Successful Treatment with Methylnaltrexone and IVIG for Paraneoplastic Syndrome–Associated Intestinal Pseudo-Obstruction

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Paraneoplastic syndromes are systemic disorders that are associated with malignancy but are not directly due to the local effects of a tumor mass or its metastases. These syndromes are most commonly associated with small cell lung cancer or thymoma.[1] Paraneoplastic syndromes frequently present with gastrointestinal dysmotility and can lead to intestinal pseudo-obstruction. Many patients with paraneoplastic syndromes have detectable anti-Hu antibodies in the serum. We report a patient with non–small cell lung cancer who presented with pseudo-obstruction of the entire gastrointestinal tract that was successfully treated with intravenous immunoglobulin (IVIG) and subcutaneous methylnaltrexone (Relistor, Salix).

Case Report

A 60-year-old man with no significant medical history initially presented with progressively worsening paresthesias of the hands and feet over approximately 3 months. Findings from his physical examination were unremarkable; however, his neurologic examination revealed decreased pinprick sensation in his extremities. Shortly after his initial presentation, the patient began complaining of constipation, bloating, abdominal distention, nausea, vomiting, and decreased appetite, and he lost approximately 50 lbs over the subsequent 6 weeks. The patient's constipation worsened to the point where he had no bowel movements for approximately 2 weeks prior to his hospital admission.

The patient underwent a colonoscopy and esophagogastroduodenoscopy, both of which had unremarkable findings. A gastric emptying study demonstrated a residuum of 56% 4 hours after ingestion of a meal, which is consistent with severe gastroparesis (normal, <10% at 4 hours). A whole-gut transit test (SmartPill) was unsuccessful, as the capsule remained in the stomach for 5 days before it passed spontaneously. A computed tomography (CT) scan of the abdomen and pelvis showed severe extrahepatic and mild intrahepatic biliary duct dilation associated with marked distension of the gallbladder; the CT scan also showed mild scattered foci of colonic wall thickening involving the cecum, proximal ascending colon, and portions of the descending colon, with no evidence of associated pericolic inflammatory change (Figure 1). Due to concern for biliary duct obstruction, the patient underwent an endoscopic retrograde cholangiopancreatography (ERCP), which demonstrated severe common bile duct (CBD) dilation with no stones (Figure 2). A distal CBD stent was subsequently placed. Cytology analysis of CBD brushings obtained during the procedure was unremarkable. Within 24 hours of the ERCP, the patient developed worsening abdominal pain. Another CT scan was performed to evaluate the patient's acute symptoms; although this scan did not demonstrate acute pancreatitis, it showed severe colonic wall thickening involving the cecum, ascending colon, transverse colon, and proximal descending colon that was increased from the CT scan that had been performed 2 days earlier. A flexible sigmoidoscopy to the splenic flexure showed normal colonic mucosa.

Initial laboratory tests were notable for normocytic anemia, an alanine transaminase level of 62 IU/L (normal, 0–40 IU/L), an alkaline phosphatase level of 144 IU/L (normal, 40–130 IU/L), an erythrocyte sedimentation rate of 60 mm/hr (normal, 0–15 mm/hr), and a C-reactive protein level of 200.2 mg/L (normal,

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Figure 1. A cross-sectional view of a computed tomography scan of the abdomen and pelvis revealing moderate dilation of the colon and thickening of the colonic wall.

Figure 2. An endoscopic retrograde cholangiopancreatography demonstrating dilation of the common bile duct.

0–5 mg/L). Due to concern for a paraneoplastic syndrome, testing for anti-Hu antibodies was performed and returned with a titer of 1:640 by Western blot.

Upon hospital admission, a nasogastric tube (NG) was placed and total parenteral nutrition (TPN) was started. During the first day of admission, NG suction output was approximately 1 L. Intravenous metoclopramide (10 mg) and ondansetron (4 mg 3–4 times per day) did not improve the patient's symptoms or his NG output. IVIG (0.5 g/kg/day) was started on Day 7 of his admission. After 4 days of IVIG therapy, the patient's symptoms had not improved and the decision was made to begin treatment with methylnaltrexone (8 μg subcutaneous injection). Within 24 hours of the first dose of methylnaltrexone, the patient started to pass gas and have bowel sounds, which had been absent since his admission 10 days earlier. His NG tube output decreased to 500 mL per day. After receiving the second dose of methylnaltrexone (12 μg subcutaneous injection) on the second day, the patient's gastric residue significantly decreased (to 50 mL) and he started to have bowel movements. The patient's symptoms quickly improved, and on Day 12 after admission, he was discharged on a clear liquid diet (which he tolerated) and TPN (because of malnutrition). In total, he received 4 doses of subcutaneous methylnaltrexone before discharge.

