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Synchronous endocrine tumors of small intestine: Report of a case

İnce barsakta senkron endokrin tümörler: Olgu sunumu

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As with most endocrine tumors, the malignant potential depends on evidence of local or distant invasion (metastasis), so it is important to differentiate synchronous/metachronous endocrine tumors from their metastases. A 90-year-old man was operated due to tumor of the ampulla of Vater. As the surgical specimen was examined macroscopically, a second tumor focus, measuring 1 cm in diameter, was detected at the duodenum. There were no clinical syndromes due to hormone hypersecretion. Microscopically, the ampullary tumor had trabecular and rosette-like patterns, with many necrotic areas. It had invaded the muscularis mucosa at the duodenal wall. The latter duodenal tumor was located in the submucosa and had distinct borders. This tumor consisted of trabecular structures with stroma rich in lymphoid aggregates. Immunohistochemistry revealed positivity for synaptophysin and gastrin and negativity for somatostatin. In addition, the whole antral portion of the Whipple resection material showed diffuse parietal cell hyperplasia. The tumors were diagnosed as well-differentiated endocrine carcinoma in the ampulla of Vater according to the WHO classification 2000, a gastrin-producing well-differentiated endocrine tumor in the first portion of the duodenum without regional lymph node metastases, and a diffuse parietal cell hyperplasia at the antral portion of the stomach.
In conclusion, clinical findings and the postoperative diagnosis suggest that this patient had primary synchronous neuroendocrine tumors of the small intestine.

Key words: Synchronous, neuroendocrine tumor, ampulla of Vater, gastrinoma, duodenum.

Çoğu endokrin tümörlerde malign potansiyel, lokal invazyon ya da uzak metastazın varlığına bağlı olduğu için, senkron/metasenkron tümörleri metastazlarından ayırt etmek önemlidir. Doksan yaşındaki erkek hasta, ampulla Vateri'deki tümöründen dolayı opere edildi. Makroskopik olarak cerrahi spesmen incelendiğinde, duodenumda, 1 cm çapında ölçülen ikinci bir tümör odağı tespit edildi. Hormon hipersekresyonuna bağlı klinik sendromları yoktu. Mikroskopik olarak ampullar tümör, birçok nekrotik alan ile birlikte trabeküler ve rozet benzeri paternlere sahiptir. Tümör, duodenum duvarında muskularis mukozayı invaze etmiştir. Duodenumdaki tümör submukozada lokalizedir ve keskin sınırlıdır. Bu tümör, lenfoid agregatlardan zengin stromayla birlikte trabeküler yapılardan oluşmaktadır. İmmunohistokimya sinaptofizin ve gastrin için pozitif, somatostatin için negatif saptandı. Ek olarak, Whipple rezeksiyon materyalinin antral bölümünün tamamı diffüz parietal hücre hiperplazisi göstermekteydi. WHO 2000 sınıflamasına göre, ampulla Vater'deki tümör iyi diferansiye endokrin karsinom, bölgesel lenf nodu metastazı içermeyen duodenum birinci bölümdeki tümör gastrin üreten iyi diferansiye endokrin tümör ve midenin antral bölümünde diffüz parietal hücre hiperplazisi olarak tanı aldı. Sonuç olarak, klinik ve postoperativ bulgular hastada, ince barsakta primer senkron endokrin tümörler olduğunu düşündürmektedir.

Anahtar kelimeler: Senkron, nöroendokrin tümör, ampulla Vater, gastrinoma, duodenum

INTRODUCTION

As with most endocrine tumors, malignant potential depends on evidence of local or distant invasion (metastasis), so it is important to make the differential diagnosis between synchronous/metachronous endocrine tumors and their metastases prior to making a protocol of the treatment. Multiple endocrine tumors of the small intestine, without MEN (multiple endocrine neoplasia) syndrome are not uncommon; however, it is not always easy to exactly recognize their origin (1).

In this article, we present the clinicopathologic features of a patient with synchronous endocrine tumors of the small intestine.

CASE REPORT

A 90-year-old man was admitted to Pamukkale University Hospital with the complaints of abdo-

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minal pain, nausea, vomiting, and dark colored urine. He had a 20-year history of hypertension. There was no family history of cancer. On physical examination, there were no remarkable signs except high blood pressure and fever. The routine laboratory data were normal. Ultrasonography and computed tomography scan revealed a tumor at the ampulla of Vater. Pancreaticoduodenectomy with extensive lymph node dissection was performed.

