THE ROLE OF SURGERY IN A PATIENT WITH CARCINOID SYNDROME, COMPLICATED BY CARCINOID HEART DISEASE

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Abstract

A 55-year-old female patient was admitted for flushing and abdominal pain in the right upper quadrant. Her past medical history revealed high blood pressure and a recent echocardiography showed thickened appearance of tricuspid valve with coaptation defect and grade II tricuspid regurgitation. Contrast enhanced abdominal CT scan and MRI were subsequently performed and revealed a large macronodular liver mass, as well as other micronodular lesions disseminated in the liver parenchyma. CT guided biopsy from the main liver mass revealed neuroendocrine tumor of unknown origin (probably GI) with Ki-67 of 8%. Surgical exploration was decided. During laparotomy, the primary tumor was found in the proximal ileum and the patient underwent segmental enterectomy. Non-anatomical hepatectomy was also performed to remove the bulk of the tumor burden (more than 90%). Postoperative course was uneventful and the carcinoid syndrome relieved. At present, 15 months postoperatively, the patient is under treatment with somatostatin analogue for its antiproliferative effect, with good clinical, biochemical and tumoral control and stable heart disease. In patients with neuroendocrine liver metastases from unknown primary, surgical exploration could allow detection (and resection) of the primary tumor and surgical debulking of liver metastases to control carcinoid syndrome and carcinoid heart disease.

Key words: neuroendocrine tumor, carcinoid heart disease, carcinoid syndrome, liver metastasis, cytoreductive surgery.

INTRODUCTION

The most frequent site for carcinoid tumors is the gastrointestinal (GI) tract (67.5%)(1). Within the GI tract, most carcinoid tumors occurred in the small intestine (41.8%), rectum (27.4%), and stomach (8.7%)(1). Identification of the intestinal carcinoid is usually difficult if octreotide scintigraphy or PET/CT are not

available, due to the low-sensitivity of CT scan and MRI (2). Most carcinoids (40-95%) are metastatic at diagnosis (3), frequently in the liver (1). About 8.4% of carcinoid patients will develop carcinoid syndrome (CS)(4) which frequently is not easily manageable (5–7). Among the systemic complications of CS, the most life-threatening is carcinoid heart disease (CHD – Hedinger syndrome). The syndrome consists in a combination of right-sided valve dysfunction associated with a morphological alteration, such as valve leaflet thickening, retraction, and/or insufficient co-optation (8). A prospective study followed 252 patients with CS and the incidence of CHD was 19.4% after a median follow-up of 29 months (9). To decrease the risk of heart complications it is mandatory to achieve a good control of the CS.

When complete resection (R0) of the liver metastasis is not possible, cytoreductive resection of hepatic metastases could be beneficial to control CS(10) (if optimal cytoreduction is achieved – resection of more than 90% of metastatic burden).

Chambers *et al.* (11) revealed that overall symptoms of CS improved in 86% of patients who underwent hepatic cytoreduction, while only 64% of patients receiving medical therapy alone experienced symptoms relief. Thus, most authors (10, 12, 13) recommend cytoreductive hepatectomy whenever possible.

Hereby are presented the diagnostic and therapeutic challenges in a patient with CS and CHD due to the liver metastasis from an ileal carcinoid tumor (discovered only at laparotomy).

CASE REPORT

A 55-year-old female patient was admitted for flushing, diarrhea and abdominal pain, mainly in the right upper quadrant. Recent cardiologic evaluation for

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fatigue and dyspnea on exertion revealed mild bilateral leg edema, high blood pressure controlled under medical treatment with Nebivolol (5 mg daily) and systolic murmur in the tricuspid area. Echocardiography showed thickened appearance of tricuspid valve with coaptation defect and grade II tricuspid regurgitation. Evaluation of NT proBNP was not recommended. She was diagnosed with NYHA II heart failure and grade II high blood pressure and received treatment with Bisoprolol (5 mg daily), Candesartan (8 mg daily) and Indapamide (1.5 mg daily). Abdominal CT scan and MRI (Fig. 1) revealed a large macronodular liver mass (95/85 mm diameter) located in segments 5-6 with heterogenic structure, as well as other micronodular lesions disseminated in the liver parenchyma, but inconclusive regarding the type of the tumor. Upper and lower GI endoscopies showed normal aspects. Laboratory tests were unremarkable, including viral and tumoral markers. A CT-guided biopsy from the liver mass was performed. The immunohistochemistry assay revealed neuroendocrine tumor of unknown origin (probably GI) with Ki-67 of 8%. Thus, the flushing and

diarrhea along with the failure of the tricuspid valve and right heart failure were considered as consequences of the CS. The multidisciplinary board recommended laparotomy in order to resect the main tumor bulk (to relieve the CS) and perform a thorough exploration of the abdominal cavity with the hope of identifying the primary tumor. Somatostatin analogues (SSA) were administered to prevent intraoperative carcinoid crisis and hypotension(14). During laparotomy, the primary tumor was found in the proximal ileum and, in the liver, were discovered a large liver mass and bilobar small liver metastasis (less than 2 cm) (Fig. 2). A non-anatomical liver resection of segments 5 and 6 was performed (Fig. 3) to remove the bulk of the tumor burden (representing more than 90% of metastatic burden – based on preoperative CT scan volumetric evaluation). The ligation of vasculo-biliary pedicles was performed with stich sutures, although some authors (15,16) revealed a benefit from the use of mechanical devices.

Figure 1. MRI scan- large macronodular liver mass (arrow).

Figure 3. Non-anatomical liver resection of segments 5 and 6.

