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Carcinoid tumor of the stomach A rare form of gastrointestinal carcinoid tumor: A report on three cases*

Mide karsinoid tümörü Gastrointestinal karsinoidlerin nadir bir tipi: Üç olgu sunumu*

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Between 1994 and 1999 three patients with gastric carcinoid tumors were diagnosed at Yüzüncü Yıl University Medical Faculty, Department of Surgery. Their ages were 65, 80, and 50 years, and all were male. The major complaints were epigastric pain, dysphagia, loss of appetite and weight, postprandial vomiting and in one patient, hematemesis and melena. None of the patients had carcinoid syndrome. The tumor was located in the upper portion of the stomach in one case and distal portion of the stomach in two cases. All three patients were initially diagnosed as adenocarcinoma of the stomach due to the endoscopic appearance of the tumor and histologic evaluation of the endoscopic biopsy. Because of the diagnosis of gastric carcinoma, two of them underwent subtotal gastrectomy and the other had a total gastrectomy. Histological examination of the resected materials showed well differantiated carcinoid tumors. Two cases had lymph node metastasis. Tumor cells in the stomach were immunoreactive for chromogranin A and neuron specific enolase and Grimelius positive for argyrophil cell detection. This paper presents a literature review and describes these three cases.

Key words: Carcinoid tumor, stomach.

1994-1999 yılları arasında Yüzüncü Yıl Üniversitesi Tıp Fakültesi Genel Cerrahi Kliniğinde üç olguda mide karsinoid tümörü saptandı. Olguların tümü erkek , 65, 80 ve 50 yaşlarında idiler. Epigastrik ağrı, disfaji, iştahsızlık, kilo kaybı, yemek sonrası kusma ve bir olguda hematemez ve melena şikayetleri vardı. Karsinoid sendrom bulguları hiçbir olguda saptanmadı. Bir olguda tümör proksimalde, iki olguda distalde lokalize idi. Her üç olguda endoskopik ve endoskopik biopsi tanısı mide adenokarsinomu idi. İki olguya subtotal, bir olguya total gastrektomi yapıldı. Ameliyat materyallerinin histopatolojik değerlendirimesi ile karsinoid tümör tanısı konuldu. İki olguda lenf nodülü metastazı saptandı. Tümör hücreleri chromogranin A ve neuron specific enolase için immunoreactive bulundu. Argyrophil hücre için yapılan Grimelius pozitif bulundu.

Anahtar kelimeler: Karsinoid tümör, mide.

INTRODUCTION

Carcinoid tumors are endocrine and usually originate from so-called enterochromaffin-like (ECL) cells. They can be easily identified by argentaffin silver staining reactions related to the presence of serotonin in tumor cells (1). Carcinoid tumors have been identified in sites as diverse as the lung, ovary, biliary system and throughout the gastrointestinal tract (2). In a combined series of 8.305 cases, nearly 74 % of all carcinoid tumors were found in the gastrointestinal tract while the second most frequent site for carcinoid formation was the tracheobronchopulmonary complex (25.09 %) (2). The most frequent location in the gastrointestinal tract is the small bowel, with the highest frequency then the ileum, appendix and large bowel. Gastric carcinoids are rare and account for less than 1 % of all gastric tumors (3,4). They tend, like those in the small and large intestine, to be infiltrative, aggressive tumors that metastasize in about one third of cases (5).

CASE REPORT

Case 1: A 65-year-old man with complaints of dysphagia and loss of weight and appetite was admitted to Yüzüncü Yıl University Hospital in

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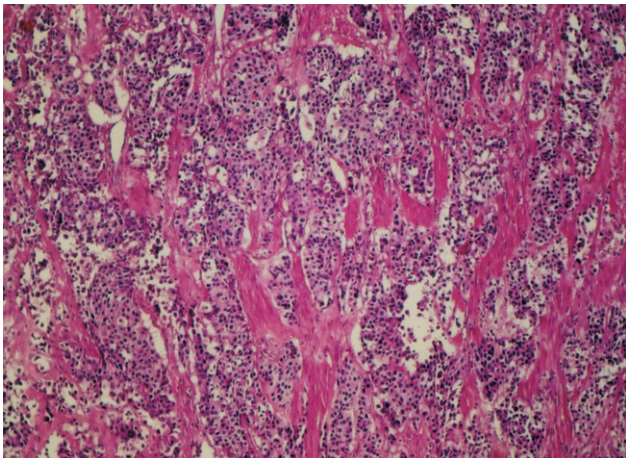

Figure 1. Carcinoid tumor with insular pattern of growth (H-E X 125).

