The Value of Biochemical Tests in the Diagnosis of Gastric Carcinoid Tumors: Case Report

Gastrik Karsinoid Tümörlerin Tanısında Biyokimyasal Testlerin Değeri

F. Emel KOÇAK,[a]
Cengiz KOÇAK,[b]
Salim İ. KELEŞOĞLU[c]

[a]Department of Clinical Biochemistry,
Dumlupınar University Faculty of Medicine,
Clinics of
[b]Pathology,
[c]General Surgery,
Dumlupınar University
Evliya Çelebi Research and
Training Hospital, Kütahya

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Yazışma Adresi/*Correspondence:*
F. Emel KOÇAK
Dumlupınar University Faculty of Medicine,
Department of Clinical Biochemistry,
Kütahya,
TÜRKİYE/TURKEY
dremelk@hotmail.com

ABSTRACT Gastric carcinoid tumors can be classified into 3 types. Type 1 tumors originate from the mucosal enterochromaffin-like (ECL) cells and are very rarely observed in stomach. These tumors are usually associated with chronic atrophic gastritis, achlorhydria and hypergastrinemia. Discerning the tumor type is critical to develop an appropriate therapeutic strategy and identify prognostic markers. The measurement of biochemical markers, such as gastrin, chromogranin A (CgA) and 5-hydroxyindolacetic acid (5-HIAA), is useful for both diagnosis and typing of tumors. In this manuscript, we report, a rare case of type 1 multiple gastric carcinoid tumor associated with hypergastrinemia and developed based on chronic atrophic gastritis. Our study highlights the importance of biochemical tests in diagnosis and typing, as elevated levels of CgA, 5-HIAA and gastrin were associated with this type 1 tumor.

Key Words: Carcinoid tumor; chromogranin A

ÖZET Gastrik karsinoid tümörler 3 tip olarak klasifiye edilebilirler. Tip 1 gastrik karsinoid tümörler, mukozal enterokromaffin-like (ECL) hücrelerden kaynaklanırlar ve midede oldukça nadir görülürler. Bu tümörler genellikle kronik atrofik gastrit, aklorhidri ve hipergastrinemi ile birliktedir. Tip ayrımının yapılması, uygun bir terapötik strateji geliştirilmesi ve prognozun belirlenebilmesi açısından önemlidir. Gastrin, kromogranin A (KgA), 5-hidroksiindolasetik asid (5-HİAA) gibi bazı biyokimyasal belirteçlerin ölçümü, tümörün tanısı ve tiplendirilmesinde faydalıdır. Bu makalede, nadir görülmesi nedeniyle, kronik atrofik gastrit zemininde gelişen ve hipergastrinemi ile seyreden bir tip 1 multipl gastrik karsinoid tümör olgusu bildirilmiştir. Bizim çalışmamız, bu tip 1 tümörle, yükselmiş gastrin, KgA ve 5-HİAA düzeylerinin birlikteliğinde olduğu gibi, teşhis ve tiplendirmede biyokimyasal testlerin önemini vurgulamaktadır.

Anahtar Kelimeler: Karsinoid tümör; kromogranin A

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Carcinoid tumors can arise in all organs that are derived from the endoderm. Gastric carcinoid tumors are derived from enterochromaffin-like cells (ECL) that contribute approximately 35% of the gastric endocrine cell mass. Enterochromaffin like cells are predominantly located in the gastric fundus. The majority of gastric carcinoid tumors develop on the basis of ECL cell hyperplasia caused by hypergastrinemia associated with achlorhydria. It is now known that hypergastrinemia and carsinoid tumor formation are linked with acid suppression, and the increase in and the duration of increased plasma gastrin levels. The prevailing hypothesis is that serum gastrin level becomes elevated in patients with gastric carcinoma due