Figure 2. Large liver mass and bilobar small liver metastases - less than 2 cm (arrows).

Figure 4. Enterectomy specimen including the primary tumor.

Also, an enterectomy including the primary tumor was performed (Fig. 4), followed by an entero-enterostomy. Postoperative outcome was favorable with the remission of the carcinoid syndrome. The patient was discharged on the 15th postoperative day with good overall condition. At present, 15 months postoperatively, the patient is under treatment with SSA for its antiproliferative effect, with good clinical, biochemical and tumoral control. Cardiologic evaluation showed controlled cardiovascular symptoms and unchanged echocardiographic findings, recommending the same treatment and timely evaluation (6 months) for potential surgical valve replacement.

DISCUSSION

The location of a primary NET is not always easy to find by preoperative examinations, because carcinoids are small tumors frequently located in the small bowel.

Octreoscan and PET/CT scan with new radiopharmaceutical - 68 gallium labelled somatostatin analogues (DOTATOC, DOTANOC, DOTATATE) (17–20) are the most useful diagnostic investigations, with a sensitivity in detection of the primary NET higher than 72% (21). In a recent study (22), 68GA-DOTA-TATE PET demonstrated a significantly higher sensitivity (94% vs. 63%, $p = 0.005$) and a significantly higher accuracy (87% vs. 68%, $p = 0.003$) than contrast enhanced CT scan in identification of the primary. Furthermore, for poorly-differentiated NETs, Octreoscan proved significantly less sensitive than PET (p value = 0.02)(21).

When these new diagnostic tools are not available, surgical exploration of patients with neuroendocrine liver metastases (NELMs) of unknown origin seems to represent the most effective approach in identification of the primary(10). Even recent studies (23–25) revealed that in patients with “unknown primary NELMs”, laparotomy offers the highest detection rate of the primary GI-NETs (the primary tumor site could be identified in more than 84% cases).

Identification of the primary tumor is useful, because its resection might improve progression-free survival (PFS) and overall survival (OS) in patients with abdominal carcinoid neoplasia and liver metastasis (26–28), even when resection of liver metastases is not possible (29). Thus, in a series of 139 patients with symptomatic, liver-metastatic, well-differentiated NETs, multivariate analysis showed that primary tumor resection was an independent positive prognostic factor ($HR = 3.17$, 95% CI: 1.77-5.69, $p < 0.001$)(27).

Moreover, most studies (30–34) suggest that an aggressive management of NELMs significantly increases survival. Obviously, complete resection of the primary tumor, lymph nodes and distant metastasis (26) represents the treatment of choice in mid gut NETs. Unfortunately, in most patients, NELMs are not completely resectable at diagnosis. However, unlike other malignant diseases, NELM patients seem to benefit from cytoreductive surgery. Thus, aside symptoms control (31, 35, 36), surgical debulking is able to improve OS rates in NELM patients undergoing cytoreductive hepatectomy (11, 37–39). Norlén *et al.* (40) reported 5- and 10-year OS rates of 75% and 51%, respectively, in surgical cytoreduction group, *versus* 28% and 6%, respectively, in the non-resected group. Similar findings were also reported by Bergestuen *et al.* (41) in 258 patients with small bowel NETs.

However, it is not clearly defined yet, which is the volume of the tumor burden that should be removed to achieve an optimal cytoreduction (that will enable significantly prolonged survival rates). Most authors consider that this goal could be achieved if more than 90% of the tumor load is resected (42). Thus, a recent paper revealed that in patients with small bowel NETs, resection of more than 90% of tumor burden offers the best OS rates, without statistical significant differences between patients undergoing 99–100% resection of tumor burden vs. 91–98% cytoreduction.

In patients with CS, the presence of CHD significantly reduces life expectancy (43), the median survival being 11 months in CHD patients with class III or IV NYHA heart failure (44). The major role in development and progression of tricuspid regurgitation is played by serotonin, which activates 5-HT_{2B} receptors and induces overexpression of TGF- β 1, leading to the deposition of fibrous plaques in right-sided heart valves (45). Thus, in CHD patients with NYHA class I or II, the control of CS is tremendously important, because decreasing the level of serotonin may slow/prevent the progression of valvular dysfunction. It could be hypothesized that in the patient presented here, the removal of the primary tumor and optimal cytoreductive liver resection were able to decrease the level of serotonin, avoiding the progression of CHD. Regarding the control of serotonin level in CHD, there is no current evidence to suggest that medical interventions such as SSA, hepatic artery embolization or systemic chemotherapy have a beneficial effect on the progression of valvular disease (46). The only treatment reported to slow cardiac disease progression was hepatic resection (47). Thus, Bernheim *et al.* (47)

revealed that optimal cytoreductive hepatic resection significantly improved 5-yr survival in CHD patients (86.5% for resected vs. 29% for unresected patients, p value < 0.01), although valve surgery is the only definitive treatment option for those with severe CHD (43,48).

In conclusion, in patients with unknown primary NELM, surgical exploration could detect the primary tumor location, allowing its resection. An efficient cytoreductive surgery (resection of more than 90% of tumor burden) significantly increases OS in patients with small bowel NETs. Optimal debulking of liver metastases offers an increased rate of CS control, improving the life-expectancy, especially in patients with CHD and class I or II NYHA cardiac failure.

Conflict of interest

The authors declare that they have no conflict of interest.

Abbreviations

CS – carcinoid syndrome; GI- gastrointestinal; CHD – carcinoid heart disease; NETs – neuroendocrine tumors; GI-NETs – gastrointestinal neuroendocrine tumors; NELMs – neuroendocrine liver metastases; SSA – somatostatin analogues.

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