Korean J Gastroenterol Vol. 72 No. 4, 217-221
https://doi.org/10.4166/kjg.2018.72.4.217
pISSN 1598-9992 eISSN 2233-6869

CASE REPORT

주유두와 부유두에 동시에 발생한 신경내분비종양에 대한 내시경 유두절제술 증례

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Endoscopic Papillectomy for Synchronous Major and Minor Duodenal Papilla Neuroendocrine Tumors

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Neuroendocrine tumor (NET) of the major duodenal papilla is a rare occurrence. However, that of the minor duodenal papilla is even rarer. To date, only a few cases have been reported. Herein, we present a rare case of NETs detected at the major and minor duodenal papilla synchronously, which were successfully treated with endoscopic papillectomy without procedure-related complication. To the best of our knowledge, this is the first report of this kind in the world. Photomicrograph of the biopsy specimen stained immunohistochemically for synaptophysin showed a positive reaction of tumor cells. All resection margins were negative. Further experience with more cases will be needed to establish the exact indication of endoscopic papillectomy for duodenal papillary NETs. **(Korean J Gastroenterol 2018;72:217-221)**

Key Words: Neuroendocrine tumors; Major duodenal papilla; Minor duodenal papilla

INTRODUCTION

Duodenal papillary neuroendocrine tumor (NET) is a rare occurrence, accounting for less than 1% of all gastrointestinal NETs. Therefore, the natural history of this disease entity has not been well established.[1] It has been postulated that the prognosis is generally good, although a small percentage of duodenal papillary NETs can show more aggressive behaviors, such as distant metastasis. Thus, the standard treatment for this lesion has been complete surgical resection.[2] However, pancreaticoduodenectomy, although it allows complete resection, has been shown to be associated with relatively high morbidity and moderate mortality.[1] Local excision shows satisfactory results in tumors <2 cm.[1]

Recently, endoscopic papillectomy has been used as a reliable treatment option for duodenal papillary tumors.[3,4] Endoscopic papillectomy is increasingly being performed on patients with NET of the minor papilla and of the major duodenal papilla as a minimally invasive alternative to radical surgery.[5] Nevertheless, a review of related articles revealed, to the best of our knowledge, that a diagnosis of NET in the major and minor duodenal papilla, simultaneously, which were sub-

Received March 18, 2018. **Revised** May 14, 2018. **Accepted** May 23, 2018.

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Financial support: None. Conflict of interest: None.

sequently treated with endoscopic resection, has never been reported to date. We report one such case, with a brief literature review.

CASE REPORT

A 42-year-old woman with pain and soreness at the epigastric area underwent esophagogastroduodenoscopy (EGD) at a local facility. The biopsy specimen was highly suspicious for adenocarcinoma of the minor papilla. She was then referred to our facility for closer examination. The patient had no history of hypertension or diabetes mellitus, and no drinking or smoking history. At the time of admission, blood pressure was 120/80 mmHg, pulse was 56 beats/minute, respiration was 20 breaths/minute, and temperature was 36.0°C. There were no abnormalities on physical examination. Laboratory findings revealed the following values: total bilirubin 0.60 mg/dL (0.2-1.0 mg/dL); AST 18 U/L (10-33 U/L); ALT 16 U/L (4-50 U/L); ALP 165 U/L (104-338 U/L); BUN 15.0 mg/dL (8-20 mg/dL); and creatinine 0.69 mg/dL (0.6-1.2 mg/dL). Complete blood count, urine analysis, and serum electrolytes were all within normal limits. CA 19-9 was <0.600 IU/L (0-34 IU/mL) and CEA was 1.18 IU/L (0-4.7 ng/mL).

