



Case Report

Lung Adenocarcinoma Presenting with WDHA Syndrome and Marie-Bamberger Syndrome: A Case Report

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Introduction

Watery diarrhea, hypokalemia, and achlorhydria (WDHA syndrome), also known as Vermer-Morrison syndrome or vipoma syndrome, was first reported by Verner and Morrison in 1958 [1]. It is characterized by watery diarrhea, hypokalemia and achlorhydria (or metabolic acidosis), most commonly associated with pancreatic islet cell tumors in adults [2]. Pancreatic vipoma accounts for 90% of WDHA syndrome cases [3] and is exceedingly uncommon to be caused by non-pancreatic tumors.

Marie-Bamberger syndrome, also known as hypertrophic osteoarthropathy (HOA), is characterized by clubbed fingers, arthralgia and painful periostitis of the extremities. This triad is most commonly associated with lung cancer, cardiac disease, or infection [4].

Here we report a case of a 61-year-old man who presented with WDHA syndrome immediately preceding the diagnosis of lung adenocarcinoma with Marie-Bamberger syndrome. To our knowledge, this is the first reported case of lung adenocarcinoma-associated synchronously with WDHA syndrome and Marie-Bamberger syndrome.

Case Report

A 61-year-old caucasian man with a 35-pack-year smoking history, presented with persistent watery diarrhea, progressively worsening bilateral knee pain for 2 months, accompanied by 30-pound weight loss. He was evaluated several times at a local emergency room for hypotension and hypokalemia and received intravenous hydration and repletion of potassium. His symptoms persisted and he was eventually admitted for further workup and treatment in August, 2011.

Upon admission, physical examination revealed a cachexic bed-ridden man; vital signs were temperature 98.4°F, blood pressure 95/53 mmHg, pulse rate 145 beats/minute, and respiration rate 26/minute. Pertinent physical findings included: severe finger clubbing,

severe tenderness around both knees, and 3+ pitting edema up to both his knees. Electrocardiogram revealed atrial fibrillation with rapid ventricular response. Laboratory studies revealed metabolic acidosis and were significant for hypokalemia, 2.6 mmol/L, hypoalbuminemia, 1.8 g/dL, and bicarbonate of 18. He reported severe frequent watery diarrhea, 20 to 30 times a day, including 5 to 6 times at night, amounting to approximately 3 to 5 liters in volume per day. It was so watery that he was initially suspected to have urinary fistula, which was ruled out with retrograde cystography. Double contrast upper GI series and small bowel study showed a very rapid transit of contrast through the small bowel, entering the colon within 15 minutes (transit is considered normal when it is at least 30 minutes), indicating hyperperistalsis of the small bowel. Both esophagogastroduodenoscopy (EGD) and colonoscopy were unremarkable. An extensive workup to rule out infectious etiology was also negative for infection. Surprisingly, as part of the workup for a suspected neuroendocrine tumor, a chest computed tomography (CT) revealed a 6.6 x 5.2 cm mass in the left upper lobe of the lung, highly suspicious for malignancy Figure 1A. A CT-guided biopsy was performed, and pathology revealed adenocarcinoma (hematoxylin and eosin Figure 2A, strongly positive for both TTF-1 Figure 2B and CK 7 Figure 2C, and negative for CK 20 Figure 2D, consistent with primary non-small cell lung cancer.

His atrial fibrillation was eventually controlled with diltiazem, metoprolol, and digoxin. He received aggressive hydration and repletion of electrolytes initially, but did not improve clinically. In addition, his diarrhea was very difficult to manage and did not respond well to high dose loperamide. His albumin dropped to 1.1 g/dL despite the use of total parenteral nutrition (TPN) support. Octreotide was initiated to control his diarrhea, with slight improvement. Workup included measurement of VIP (vasoactive intestinal peptide) 68 pg/mL (reference range 20 - 42) and chromogranin A 42 ng/mL (reference range 1.9 - 15). This is in line with his initial presentation of water diarrhea, dehydration, hypokalemia and acidosis, supporting the diagnosis of WDHA syndrome. Due to the patient's extremely poor performance status and poorly controlled diarrhea, he was considered a poor candidate for systemic chemotherapy and only palliative radiotherapy was offered. He received a total of 31 Gy of radiation to the left upper lobe mass over 11 fractions, and was subsequently transferred to an inpatient rehabilitation service. His diarrhea improved and completely resolved 10 days after completion of radiation. Octreotide was continued at 100 mcg intramuscularly twice a day; loperamide was discontinued by the patient.