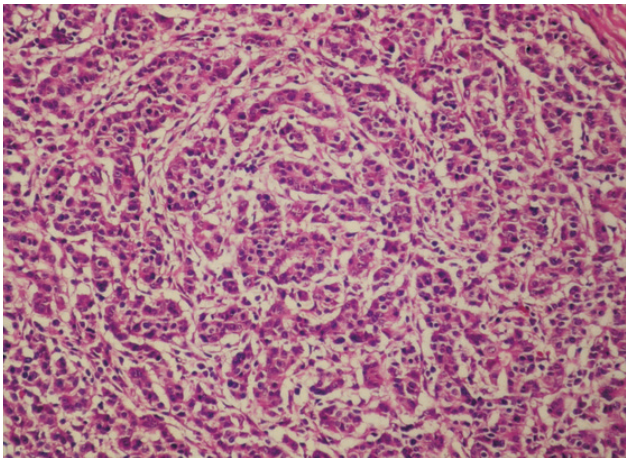

Figure 2. Carcinoid tumor with trabecular pattern of growth (H-E X 125).

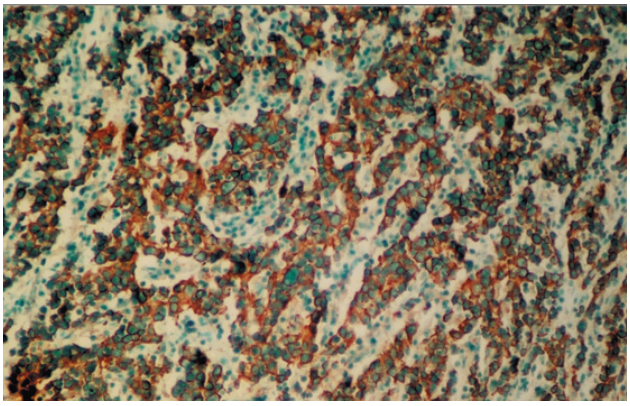

Figure 3. Tumor cells showing immunohistochemical positivity for NSE (ImmunperoxidaseX 125).

February 1999. He was found to be anemic with hemoglobin of 8.1 g/dL. Gastroscopic examinaton revealed a polypoid and superficially ulcerated tumor mass with a diameter of 3-4 cm. located in the upper portion of the stomach. Biopsy was performed and the histological work-up revealed poorly differentiated adenocarcinoma. Total gastrectomy with a Roux-en-Y reconstruction was performed. At operation serosal involvement was found to be present but there was no liver metastasis. Postoperative recovery was uneventful. Gross examination of the resected material revealed a 9cm x 8cm x 6cm tumor with serosal involvement located on the upper portion of the stomach. Microscopically, the tumor had a predominantly insular growth pattern (Figure 1). The nuclei were minimal pleomorphic and normochromatic and mitoses were scanty (3-4 mitoses in each 20Xmagnification areas). Necrosis was minimal. The tumor cells were positive for chromogranin and neuron specific enolase (NSE). One of the seven resected lymph nodes had tumor metastasis.

Case 2: An 80-year-old man was admitted in January 1999, with a history of epigastric pain and postprandial vomiting. Hematological investigations revealed a hemoglobin of 8.7 g/dL. At gastroscopy, he was found to have a vegetating, ulcerated mass causing gastric outlet obstruction. Endoscopic biopsy was performed and histology revealed adenocarcinoma. At surgery, a 5 cm x 6 cm x 6 cm. mass in the antro-pyloric junction was found. Subtotal gastrectomy was performed. Gross examination of the resected specimen revealed an 8 cm x 8 cm x 1.5 cm tumor which had serosal involvement. Microscopically the tumor had a predominantly trabecular growth pattern (Figure 2). The nuclei were regular and normochromatic while mitoses were scanty (1-2 mitoses in each 20X magnification areas). Necrosis was absent. Grimelius stain showed argyrophilia and the tumor cells were positive for chromogranin and NSE. (Figure 3). None of the 11 resected lymph nodes had tumor involvement.