A positron emission tomography scan performed after discharge showed an enlarged cervical lymph node, and a biopsy revealed metastatic non–small cell lung cancer.

Discussion

Our patient presented with a 3-month history of sensory neuropathy followed by the development of diffuse gastrointestinal dysmotility, was found to be positive for anti-Hu antibodies, and was subsequently diagnosed with a non–small cell carcinoma of the lung. His gastrointestinal symptoms responded to treatment with IVIG and methylnaltrexone, which resulted in the successful reinstitution of oral intake as well as discharge from the hospital. To date, this case study is the first report of successful treatment with IVIG and methylnaltrexone for paraneoplastic syndrome–associated intestinal pseudo-obstruction.

The most common presentations of paraneoplastic syndromes are neurologic symptoms, including paraneoplastic sensory neuropathy (59–69%), encephalomyelitis/seizure (16–21%), cerebellar dysfunction (13–23%), motor weakness (14%), and brainstem dysfunction (10%). When the inflammatory infiltrate is localized to the myenteric plexus in the gastrointestinal system, intestinal motor dysfunction is the primary manifestation, including gastroparesis (50%), intestinal pseudo-obstruction (21%), dysphagia (11%), esophageal achalasia (11%), pyloric stenosis (5%), and anal spasticity (3%).[1-3]

The role of Hu antibodies in the pathogenesis of paraneoplastic syndromes is unknown. In addition to being present in underlying tumors, Hu antigen is also expressed in the nucleus and cytoplasm of neurons (particularly within the myenteric ganglia) in the gastrointestinal tract.[1,4,5] One hypothesis is that anti-Hu antibodies elicit a cellular immune response that results in the infiltration of mononuclear cells into the nervous system.[1,2,6]

Management of paraneoplastic syndrome–associated intestinal pseudo-obstruction is difficult and

largely unsuccessful. When a malignancy is detected, the treatment of choice is treating the tumor. However, when a malignancy is not detected, treatment usually consists of supportive therapy.[1] Immunosuppression with corticosteroids, cyclophosphamide, azathioprine, plasma exchange, IVIG, or immunoabsorption has been used with variable results for treatment of paraneoplastic neuropathy with or without the association of anti-Hu antibodies.[7-9] In a case report of a patient without detectable neoplasia, after the failure of oral steroids and IVIG, rituximab (Rituxan, Genentech) was used to successfully treat anti-Hu–associated sensory neuropathy and gastric pseudo-obstruction.[10]

After receiving a 4-day course of IVIG followed by subcutaneous injection of methylnaltrexone, our patient's gastrointestinal dysmotility quickly improved. Methylnaltrexone is a quaternary derivative of the opioid antagonist naltrexone. By selectively binding to the opioid μ-receptor, methylnaltrexone reverses morphine-induced inhibition of electrically stimulated contraction in isolated guinea pig ileum and human small intestinal smooth muscle cells. Methylnaltrexone has been shown to reverse morphine-induced prolonged oral–cecal transit time in healthy human volunteers.[11]

We propose 2 hypotheses to explain the mechanism of action for methylnaltrexone treatment of intestinal pseudo-obstruction. The first hypothesis involves an effect on the infiltrating lymphocytes. In a previously reported case of anti-Hu–associated intestinal pseudo-obstruction, samples taken from the entire intestinal tract showed absent or severely reduced mucosal and myenteric nervous tissue. The remaining areas of the nerve plexus were infiltrated or surrounded by a mononuclear infiltrate.[4] Activated lymphocytes have increased expression of opioid peptides and home preferentially to injured tissue, where they secrete endogenous opioids. Prompted by local inflammatory factors—such as corticotropin-releasing factor and interleukin-1β—immunocytes release β-endorphin, an endogenous opioid.[12] Endogenous opioids have been shown to affect colonic inflammation. μ-opioid receptor agonists significantly reduced inflammation in experimental models of colitis induced by 2,4,6-trinitrobenzene sulfonic acid in mice.[13] In inflammatory bowel disease patients, μ-opioid receptors are upregulated in lamina propria mononuclear cells, as well as in neuronal cell bodies located in the submucosal and myenteric plexuses.[14] Therefore, we postulate that in anti-Hu–associated intestinal pseudo-obstruction, after binding to Hu antigen, anti-Hu antibodies elicit immune-mediated inflammation in the small intestinal myenteric plexus through the recruiting of mononuclear cells. Due to the subsequent release of endogenous opioids by activated immunocytes, peristaltic activity or contraction of the intestine is inhib-

ited. Methylnaltrexone, an opioid antagonist, can counteract the effects of endogenous opioids.

