Occult Non-small Cell Lung Cancer Presenting as Paraneoplastic Gastroparesis: A Case Report and Literature Review

Muhammad A. Baig 1, Tejinder Randhawa 2, Muhammad B. Majeed 2, Rohit Agrawal 1, Seema R. Gandhi 3

1. Internal Medicine, John H. Stroger, Jr. Hospital of Cook County, Chicago, USA 2. Internal Medicine, John H. Stroger Jr. Hospital of Cook County, Chicago, USA 3. Gastroenterology and Hepatology, John H. Stroger Jr. Hospital of Cook County, Chicago, USA

Corresponding author: Muhammad A. Baig, mbaig2@cookcountyhhs.org

Abstract
Paraneoplastic gastrointestinal syndromes rarely precede the actual detection of an overt cancer with gastroparesis being a very rare initial presentation. To increase the clinical awareness of this rare clinical entity, we present a case of severe gastroparesis that was later proven to be associated with an occult poorly differentiated non-small cell lung cancer. We then continue to briefly review the relevant literature on paraneoplastic gastrointestinal syndromes to date.

A 61-year-old African-American man presented with two months history of severe post-prandial nausea, vomiting and bloating associated with unintentional weight loss of 20 pounds. General physical examination revealed cachexia, temporal muscle wasting and clubbing of nails in both hands. The following investigations were normal or negative: basic metabolic panel, liver function tests, chest X-ray and esophagogastroduodenoscopy. Computed tomography (CT) scan of the abdomen showed residual food in the stomach and scintigraphic gastric emptying studies were consistent with gastroparesis. CT scan of the chest was performed which revealed a spiculated nodule sized 9 mm in right upper lobe of the lung with right hilar lymphadenopathy. Positron emission tomography (PET) scan revealed hyper-metabolic activity in the right upper lobe nodule and right hilar adenopathy. Nodule resection and biopsy revealed a poorly differentiated non-small cell lung carcinoma. Due to the concern of paraneoplastic origin of his gastroparesis further serological testing showed positive anti-neuronal nuclear antibodies type 1 (Anti-Hu) and cytoplasmic purkinje cell antibodies (Anti-Yo). The patient was started on a chemotherapy combination of Carboplatin and Paclitaxel with a three-week course of local radiation therapy. Moreover, for the relief of his severe gastrointestinal (GI) symptoms dietary modifications, pro-kinetic agents and psychological counseling were used with gradual clinical improvement observed on follow-up visits.

Introduction
Gastroparesis is a disorder of delayed gastric emptying that commonly presents with nausea, vomiting, abdominal bloating and early satiety. Although the majority of gastroparesis cases are idiopathic or secondary to diabetic and post-surgical etiologies, a rare etiology of gastroparesis is paraneoplastic syndrome. This is most commonly seen in pancreatic, ovarian, gallbladder, lung, and soft tissue cancers [1, 2]. Paraneoplastic gastroparesis (PG) is an important diagnosis for two reasons: (1) the presentation of gastroparesis frequently precedes the diagnosis of the underlying malignancy and (2) treatment of the underlying malignancy may resolve the gastroparesis [3]. The pathophysiology of PG is not well understood; however, studies have demonstrated an immune-mediated destruction of the interstitial cells of Cajal and neurons within the myenteric plexus as the primary histologic change in PG [4, 5]. Serologic testing for autoantibodies, specifically anti-neuronal nuclear autoantibodies type 1 (ANNA-1) or anti-Hu antibodies, which mediate the degeneration of neurons may aid in making the difficult diagnosis of PG. Herein, we report a case of PG with positive serologies as well as present a review of the literature on the subject.

Case Presentation
A 61-year-old African-American man presented with two months history of severe post-prandial nausea, vomiting and bloating. He also reported generalized fatigue, anorexia and unintentional weight loss of 20 pounds. He remained an active smoker with a 20-pack-year smoking history but denied any alcohol consumption or illicit substance use. His medications included ondansetron and pantoprazole tablets with minimal symptom relief. On admission, vital signs were only significant for slight tachycardia of 94 beats per minute. General physical examination revealed cachexia, temporal muscle wasting and clubbing of nails in both hands. The remainder of his examination was unremarkable. At this point, our differential diagnoses for his symptoms included gastrointestinal (GI), endocrine, metabolic, and psychiatric causes. From a GI perspective, we considered gastroparesis, gastric outlet obstruction, GI malignancy and cyclical vomiting.
Investigations

The following investigations were normal or negative: blood urea nitrogen, serum creatinine, serum potassium, serum total calcium, bilirubin, alanine aminotransferase, aspartate aminotransferase, serum lipase, urinalysis, chest X-ray and electrocardiogram. In addition, the patient had a computed tomography (CT) scan of the abdomen and pelvis on admission demonstrating residual food and fluid in his stomach despite fasting concerning for delayed gastric emptying. An esophagogastroduodenoscopy (EGD) was performed early in the admission and was seen to be normal. Scintigraphic gastric emptying studies were performed and gastric emptying time was calculated from anterior images acquired for approximately 90 minutes. The percentage of residual tracer within the stomach at two hours was 75% consistent with delayed gastric emptying or gastroparesis. A small bowel follow was also consistent with generalized GI hypo-motility disorder of unclear etiology.

