

간 전이를 동반한 VIPoma에서 간동맥 색전술을 이용한 현저한 증상 호전

울산대학교 의과대학 서울아산병원, ¹내과, ²영상의학과, ³병리과

최윤숙¹ · 고기영² · 류민희¹ · 강신광³ · 김정은¹ · 송준선³ · 강윤구¹

Significant Symptom Relief with Hepatic Artery Embolization in a VIPoma with Liver Metastases

Yun-Suk Choi¹, Gi-Young Ko², Min-Hee Ryu¹, Shin Kwang Khang³, Jeong-Eun Kim¹, Joon Seon Song³, and Yoon-Koo Kang¹

*Departments of ¹Internal Medicine, ²Diagnostic Radiology, and ³Pathology, Asan Medical Center,
University of Ulsan College of Medicine, Seoul, Korea*

Vasoactive intestinal polypeptide-secreting tumors (VIPomas) cause VIPoma syndrome, which is characterized by watery diarrhea, hypokalemia, and achlorhydria. The treatment options for metastatic VIPomas include somatostatin analogs, cytoreductive surgery, and chemotherapy. We report the case of a 54-year-old male who presented with a peripancreatic mass with multiple hepatic metastases on computed tomography. After resection, the peripancreatic mass was demonstrated pathologically to be a neuroendocrine tumor. Although the patient received systemic chemotherapy and somatostatin analogs for the hepatic metastatic masses, the tumor increased in size. The patient then experienced severe diarrhea, despite treatment with the somatostatin analogs. Elevated serum VIP levels (3,260 pg/mL) and typical symptoms confirmed the diagnosis of VIPoma. We performed hepatic artery embolization (HAE) to reduce the tumor volume and control his symptoms, which led to a very rapid symptomatic response. The patient has remained symptom-free for 18 months with repeated HAE. (Korean J Med 2014;87:363-368)

Keywords: VIPoma; Liver metastases; Hepatic artery embolization; Diarrhea

INTRODUCTION

Vasoactive intestinal polypeptide (VIP)-secreting tumors (VIPomas) are very rare, with an annual incidence estimated

to be < 0.2-0.5 per million individuals annually [1]. The excessive amounts of VIP secreted by these tumors causes watery diarrhea, hypokalemia, and achlorhydria (WDHA) syndrome [2]. Complete surgical resection is the only curative

Received: 2008. 8. 3

Revised: 2008. 8. 14

Accepted: 2008. 10. 6

Correspondence to Min-Hee Ryu, M.D., Ph.D.

Division of Oncology, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 138-736, Korea

Tel: +82-2-3010-5935, Fax: +82-2-3010-6961, E-mail: miniryu@amc.seoul.kr

Copyright © 2014 The Korean Association of Internal Medicine

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>) which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

treatment for localized VIPomas. However, the treatment of advanced VIPomas is mostly palliative, such as systemic chemotherapy and the treatment of symptoms using cytoreductive surgery or somatostatin analogs [3,4]. To our knowledge, the use of hepatic artery embolization (HAE) has been reported in only a small number of VIPoma cases [5]. Here, we report a 54-year-old male with metastatic VIPomas whose profound diarrhea and abnormal biochemical profiles were resolved successfully and rapidly using HAE.

CASE REPORT

A 54-year-old male presented with reduced stool caliber that had persisted for more than 1 month. Abdominal and pelvic computed tomography (CT) were performed in a community hospital, and revealed a 5-cm inhomogeneous enhancing mass anterior to the head of the pancreas, and four additional enhancing masses in hepatic segments VI, VII, and VIII. He was referred to our hospital, a tertiary referral hospital, for further work-up and treatment. A colonoscopy showed no abnormalities. According to the results of the enhanced CT, we determined that the tumors could be Castleman's disease, leiomyosarcomatosis, or multiple desmoid tumors. Because

the masses seemed hypervascular on CT, a needle biopsy was not performed. Instead, we performed an exploratory laparotomy to confirm the diagnosis and reduce the tumor-mass effect to the greatest extent possible. We located and resected a 5-cm tumor, which was a hard omental lesion without invasion or infiltration to the adjacent structures. Eight metastatic hepatic masses were also detected, the largest of which was 2 cm in diameter. No lymph node metastasis was detected. Because the tumor stained positive for chromogranin, cytokeratin, and synaptophysin, it was diagnosed pathologically as a neuroendocrine tumor (Fig. 1). Although no pancreatic mass was found on the CT or during the exploratory laparotomy, our histological analyses did not exclude the possibility of a metastatic pancreatic islet cell tumor. The neuroendocrine tumor was considered to be nonfunctioning because the patient had no remarkable symptoms (e.g., diarrhea, flushing, or hypoglycemia).