A second potential mechanism is that anti-Hu antibodies bind directly to the opioid receptor in the gastrointestinal tract, causing a motility disorder. By blocking the binding of anti-Hu antibodies to the opioid receptor, methylnaltrexone could relieve anti-Hu–associated gastrointestinal dysmotility.

In our patient, it is difficult to separate the effects of IVIG and methylnaltrexone. In the largest series reported to date of patients with paraneoplastic neurologic syndromes who were treated with IVIG, all patients received 1–26 cycles of a 5-day course of IVIG (mean, 5.8 cycles). Only 1 patient, who received both antitumor treatment and 13 complete cycles of IVIG, showed improvement in peripheral nervous system symptoms.[7] To date, IVIG treatment for paraneoplastic syndromes has been very disappointing. However, the symptoms of our patient significantly improved within 24 hours of receiving a subcutaneous injection of methylnaltrexone. Upon improvement, he had received only 4 doses of IVIG. Therefore, it is likely that his improvement in gastrointestinal function is mostly, if not completely, due to methylnaltrexone treatment.

In addition to gastroparesis and intestinal pseudo-obstruction, our patient developed biliary duct dilation and distention of the gallbladder. However, an ERCP did not find biliary duct obstruction. Therefore, the patient's biliary duct dilation and distention of the gallbladder are most likely other manifestations of paraneoplastic syndromes. To date, only 3 cases of paraneoplastic syndromes have been documented as the cause of biliary dilation.[15] However, the anti-Hu antibody status of these 3 cases is unknown.

Conclusion

This case study suggests a possible new therapeutic approach (subcutaneous methylnaltrexone) for anti-Hu–associated intestinal pseudo-obstruction. The results from our patient are promising; however, a randomized clinical trial is required to validate this therapy.

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Review

Treatment with Methylnaltrexone and IVIG for Paraneoplastic Gastrointestinal Dysmotility

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Gastrointestinal (GI) dysmotility that occurs in the setting of malignancy may not result from direct tumor invasion, infections, metabolic derangements, or chemotherapy. Such disorders of motility are characterized as paraneoplastic GI dysmotility. This condition is most commonly associated with small cell lung cancer (SCLC), with symptoms usually preceding the diagnosis of cancer.[1] Paraneoplastic GI dysmotility has a wide spectrum of clinical presentations, including achalasia, gastroparesis, chronic intestinal pseudo-obstruction, and constipation. Diagnosis often requires a high degree of clinical suspicion as well as serologic testing with widely available onconeuronal antibodies such as type 1 anti–neuronal nuclear antibody (ANNA-1), also known as anti-Hu antibody (which is directed against the Hu family of RNA nuclear binding proteins). This test has become the first line of testing when paraneoplastic dysmotility is suspected.

The pathophysiology of paraneoplastic GI dysmotility is not completely understood. Lymphoplasmacytic destruction of myenteric plexus neurons has been proposed based on histologic studies that show a decreased number of ganglion cells, replacement of neurons by Schwann cells and collagen, or a decrease in interstitial cells of Cajal; however, smooth muscle cells are typically spared.[2,3] The destruction of myenteric neurons is thought to result from autoimmune mechanisms. This is consistent with recent reports of non-neoplastic autoimmune GI dysmotility. Thus, in addition to ANNA-1, voltage-gated calcium channel antibodies, neuronal nicotinic acetylcholine receptor antibodies, and Purkinje cell cytoplasmic antibodies have been seen in patients with paraneoplastic GI dysmotility.[1]

Although SCLC is the cancer most commonly associated with paraneoplastic GI dysmotility, cancers arising in the ovaries, breasts, stomach, esophagus, and bronchial carcinoids have also been associated with paraneoplastic GI dysmotility. A subset of ANNA-1–positive SCLC patients in 1 study were found to have synchronous malignancies.[4] Subacute (<6 months) onset of rapidly progressive, disabling symptoms in high-risk patients (eg, age >50 years, history of smoking) should prompt suspicion for a paraneoplastic phenomenon.[5] Gastroparesis and chronic intestinal pseudo-obstruction are the 2 most common paraneoplastic GI dysmotility syndromes. Unfortunately, the diagnosis of paraneoplastic GI dysmotility is difficult because dysmotility symptoms have poor specificity for paraneoplastic processes and poor negative predictive values in the absence of antibodies. To exclude the possibility of a false-positive serology test, a more aggressive search with mediastinal computed tomography imaging and bronchoscopy is generally recommended to detect an

