosis is identified, it is important to differentiate the
hereditary form from the senile form (wild-type). This can be accomplished by genotyping on peripheral blood. Although therapeutic options for both forms are limited, a genetics consultation for those with the hereditary form, and their family members, is important.

AL amyloidosis is typically treated with chemotherapy. If the patient meets clinical eligibility criteria, myeloablative chemotherapy followed by hematopoietic stem cell transplant has been used with good results.10 Therapy for AA amyloidosis consists of controlling the underlying inflammatory disease. Treatment options for hereditary amyloidosis are somewhat limited. Certain hereditary subtypes, especially those with sequence variations in hepatically produced proteins, have been shown to respond to liver transplant, especially if recognized early in the disease.8 Otherwise, there are no specific therapies available for hereditary amyloidosis. Although several drugs with antifibril activity (tafamidis, diflunisal) have been developed and shown efficacy in animal models, they are still in the process of being approved for clinical use.1 No specific treatment is available for senile amyloidosis.

Physicians should be aware of the amyloid subtypes and proceed with subtype identification before prescribing treatment. Misdiagnosis has occurred.10 Not all patients with a monoclonal protein have AL amyloidosis. Patients with senile amyloidosis can have monoclonal gammopathy of undetermined significance, and patients with hereditary amyloidosis may not have a family history of the disease. With the advent of mass spectroscopy, subtyping can be performed easily and accurately.

Our patient presented with a constellation of signs and symptoms that could be consistent with a diagnosis of AL amyloidosis. However, additional investigation showed that our patient had senile amyloidosis. Treatment with chemotherapy would not have been helpful and would have put the patient at unnecessary risk.

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REFERENCES

CORRECT ANSWERS: 1. d. 2. a. 3. b. 4. e. 5. b.