Case 3: 50-year-old man was admitted in February 1998, with complaints of epigastric pain, postprandial vomiting, hematemesis and melena. At gastroscopy, a necrotic based ulcerated tumor mass was found in the pylorus. A biopsy was taken and histology revealed adenocarcinoma. Subtotal gastrectomy was performed. Macroscopic evaluation of the resected material revealed 11 cm x 8 cm x 1.5 cm tumor mass with serosal involvement. Microscopically, the tumor had a similar growth pattern to that of case 2. The nuclei were regular and normochromatic, mitoses were scanty (one-two mitoses in each 20X magnification area) and necrosis was minimal. Grimelius stain showed argyrophilia. The tumor cells were positive for chromogranin and NSE. Three of the 14 resected lymph nodes had tumor metastasis.

Tissues were routinely processed and stained with hematoxylin and eosin for conventional histopathology and with silver impregnation methods (Grimelius) for argyrophil cell detection. Immunohistochemical tests for general neuroendocrine markers chromogranin A and NSE were performed. Endocrine tumors were diagnosed as well-differentiated or poorly differentiated following conventional histopathologic criteria and tumor analysis comprised determining the size, site, number of growths and level of infiltration. Clinicopathologic analysis included the age, sex and presence of local or distant metastasis. Based on these criteria, the three cases were diagnosed as well differentiated sporadic type 3 carcinoid tumor of the stomach. They had no symptoms of flushing, palpitations or diarrhea, no finding of pernicious anemia, chronic atrophic gastritis or Zollinger-Ellison syndrome and no history of treatment with omeprazole. A 24-hr urine 5-Hdroxy indol acetic acid was negative after the diagnosis of the carcinoid tumor.

DISCUSSION

Carcinoids are the most frequently occurring neuroendocrine tumors (6). Although they were initially believed to be mostly benign, these neoplasms have since been found to exhibit a malignant course. Unfortunately, in this class of neoplasia the criteria for establishing the degree of malignancy are not clear. The best indicator of prognosis and malignancy is evidence of invasive growth and the presence or absence of regional or distant metastases (2). Tumor size of gastric carcinoids appears to be a fundamental risk factor for metastatic dissemination, and surgical management is commonly based on the size of these lesions (1,7,8).

Until recently, gastric carcinoids were considered to be rare tumors, accounting for no more than 0.3% of all gastric tumors and only about 2% to 3 % of all neuroendocrine gut neoplasms, (9,10). According to recent studies, however, the incidence of gastric carcinoids accounts for at least 10 % or more of all such tumors (11-13). This remarkable increase in the incidence of gastric carcinoids probably represents increased recognition rather than a true increase in incidence because it has occured since endoscopic examination of the stomach became widespread (8,13,14). The percentage of gastric carcinoids in relation to all gastric cancers has also increased (1,14).

In most centers, gastric carcinoids are still rare tumors and are unlikely to account for more than 5% to 10% of gastrointestinal carcinoids (1,10). In our department, only three (2.4%) out of 123 patients who had undergone surgery for gastric malignant lesions were found to have carcinoid tumor.

The association between low acid states (atrophic gastritis, pernicious anemia) and gastric ECL cell hyperplasia and subsequent neoplasia has been demonstrated in both human and animal models (14-18). This is believed to be due to a chronic hypergastrinemia, resulting in chronic stimulation of ECL cells, which in turn leads to hyperplasia, metaplasia and ultimately neoplasia (3,19). Although gastric carcinoid tumors have not specifically been linked with major acid inhibitory therapy, ECL cell hyperplasia has been these patients (14-18). None of our three patients had pernicious anemia, chronic atrophic gastritis, Zollinger-Ellison syndrome or a history of long term treatment with omeprazole.

Based on their association with several hypergastrinemic conditions that occur sporadically a single tumors usually arising in normal mucosa, well-differentiated ECL cell tumors (carcinoids) were subclassified as type1: associated with chronic atrophic gastritis; type 2: associated with hypertrophic gastropathy, usually in conjunction with type 1 multiple endocrine neoplasia and Zollinger-Ellison syndrome type 3: sporadic, not associated with any specific gastric pathology (8,12-14). Enterochromaffin-like cells are the