Macroscopically, Whipple's specimen measured 26x10x5 cm in diameter and revealed an ampullary submucosal lesion measuring 8x5x4 mm that was protruding towards the luminal surface. In addition, at the first portion of the duodenum, a second lesion was determined as a nodular, submucosal tumor that measured 10x10x10 mm. The distance between the first and second lesions was 8.5 cm. Moreover, rugae of the antral portion of the stomach were thick and irregular. This area was approximately 10x2.5x1 cm in diameter. Totally, four lymph nodes were dissected, including at one perigastric and three peripancreatic locations.

Microscopically, the ampullary tumor had trabecular and rosette-like patterns, with many necrotic areas (Figure 1). It had invaded the muscularis mucosa at the duodenal wall. Tumor cells had large and pleomorphic nucleus containing coarse chromatin and rarely nucleolus. Their cytoplasms were scanty and cytoplasmic borders were indistinct. Atypical mitoses were frequent, with 12 mitoses counted in x10 high power field. In addition, Ki-67 proliferation index was 90%. There were dysplastic changes at the mucosa adjacent to the tumor. Immunohistochemical staining of the tumor cells were diffuse positive for synaptophysin, chromogranin and EMA, and negative for gastrin, somatostatin and p53. There was vascular invasion; however, lymph node metastases were not observed.

The latter duodenal tumor, measuring 0.8 cm in diameter microscopically, was located in the submucosa and had distinct borders. This tumor consisted of trabecular structures with stroma rich in lymphoid aggregates (Figure 2). Tumor cells had mild nuclear pleomorphism, granular chromatin pattern and scanty cytoplasm. Immunohistochemical investigation of this tumor clarified that the tumor cells were positive for synaptophysin and gastrin (Figure 3) and negative for somatostatin. Vascular invasion and mitosis were not observed; however, Ki-67 proliferation index was 3-4%.

In addition, the antral portion of the stomach had an increased number of hypertrophic parietal cells like oxyntic type mucosa (Figure 4). There was no atrophy or endocrine cell hyperplasia anywhere in the stomach. Immunohistochemical examination revealed positivity for chromogranin in the neuroendocrine cells of the submucosa, but parietal cells were negative. Surgical borders of the Whipple resection were intact and no regional lymph node metastasis was seen.

Finally, the tumors were diagnosed as well-differentiated endocrine carcinoma in the ampulla of Vater according to the World Health Organization

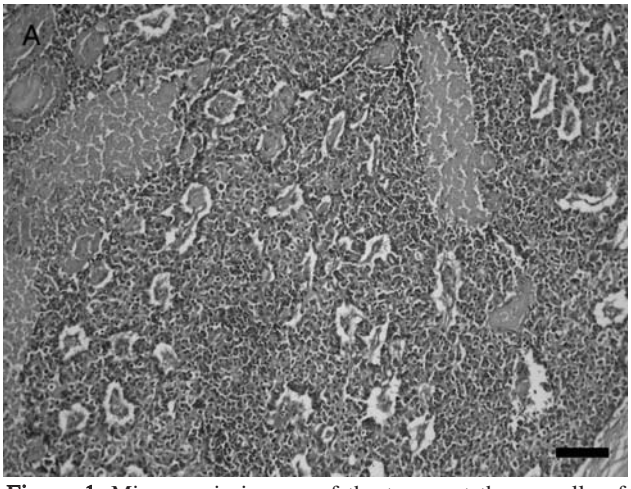

Figure 1. Microscopic images of the tumor at the ampulla of Vater. Solid structures with central necrosis (hematoxylin and eosin stain, scale bar=100 μm).

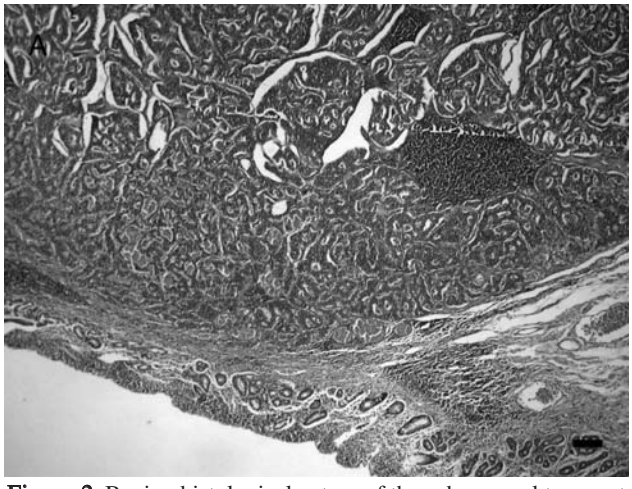

Figure 2. Benign histological nature of the submucosal tumor at the duodenum. Trabecular structures including lymphoid aggregates are seen (hematoxylin and eosin stain, scale bar=20 μm).