The patient was transferred to our center in November 2011. His performance status and nutritional status were significantly improved from the initial hospitalization at the other hospital. Clinically, he did not have diarrhea, but continued to have severe bilateral knee pain. His electrolytes including potassium were normal and albumin was 3.4 g/dL. Interestingly, additional immunohistochemistry studies on the original biopsy of lung mass did not reveal any evidence of neuroendocrine components (negative for synaptophysin Figure 2E, chromogranin Figure 2F, VIP Figure 2G, and growth factor Figure 2H) VIP, serotonin, and chromogranin A and 24-hour urine 5-HIAA level were all in the normal range. He also underwent an esophagogastroduodenoscopy, colonoscopy, and enteroscopy

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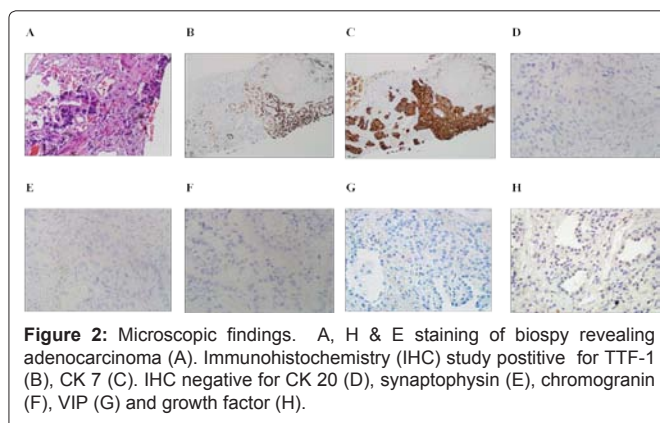
Received: May 31, 2013 Accepted: June 03, 2013 Published: June 28, 2013

that were unrevealing. PET/CT (18-fluorodeoxyglucose positron emission tomography with computed tomography) showed a FDG-avid lesion in the left upper lobe of the lung, and likely physiologic uptake in the mediastinum Figure 1C. X-ray of the bilateral knees showed periostitis along the femur and tibia Figure 1B, (see arrows), providing the radiographic evidence of Marie-Bamberger syndrome.

A repeat lung tumor biopsy was performed, confirming the diagnosis of lung adenocarcinoma. With the improvement in his performance status, a mediastinoscopy was performed as part of preoperative assessment for possible primary lung tumor resection. Mediastinal lymph node involvement was identified, so surgical resection was aborted. Immunohistochemistry studies were repeated on the lung biopsy and involved resected mediastinal lymph nodes, and these were negative for neuroendocrine tumor markers and VIP (data not shown). This patient was discussed at our multidisciplinary tumor board, with the consensus recommendation to re-irradiate FDG-avid areas concurrently with weekly carboplatin and paclitaxel given his improving performance status. Intensity-modulated radiation therapy was administered to the left upper lobe pulmonary mass and left mediastinal-hilar adenopathy at 1.8 Gy per fraction to a total cumulative dosage maximum of 45 Gy concurrently with the chemotherapy. Taking into consideration the radiobiological effects from the prior palliative radiation therapy and the length of time since its administration – 4½ months, the proposed maximum re-irradiation dosage 45 Gy, combined with the prior radiation dosage 31 Gy, was estimated to be roughly equivalent to a “curative dosage” of radiation therapy, but in a somewhat prolonged split course.

He tolerated the concurrent chemoradiation therapy with weekly carboplatin (AUC of 2) and paclitaxel (50 mg/m²) very well without any treatment-related complications. His diarrhea never recurred. His bilateral knee pain improved substantially to his baseline level upon completion of the treatment.

He did well clinically for approximately 6 months, and then he began to experience progressively worsening dyspnea and deteriorating performance status. Restaging CT showed local



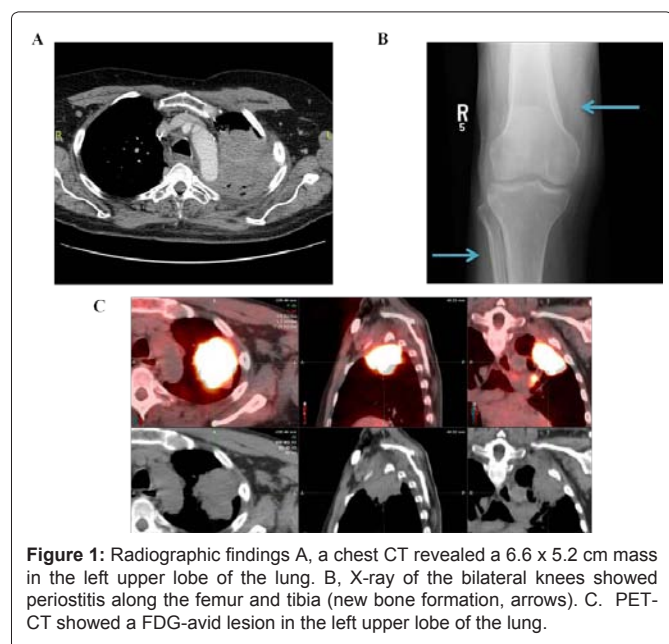
progression of the lung mass, which invaded his aorta and cardiac wall, resulting in severe atrial fibrillation with rapid ventricular response. His diarrhea never recurred, although his bilateral knee pain was worsened, requiring high dose narcotics for pain control. Repeat VIP and chromogranin levels were within normal range. In view of poor performance status and cardiac dysfunction due to mechanical compression, he was transferred to hospice care, and died 2 months later.