to achlorhydria associated with chronic atrophic gastritis. Subsequently, ECL hypertrophy or hyperplasia can develop, mostly because of chronic stimulation by high gastrin.[1,2] Gastric carcinoid tumors are relatively rare lesions, as they constitute about 7% of all carcinoid tumors and less than 1% of all stomach neoplasms.[3] However, the incidence of these tumors has increased at a rate of 3%-10% per year over the past 3 decades. This most likely reflects: increased use of endoscopy for detection, advances in immunohistochemical pathology, increased awareness of the disease among physicians and a true increase in tumor incidence.[4] Carcinoid tumors contain many neurosecretory granules including serotonin, histamine, prostaglandins, kallikrein, bradykinins, substance P, gastrin, CgA and neuron specific enolase. The most prominent of these substances is serotonin. The measurement of the secretory products of carcinoid tumors is helpful in 3 respects: to assist with initial diagnosis, to assess the efficacy of treatment and to assess changing prognosis.[5-7] Gastric carcinoid tumors are unique in that 3 types have been described based upon their unique pathophysiologies: Type I gastric carcinoids account for 70% to 80% of these tumors and are characterized by multiple small lesions; they are also associated with hypergastrinemia secondary to chronic atrophic gastritis and achlorhydria. These type of malignancies are more common in women. Type 2 gastric carcinoid tumors are related to multiple endocrine neoplasia type 1 (MEN-I) and Zollinger-Ellison syndrome (ZES) and associated with hypergastrinemia. Type 3 tumors are generally sporadic and are not associated with elevated gastrin. Chromogranin A levels are elevated in all 3 types.[7,8] Here, we report an extremely rare case of a 58-year-old woman diagnosed with a type 1 multiple gastric carcinoid tumor with accompanying hypergastrinemia and chronic atrophic gastritis. We informed and then, received informed consent from patient.

CASE REPORT

A 58-year-old woman was admitted to the Department of General Surgery with a complaint of dyspepsia; the history of this patient was unremarkable. An endoscopic biopsy from the upper tract of gastrointestinal system was performed. Upon endoscopic examination, multiple polypoid lesions were observed on the anterior and posterior walls of the gastric corpus and endoscopic biopsies were taken from these polypoid lesions. Biopsy samples were subjected to both pathology and immunohistochemical evaluation. Hematoxylin and eosin (H&E) staining revealed that the neoplasm consisted of cells with ovoid, hyperchromatic, uniform nuclei and with a narrow cytoplasm. In addition, there was involvement of the lamina propria, muscularis mucosa, submucosa and grown as solid islets, cordons and nests (Figure 1). Upon immunohistochemical examination (Roche Ventana Benchmark-Bios, Arizona, USA and Thermo Fisher Scientific Inc. MI, USA), the neoplastic cells showed immunoreactivity for pan-cytokeratin, neuron specific enolase (NSE), chromogranin A and synaptophysin (Figures 2-4). Intense atrophic gastritis and incomplete intestinal metaplasia were seen in non-neoplastic gastric tissue. Considering all these features, the pathological diagnosis was one of low-grade carcinoid tumor accompanied with chronic atrophic gastritis and intestinal metaplasia. Biochemically, 5-hydroxyindolacetic acid (5-HIAA) in 24-h urine, serum gastrin and plasma chromogranin A levels were measured. 5-HIAA was measured using the

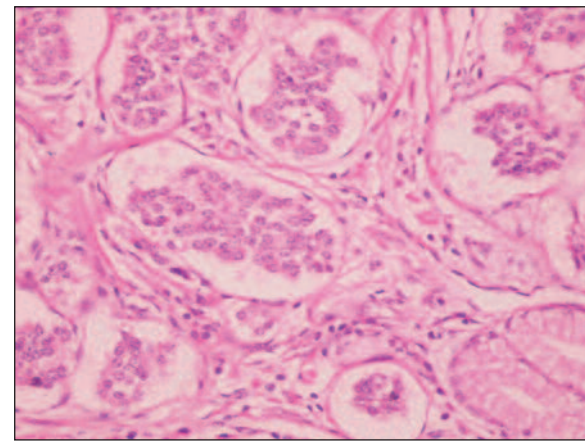

FIGURE 1: Nests of carcinoid tumor cells in mucosa, HE x 40.
(See color figure at
http://www.turkiyeklinikleri.com/journal/journal-of-medical-research-case-reports/1300-0284/)