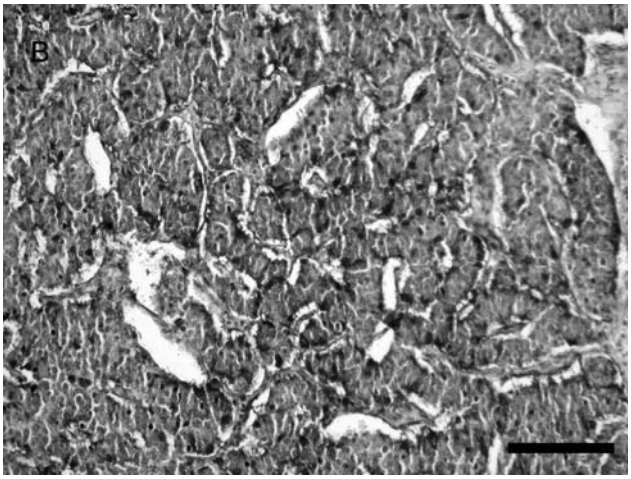

Figure 3. Gastrin positivity in the submucosal tumor at the duodenum (anti-gastrin immunostaining, scale bar=100 μm).

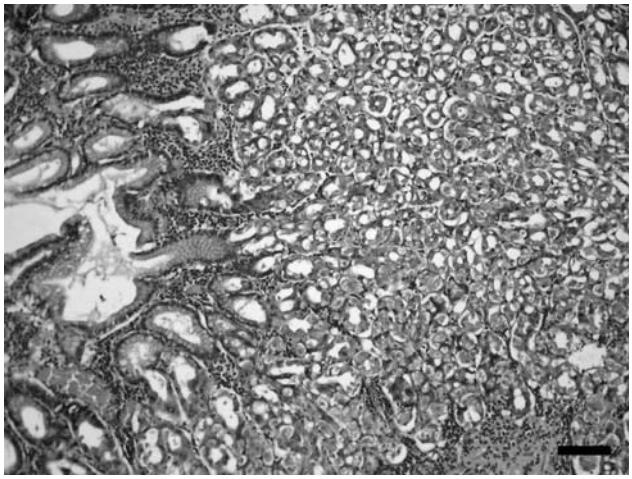

Figure 4. Diffuse parietal cell hyperplasia at the antral portion of the stomach (hematoxylin and eosin stain, scale bar=100 μm).

(WHO) classification 2000, a gastrin-producing well-differentiated endocrine tumor for the first portion of the duodenum without regional lymph node metastases, and a diffuse parietal cell hyperplasia at the antral portion of the stomach (2). The well-differentiated gastrin-producing endocrine tumor of the first portion of the duodenum had benign behavior, because tumor size was 1 cm, without vascular invasion and clinical syndrome, except for Ki-67 proliferation index of >2% (2-4).

The patient's postoperative course was uneventful. The patient died in the sixth postoperative month of causes unrelated to the cancer.

DISCUSSION

Ampullary endocrine tumors become evident with the signs of bile duct obstruction like jaundice and bleeding (5). Our patient was admitted to the hospital with the complaint of dark urine as a sign of bile duct obstruction. The other gastrin-producing well-differentiated endocrine tumor at the first portion of the duodenum was discovered postoperatively. Gastrinomas are small, and thus preoperative localization procedures often fail. According to the literature, duodenal gastrinomas are often malignant and two-thirds have already metastasized to the liver or regional lymph nodes at the time of diagnosis (6). Though advanced age of the patient increases the risk of malignant behavior of gastrin-producing endocrine tumors, in this elderly case, one might presume that it had metastasized to the ampulla of Vater. If this statement was true, first, gastrin expression in both tumors should be expected. Second, it would be surprising to find a metastasis at the ampulla of Vater due to such gastrin-producing well-differentiated endocrine tumor before metastasis to the lymph nodes or liver. However, the metastatic potential of most small duodenal gastrinomas seems to be restricted to the regional lymph nodes (7,8). In our case, lymph node metastases were not detected, supporting the synchronous nature of these tumors. Additionally, the histochemical and immunohistochemical profiles of these two tumors of the ampulla of Vater and the duodenum differ considerably: the former consisted of tumoral cells with numerous atypical mitoses and necrosis, while the latter was very organized with trabecular structure without atypia. We then considered this case as having two synchronous endocrine tumors without MEN-1. Primary duodenal gastrinomas are now recognized as a common etiology in patients with sporadic Zollinger-Ellison syndrome (ZES). The presence of prominent gastric body folds is an important clue to the diagnosis of ZES. Histopathological findings of ZES have been described as gastric mucosal hypertrophy and parietal cell hyperplasia. In this case, the existence of parietal cell hyperplasia might be due to silent ZES. We tried to explain the increase in parietal cells at the antrum with gastrin hypersecretion; however, we were unable to learn the serum gastrin level of this patient in the preoperative period. It has been demonstrated that hypergastrinemia invariably results in increased parietal cell mass and enterochromaffin-like (ECL) cell proliferation. Long-term hypergastrinemia induces ECL cell hyperplasia as well and, if continued, results in neoplasi-