He was screened for potential underlying causes for his gastroparesis. His fasting plasma glucose and hemoglobin A1c levels were normal ruling out diabetes mellitus. Hypothyroidism and connective tissue disorders were also ruled out by normal thyroid stimulating hormone levels and negative autoimmune panel, respectively. His neurological examination was entirely normal and had no history of recent viral illness or prior gastric surgery. None of his medications were particularly associated with a delay in gastric emptying. In view of his significant weight loss and active smoking a CT scan of the chest was performed which revealed a spiculated nodule sized 9 mm in right upper lobe of the lung (Figure 1) along with right hilar lymphadenopathy (Figure 2). A positron emission tomography (PET) scan was performed with hyper-metabolic activity in the right upper lobe nodule (Figure 3) and right hilar lymphadenopathy (Figure 4). Nodule resection and biopsy revealed a poorly differentiated non-small cell lung carcinoma (Figure 5) with no evidence of local or distal metastasis on PET scan and CT scan of the brain with intravenous contrast. Due to the concern for paraneoplastic origin of his gastroparesis further serological testing revealed positive anti-neuronal nuclear antibodies type 1 (Anti-Hu) and cytoplasmic purkinje cell antibodies (Anti-Yo).

FIGURE 1: Computed tomography (CT) chest showing a sub-centimeter spiculated nodule in right upper lobe of the lung.
FIGURE 2: Computed tomography (CT) chest showing right hilar lymphadenopathy.

FIGURE 3: Positron emission tomography (PET) scan showing hyper-metabolic activity in right upper lobe nodule.
FIGURE 4: Positron emission tomography (PET) scan showing hypermetabolic activity in right hilar lymphadenopathy.

FIGURE 5: Biopsy of right upper lobe nodule showing poorly differentiated non-small cell lung cancer.

Treatment and outcome
The patient was diagnosed with a paraneoplastic gastroparesis secondary to occult non-small cell lung cancer. He was started on a chemotherapy combination of Carboplatin and Paclitaxel with a three-week course of local radiation therapy. Moreover, for the relief of his severe GI symptoms dietary modifications, pro-kinetic agents and psychological counselling were used with gradual clinical improvement observed on follow-up visits.

Discussion
Gastroparesis cases can be attributed to idiopathic, diabetic, or post-surgical etiologies in majority of the cases. In the absence of these common etiologies, and with appropriate risk factor assessment, clinicians should consider a paraneoplastic syndrome causing gastroparesis [1]. Early evaluation and diagnosis of malignancy can have a profound effect on the overall treatment course. Yet, the diagnosis of paraneoplastic gastroparesis can be extremely challenging. The Paraneoplastic Neurological Syndrome Euronetwork (PNSE) has established diagnostic criteria for paraneoplastic neurologic syndromes including paraneoplastic gastroparesis. Gastroparesis can be classified as definite paraneoplastic syndrome when there is presence of positive onco-neural antibodies or onset of symptoms is within five years of the development of cancer [6]. PNSE recognizes that the onco-neural antibodies in their criteria are limited to those that are well-studied (anti-Hu antibody, anti-Yo antibody, anti-collapsin response mediator protein 5 antibody, anti-neuronal nuclear antibody type 2, anti-Ma2 antibody, anti-amphiphysin antibody). However, they concede that other antibodies could be used in the diagnosis once they are further characterized. In our study we identified four more antibodies (ganglionic acetylcholine receptor antibody, anti-ganglioside GM1 antibody, P/Q-type voltage-gated calcium channel antibody, N-type voltage-gated calcium channel antibody) that are known to target autonomic and motor neurons and are potential areas for further study to establish their utility in diagnosis of PG [4, 7]. Once the diagnosis of PG is made, the treatment (irrespective of etiology) is usually a combination of several recommendations: dietary modifications including frequent fiber intake, low-fat diet, frequent meals; daily use of pro-kinetic agents such as metoclopramide or erythromycin; and daily use of anti-emetics [1, 8]. In PG, interestingly, there is evidence that successful treatment of the primary malignancy may improve symptoms of gastroparesis [3].