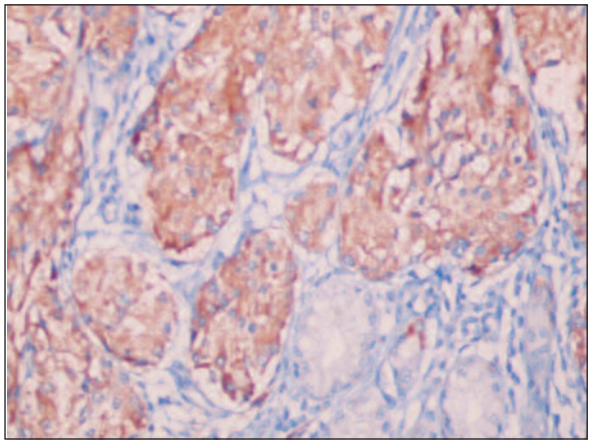

FIGURE 2: Immunreactivite (+)for Synaptophysin, x40.
(See color figure at
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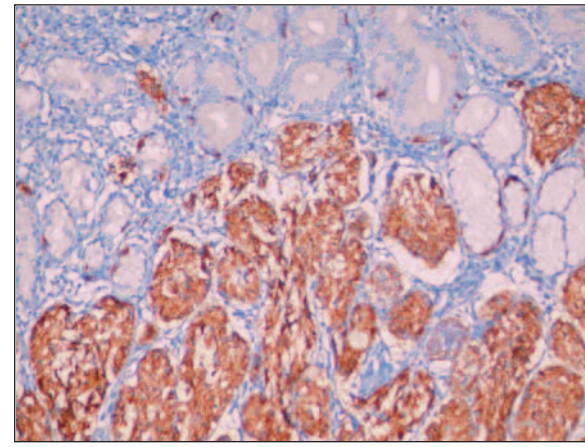

FIGURE 3: Immunreactivite (+) for Chromogranin A, x10.
(See color figure at
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microcolumn liquid chromotography method (FAR, Verona, Italy). Serum gastrin was measured on a Siemens Immulite®1000 immunoassay system and by using original reagent. Plasma CgA was measured with an enzyme-linked immunosorbent assay (ELISA) method (LDN, Labor Diagnostica Nord GmbH&Co KG, Nordhorn, Germany). Gastrin level was 1480 pg/mL (25-125 pg/mL), chromogranin A level was 217 U/L (2-18 U/L), 5-HIAA level was 22.8 mg/day (2-9 mg/day). In addition, the serum vitamin B12 level was 207 pg/mL (191-663 pg/mL) and ferritin level was 10 ng/mL (13-150 ng/mL). Vitamin B12 and ferritin analyses were performed on a Roche Cobas 6000 system and by using original reagents. The analytical method was an electrochemiluminescence immunoassay (ECLIA). The biochemical analysis results correlated with the pathological diagnosis and also supported the diagnosis. Carcinoid tumor was identified as type 1 on the basis of the pathological and biochemical results. In summary, the pathological diagnosis of chronic atrophic gastritis and biochemical diagnosis of hypergastrinemia were both correlated with the presence of the tumor. The patient then underwent total gastrectomy and the removed tissue was subjected to a pathology analysis. In the gastrectomy specimen, common atrophic areas, endoscopic excision areas in these atrophic areas and multiple foci that were slightly elevated in comparison to those in the mucosa were seen in gastrectomy specimen (Figure 5). A residual neoplasm had invaded the lamina propria and sub-

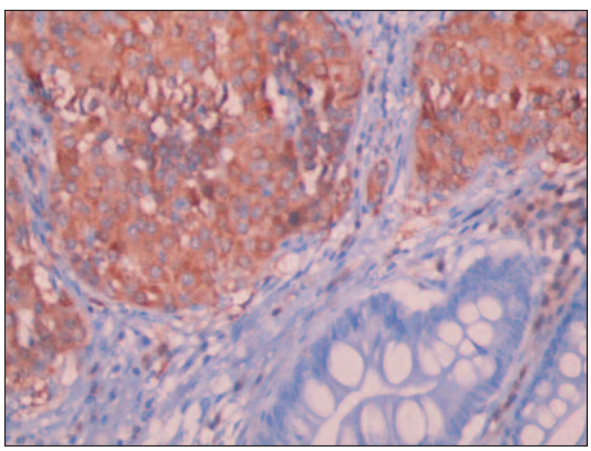

FIGURE 4: Immunreactivite (+) for NSE, x40.
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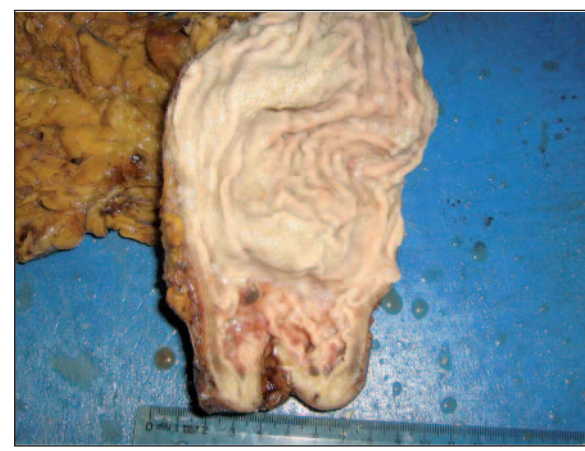

FIGURE 5: The macroscopic view of tumor and atrophy in stomach.
(See color figure at
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mucosa and was observed upon microscopic examinations of samples from these foci. Metastasis was not detected for the dissected regional lymph nodes.

