Analysis of 23 patients with carcinoid tumors: Emphasis on the relationship between carcinoid syndrome and liver involvement

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A prospective and retrospective analysis of 23 patients with carcinoid tumors diagnosed, treated, and followed up at Hacettepe University Hospital between 1968-1992 was undertaken. The most common sites of primary tumors were the appendix (34%), and jejunoileum (22%). The most common initial symptoms were abdominal pain and flushing. The carcinoid syndrome including flushing, diarrhea and elevated urinary 5-hydroxyindole acetic acid (5-HIAA) concentrations was manifested by five patients (two patients with jejunoileal, two with bronchial and one with unknown origin). Elevated urinary 5-HIAA was found in seven patients. While the appendiceal and rectal carcinoids were usually benign and showed no distant metastasis, jejunoileal and bronchial ones were usually metastatic. Although heavily hepatic involvement was detected in all five jejunoileal carcinoid tumors, carcinoid syndrome was seen in two of these patients and was not seen in a colorectal carcinoid tumor patient with severe liver involvement. We concluded that carcinoid syndrome can not develop in every patients with severe liver involvement. [Turk J Med Res 1993; 11(3): 120-125]

Key Words: Carcinoid tumor, Carcinoid syndrome, Liver

The carcinoid tumor is a neuroendocrine neoplasm with malignant potential and the most frequent of all endocrine gut tumors. Carcinoid tumors arise from enterochromaffin or enterochromaffin-like. cells and can be found anywhere of the gastrointestinal system, from esophagus to the rectum. The most frequent enteral localizations are the appendix, terminal ileum and rectum. The stomach, duodenum, colon and Meckel's diverticulum are less frequently involved. Bronchial carcinoids originate from the enterochromaffin cells in the epithelium of the bronchial tree and are reported with increasing frequency (1). Carcinoid tumors secrete a variety of humoral substances including seratonin, 5-hydroxytryptophan histamine, bradykinin, kallikrein, calcitonin, catecholamins, prostoglandins, insulin, ACTH, glucagon, gastrin, PTH, vasoactive intestinal peptide (VIP), gastric-inhibiting polypeptide (GIP), vasopressin, substance P and motilin. Seratonin is the most common secretory product of carcinoid tumors of intestinal origin. In normal individuals 99% of dietary tryptophan is converted to niacin and protein and only 1% is metabolized to seratonin. Therefore, the patients with carcinoid tumor may be use 60% of dietary tryptophan to produce seratonin. As a result of this metabolic effect of tumor, the principal urinary excretion product of seratonin metabolism, 5-hydroxyindole acetic acid (5-HIAA) increase excessively in urine. Approximately 10% of all patients with carcinoid tumors exhibit one or more symptoms of carcinoid syndrome: facial flushing, diarrhea, right sided valvular heart disease and less commonly bronchoconstriction, telengiectasias, paroxysmal hypotension, abdominal cramps and pellegra-like skin lesions. It has been reported that these signs and symptoms are related with hormone production in carcinoid tumors (2-6).

The majority of patients with functional carcinoid tumor (carcinoid syndrome) have flushing or diarrhea or both and a large liver or tumor metastasis in the liver. Measurement of 24 hours urinary 5-HIAA excretion is the most useful diagnostic test and approximately 75 percent of patients excrete more than 15 mg/day. Since most patients with carcinoid syndrome have metastasis; liver biopsy, with the sample taken under ultrasonic guidance, will reveal histologic diagnosis of carcinoid (7).

Surgery plays a limited role in the treatment of the carcinoid syndrome. More than 90 percent of patients have extensive metastatic disease, and therefore curative surgery can be offered only to rare patients with a primary ovarian or bronchial tumors.

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The surgical removal of ileal or other gastrointestinal primary tumors with secondary metastasis may be indicated if the primary lesion is large or causing local problems such as intestinal obstruction, bleeding or vascular insufficiency (8).