Discussion

WDHA is a rare, but well-defined clinical syndrome that is most commonly caused by VIP-producing tumors. These tumors have a strong predilection for the gastrointestinal tract, with up to 90% cases originating from the pancreas. The annual incidence of pancreatic VIPoma is estimated to be about 1 per 10,000,000 individuals in adults [2]. VIPomas have also been reported from other sites such as liver, adrenal gland, bronchus or sympathetic ganglia [5]. Over secretion of VIP in these tumors stimulates excessive production of adenosine 3', 5'-cyclic phosphate (cAMP) by the intestinal tract, resulting in profuse watery diarrhea and severe hypokalemia and metabolic acidosis (or achlorhydria), defining the WDHA syndrome [2].

The patient presented with classic symptoms of WDHA syndrome which was supported by the findings of hyperperistalsis by the double contrast study of the small bowel. Extensive imaging and pathological studies confirmed the diagnosis of lung adenocarcinoma. Palliative radiation to the lung mass completely reversed the WDHA symptoms, while his plasma VIP and serotonin levels returned to normal after this intervention. His disease course convincingly demonstrated that it was the lung mass that caused WDHA syndrome via producing neurotransmitters including VIP. More interestingly, the immunohistochemistry studies of the lung biopsies and removed lymph nodes from mediastinoscopy did not reveal any evidence of neuroendocrine tumor. It is quite intriguing how his lung adenocarcinoma led to elevated VIP. We suspect that VIP might have been released from the tumor cells so rapidly that no VIP was detectable in the tumor cells due to low concentration which has been shown previously in pancreatic VIPoma [6]. Alternatively, although less likely, the neuroendocrine component of the tumor might have been missed due to random sampling.

Endocrine paraneoplastic syndrome occurs in approximately 20% patients with lung cancer. However, it is more commonly associated with small cell lung cancer or carcinoid tumors due to their neuroendocrine origin. WDHA syndrome was previously reported in



small or large cell lung cancer [7,8]. A Medline search found no other reports associating WDHA syndrome with lung adenocarcinoma, and to the best of our knowledge this case appears to represent the first such report.

Finger clubbing is regarded as the oldest clinical sign, was first documented by Hippocrates [9]. The association of digital clubbing and arthritis with lung and heart disease was initially reported by von Bamberger, in Vienna, in 1889 and Marie, in Paris, in 1890 [10]. Marie-Bamberger syndrome or HOA is manifested clinically as a triad: clubbed fingers, arthralgia, and painful periostitis. The periosteal new bone formation of periostitis can be demonstrated radiographically by X-ray as with this patient or via other imaging studies. Up to 12% of lung cancer patients, in particular, those with squamous cell lung cancer, present with Marie-Bamberger syndrome, accounting for approximately 90% of reported malignant cases [11,12]. The pathogenesis of HOA remains elusive to date. Emerging evidence suggests that megakaryocytes or platelet clumps fail to enter the pulmonary vasculature in the presence of extrapulmonary shunting, instead they enter the systemic circulation impacting at the most distal sites, resulting in clubbing [9]. Vascular endothelial growth factor (VEGF) is postulated to play a central role in the development of HOA in patients with lung cancer. It is a platelet-derived factor induced by hypoxia, and also well-known to be over-produced by a wide variety of malignancies including lung cancer. Elevated VEGF leads to vascular hyperplasia, edema, and osteoblast proliferation – the very mechanism implicated in pathogenesis of HOA [4]. Bevacizumab, an anti-VEGF antibody, in combination with chemotherapy was shown to prolong survival in patients with non-small cell lung cancer [13]. It would be interesting to find out if bevacizumab is beneficial to HOA. Other hormones such as growth hormone, adrenocorticotropic hormone (ACTH), VIP, etc. have also been implicated in the development of HOA. Interestingly, octreotide, an somatostatin analogue, generally functions as a hormone inhibitor, has been reported to relieve the pain secondary to HOA [14]. Surgical resection of tumor or chemotherapy has also been shown to improve or reverse HOA in some patients [15,16]. In the present case, immunohistochemical staining of the tumor samples did not reveal any evidence of VIP or growth factor. VEGF plasma level was not measured. The patient indeed had modestly elevated VIP; however, his knee pain failed to respond to octreotide injection or palliative radiation, but improved dramatically after completion of concurrent chemoradiation. Moreover, the progression of lung cancer in this patient resulted in recurrence of his knee pain, yet at that time a repeat VIP level was normal. Taken together, his disease course seems to suggest that elevated VIP is not causative for his HOA.

In summary, to our knowledge, we report here the first case of lung adenocarcinoma which presented with both WDHA syndrome and Marie-Bamberger syndrome. Concurrent chemoradiation resulted in resolution of both syndromes. Progression of his lung adenocarcinoma resulted in worsening painful HOA, but no elevation of VIP and no recurrence of WDHA syndrome.

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