Clinical presentation and management of gastro-intestinal and pancreatic secondary metastatic tumors

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Summary

Purpose: As progress regarding the treatment has occurred over recent years in oncology, more patients with metastatic disease are presented for diagnosis and further management. The purpose of this study was to reveal the incidence, location and to describe the clinical characteristics and outcome in a series of patients diagnosed with pancreatic, small and large bowel metastatic tumors that underwent metastasectomy.

Methods: A total of 12 patients (7 male and 5 female) diagnosed with extrahepatic gastrointestinal (GI) and pancreatic metastases from 2001 to 2013 were operated for resection of secondary metastatic tumors to the small and large bowel and the pancreas. Four out of 12 patients were asymptomatic and a secondary tumor was detected during follow up.

Results: The median interval revealing the metastatic tumor since the management of the primary tumor was 6.5 years (range 1-27). Primary tumors were malignant melanoma (4 patients), renal cell carcinoma (RCC; 2 patients), leiomyosarcoma of the uterus (2 patients), lobular breast cancer, mesenchymal chondrosarcoma of the skull, endometrial adenocarcinoma and a non-Hodgkin lymphoma (one case each). The median follow-up was 15 months (range 4-120).

Conclusions: Metastatic secondary tumors have to be considered especially when the patient’s medical history includes a previous malignancy. They may also occasionally present as the initial manifestation of an occult primary lesion leading to diagnostic difficulty. Although radical surgery is the most effective approach, treatment and survival grossly depend on histological type and the stage of the primary disease. Hence, management of these patients should be individualized by a multidisciplinary team.

Key words: gastrointestinal, metastasectomy, metastatic tumors, pancreas, secondary tumors

Introduction

Secondary metastatic tumors of the extrahepatic GI tract and pancreas are commonly observed in patients with malignancies. They are more often presented in patients with primary lesions such as malignant melanoma, breast, lung and renal cell carcinoma [1-3]. The identification of these tumors is straightforward during the short follow up period after the initial management of the primaries. Since the time from diagnosis of the primary tumor to the development of metastases varies widely, clinical presentation and judgment is challenging when they appear significantly later in the sense that, to distinguish these tumors from a second primary neoplasm can be difficult. For example, in patients with malignant melanoma these metastases may appear several decades later [4,5].

These metastases are relatively asymptomatic but sometimes manifest themselves by serious complications such as painless jaundice, bowel...
obstruction, GI bleeding, GI perforation and intussusception. In certain cases, the tumors may be clinically silent discovered in follow-up imaging studies [6-8].

The management of these patients and the therapeutic interventions may be affected by the extent of the metastatic disease and its chances to respond to anticancer treatment. Experience with resections for the treatment of isolated metastatic lesions is limited. As a result, there are few guidelines that exist regarding the appropriate management of such lesions. In this study, our aim was to describe the clinical characteristics and outcome in a series of patients who underwent metastasectomy, diagnosed with pancreatic, small and large bowel metastatic tumors. We report a series of twelve cases and their outcome after surgical treatment with a review of the literature.

**Methods**

Following our hospital ethics committee approval, we performed a retrospective study using our data from patients diagnosed with extrahepatic GI and pancreatic metastases. A total of 12 patients (7 male and 5 female) were identified from 2001 to 2013 who were operated in our department regarding secondary metastatic tumors to the small and large bowel and the pancreas. Four patients were asymptomatic and a secondary tumor was detected during the follow up assessment. The diagnostic approach varied from case to case and a small bowel endoscopic examination with capsule (PillCam, Given Imaging LTD, GA) was performed in 2 patients who presented with melena and negative upper and lower GI endoscopy.

**Results**

The median interval revealing the metastatic tumor since the management of the primary tumor was 6.5 years (range 1-27). At diagnosis, the patient median age was 65 years (range 26-82). Past medical history regarding their primary tumors identified cutaneous melanoma (4 patients), RCC (2 patients), leiomyosarcoma of the uterus (2 patients), lobular breast cancer, mesenchymal chondrosarcoma of the skull, endometrial adenocarcinoma and a non-Hodgkin lymphoma (one case each) (Table 1).