Subsequently, EGD was performed again, with endoscopic biopsy due to the ectatic vessels and mild enlargement of the duodenal major and minor papilla were observed. The results showed inflammation with erosion of the major papilla, with the minor papilla showing NET (Grade 1). Abdominal CT showed a suspicious small nodular lesion with faint contrast enhancement in the duodenal papillary region. However, there were no abnormal findings in the bile duct, pancreatic duct, or other organs in the abdomen. Enlargement of the surrounding lymph nodes were not observed. Bile duct and pancreatic

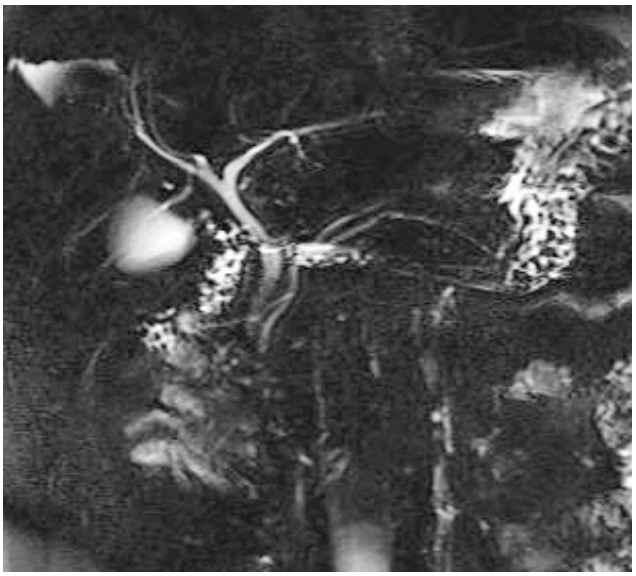

Fig. 1. MRCP image showing clinically normal biliary tree and pancreatic duct. MRCP, magnetic resonance cholangiopancreatography.

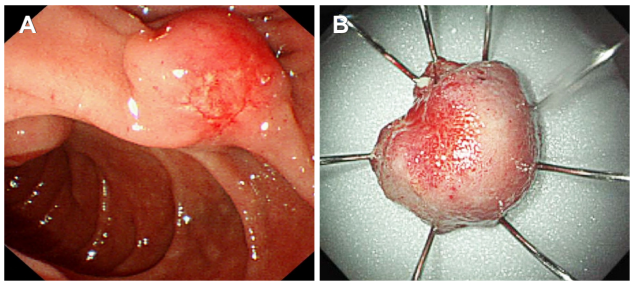

Fig. 2. Side-viewing duodenoscopic findings for minor duodenal papilla. (A) Endoscopy showing an enlarged tumor at the minor duodenal papilla, with shallow ulcers and ectatic vessels at the top of the tumor. (B) Gross finding of the resected specimen after endoscopic snare minor papillectomy.

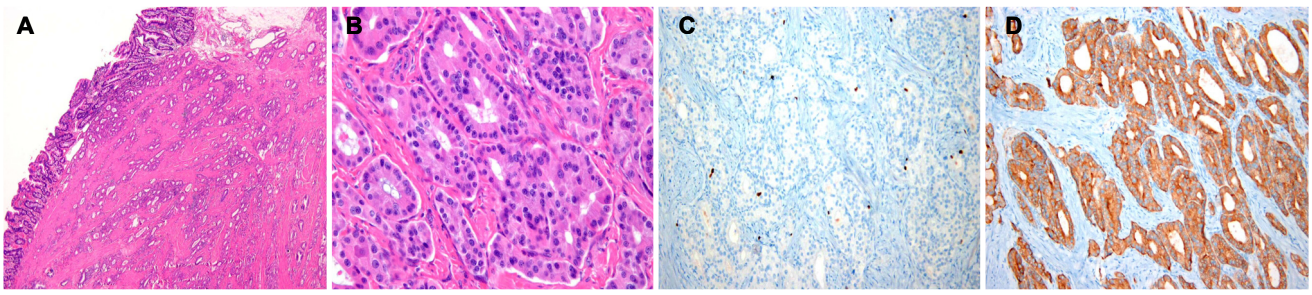

Fig. 3. Pathologic findings of a neuroendocrine tumor of the minor duodenal papilla. (A) On low-power view, glandular proliferation of tumor cells was seen in mucosa and submucosa. Lymphovascular and perineural invasion was not observed (H&E, ×40). (B) On high-power view, tumor cells were monomorphic and uniform-sized, showing a trabecular, rosette pattern with small round cells featuring small round nuclei and pink-to-pale cytoplasm (H&E, ×400). (C) Tumor cells showing positivity for Ki-67 (Ki-67 stain, ×200). (D) Tumor cells were reactive to synaptophysin immunohistochemistry, evidence of neuroendocrine neoplasm (synaptophysin stain, ×200).

duct dilatation were not observed on the magnetic resonance cholangiopancreatography (Fig. 1).