After the operation, the four enhancing liver masses were regarded as hepatic metastases, and additional tiny nodules of unknown significance and with omental infiltration anterior to gastric antrum were detected on CT. To control the residual hepatic metastases, the patient was treated using systemic chemotherapy consisting of etoposide (100 mg/m²/day on

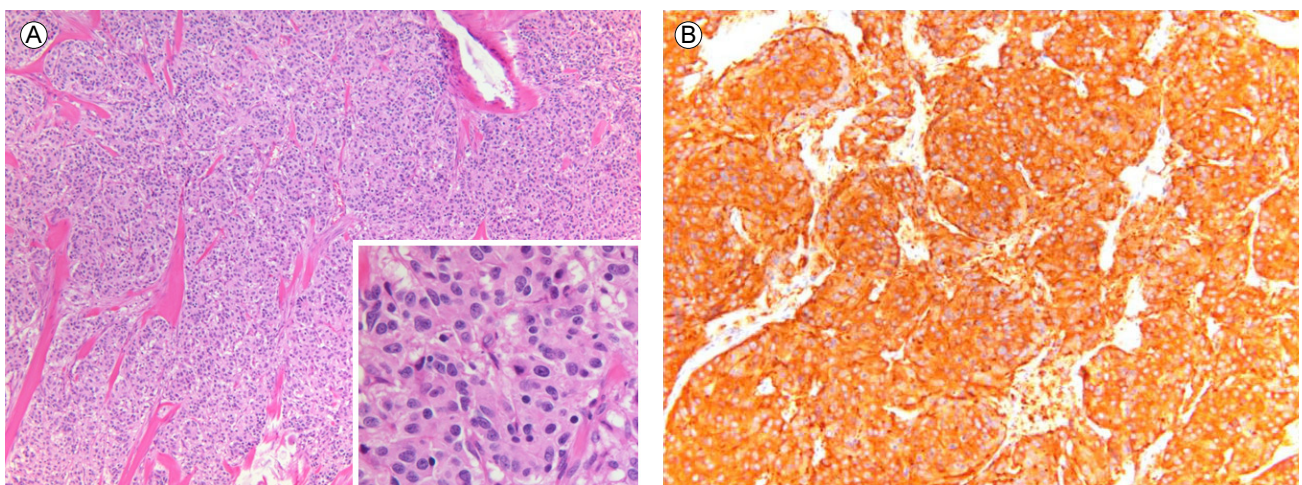


Figure 1. Tumor histology. (A) The tumor exhibited a solid and trabecular pattern with fibrovascular cores ($\times 100$). On high magnification ($\times 400$), the tumor cells were uniform and polygonal, with relatively small nuclei, finely granular chromatin, and abundant eosinophilic granular cytoplasm. (B) The tumor cells were strongly positive for synaptophysin, supporting the diagnosis of a neuroendocrine tumor. The tumor cells were also immunopositive for chromogranin and cytokeratin (not shown).

days 1-3) and cisplatin (70 mg/m^2 on day 1) every 3 weeks. After six cycles of chemotherapy, the nodules adjacent to the gastric antrum were largely unchanged in size, whereas the size of the metastatic mass located on the inferior tip of right liver was increased slightly. Because this was considered evidence of disease progression, the chemotherapy was discontinued.

The hepatic metastatic masses and nodules anterior to the gastric antrum remained unchanged until 5 months after the discontinuation of chemotherapy, after which CT revealed that the size and number of the hepatic masses on the right hepatic lobe were increased significantly. A 1-cm nodule anterior to the gastric antrum had also developed, but there were no new lesions in other organs. To stabilize the tumor masses, we administered a 20-mg intramuscular dose of a long-acting release (LAR) preparation of octreotide (Sandostatin[®] LAR[®]). After one month, the patient presented with severe watery diarrhea and was admitted to our hospital complaining of both arm and leg weakness. A physical examination revealed severely dehydrated tongue and skin. The patient's serum sodium (123 mEq/L), potassium (1.6 mEq/L), and bicarbonate (7.0 mEq/L) levels had decreased markedly, and his serum blood urea nitrogen (BUN; 43 mg/dL) and creatinine (1.7 mg/dL) had increased. His serum calcium, phosphorus, and glucose levels were 10.3 mg/dL , 1.3 mg/dL , and 235 mEq/L , respectively. The patient was

treated with fluid resuscitation and with potassium, bicarbonate, and phosphorus supplements. To control the diarrhea, he was treated with 500- μg octreotide subcutaneously three times per day for 4 days. Despite this treatment, the frequency of his stools increased to > 20 per day, and the volume of diarrhea increased to 10 L/day . The patient's blood pressure in the supine position fell to $74/47 \text{ mmHg}$, and his serum potassium and bicarbonate levels did not improve despite supplementation with large amounts of electrolytes for 1 month after admission.