Literature review
To further investigate the association between various cancers and paraneoplastic gastroparesis and to find out the clinical utility of serological testing in the diagnosis of this complex and challenging clinical entity we conducted a literature search using the electronic database engines MEDLINE through PubMed, EMBASE, Ovid and Scopus from inception to December 2018. The combinations of keywords used were ("malignancy" or "cancer" or "carcinoma" or "paraneoplastic") and ("gastroparesis" or "hypo-motility"). The reference list of all eligible reports was reviewed to identify additional reports. Reports were excluded if
(1) they were not written in English, (2) no malignancy was found in the reported patient or (2) reports were published as abstracts only. Eventually, 16 reports, including 22 cases, were identified as listed in Table 1. Characteristics of the patient population are listed in Table 2. Management and prognosis of the included patients are summarized in Table 3.

| Study                  | Year | Country of Publication |
|------------------------|------|------------------------|
| Gerl et al. [9]        | 1992 | United States          |
| Kelly et al. [10]      | 2014 | Ireland                |
| Moskovitz and Robb [11]| 2002 | Canada                 |
| Hejazi et al. [12]     | 2009 | United States          |
| Vaidya et al. [8]      | 2014 | United States          |
| Argyriou et al. [13]   | 2012 | United Kingdom         |
| Burger et al. [14]     | 2013 | Netherlands            |
| Franco and Koulaeva [15]| 2014 | Australia              |
| Pardi et al. [4]       | 2002 | United States          |
| Ghoshal et al. [16]    | 2005 | India                  |
| Bernardis et al. [17]  | 1999 | Switzerland            |
| Liang et al. [18]      | 1994 | United States          |
| Lautenbach and Lichtenstein [19] | 1995 | United States |
| Nguyen-tat et al. [3]  | 2008 | Germany                |
| Caras et al. [20]      | 1996 | United States          |
| Chinn and Schuffler [5] |     | 1988 United States     |

TABLE 1: Characteristics of included studies.

| Study                  | Age | Gender | Type of Cancer      | Time Elapsed between GI Symptoms and Cancer Diagnosis | Antineuronal Antibodies |
|------------------------|-----|--------|---------------------|------------------------------------------------------|-------------------------|
| Gerl et al. [9]        | 53  | F      | Bronchial carcinoid | Four years after cancer diagnosis                    | Not reported             |
| Kelly et al. [10]      | 69  | F      | SCLC                | One year prior to cancer diagnosis                    | Anti-Hu -ve, Anti-Yo -ve |
| Moskovitz and Robb [11]| 57  | F      | SCLC                | Six months prior to cancer diagnosis                  | Anti-Hu +ve              |
| Hejazi et al. [12]     | 56  | M      | SCLC                | Six months prior to cancer diagnosis                  | Anti-Hu +ve, ANNA-2 -ve  |
| Vaidya et al. [8]      | 87  | M      | Lung adenocarcinoma | Two weeks prior to cancer diagnosis                   | Anti-Hu -ve, ANNA-2 -ve  |
| Argyriou et al. [13]   | 70  | F      | SCLC                | Eight weeks prior to cancer diagnosis                 | Not reported             |
| Burger et al. [14]     | 74  | M      | SCLC                | Eight months prior to cancer diagnosis                | Anti-Hu +ve              |
| Franco and Koulaeva    | 72  | M      | Pancreatic neuroendocrine | One month after cancer diagnosis                    | Not reported             |
TABLE 2: Characteristics of patients in included studies.

| Study                    | Type of Cancer   | Cancer Treatment                          | GI Symptoms Treatment | Prognosis                                                                 |
|--------------------------|------------------|-------------------------------------------|-----------------------|---------------------------------------------------------------------------|
| Gerl et al. [9]          | Bronchial carcinoid | Pneumonectomy and lymph node dissection  | Prokinetics and TPN   | No clinical improvement. Patient passed away 10 months after the onset of GI symptoms. |
|                          |                  |                                           |                       | No a candidate for                                                         |