According to the pathologic report, endoscopic snare papillectomy was performed for accurate diagnosis and treatment, which was based on patient's hesitancy to undergo surgery (Fig. 2). At the time of the procedure, red infiltrative changes were observed in the bottom of the major papilla, and a further biopsy was performed concurrently. The resected specimen measured 1.7×1.3 cm. The patient was discharged after the procedure, without complications, such as bleeding or perforation. The pathologic examination of the minor papilla showed that the lesion was localized to the deep mucosal layer and submucosa, and there was no involvement of the resection margin. According to microscopy, the tumor cells were arranged in a fibrous or rosette form, with a round nuclei and granular chromatin; mitosis was rarely observed (1 per 10 high-powered fields). On immunohistochemistry, both synaptophysin and Ki-67 were positive. The Ki-67 index was <2%, which was consistent with NET (Fig. 3). The tumor diameter was 1.2×1.1 cm, suggesting a well-differentiated, low-grade NET with a World Health Organization (WHO) grade of I.

The patient was later re-admitted because NET was also observed on histologic examination of the major papilla. Positron emission tomography was performed, but showed no suspicious metastases. Endoscopic papillectomy was also performed of the major papilla (Fig. 4), and a tumor with a size of 1.6×1.2 cm was observed. The tumor was limited to the sphincter of Oddi and perisphincteric submucosa. There was no tumor involvement at the resection margins. Microscopic and immunohistochemistry findings were the same as those of the minor papilla (Fig. 5). Since the diagnosis, the patient has undergone follow-up for 16 months without recurrence on repeated EGD and CT.

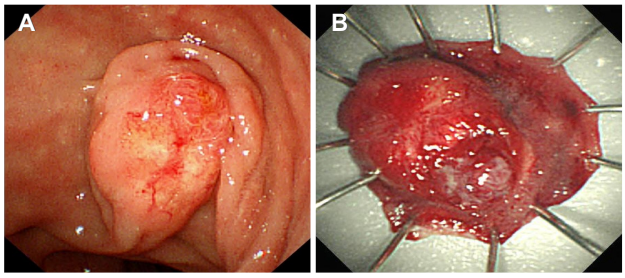

Fig. 4. Side-viewing duodenoscopic findings for major duodenal papilla. (A) Endoscopy showing a rather prominent major duodenal papilla, but with preserved configuration. There were hyperemic granular changes and ectatic vessels. (B) Gross finding of the resected specimen after endoscopic snare major papillectomy.

DISCUSSION

The Surveillance, Epidemiology, and End Results Program from the National Cancer Institute reported only 1.35% of NETs among all malignant neoplasms of the ampulla of Vater (AOV).[6] However, the incidence rate has apparently increased in recent years, likely due to the generalization of EGD for screening and the development of diagnostic technologies.[7] The behavior of duodenal papillary NET has not been fully elucidated to date due to their rare occurrence. Moreover, surgical outcomes of duodenal papillary NETs are limited to only case reports.[8] Previous studies have recommended pancreaticoduodenectomy over local resection for duodenal papillary NET, regardless of tumor size due to frequent nodal metastasis, compared to duodenal NETs, with tumor sizes as small