Various combinations of chemotherapeutic agents (streptozocin, fluorouracil, cylophosphamide and doxorubicin) and human leucocyte interferon induce objective responses in about half of patients with metastatic disease. In recent years a long action analogue of somatostatin (octreotid) has been shown to supress carcinoid symptoms successfully (9-11).

In this study, we reevaluated retrospectively 18 patients (12) and evaluated prospectively 5 cases of carcinoid tumor. Special attention was paid to the localization of primary tumor, metastasis, and the occurence of carcinoid syndrome. Therefore we particularly focused about how much carcinoid syndrome is related to liver involvement.

PATIENTS AND METHODS

During the 24-year period (1968-1992) 23 patients with carcinoid tumors (16 men, 7 women) were seen at Hacettepe University Hospital. In twenty of the 23 patients, histologic confirmation of diagnosis was available. In three patients who refused biopsy, symptoms of carcinoid syndrome and high 24-hr urinary 5-HIAA levels suggested the diagnosis. Routine analysis of blood and urine, including hemoglobin content, leucocyte and platelet counts, liver enzymes, serum creatinine, electrolytes and blood glucose were tested and urinary 24-hr 5-HIAA levels were studied. All patients were evaluated by roentgenography of the lungs and gastrointestinal tract and liver scintigraphy. In most patients ultrasonography and/or computerized tomography (CT) were used for investigations of primary site of tumor and evaluation of metastatic lesions (Fig. 1-3). Sonography-guided liver needle biopsy was made in all patients suspected hepatic metastasis (Fig. 5-6), including severe liver involved patients without carcinoid syndrome.

Appendectomy was made in all patients with appendiceal carcinoids. Surgical treatment plus chemotherapy have been performed all of the jejunoileal carcinoids. One of the patients underwent segmental ileal resection (Fig. 4) and was adminestered 5-flourouracil therapy. The second patient have received right hemicolectomy, left lateral segmentectomy of the liver and 5-FU therapy. The third patient underwent segmental jejunal resection and 5-FU plus mithomycin-C therapy. The fourth patient have been treated with segmental ileal resection and interferon. The last patient have received segmental ileal resection and streptozocin plus 5-FU chemotherapy and after that interferon therapy. Two of these patients had clinical carcinoid syndrome. In two patients with rectal carcinoids, polypectomy was performed in one and anterior resection and temporary colostomy in the other. Both were diagnosed during rectoscopic examination for bowel dysfunction. One of the patients with gastric carcinoid was treated by subtotal gastrec-

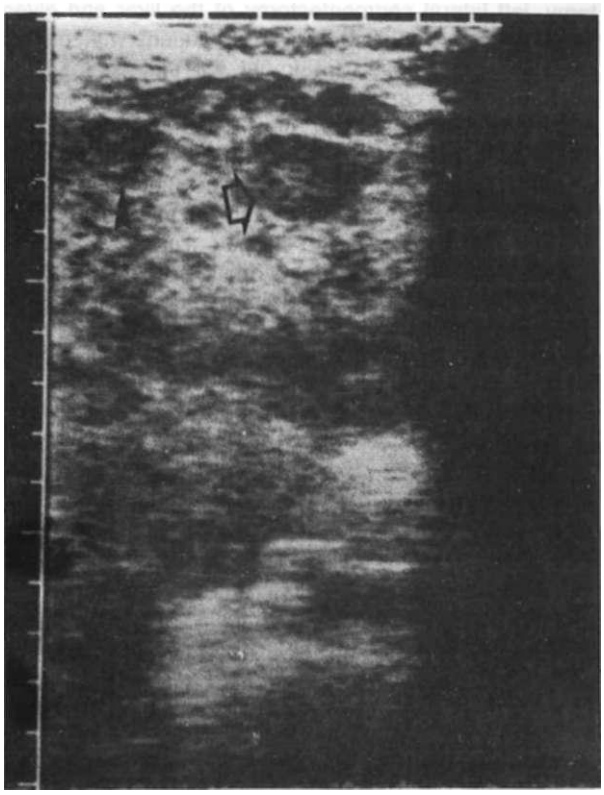

Figure 1. Ultrasonography shows multiple small hypoechoic lesions (arrows).