SCLC: Small cell lung cancer; Anti-Hu: Anti-neuronal nuclear antibodies type 1; Anti-Yo: Cytoplasmic purkinje cell antibodies; ANNA-2: Anti-neuronal nuclear antibodies type 2; G-AchR antibody: Ganglionic acetylcholine receptor antibody; Anti-GM1 antibody: Anti ganglioside GM1 antibody; +ve: Positive; -ve: Negative.
| Study                        | Diagnosis          | Treatment                     | Prokinetics | Outcome                                                                 |
|------------------------------|--------------------|-------------------------------|-------------|------------------------------------------------------------------------|
| Kelly et al. [10]            | SCLC               | chemotherapy/radiotherapy     | Prokinetics | Symptoms resolved with prokinetics.                                    |
| Moskovitz and Robb [11]     | SCLC               | Chemotherapy and radiotherapy | Prokinetics and TPN | No clinical improvement.                                               |
| Hejazi et al. [12]           | SCLC               | Chemotherapy and radiotherapy | Antibiotics and laxatives | Symptoms improved after chemotherapy                                    |
| Vaidya et al. [8]            | Lung adenocarcinoma| Not reported                  | Prokinetics | Symptoms improved with prokinetics.                                    |
| Argyriou et al. [13]         | SCLC               | Not reported                  | Prokinetics, TPN, gastric pacing | Patient passed away one week afterwards from respiratory tract infection. |
| Burger et al. [14]           | SCLC               | Chemotherapy                  | Prokinetics, NJ tube, TPN | No clinical improvement                                                 |
| Franco and Koulalova [15]    | Pancreatic neuroendocrine tumor | Not a candidate for chemotherapy/radiotherapy | Prokinetics, IV erythromycin, TPN | Symptoms improved with IV erythromycin which was later transitioned to PO erythromycin. |
| Pardi et al. [4]             | SCLC               | Not reported                  | Domperidone and jejunostomy tube | Not reported                                                             |
| Ghoshal et al. [16]          | Cholangiocarcinoma | Not reported                  | Dietary modification, prokinetics, NJ tube, TPN | Patient passed away six months after the onset of GI symptoms.          |
| Bernardis et al. [17]        | Leiomyosarcoma     | Surgical resection            | Antiemetics, prokinetics | Symptoms improved after resection.                                     |
| Liang et al. [18]            | SCLC               | Chemotherapy                  | TPN, surgical exploration | No improvement. Passed nine months after diagnosis of cancer.          |
| Lautenbach and Lichtenstein [19] | Leiomyosarcoma | Surgical resection            | Prokinetics | Symptoms improved after resection.                                     |
| Nguyen-tat et al. [3]        | SCLC               | Chemotherapy                  | Prokinetics, jejunostomy tube | No clinical improvement                                                 |
| Caras et al. [20]            | Pancreatic adenocarcinoma | Chemotherapy and radiotherapy | Antiemetics, prokinetics | Symptoms improved initially with treatment but patient passed away eight months after diagnosis. |
| Chinn and Schuffler Case 1 [5] | SCLC               | Cancer found post-mortem     | Prokinetics | No clinical improvement. Patient passed away nine months after the onset of GI symptoms. |
| Chinn and Schuffler Case 2 [5] | SCLC               | Chemotherapy                  | Prokinetics | No clinical improvement. Patient passed away five months after the onset of GI symptoms. |
| Chinn and Schuffler Case 3 [5] | SCLC               | Chemotherapy                  | Prokinetics | No clinical improvement. Patient passed away six months after the onset of GI symptoms. |
| Chinn and Schuffler Case 4 [5] | SCLC               | Lung carcinoid                | Prokinetics | Symptoms improved with prokinetics and surgical resection. Patient was alive 57 months after the onset of GI symptoms. |
| Chinn and Schuffler Case 5 [5] | SCLC               | Cancer found post-mortem     | Prokinetics | No clinical improvement. Patient passed away four months after the onset of GI symptoms. |
| Chinn and Schuffler Case 6 [5] | SCLC               | Chemotherapy                  | Prokinetics | No clinical improvement. Patient passed away five months after the onset of GI symptoms. |
| Chinn                         |                    |                               |             | Symptoms improved with prokinetics.                                    |
The population ranged in age from 20 to 87 years with a mean age of 63.9 years and there was a male to female ratio of 1:1.2. The majority of cases had an underlying small cell lung cancer diagnosis (14/22 cases), however cases of pulmonary carcinoid, cholangiocarcinoma, pancreatic neuroendocrine tumor, pancreatic adenocarcinoma, and leiomyosarcoma are also represented. In 19 cases, GI symptoms of dysmotility preceded the diagnosis of cancer, with an average of 6.4 months between onset of gastroparesis and the diagnosis of malignancy.

In our literature review, eight cases included testing for anti-Hu antibodies, of these seven were in the setting of small cell lung cancer (SCLC) and one was adenocarcinoma of the lung. The case of adenocarcinoma of the lung had a negative anti-Hu serology. In six out of the seven cases of SCLC with PG a positive anti-Hu antibody was seen. Anti-Hu antibodies have not been well studied in cases of PG outside of SCLC, in large part due to the rarity of the syndrome. Our review of the literature is consistent with the case series conducted by Lee et al. [2] where they found that eight out of nine patients presenting to the Mayo Clinic with PG secondary to SCLC were found to have positive anti-Hu serology.

In our review, 14 cases underwent surgical resection or chemotherapy/radiotherapy to treat their cancer, and in six cases symptoms of gastroparesis improved or resolved after therapy.

Conclusions

Paraneoplastic gastroparesis is a rare and challenging diagnosis, however accurate identification can have significant implications for patients. Symptoms of gastroparesis frequently present before the diagnosis of cancer in PG. The challenge of recognizing PG can be made less burdensome with serologic evaluation, though more studies are needed.

Additional Information

Disclosures

**Human subjects:** Consent was obtained by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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