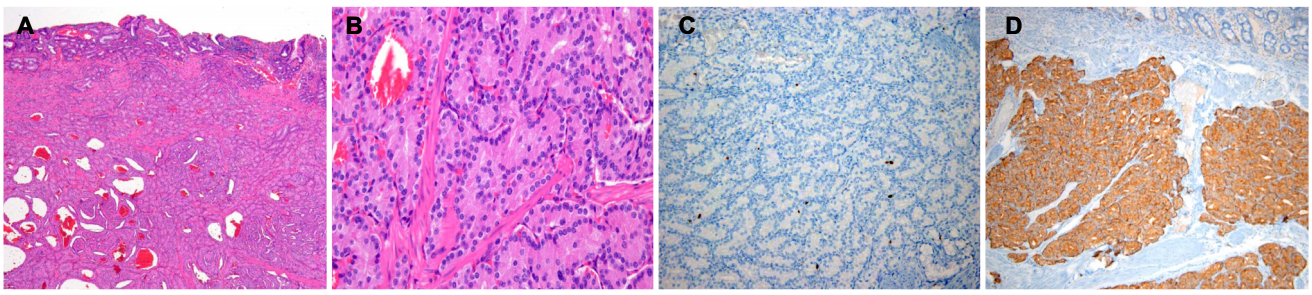

Fig. 5. Pathologic findings of a neuroendocrine tumor of the major duodenal papilla. (A) On low-power view, tumor cells were limited to submucosa. Lymphovascular and perineural invasion was not seen (H&E, ×40). (B) On high-power view, tumor cells were monomorphic, uniform-sized, and showed a trabecular, rosette pattern with small round cells featuring small round nuclei and pink-to-pale cytoplasm (H&E, ×400). (C) Tumor cells showing positive reaction for Ki-67 (Ki-67 stain, ×200). (D) Tumor cells were reactive to synaptophysin immunohistochemistry, evidence of neuroendocrine neoplasm (synaptophysin stain, ×100).

as 2.0 cm.[9,10]

Despite frequent regional lymph node metastases, the prognosis of duodenal papillary NETs has generally been good: 5-year survival is 90%, with only 6% dying from metastatic disease or progressive tumors.[1] According to the WHO 2010 tumor grading classification, small tumor size (<2 cm) and G1/G2 NETs showed favorable prognosis.[11] Currently, endoscopic resection and surgical ampullectomy have been considered to be safe for small NETs of the AOV (<2 cm) or in patients with severe comorbidities.[12,13]

NETs located in the minor duodenal papilla are extremely rare, and as of 2016, only 15 cases have been described in the English literature.[14] However, in a single autopsy and surgical specimen study, NETs of the minor duodenal papilla were twice as common as those of the major duodenal papilla.[15] The reason NETs of the major duodenal papilla are discovered more frequently than those of the minor duodenal papilla in the clinical practice may be that the former is more likely to cause symptoms, such as jaundice or abdominal pain due to papillary obstruction. Conversely, NETs of the minor duodenal papilla seldom cause symptoms, as there is no biliary or pancreatic obstruction.[16] Moreover, NETs arising from the minor papilla are not easy to diagnose preoperatively due to its relatively small size and submucosal location.[17]

The frequency of lymph node metastasis from duodenal papillary NETs is 60-66%, although it has been shown that this variant is not related to the overall survival, as the 5-year survival rate is about 90%. However, the prognosis is rather poor, especially when there are hepatic metastases; the prognosis for minor papilla NETs remains unknown.[8] The Japanese-language literature reports 19 cases who underwent pancreaticoduodenectomy for NET of the minor duodenal papilla. Most patients with tumors measuring 1.0-2.0 cm had lymph node metastasis; it appears that NETs arising from the minor duodenal papilla have a high propensity for lymph node metastasis, like the major duodenal papilla.[18]

The treatment of choice for NETs of the duodenal papilla is complete resection, and the standard treatment modality is pancreaticoduodenectomy.[10] Although a pancreaticoduodenectomy enables complete resection of the tumor, this procedure seems to be associated with disadvantages due to relatively high morbidity, as well as moderate levels of mortality.[1] Local excision shows satisfactory results in tumors smaller than 2 cm.[1] Compared to local resection, endoscopic papillectomy is much less invasive because it does not require laparotomy or duodenectomy.

Complications related to endoscopic snare papillectomy are self-limiting.[3] In a recently published article, complications occurred in 18.5% (n=10/54) of cases: bleeding (n=3); pancreatitis (n=7), and perforation (n=1; the only case requiring rescue surgical intervention). There was no intervention-related death (mortality, 0%).[4] Endoscopic snare papillectomy may be considered as the first step in the management of small NETs (<1 cm) of the AOV when radical resection appears to be difficult or poorly tolerated.[19] In this case, pancreaticoduodenectomy was initially recommended; however, the patient refused to undergo surgery. Endoscopic papillectomy was successfully performed sequentially.

We report the first case of endoscopic papillectomy of simultaneous neuroendocrine tumors in the major and minor duodenal papilla. Long-term follow-up is needed to better determine the ultimate outcome. Endoscopic papillectomy is considered a treatment option when radical surgery seems to be difficult or poorly tolerated.

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