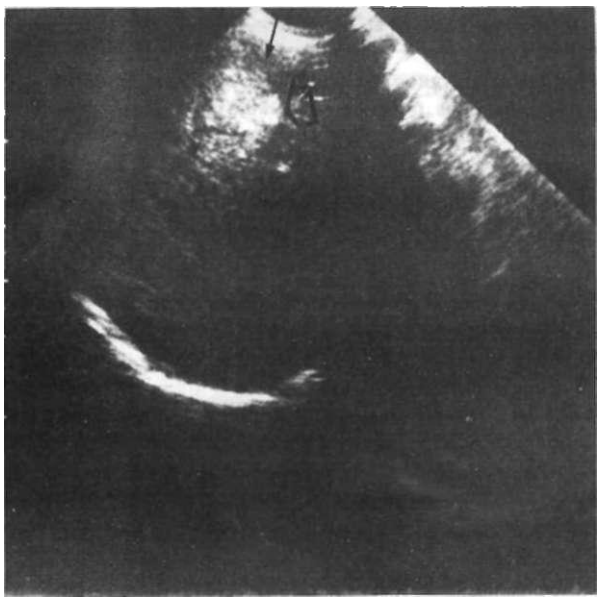

Figure 2. Ultrasonogram, belonging the same patient (Fig. 1) shows an hyperechoic mass lesion (arrow) being hypoechoic before treatment two years ago.

tomy, left lateral segmentectomy of the liver and given 5-FU therapy. However the other patient with gastric carcinoid was refused treatment. Of the two patients with colorectal carcinoid, ileotransversostomy in one and right hemicolectomy plus 5-FU therapy in the other were performed. Preoperative diagnoses were Chron's disease and carcinoma of cecum, respectively. The third patient with colorectal carcinoid was diagnosed with colonoscopic biopsy from cecum and treated with hemicolectomy and ileotransversostomy. Two of the bronchial carcinoids underwent surgical treatment. Left lobectomy and left pnomonectomy have been performed for these patients. The third patient with bronchial carcinoid refused any treatment. Two of these patients had carcinoid syndrome.

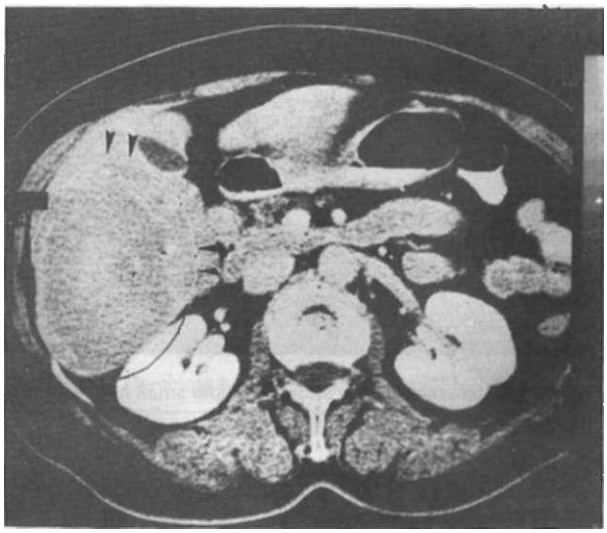

Figure 3. Computerized tomography demonstrates multiple hypodens lesions, one of them is on the figure (arrows).