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occult neoplasm (eg, SCLC) in the presence of both suggestive dysmotility symptoms and ANNA-1.[1]

The treatment of paraneoplastic GI dysmotility centers on management of the underlying malignancy. However, dysmotility can persist even after the cancer is in complete remission.[6] The usual management of dysmotility (with antiemetics, prokinetics, or laxatives) is often suboptimal, leading to severe malnutrition and wasting, even though the cancer itself may be under control. There is an unmet clinical need for management of paraneoplastic GI dysmotility. Targeting the autoimmune pathogenesis with high-dose corticosteroids, cyclophosphamide, intravenous immunoglobulin (IVIG), rituximab (Rituxan, Genentech), or plasmapheresis has been associated with limited success to date.[7]

The case reported by Zhang and colleagues described a patient who had metastatic non-SCLC confirmed by a positron emission tomography scan and a biopsy of a cervical node and who had presumed paraneoplastic GI dysmotility (gastroparesis and diffuse colonic dilation).[8] The patient failed initial treatment with a 4-day course of IVIG—although the usual dose for the treatment of autoimmune dysmotility is six 5-day cycles—but he was successfully treated with methylnaltrexone (Relistor, Salix).[8] The case report also highlighted nonobstructive biliary dilation as a rare manifestation of paraneoplastic GI dysmotility.

It is unclear from the case report by Zhang and colleagues whether there was metastatic spread beyond the cervical node, and it is assumed that the potential adverse effects of opioid use were excluded when the patient was enrolled in a comprehensive strategy to manage the presumed paraneoplastic GI dysmotility.[8] After failure of IVIG therapy, a significant improvement in bowel function was noted with a single dose of methylnaltrexone. Additional clinical clues supported the potential role of increased endogenous opioid function in this patient. Thus, the presence of colonic dilation and bile duct dilation was suggestive of high opioid effects. As the sphincter of Oddi has a high density of µ-opioid receptors, the nonobstructed dilation of the bile duct suggests a dysfunction or spasm of the sphincter.[9,10] Opioid agonism is associated with gastroparesis and colonic motor dysfunction, including dilation.[11]

Methylnaltrexone is a subcutaneously administered, peripherally acting, µ-opioid receptor antagonist that is approved by the US Food and Drug Administration for treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care and have not received sufficient relief from laxative therapy. N-methylation of the systemic opioid antagonist naltrexone limits its ability to cross the blood–brain barrier, thus preserving central analgesic effects of co-administered opioids and reversing the effects of those opioids in the periphery, specifically in the GI tract. Methylnaltrexone has reversed morphine-induced delay in gastric emptying and oral–cecal transit time without affecting analgesia in healthy volunteers and has also been shown to reverse methadone-associated constipation and GI dysmotility.[12-14] In a phase III clinical trial, 133 patients with terminal disease (58% cancer) who were taking opioids for analgesia for at least 2 weeks and who were having fewer than 3 bowel movements despite taking laxatives during the previous week were randomized to either methylnaltrexone at a dose of 0.15 mg/kg body weight or placebo every other day for 2 weeks.[15] In the methylnaltrexone group, significantly more patients achieved laxation within 4 hours of the first study dose compared to patients in the placebo group (48% vs 15%). Abdominal pain and flatulence were the most commonly reported adverse effects.

Zhang and associates proposed 2 potential mechanisms to explain their patient's improved gut motility, including a reduction in the effects of endogenous opioids in the autoimmune destruction of enteric neurons and competitive inhibition of anti-Hu antibody binding to opioid receptors.[8] Additional studies are required to investigate these potential mechanisms. Opioids may also have other roles in the enhancement of cancer progression, which may have been inhibited by methylnaltrexone. Thus, reduced exposure to opioids via regional anesthesia has been associated with a decreased risk of cancer recurrence, and overexpression of µ-opioid receptors in a human non-SCLC cell line has been shown to increase in vitro and in vivo measures of tumor growth and metastasis.[16,17] Other potential effects of methylnaltrexone include inhibition of opioid-induced endothelial cell proliferation and migration via inhibition of the vascular endothelial growth factor receptor.[18]

Overall, the case reported by Zhang and coworkers raised interesting concepts on the mechanism of paraneoplastic GI dysmotility and documented the potential utility of methylnaltrexone for treatment of this condition; however, these observations must be replicated and systematically studied before this drug can be recommended as a treatment option.[8]

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