We suspected that the patient's neuroendocrine tumor might have become functional; therefore, we measured his serum levels of VIP, somatostatin, gastrin, and serotonin, and 24-h urinary 5-hydroxyindolacetic acid (5-HIAA) levels. His serum VIP was elevated dramatically to $3,260 \text{ pg/mL}$ (upper normal limit, 100 pg/mL), whereas the serum levels of somatostatin (19.0 pg/mL), gastrin (39.0 pg/mL), and serotonin (10.9 ng/mL), and the 24-hour urinary 5-HIAA (1.2 mg/day) levels were within the normal ranges. Therefore, the patient was diagnosed with VIPoma. To reduce the tumor volume and provide symptomatic relief, we performed hepatic artery embolization (HAE) by infusing Gelfoam and lipiodol into both hepatic arteries. One day after the first HAE, the amount of diarrhea was reduced dramatically from 10 L/day to $< 2 \text{ L/day}$, and his serum concentrations of potassium and bicarbonate improved to 3.9 mEq/L and 21.2 mEq/L , respectively. The

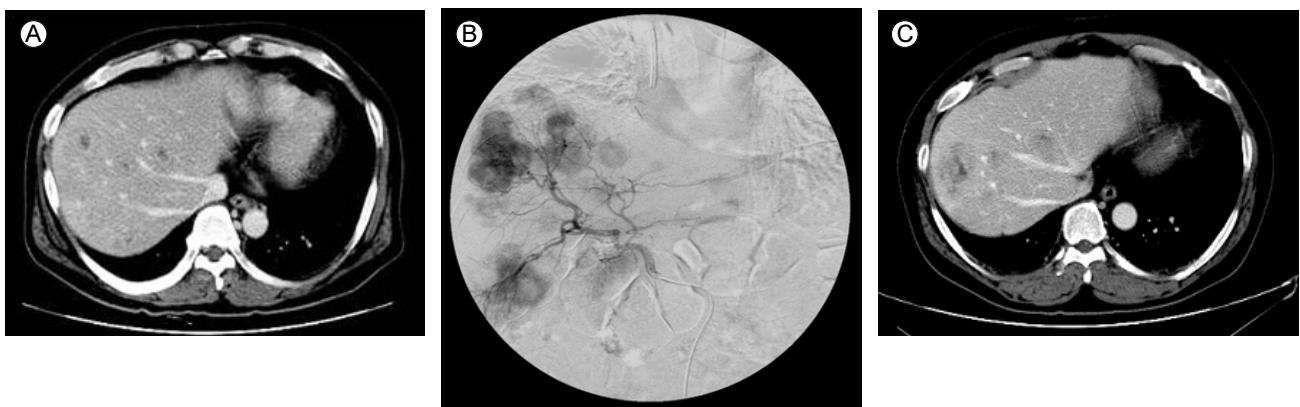


Figure 2. (A) CT scan immediately prior to the first HAE (0 month), showing multiple ill-defined and low-density masses. (B) Angiography following the first HAE, showing multiple hypervascular tumor staining in both hepatic lobes. (C) CT scan after the sixth HAE (18 months after the first HAE) showing the slow growth of the metastatic tumors.

patient was discharged and had no further requirement for intravenous fluids. The HAE has since been repeated six times at 2-6-month intervals, depending on the severity of the symptoms and biochemical abnormalities, with no complications. According to the Response Evaluation Criteria In Solid Tumors (RECIST) criteria [6], the sum of the longest diameter of five representative tumor lesions in the liver at baseline (0 month), and after the first (1 month), second (3 months), third (8 months), fourth (11 months), fifth (15 months), and sixth HAE administration (18 months) was 16.7, 9.7, 13.3, 10.1, 16.9, 15.5, and 17.5 cm, respectively. No new lesions were found in the liver or other organs during the follow-up period (Fig. 2). Subsequently, patient has been free from life-threatening symptoms, such as voluminous diarrhea, hypokalemia, and acidosis, for 18 months, and lives a normal life.