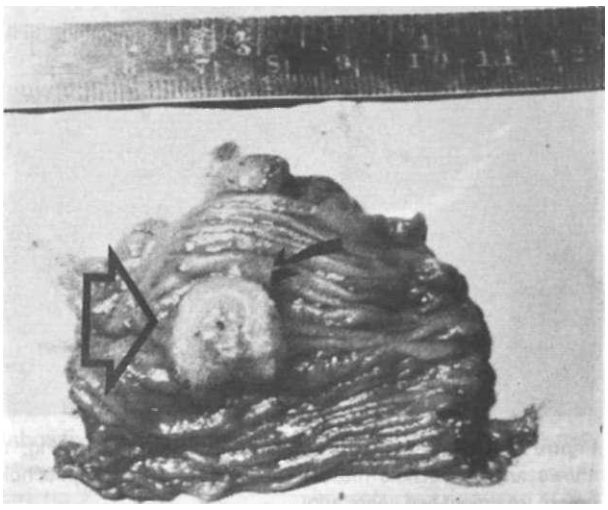

Figure 4. A carcinoid lesion located ileum is relatively small (arrow), but as seen Fig. 3, metastatic lesions in the liver are huge.

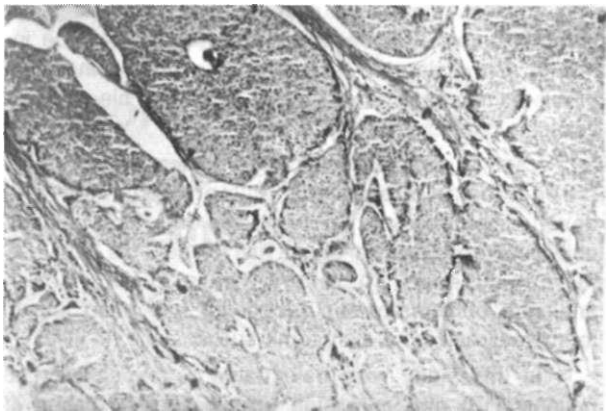

Figure 5. Carcinoid metastatic tumor in the liver, heavily uniform cells seperated by fine fibromuscular stroma (x 115 H+E).

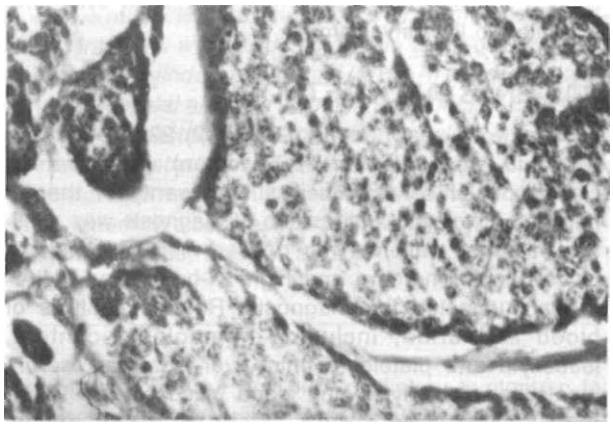

Figure 6. Microscopic examination shows carcinoid tumor islands composed of round, oval, uniform cells with fine granules containing cytoplasm (x 460 H+E).

RESULTS

The median age at diagnosis for all patients was 43.6 years, ranging from 18 to 74 years. A prominent predominance of men was seen in the total group (males/females: 16/7).

In seven patients (34%) the primary tumor was localized to the appendix, whereas five patients had jejunoileal carcinoid tumors, two had gastric, three had colorectal, three had bronchial and two had rectal carcinoid tumors. In one patient with carcinoid syndrome, the primary site of the tumor was unknown because she refused biopsy and further investigations (Table 1).

As shown in Table 2, the first symptoms were abdominal pain in 14 patients, flushing in three patients, cough in two patients, diarrhea in one, dyspnea and diarrhea in one, constipation in one and painful defecation in one patient. In six of the patients, 24-hr urine 5-HIAA excretion was higher than 10mg.