Bowel obstruction clinically manifested was registered in 2 patients due to metastatic tumors from endometrial adenocarcinoma to the jejunum (case #1), and metastatic breast cancer to the ascending colon (case #2) (Figure 1). Obstructive jaundice presented in 1 patient due to a metastatic tumor from RCC in the Vater’s ampulla (case #3).
Secondary gastrointestinal and pancreatic tumors

Clinical manifestation of melena and GI bleeding was diagnosed in 3 patients due to a metastatic melanoma in the small and large bowel (cases #4, 5, 6) and from metastatic RCC to the Vater’s ampulla in 1 patient (case #7) (Figures 2,3).

Obstructive jaundice was registered in one patient with a non-Hodgkin lymphoma (case #8). A tumor of the head of the pancreas was subsequently diagnosed and preoperative diagnosis of pancreatic adenocarcinoma was established following ultrasound endoscopy and FNA cytology of the tumor. This patient underwent a Whipple procedure and the pathology report revealed infiltration of the pancreas by a non-Hodgkin lymphoma (Figure 4).

In asymptomatic patients, imaging studies during follow up revealed secondary metastatic tumors from leiomyosarcoma of the uterus to the pancreas and to the small bowel (cases #9,10), from chondrosarcoma of the skull to the pancreas (case #11) and from a cutaneous melanoma to the omentum (case #12) (Figures 5 a,b).

All patients underwent an exploratory laparotomy and surgical treatment according to the preoperative diagnosis and intraoperative findings (Table 1). Metastatic lesions were defined pathologically and in one case by immunohistochemical staining (Figure 6). The median follow-up was 15 months (range 4-120). The clinical characteristics and management concerning these 12 case series are summarized in Table 1.

Discussion

Extrahepatic metastatic tumors of the GI system and pancreas are usually low on the differential diagnosis list when space-occupying lesions are detected. However, they are not as rare as considered and they are commonly observed in patients with malignancies. They may originate from the breast, lung, malignant melanomas and RCC or other rare tumors such as, neuroblastomas, nephroblastomas and mesenchymal tumors of different origins [7,9,10-13].

Although in the pancreas usually develop primary tumors, it is probably the most frequent site of GI metastatic malignancies if liver is to be excluded. Pancreatic metastasectomies account for approximately 4% of all pancreatic resections [14].

Most reports on such tumors concern RCCs and in many cases the interval after the diagnosis to the development of metastasis was several years. It has been suggested that nearly two-thirds of patients with primary RCC experience metastatic disease [15]. Other secondary tumors of the pancreas may derive from the colon and rectum, the lungs and pleura, the thyroid gland, or other rare tumors such as lymphomas, neuroblastomas, nephroblastomas, and mesenchymal tumors of different origins [7,16]. Isolated metastatic disease of the pancreas may be asymptomatic in 69% of the patients or it may manifest with pancreatitis-like symptoms, upper GI bleeding, and

Figure 4. Pancreatic specimen infiltrated by lymphocytes with atypical nuclei in a patient with non-Hodgkin lymphoma and infiltration by pancreatic adenocarcinoma (arrow) (H&E x10).

Figure 5. a. Metastatic leiomyosarcoma (white arrow) to the pancreas (white arrowhead) (HE x25). b. Metastatic leiomyosarcoma (black arrow) to the small bowel (black arrowhead) (H&E x 25).