DISCUSSION

In this case, HAE was very effective for relief of the symptoms of VIPoma, including diarrhea, hypokalemia, and acidosis. HAE can reduce the blood supply to tumor lesions and induce tumor cell death, which decreases the secretion of VIP by the tumor cells and amelioration of the VIPoma symptoms [7]. HAE might be effective not only for controlling the VIPoma symptoms but also for stabilizing tumor growth. However, the symptomatic responses might not always parallel the radiological responses, as evidenced by the slight increase in tumor size on a follow-up CT scans, despite the well-controlled symptoms.

To date, there have been only a small number of reports using HAE to relieve VIPoma symptoms [3,5,8]. Most reports of HAE in patients have been with neuroendocrine tumors that were not specified as VIPomas. HAE using only a vaso-occlusive material, such as Gelfoam, effectively decreased tumor size and hormone levels in most patients [7]. Chemoembolization is a similar procedure, except that chemotherapeutic agents such as emulsified doxorubicin, 5-fluorouracil or cisplatin are administered directly into the hepatic artery.

Although chemoembolization was recently shown to be effective for unresectable malignant endocrine tumors, it might not offer therapeutic advantages over particulate embolization alone [9]. Because of the rarity of neuroendocrine tumors, no randomized studies have compared chemoembolization with embolization alone. We performed HAE on our patient rather than chemoembolization because the tumors were refractory to chemotherapy. We also predicted that hepatic arterial occlusion alone would be sufficient to inhibit the function of the hepatic metastatic tumors, which derive most of their blood supply from the hepatic artery.

Other treatment options for metastatic neuroendocrine tumors include chemotherapy and somatostatin analogs. The response rates to chemotherapy vary, and the effects with metastatic neuroendocrine tumors are often short lasting [10]. One randomized study of 106 patients with advanced islet cell tumors showed that combination therapy with streptozotocin and doxorubicin resulted in the best outcome, with a 69% response rate [11]. In a trial of 14 patients with endocrine pancreatic tumors, seven patients responded biochemically and five (36%) responded radiologically to the combination of etoposide and cisplatin, with a median response duration of 9 months [12]. Because streptozotocin is not available at our hospital, we selected the combination of etoposide and cisplatin, which was ineffective. Because of the small number of patients studied to date, there is no widely accepted standard chemotherapy regimen for neuroendocrine tumors. Moreover, most studies do not specify the specific type of neuroendocrine tumor, and the efficacy of systemic chemotherapy in patients with VIPomas is unclear.

Octreotide, a synthetic somatostatin analog, and its long-acting release (LAR) preparations (e.g., Sandostatin LAR and lanreotide) can reduce hormone secretion by > 50% in 60-80% of patients with neuroendocrine tumors [13]. In addition, these compounds can reduce neoplastic proliferation in some patients by blocking the somatostatin receptors that are expressed in > 80% of neuroendocrine tumors [13]. Patients with VIPomas were reported to respond well to octreotide and its LAR preparations, with > 80% of patients showing

the relief of symptoms such as diarrhea [14]. In addition, octreotide could stabilize disease [14]. However, although most patients exhibit good initial responses, the benefits of octreotide are generally short-lived, thus requiring higher doses [1]. Our patient did not show any symptomatic improvement after treatment with somatostatin analogs, which might be due to the exacerbation of diarrhea via an adverse effect of octreotide, little or no somatostatin receptor expression by the tumors, or the administration of insufficient doses of octreotide.

A number of new molecular-targeted therapies for neuroendocrine tumors were introduced recently. Neuroendocrine tumors express several angiogenic molecules, including vascular endothelial growth factor (VEGF), epithelial growth factor receptor (EGFR), insulin-like growth factor-1 receptor, phosphoinositide-3-kinase, RAC- α serine/threonine-protein kinase (AKT), and mammalian target of rapamycin (mTOR). Although < 20% of patients exhibit a radiological response to angiogenesis inhibitors (e.g., bevacizumab, sunitinib, sorafenib, and vatalanib) and mTOR inhibitors (e.g., everolimus and temsirolimus), these agents remain promising [14,15]. Novel drugs that target some of these molecules are currently being assessed in early clinical trials for the treatment of neuroendocrine tumors.

