

Type 1 gastric carcinoid tumor: another extrahepatic manifestation of hepatitis C virus infection?

Tip 1 gastrik karsinoid C tümör: Hepatit C virüs infeksiyonunun bir başka ekstrahepatik manifestasyonu mu?

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A 67 year-old female with a 10-year history of cirrhosis due to hepatitis C virus who developed a gastric carcinoid tumor of the corpus is described. Carcinoid tumor was identified during her last routine gastroscopic evaluation for portal hypertension. In the case, serum parietal cell antibodies, hypergastrinemia and atrophic gastritis were also found. Chronic hepatitis C virus infection is known to induce clinical and laboratory signs of autoimmunity. But the question of whether hepatitis C virus plays a pathogenic role in the development of gastric carcinoid tumor is unknown. As far as we know, this is the first report describing gastric carcinoid tumor in hepatitis C virus induced chronic liver disease. We suggest that the possibility of the development of autoimmune atrophic gastritis and carcinoid tumors should be considered in patients with chronic hepatitis C that coexists with autoimmune diseases and has positive parietal cell antibodies.

Key words: Hepatitis C virus, gastric carcinoid tumor, atrophic gastritis

INTRODUCTION

Carcinoid tumors are relatively rare neuroendocrine malignancies that most commonly arise in the gastrointestinal tract. Gastric carcinoid tumors were previously believed to constitute only 1-2% of all carcinoid tumors (1). But recent studies have demonstrated that the proportion may be as high as 11-30% (2, 3). A relationship between gastric carcinoid tumor and autoimmune gastritis has been recognized (1, 4).

In the previous publications it was clearly reported that there was an accompaniment of carcinoid tumors with primary biliary cirrhosis and autoimmune hepatitis (5, 6). However, no data showing the relationship between chronic hepatitis C and carcinoid tumors have been obtained so far.

We report an unusual case with cirrhosis due to hepatitis C virus (HCV) infection who developed a gastric carcinoid tumor. The literature on the subject is also reviewed.

Hepatit C'ye bağlı sirozu olan 66 yaşında bayanda gelişen midedin karsinoid tümörü olgusu tanımlandı. Karsinoid tümör, hastanın portal hipertansiyonuna yönelik rutin gastrokopik incelemesinde saptandı. Olguda aynı zamanda serum parietal hücre antikoru, hipergastrinemi ve atrofik gastrit mevcuttu. Kronik hepatit C'nin, otoimmün hastalıkların laboratuvar ve klinik bulgularının ortaya çıkmasını kolaylaştırdığı bilinmektedir. Bildiğimiz kadarıyla bu olgu, hepatit C virusüne bağlı kronik karaciğer hastalığında tanımlanan ilk gastrik karsinoid olgusudur. Biz otoimmün hastalığı ve parietal hücre antikörleri pozitif olan kronik hepatit C olgularında otoimmün gastrit ve karsinoid tümör gelişme olasılığının göz önünde bulundurulması gerektiğini düşünüyoruz.

Anahtar kelimeler: Hepatit C virüsü, gastrit karsinoid tümör, atrofik gastrit

CASE REPORT

A 67-year-old female with a 10-year history of biopsy-proven cirrhosis due to HCV was found to have a gastric carcinoid tumor during her last routine endoscopic examination. There was no evidence of diarrhea, abdominal pain, flushing, wheezing or palpitations. Past medical history included intermittent itchy skin lesions for 10 years, biopsies of which were in keeping with urticaria. She had no history of risk of HCV. The timing of her exposure with HCV was not defined. In 1992, interferon (IFN) treatment was started, but three months later the treatment program had to be stopped due to thyroiditis. In 1997, esophageal varices and portal gastropathy were found at endoscopic examination and she was treated for portal hypertension (propranolol, famotidine). Ascites, which progressed subsequently, was brought under control by spironolactone treatment. Neither gastric bleeding nor encephalopathy developed at any stage.

On examination she was overweight. Splenomegaly was present. Laboratory results revealed: Hb: 14.7 g/dl, leukocyte: 9600/mm³, platelet: 141,000/mm³, erythrocyte sedimentation rate: 32 mm/h, AST: 183 U/L, ALT: 137 U/L, GGT: 110 U/L, total protein: 6.5 g/dl, and albumin: 3.1 g/dl. Prothrombin time, thyroid function tests, and parathormone levels were normal. Serum vitamin B₁₂: 57.2 ng/ml (Normal: 180-950 ng/ml), serum gastrin: 800.00 pg/ml (Normal: 25-125 pg/ml), urinary 5-hydroxyindole acetic acid: 24 Umol/24 h. (Normal: 10.40-31.20 Umol/24 h), serum parietal cell antibodies (PCA): 1/20 positive. ANA, anti DNA, ASMA, and AMA autoantibodies were negative. No kind of tumor was identified on chest x-ray or abdomen and pelvis computerized tomography (CT). At endoscopy, portal hypertensive gastropathy and grade 2 esophageal varices were present. A 1 cm sessile polyp was found in the gastric corpus. *Helicobacter pylori* was negative.

On histopathological examination of the polyp, tumor was observed in two foci (1mm and 3mm each) in the deep mucosa. It was infiltrating into the muscularis mucosa and submucosa. Tumor was composed of a uniform population of small tumor cells that were arranged in cords and sheets with acinar formation (Fig 1). Immunohistochemically, tumor cells were positive for cytokeratins (AE1 & AE3, Zymed, USA) and chromogranin A (Dako, USA) (Figs 2, 3). Tumor cells were granulated with grimalius stain. Mucin was negative in the tumor. Immunohistochemical staining for HCV (Biogenex, USA) was negative in tumor tissue. The surrounding mucosa revealed atrophic gastritis and intestinal metaplasia.