a (9). Additional factors associated with atrophic corporal gastritis or MEN-I are therefore necessary for such progression (10). In our case, no typical carcinoid was determined in the stomach or any condition like pernicious anemia. Moreover, there was no atrophy anywhere in the stomach. It lacked all features of ZES like diarrhea, steatorrhea or duodenal ulcer, but one of the symptoms was abdominal pain. We finally concluded that the tumor located in the duodenum could be considered a sporadic and clinically non-functioning gastrinoma. We think that the association of silent ZES is still debatable in view of the presence of parietal cell hyperplasia, even though ZES was not biochemically proven.

Synchronous multiple neuroendocrine tumors have been reported in the gastrointestinal tract (5,11). In the report of Andaker et al. (11), multiple synchronous carcinoid tumors were found in 14 of 102 patients and interestingly, all of them were men. This case is compatible with their data according to male incidence. However, there is very poor information about synchronous/metachronous endocrine tumors at different grades of differentiation.

In summary, in this case we considered that the gastrin-negative tumor of the ampulla of Vater and the gastrin-positive tumor of the duodenum were two distinct tumors rather than one being a metastasis of the other. For this reason, we accepted this case as two synchronous/metachronous endocrine tumors at different grades of differentiation. The possible synchronous occurrence of several such tumors should not be ignored preoperatively and should be differentiated from metastatic endocrine tumors. Preoperative diagnostic biochemical and imaging tests should include serum gastrin level, computerized tomography, ultrasonography, and somatostatin receptor scintigraphy (SRS) to exclude diffuse metastasis and ZES.

REFERENCES

1. Nassar H, Albores-Saavedra J, Klimstra DS. High-grade neuroendocrine carcinoma of the ampulla of Vater: a clinicopathologic and immunohistochemical analysis of 14 cases. Am J Surg Pathol 2005; 29: 588-94.
2. Solcia E, Klöppel G, Sobin LH. Histological Typing of Endocrine Tumours. New York: Springer, 2000.
3. Bordi C, D'Adda T, Pizzi S, et al. The assessment of malignancy in endocrine tumours of the gastrointestinal tract. Curr Diagn Pathol 2002; 8: 421-9.
4. Kloeppel G, Anlauf M, Lüttges J. Klassikation und pathologie der neuroendokrinen tumoren des magen- darmtrasks und pankreas. Onkologe 2004; 10: 570-9.
5. Witzigmann H, Loracher C, Gesissler F, et al. Neuroendocrine tumors of the duodenum: clinical aspects, pathomorphology and therapy. Langenbeck's Arch Surg 2002; 386: 525-33.
6. Kisker O, Bastian D, Bartsch D, et al. Localization, malignant potential, and surgical management of gastrinomas. World J Surg 1998; 22: 651–8.
7. Solcia E, Rindi G, Larosa S, et al. Morphological, molecular and prognostic aspects of gastric endocrine tumors. Microsc Res Tech 2000; 48: 339-48.
8. Takasu A, Shimosegawa T, Fukudo S, et al. Duodenal gastrinoma–clinical features and usefulness of selective arterial secretin injection test. J Gastroenterol 1998; 33: 728-33.
9. Waldum HL, Brenna E, Sandvik AK. Relationship of ECL cells and gastric neoplasia. Yale J Biol Med 1998; 71: 325-35.
10. Bordi C, D'Adda T, Azzoni C, et al. Pathogenesis of ECL cell tumors in humans. Yale J Biol Med 1998; 71: 273-84.
11. Andaker L, Lamke LO, Smeds S. Follow-up of 102 patients operated on for gastrointestinal carcinoid. Acta Chir Scand 1985; 151: 469-73.