In the current case, CT scans did not reveal the site of the primary tumor, suggesting that somatostatin receptor scintigraphy might have been needed to determine the primary site precisely [16]. Our patient was not diagnosed with a VIPoma initially because it might be difficult to distinguish from other neuroendocrine tumors pathologically. Rather than microscopic morphology, which can be ambiguous, the presence of elevated levels of serum VIP and symptoms typical of VIPomas are critical for the accurate diagnosis of these tumors [17]. Because nearly complete symptomatic relief was achieved despite the presence of residual disease in some patients with VIPomas that were treated using cytoreductive surgery or HAE, it is likely that there is a threshold level of VIP that is necessary to induce these symptoms. Our patient experienced periodic symptomatic exacerbation even after the first

HAE, suggesting tumor regrowth and a resultant increase in VIP levels above the threshold concentration. However, repeated HAE ameliorated his symptoms. Generally, this procedure does not confer a survival advantage. Nevertheless, in our patient, who was refractory to somatostatin analogs and chemotherapy, HAE undoubtedly abrogated the life-threatening symptoms of VIPoma and allowed his continuing survival 18 months after the first HAE.

CONCLUSION

We encountered a patient with metastatic VIPoma who experienced diarrhea and abnormal biochemical profiles. These symptoms were resolved successfully and rapidly using HAE, which resulted in long-term relief from symptoms. HAE should be considered as the first treatment option in patients with VIPomas and hepatic metastases that are unresectable and refractory to somatostatin analogs.

중심 단어: VIPoma; 간전이; 간동맥 색전술; 설사

REFERENCES

1. Modlin IM, Lewis JJ, Ahlman H, Bilchik AJ, Kumar RR. Management of unresectable malignant endocrine tumors of the pancreas. *Surg Gynecol Obstet* 1993;176:507-518.
2. Grier JF. WDHA (watery diarrhea, hypokalemia, achlorhydria) syndrome: clinical features, diagnosis, and treatment. *South Med J* 1995;88:22-24.
3. Smith SL, Branton SA, Avino AJ, et al. Vasoactive intestinal polypeptide secreting islet cell tumors: a 15-year experience and review of the literature. *Surgery* 1998;124:1050-1055.
4. Remme CA, de Groot GH, Schrijver G. Diagnosis and treatment of VIPoma in a female patient. *Eur J Gastroenterol Hepatol* 2006;18:93-99.
5. Case CC, Wirfel K, Vassilopoulou-Sellin R. Vasoactive intestinal polypeptide-secreting tumor (VIPoma) with liver metastases: dramatic and durable symptomatic benefit from hepatic artery embolization, a case report. *Med Oncol* 2002; 19:181-187.
6. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors: European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States,

- National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205-216.
7. Marlink RG, Lokich JJ, Robins JR, Clouse ME. Hepatic arterial embolization for metastatic hormone-secreting tumors: technique, effectiveness, and complications. *Cancer* 1990;65:2227-2232.
8. Ito S, Kasturagi M, Otsuji H, et al. Transcatheter embolization of metastatic liver VIPoma: report of a case. *Rinsho Hoshasen* 1987;32:1169-1172.
9. Ajani JA, Carrasco CH, Wallace S. Neuroendocrine tumors metastatic to the liver: vascular occlusion therapy. *Ann N Y Acad Sci* 1994;733:479-487.
10. Nguyen HN, Backes B, Lammert F, et al. Long-term survival after diagnosis of hepatic metastatic VIPoma: report of two cases with disparate courses and review of therapeutic options. *Dig Dis Sci* 1999;44:1148-1155.
11. Moertel CG, Lefkopoulo M, Lipsitz S, Hahn RG, Klaassen D. Streptozocin-doxorubicin, streptozocin-fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma. *N Engl J Med* 1992;326:519-523.
12. Fjällskog ML, Granberg DP, Welin SL, et al. Treatment with cisplatin and etoposide in patients with neuroendocrine tumors. *Cancer* 2001;92:1101-1107.
13. Wymenga AN, Eriksson B, Salmela PI, et al. Efficacy and safety of prolonged-release lanreotide in patients with gastrointestinal neuroendocrine tumors and hormone-related symptoms. *J Clin Oncol* 1999;17:1111.
14. Modlin IM, Oberg K, Chung DC, et al. Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncol* 2008;9: 61-72.
15. Khanna G, O'Dorisio SM, Menda Y, Kirby P, Kao S, Sato Y. Gastroenteropancreatic neuroendocrine tumors in children and young adults. *Pediatr Radiol* 2008;38:251-259.
16. Thomason JW, Martin RS, Fincher ME. Somatostatin receptor scintigraphy: the definitive technique for characterizing vasoactive intestinal peptide-secreting tumors. *Clin Nucl Med* 2000;25:661-664.
17. Peng SY, Li JT, Liu YB, et al. Diagnosis and treatment of VIPoma in China: (case report and 31 cases review) diagnosis and treatment of VIPoma. *Pancreas* 2004;28:93-97.