DISCUSSION

Gastric carcinoid tumors are relatively uncommon and make up less than 1% of gastric neoplasms (7). They are grouped into three categories. Type 1 gastric carcinoids are associated with autoimmune chronic atrophic gastritis (AAG). Type 2 gastric carcinoids are associated with Zollinger-Ellison syndrome or multiple endocrine neoplasia type 1 (MEN I). Type 3 gastric carcinoids are known as sporadic carcinoids (4, 8).

Up to 75% percent of gastric carcinoid tumors are associated with AAG. They originate from enterochromaffin-like (ECL) cells present in the body of the stomach. Patients with AAG usually have hypergastrinemia. The ECL cell is known to be highly sensitive to gastrin stimulus. Hypergastrin-

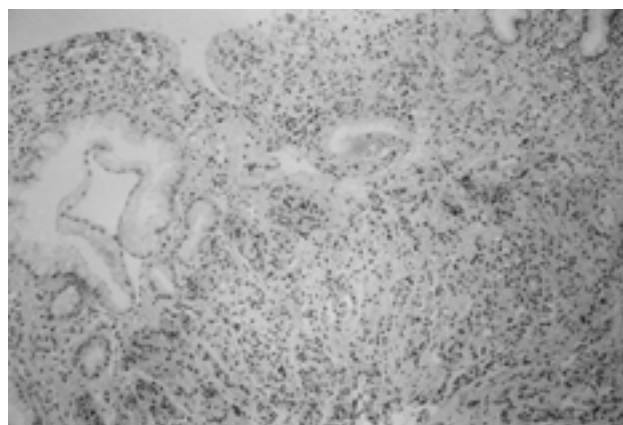


Figure 1. Tumor composed of uniform endocrine cells arranged in nests and infiltrating strands, having rib-bong acinar patterns (HE x10)

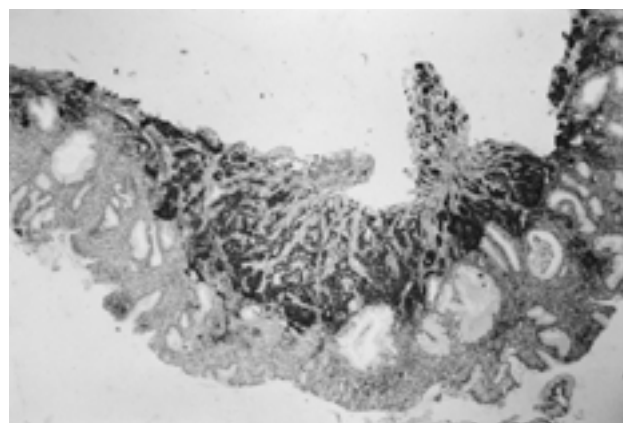


Figure 2. Chromogranin immunoreactivity in tumoral tissue infiltrating mucosa and submucosa (Immunoperoxidase x 4)

nemia is associated with ECL-cell hyperplasia and can, but does not frequently, cause progression to dysplasia and neoplasia (9, 10).

Helicobacter pylori infection has been found in 20% of patients who have Type 1 gastric carcinoid tumor. *Helicobacter pylori* is said to cause ECL-cell proliferation by leading to gastric gland atrophy (11). No sign of *H. pylori* infection was detected in our case.

Though there are different results (12, 13), many investigators have reported that serum gastrin concentrations are significantly higher in cirrhotic patients (14, 15).

Chronic HCV infection is known to induce clinical and laboratory signs of autoimmunity. As well as organ and non-organ specific autoantibodies, a wide range of extrahepatic syndromes have been described (16, 17). An increase in the production of autoantibodies has also been described in patients

undergoing IFN therapy for chronic hepatitis C (18-21). Our patient also developed autoimmune thyroiditis with the IFN treatment, and PCA tested after the identification of carcinoid tumor was found to be positive.

In much of the research conducted in the field so far, PCA frequency was found in between 4.2% and 32% of hepatitis C patients, and it has also been shown that IFN treatment did not change the frequency of PCA, which is a risk factor for atrophic gastritis and carcinoid tumors (18-22). However, no data was found in the literature about association of HCV infection with AAG.

As in the case with our patient, gastric carcinoid tumors are often seen in females and in the sixth decade of life. Since there is no specific symptom of gastric carcinoid, and most of the cases are asymptomatic, diagnosis is not established easily, and is determined incidentally in 40-60% of the patients (23). In our case, we were able to diagno-

se the patient during her last routine endoscopic control conducted due to portal hypertension.

Type 1 carcinoid tumors are usually indolent, metastasizing in less than 10% of cases, though some local recurrences have been reported. It has been suggested that lesions less than 1 cm in diameter be treated with endoscopic resection. Larger, multiple, or recurrent tumors may require local excision and gastrectomy (1, 4). In our case, the lesion was not bigger than 1 cm, so we decided to perform an accurate endoscopic and histological follow-up after endoscopic polypectomy.

It is not certain whether chronic HCV infection alone was a sufficient triggering factor to induce autoimmune atrophic gastritis in our patient. However, we suggest that the possibility of the development of autoimmune atrophic gastritis and carcinoid tumors should be considered in patients with chronic hepatitis C that coexists with autoimmune diseases and has positive PCA.

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