main endocrine cell types in type 1 and type 2 gastric neuroendocrine tumors and are highly suspectible to gastrin trophic stimulus. Gastric neuroendocrine tumor types 1 and 2 are usually considered benign with a low risk of malignancy, making it possible to avoid surgery, at least in patients at high surgical risk. Although type 3 gastric neuroendocrine tumors histologically appear to be ECL cell tumors, they may also contain other cell types. These may be composed of different endocrine cells, including poorly differantiated endocrine and exocrine cells, which grow sporadically and are a highly proliferative and malignant entity probably induced by disregulation of p53 protein function (11-13,20-24). The most common are those associated with chronic atrophic gastritis with or without pernicious anemia and arising in a background of ECL hyperplasia, induced by hypergastrinemia, a promoting growth factor for these cells. Most of these tumors are less than one cm in diameter, well differentiated and confined to the mucosa and submucosa of the upper two thirds of the stomach or in the transitional zone to the antrum (1). Lymph node metastases do occur, but in fewer than 10% of these patients and primarily when the tumors are two cm and above in diameter. They are frequently multiple and present as polypoid tumors (1,14,20-23).

Well differentiated neuroendocrine tumors arising sporadically in the gastric mucosa (type 3) are rare, frequently 2 cm or larger at the time of discovery and often show angioinvasion or invasion within the stomach wall. More than 60% of these solitary lesions have been associated with lymph node metastases and at least half of these with liver metastases (14,20-23). Our cases had large tumors that invaded serosa; angioinvasion was also seen in three cases, and lymph node metastases in two cases.

A comprehensive retrospective series of 100 patients with advanced gastric carcinoid, presented by Mizuma et al. revealed that a quarter of gastric carcinoids were located in the antral region, with the remainder in the corpus and fundus (7). Two of our cases had carcinoid tumor located in the antrum and the third had a tumor located in the upper portion of the stomach.

Gastric carcinoids usually present with symptoms of epigastric pain, vomiting, gastrointestinal bleeding and anemia. In contrast to carcinoids of the small intestine however, a carcinoid syndrome is only rarely (5%) encountered, even in patients with more advanced lesions (1,3,25). None of our patients, in spite of their advanced stage, had symptoms of carcinoid syndrome.

Endoscopic diagnosis of carcinoid tumors may be difficult in the early stage due to their submucosal location and varied endoscopic appearance (3,26,27). In the early stages, they may appear as multiple sessile nodules or gastric polypes (3). Biopsies have to be deep and multiple biopsies should be taken from the same site to involve the submucosa and obtain a histological specimen that will reveal the tumor (3).

In advanced cases, a tumor mass is seen, which may be ulcerated. Although identification of the tumor mass is not difficult, making a diagnosis of carcinoid tumor may be a problem (2,26,27). There are only subtle histological differences between undifferentiated gastric carcinoids and gastric adenocarcinomas (3). All of our three cases had initially been diagnosed as adenocarcinoma of the stomach. A literature review revealed reports of such misdiagnosed carcinoid tumors of the stomach. Eriguchi at al. reported an advanced case of carcinoid of the stomach who underwent gastric resection following a diagnosis of gastric adenocarcinoma. The carcinoid was diagnosed following histological examinaton of the resected material as in our cases (26). In a similar study evaluating eight patients with gastric carcinoid, Krishnamurthy concluded that the endoscopic appearances and endoscopic biopsy were not diagnostic (27).

Surgical resection offers the only hope of a cure or long-term palliation. Since the majority of the tumors are in the body or fundus, and because of multiplicity, a subtotal or total gastrectomy is usually needed (3,8). Resection should be extensive, with regional lymphadenectomy, according to the guidelines for management of gastric cancer even with advanced disease, due to the indolent nature of gastric carcinoid (1,3,7). The five year survival rate is 63%, which is six times that of gastric adenocarcinoma. Functioning carcinoid metastasis to the liver can be treated by hepatic resection for localised disease and hepatic artery ligation for diffuse disease.

One of our patients underwent total gastrectomy, and two underwent subtotal gastrectomy. Aggresive surgery was performed despite their

advanced stage of disease, with serosal invasion and lymph node involvement. All cases are still under follow-up and no cases have developed metastasis or tumor recurrence.

In conclusion, gastric carcinoids are rare lesions and may be difficult to detect endoscopically in the early and advanced stage. Histological examination may require specialised histochemical and ultrastructural examination techniques. Aggressive surgical resection is the treatment of choice, since gastric carcinoids have a better prognosis than gastric adenocarcinomas.

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