DISCUSSION

Gastric carcinoid tumors can be separated into 3 types: Type 1 tumors are characterized by the presence of chronic gastritis, type 2 tumors are associated with MEN and type 3 tumors are generally sporadic lesions. It has been reported that achlorhydria may play a role in carcinoid tumor development by leading to hypergastrinemia and ECL hyperplasia.[9,10] The association between low acidic states (atrophic gastritis, pernicious anemia) and gastric ECL cell hyperplasia and subsequent neoplasia has been demonstrated in both humans and in animal models.[11,12] The underlying causes of this tumor are thought to involve chronic hypergastrinemia which results in chronic stimulation of ECL cells; this in turn leads to hyperplasia, metaplasia and ultimately neoplasia.[13] Gastric carcinoid tumors that are related to hypergastrinemia derive from ECL cells that usually exist in the oxyntic mucosa and represent the majority of endocrine cells in this location.[14] Gastric carcinoid tumors are asymptomatic at early stages; therefore, there are no specific treatments available. Dyspeptic symptoms and abdominal pain are observed in some cases. Although carcinoid tumor diagnosis is basically pathological, biochemical tests are also required to support dignosis and asist in tumor typing. It has been suggested that evaluation of serum gastrin levels and plasma Cg A may facilitate diagnosis and typing. In particular, Cg A is reported to be a valuable and sensitive marker for all types of gastric carcinoid tumors.[9,15] Nobel et al. reported that levels of CgA are increased in 50% of patients with neuroendocrine tumors.[16] Chromogranins are a family of proteins that are acidic in nature and there are 3 types (A,B and C). Chromogranin is released from the secretory granules of neuron and neuroendocrine cells when they are stimulated.[17] Normally, 1 to 2% of tryptophan from food is used for serotonin synthesis, but, this rate rises to 60% in carcinoid tumor cases. Serotonin is stored in the secretory granules of carcinoid tumor cells, some of which are secreted into blood. Most of the serotonin in the blood is taken up and stored in platelets, whereas the remainder is eventually metabolized to 5-HIAA by monoamine oxidase and aldehyde dehydrogenase in the kidney and, then, excreted in the urine. One of the most widely used biochemical diagnostic methods is 24 h urinary 5-HIAA level. False positive results are related to the consumption of some fruits such as banana, kiwi, avocado. False negative results are related to the use of some drugs such as acetaminophen, salicylate and L-dopa. The sensitivity of 5-HIAA detection is 73%, and the specificity of 5-HIAA is 100%.[18] The level of 5-HIAA can rise in the urine of patients with carcinoid tumors, even in the absence of carcinoid syndrome. Other secreted molecules found at elevated levels, including neurotensin (43% of cases), substance-P (32%), motilin (14%) and somatostatin (5%) are increased in carcinoid tumors.[19-21] In a study by Okada et al. 5 cases of multiple gastric carcinoids with hypergastrinemia were analyzed. Serum gastrin levels were elevated in all cases, serum vitamin B12 levels were decreased in one cases, and all cases were immunopositive for CgA and synaptophysin.[22] Furumoto et al. reported 3 cases of gastric carcinoid with hypergastrinemia. They found that serum gastrin levels were elevated and CgA and synaptophysisn positivity was detected in all cases.[23] Hung et al. reported a case in which serum gastrin and CgA level were increased, serum vitamin B12 level was decreased, and 5-HIAA level was normal. Furthermore, according to biochemical and histopathological findings, a diagnosis of chronic atrophic gastritis leading to hypergastrinemia and ECL proliferation with carcinoid formation was confirmed.[24] In our patient, serum gastrin, plasma CgA and urinary 5-HIAA levels were all increased, serum ferritin level was decreased and vitamin B12 level was normal but near the lower limit. Furthermore, the sample was immunopositive for synaptophysin, NSE, and CgA. The identification of tumor type is important since it aids in the development of treatment strategies and in prognostic estimations. Biochemical tests are important for determining prognosis, identification

of tumor type, and monitoring of both disease progression and response to treatment. For example, a diagnosis of type 1 gastric carcinoid tumor accompanied with hypergastrinemia is associated with increased biological response to tratment and a more favorable prognosis.[25]

In recent years, an increasing number of gastric carcinoids are determined depending on various diagnostic methods such as endoscopic, immunohistochemical examinations, as well as biochemical examinations such as CgA. When a carcinoid tumor is suspected, the initial diagnosis is primarily biochemical, and the most important screening marker today is chromogranin A. In addition, 5-HIAA is also a specific marker for carcinoid tumors. In our case, an increased level of gastrin was accompanied with an increased level of 5-HIAA and chromogranin A. However, the final diagnosis should always be based on histopathology, while the neuroendocrine features of the tumor should be demonstrated by immunohistochemistry for chromogranin A, synaptophysin or NSE.[26]

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