Table 1. Some characteristics of 23 patients with carcinoid tumor

Primary site	Number of cases	Liver metastasis	Carcinoid symptoms	5-HIAA
Appendix	7	—	—	—
Rectum	2	—	—	—
Colorectal	3	1	—	1
Jejunoileal	5	5	2	4
Gastric	2	—	—	" —^ '
Bronchus	3	1	2	1
Unknown	1	1	1	
Total	23	8	5	7

Tablo2. The first symptoms and signs of the patients with carcinoid tumor

Symptoms, signs	Number of patients	%
Abdominal pain	14	60
Flushing	3	13
Cough	2	9
Diarrhea	1	4
Dyspnea	1	4
Constipation	1	4
Painful defecation	1	4

Seven appendiceal, four jejunoileal, three colorectal, two rectal, one gastric and one bronchial carcinoid tumor cases have fully recovered and are being followed. One patient with jejunoileal carcinoid still had carcinoid syndrome symptoms after surgery. After discharge, it was not possible to follow up this patient. A secondary malignant mammary carcinoma was seen in one patient with jejunoileal carcinoid in follow up period. One patient who was thought to have gastric carcinoid and another with unknown primary site of origin refused any treatment. One patient with bronchial carcinoid died six years after her first diagnosis and one other patient with bronchial carcinoid was unable to be followed.

DISCUSSION

The likelihood of developing symptoms is strongly dependent on the localization and behavior of the carcinoid tumor. For example, bronchial and other extraintestinal carcinoid tumors secrete hormone throughtly blood and produce carcinoid symptoms without any liver metastasis. Therefore intestinal carcinoids may develop characteristic carcinoid symptoms only in the presence of liver metastasis. Beside that carcinoid symptoms have been reported in the absence of any detectable hepatic metastasis in intestinal carcinoid tumors (13).

Localization of tumor is also related with systemic symptoms. In large series of patients with the carcinoid syndrome, the primary tumor was in the small intestine (usually the ileum) in 44%, the bronchus in 32%, ovary 8%, stomach 4%, and about 1% each other localizations (14).

In agreement with other large studies that were done retrospectively, the most common site for carcinoid tumors in our study was appendix. Of all appendices, removed surgically 0.3 to 0.71% have carcinoid tumors (15). Seven of our patients (34%) had appendiceal involvement. Appendiceal carcinoids had the highest survival rates in carcinoid patients. Some investigators have reported no death from carcinoid in their series of appendiceal carcinoids (16). Although rare, appendiceal carcinoids have been known to metastases in approximately 2% of all cases (17). Several factors, such as the size of the primary tumor and lymphatic and mesoappendiceal invasion have been suggested as predictors of malignant potential. Appendectomy alone is the accepted treatment unless the primary carcinoid is larger than 2cm (18). In all of our cases appendectomy alone was sufficient treatment. No cases had liver involvement.

Another site where carcinoid tumors have been seen frequently is jejunoileal localization. Jejunoileal carcinoids have usually related with liver metastasis and carcinoid symptoms. In our study we have detected liver metastasis in all of the five jejunoileal carcinoids. Carcinoid syndrome symptoms have been observed in two patients preoperatively and in one patient postoperatively. In a patients with liver metastasis there were multiple hipoechoic and round lesions not more than 2cm in diameter in sonographic examination (Fig. 1). These lesions became hiperechojenic after two years of the treatment of carcinoid tumor (Fig. 2). Although liver involvement was so severe, carcinoid syndrom symptoms did not observed. In this patient secondary mammary carcinoma was detected after two years of first diagnosis. This correlation is not clear whether the secondary tumor is a complication of treatment of carcinoid tumor or not.

The carcinoid is the most common type of bronchial adenoma (15). Bronchial carcinoids produce the most striking features of any of the variants of the carcinoid syndrome. Characteristically flushing attacts can be more prolonged and severe (19). Two of the three bronchial carcinoids cases had carcinoid syndrome symptoms. In one of them there was no liver involvement.