Figure 6. Immunostaining of metastatic breast cancer to the large bowel. a. GCDFP-15 stain (x100), b. ER stain (x100), c. PgR stain (x100).
obstructive jaundice in cases of metastatic tumors of the head of the pancreas [17]. Metastatic RCCs in Vater’s ampulla may often present GI bleeding possibly due to their hypervascular nature as well as the fact that they often also involve the ampulla of Vater [16,18]. In case of metastatic RCCs and lymphomas, they are especially prone to being mistaken for a primary pancreatic carcinoma clinically since both form solitary masses in the pancreas [16]. Lymphoma, predominantly the non-Hodgkin B cell subtype as in our patient, involves the pancreas secondarily in approximately 30% of patients with widespread disease. The disease usually spreads to the pancreas by direct extension from peripancreatic lymphadenopathy and many of these cases occur in immunocompromised hosts, particularly patients infected with HIV [15,16]. There is no established management for secondary tumors of the pancreas due to the wide variety of primary tumors and stage at the time of diagnosis. Resectional options depend on the type of primary tumor, the location of metastasis, and the extent of disease. According to these characteristics, surgical excision is the most frequent approach in isolated cases, while chemotherapy or radiotherapy may offer some benefit in inoperable cases [14,15,19,20].

The small and large bowel seem to be a preferential target in metastatic tumors from breast cancer, ovarian carcinoma, malignant melanoma, lung cancer, hepatocellular carcinoma and rarely choriocarcinoma [4,5,11]. Metastatic sites in small and large bowel from malignant melanoma and lobular breast cancer can occur after many years of freedom from disease and can represent the first site of recurrence with otherwise no evidence of active disease [11]. Presenting symptoms may include perforation, obstruction and intussusception and bleeding in cases of hypervascular lesions such as choriocarcinoma [12]. Malig-

**Table 1. Clinical characteristics and outcome of patients**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/sex</th>
<th>Symptom</th>
<th>Site of primary</th>
<th>Site of metastasis</th>
<th>Time of diagnosis (F/U -yrs)</th>
<th>Surgical intervention</th>
<th>Overall survival according to last F/U (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65/F</td>
<td>Bowel obstruction</td>
<td>Endometriat adenocarcinoma</td>
<td>Small bowel</td>
<td>6</td>
<td>SB resection</td>
<td>Dead: (18)</td>
</tr>
<tr>
<td>2</td>
<td>77/F</td>
<td>Bowel obstruction</td>
<td>Lobular breast carcinoma</td>
<td>Large bowel</td>
<td>7</td>
<td>Right colectomy</td>
<td>Dead: (8)</td>
</tr>
<tr>
<td>3</td>
<td>77/M</td>
<td>Obstructive jaundice</td>
<td>RCC</td>
<td>Duodenum (Vater’s ampulla)</td>
<td>3</td>
<td>Endoscopic ampullectomy - sphincterotomy</td>
<td>Alive: (18)</td>
</tr>
<tr>
<td>4</td>
<td>82/M</td>
<td>Melena</td>
<td>Cutaneous melanoma</td>
<td>Small bowel</td>
<td>3</td>
<td>SB resection</td>
<td>Alive: (6)</td>
</tr>
<tr>
<td>5</td>
<td>64/M</td>
<td>Melena</td>
<td>Cutaneous melanoma</td>
<td>Large bowel</td>
<td>5</td>
<td>Left colectomy</td>
<td>Dead: (16)</td>
</tr>
<tr>
<td>6</td>
<td>47/M</td>
<td>Melena</td>
<td>Cutaneous melanoma</td>
<td>Small bowel</td>
<td>7</td>
<td>SB resection</td>
<td>Alive: (120)</td>
</tr>
<tr>
<td>7</td>
<td>66/M</td>
<td>Melena</td>
<td>RCC</td>
<td>Duodenum (Vater’s ampulla)- Pancreas</td>
<td>27</td>
<td>Pancreatectomy</td>
<td>Alive: (9)</td>
</tr>
<tr>
<td>8</td>
<td>76/F</td>
<td>Obstructive jaundice</td>
<td>Non-Hodgkin lymphoma</td>
<td>Pancreas</td>
<td>9</td>
<td>Whipple’s procedure</td>
<td>Dead: (4)</td>
</tr>
<tr>
<td>9</td>
<td>66/F</td>
<td>Asymptomatic</td>
<td>Diagnosed on follow up CT</td>
<td>Leiomyosarcoma of the uterus</td>
<td>10</td>
<td>Distal pancreatectomy- splenectomy</td>
<td>Dead: (18)</td>
</tr>
<tr>
<td>10</td>
<td>64/F</td>
<td>Asymptomatic</td>
<td>Diagnosed on follow up CT</td>
<td>Leiomyosarcoma of the uterus</td>
<td>1</td>
<td>SB resection</td>
<td>Dead: (8)</td>
</tr>
<tr>
<td>11</td>
<td>26/M</td>
<td>Asymptomatic</td>
<td>Diagnosed on follow up CT</td>
<td>Mesenchymal chondrosarcoma of the skull</td>
<td>9</td>
<td>Distal pancreatectomy- Splenectomy</td>
<td>Alive: (72)</td>
</tr>
<tr>
<td>12</td>
<td>59/M</td>
<td>Asymptomatic</td>
<td>Diagnosed on follow up CT</td>
<td>Cutaneous melanoma</td>
<td>3</td>
<td>Omental resection</td>
<td>Dead: (14)</td>
</tr>
</tbody>
</table>

F/U: follow up; yrs: years; mo: months; CT: computerized tomography; RCC: renal cell carcinoma; SB: small bowel; M: male; F: female
nant melanoma is the most common tumor that metastasizes to the small bowel and it is present in more than a quarter of patients with melanoma at autopsy, though only 1-4% of patients have the diagnosis made during life [21]. About 10% of metastatic melanomas in the small bowel may act as leading points for intussusceptions and result in small bowel obstruction while lung cancer metastases often clinically present as intestinal perforation. Several factors though can make the diagnosis difficult as the rarity of the condition commonly leads to a low index of suspicion. Also, the symptoms are often non-specific and can be easily misattributed to much more common etiologies (e.g., adhesions) [11].

Metastatic tumors of the large intestine are quite less frequent than those of the small intestine and are most common in patients with breast cancer with some series showing colonic metastases in up to 12%. Rectal involvement has also been described, including rectal stenosis secondary to metastatic breast cancer [22]. The median interval between breast cancer and the diagnosis of metastasis may vary from a few months to many years (>12 yrs) [25]. Infiltrating lobular breast cancer is the predominant type metastasizing to the colon and rectum, and many authors showed a mainly diffuse limitis plastica – like infiltration of the intestinal wall [23]. Pathological diagnosis can be complicated by the signet-ring appearance which is present in most metastases with infiltrating strands of pleomorphic cells with monomorphic, round nuclei and vacuolated cytoplasm mimicking other primary tumors (i.e. gastric carcinoma) [1]. As a result, immunohistochemistry is the most useful tool to reach the correct diagnosis (Figure 6). Metastatic breast carcinomas are usually positive for gross cystic disease fluid protein-15 (GCD-FP-15), cytokeratin 7, carcinoembryonic antigen, estrogen and progesterone receptors, and negative for cytokeratin 20 [22].

Finally, remote metastatic tumors to the omentum are very rare, most often asymptomatic, and they may originate from malignant melanomas as in our patient [24].

In conclusion, as progress regarding the treatment of cancer patients with current therapeutic modalities has occurred, more uncommon presentations of metastatic disease will be presenting for diagnosis and further management. Extra-hepatic metastatic tumors of the GI system and pancreas have to be considered when the patient’s medical history includes a previous malignancy. Treatment and survival grossly depends on histological type and the stage of the primary disease, thus the latter has to be thoroughly investigated. Although radical surgery of an isolated metastasis is the most effective approach, certain data must be considered such as the role of systemic therapy after complete resection. Thus, management should be individualized for each patient by a multidisciplinary team.

References