The rectum is another site where carcinoids are found. Rectal carcinoid tumors are relatively uncommon lesions, comprising only 1.3% of all rectal tumors (16). They are usually incidental findings during proctosigmoidoscopy. When the primary tumor is larger than 2cm, it metastasis in 82% of cases (20). Some authors believe that invasion of the muscularis propria is an additional prognostic sign for tumor progression (21). In our two patients with rectal carcinoids the tumor size was 0.5cm. When local excision was performed, there was invasion of muscularis mucosa in only one patient, as revealed by histologic examination. Subsequently, anterior resection and temporary colostomy were also undertaken in this patient. The incidence of carcinoid syndrome is closely related with tumor localizations, behavior, and metastasis. We have detected five patients (22%) with carcinoid syndrome symptoms. This is a lower rate than other reports and may be for appendiceal tumor (usually non-fonctional) were seen high rates in our study. Intestinal carcinoid tumors can develop classic carcinoid sendrom symptoms only in the occurence of liver metastasis. Therefore, carcinoid symptoms have been reported without any detectable liver metastasis (22). In our study we have showed liver metastasis in all intestinal carcinoids. In intestinal carcinoid tumors with liver metastasis, substance secreted by tumor can be pass through into systemic circulation easily and carcinoid symptoms have been seen clinically. Before this, it hasn't been reported any intestinal carcinoid tumors showing excessively liver metastasis but no detectable carcinoid symptoms. In our three patients with intestinal carcinoids, we haven't noticed any carcinoid symptoms in spite of excessively liver involvement. It can be thought that the non-tumor portion of the liver can metabolise the substances which are related to producing carcinoid syndrome. Tomographic appearance of heavily liver metastasis in one of our ileal carcinoids are seen in Fig. 3 and primary ileal tumor in same case are seen in Fig. 4. It is very remarkable that primary tumor is very small despite excessively liver metastasis. In this case, during follow-up period there were no symptoms related to carcinoid syndrome.

We evaluated prospectively the eight patients with liver involvement paying extra attention to carcinoid syndrome. In three of them, despite severe liver involvement, carcinoid syndrome symptoms could not be seen during follow up period. Perhaps in these three patient liver has still capacity to metabolise the substances which are responsible producing carcinoid syndrome symptoms.

An accessory malignant neoplasm was found in only one patients during posttreatment period, which is a lower frequency than published in other reports (23).

Localization and metastasis of tumor is closely reiaied with survival. Therefore supportive and symptomatic treatment is extremely important in metastatic tumors. The five-years survival rate is about 67% in all cases (7,16). In 17 of our patients who are being controlled regularly, prognosis is favorable. One patient with bronchial carcinoid died six years and one patient with jejunoileal carcinoids died two years after surgery. Unfortunately, we don't know the prognosis of the three patients who refused treatment and one patient who didn't return to us after surgery.

It can be concluded that the most common primary site of carcinoid tumors is the appendix. While appendiceal and rectal carcinoids are usually benign; gastric, jejunoileal, colorectal, and bronchial tumors are often metastatic. Patients with carcinoid syndrome symptoms usually have liver metastasis (Fig 5-6), and high urinary 24-hr 5-HIAA levels. Carcinoid syndrome can not be seen in patients with severe liver involvement.

Karsinoid tümörlü 23 vakanın incelenmesi

Hacettepe Üniversitesi Hastanesinde 1968-1992 yılları arasında teşhis ve tedavi edilen karsinoid tümörlü 23 hastanın prospektif ve retrospektif bir analizi yapıldı. Tümörün en sık görüldüğü yer appendiks (%34) ve jejunoileum (%22) olarak tesbit edildi. En sık görülen başlangıç semptomları karın ağrısı ve flushingdi. 5-HIAA düzeyinde artış yedi hastada belirlendi. Appendiks ve rektal karsinoidler genellikle benigndi ve uzak metastaz görülmedi. Jejunoileal ve bronşial karsinoidler ise genellikle metastatikti. Tüm jejunoileal karsinoidlerde ileri derecede karaciğer tutulumu belirlenmesine rağmen sadece iki vakada karsinoid sendrom saptandı. Kolorektal karsinoidi olan bir vakada ağır karaciğer tutulumuna rağmen karsinoid sendrom görülmedi. Bu çalışma karaciğer tutulumu olan her karsinoid tümörlü hastada karsinoid sendrom olmayabileceğini göstermektedir.

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