Vagaries of clinical presentation of pancreatic and biliary tract cancer

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Summary

Pancreatic and biliary carcinomas remain a challenge to clinicians and investigators, as diagnosis is rarely achieved while the tumor is still in a curative stage. Clinical symptoms and signs of these neoplasias are non-specific and heterogeneous. We review the clinical presentation of these tumors, with an emphasis on their pathophysiology and relationship with survival. Abdominal pain is the most common presenting complaint in pancreatic and biliary tract carcinomas, regardless of their size; although severe back pain usually indicates neural compromise, and is associated with a short survival. Jaundice may also be an early sign, in fact, pancreatic tumors that present as painless jaundice have been adscribed, a relatively more favorable prognosis. Weight loss is a common finding in most patients, being usually associated with malabsorption. These neoplasias may also present as diabetes, as an acute pancreatitis episode, with venous thrombosis or malignant thrombophlebitis, as a gastrointestinal hemorrhage, with mental disturbances, or skin manifestations.

Key words: biliary, cancer, pancreas

Introduction

Pancreatic and biliary carcinomas remain a challenge to clinicians and investigators, as diagnosis is rarely achieved while the tumor is still in a curative stage. The incidence of pancreatic cancer has been increasing steadily over the last decades [1-3], which has been attributed primarily to the aging of the population [4]. Its incidence increases with age, 80% of the cases being diagnosed between the sixth and eighth decades of life. It is more prevalent in males, and in industrialized countries. The prognosis of pancreatic and biliary carcinomas remains very poor: 3 year survival is less than 5%, despite valiant therapeutic measures [5].

The etiology of pancreatic and biliary neoplasias remains unknown, although several risk factors have been described. Smoking and reduced consumption of fruits and vegetables appear to be the best established risk factors for exocrine pancreatic cancer. Chronic [6] and hereditary pancreatitis [2], diabetes [7,8], and gallstone disease [8] have also been implicated in the development of ductal adenocarcinoma. Parasite infestation of the biliary tree, disorders leading to biliary stasis (such as primary sclerosing cholangitis), and occupational exposure to rubber are widely regarded as risk factors for cholangiocarcinoma.

Clinical presentation of pancreatic and biliary carcinomas is heterogeneous. They commonly present with abdominal pain, jaundice and weight loss; although they may also be associated with malabsorption, as a palpable gallbladder or with splenomegaly, as a gastrointestinal hemorrhage, or migratory thrombophlebitis.

We will review the clinical presentation of tumors localized in the pancreas and in the extrahepatic biliary tree, restricting the description to a certain anatomical location: head of pancreas, the intrapancreatic biliary tract and the ampulla, and periampullary duodenal region. It is relevant to note that more than 98% of tumors arising from this localization are carcinomas [9], and quite often the primary site cannot be precisely established.

Approximately 60-70% of pancreatic ductal adenocarcinomas are localized in the head of pancreas, being 20-25% in the body and tail, with the remaining 10-20% of carcinomas involving the whole organ at the time of diagnosis. Tumors arising from the intrapancreatic biliary tree are almost always also adenocarcinomas. Adenocarcinomas in this anatomical area are locally very aggressive: the great majority of cases have infiltrated the peripancreatic fat and the surrounding great vessels at diagnosis.

Pain

Abdominal pain is the most common presenting complaint [1,10-12]. It is also the most frequently reported symptom in small (<2 cm) pancreatic carcinomas [13,14]. In fact, pain and/or jaundice are found in around 90% of the patients [1,11], even in a series of 106 patients with small carcinomas [15].

Pain is usually insidious in nature, and as a rule been present for one or two months at the time of diagnosis. It has a typical gnawing, visceral quality. It is generally epigastric, radiating to the sides and/or to the back. The pain is frequently worse at night, interfering with sleep, and may be worse in the postprandial period, and in the supine position. It results from mechanical compression of neighboring structures, and tumoral invasion of not only perineural tissue, but also of neural elements [16].

Severe back pain usually arises from compromise of body and tail of the pancreas. It results from splanchic nerve and/or celiac plexus infiltration, and is associated with a short survival [17].

Postprandial pain or postprandial exacerbation of the pain may be secondary to an increase in the secretory ductal pressure, due to partial or total tumoral obstruction of the pancreatic ducts.
Jaundice in the above referenced studies had unresectable catabolic metabolism induced by the tumor. Nevertheless, in Weight loss decreased food intake due to anorexia, vomiting, and the finding in patients with cancer, being generally the result of lesions, or distant metastases. Nevertheless, this presentation does not necessarily always mean a favorable stage, since some patients with painless Jaundice have been ascribed a relatively favorable prognosis [11,19], as it may correspond to a small tumor susceptible of potentially curative resection.

Jaundice

Jaundice due to biliary obstruction is typically the first clinical manifestation of tumors arising from the biliary tree. Jaundice is found in around 80% of patients with tumors in the pancreatic head, specially if tumors are larger than 2 cm (see table 1). It is even more prevalent when the tumor arises from the ampulla, in which it may be intermittent due to intraductal activation of trypsinogen [26]. In fact, the acute inflammation of the pancreatic gland may be due to Wirsung obstruction, invasion of parenchyma, tumor infiltration and islet cell destruction, but also because the tumor induces peripheral resistance to insulin [21,22]. Diabetes mellitus and glucose intolerance have been recognized as clinical signs of pancreatic cancer, particularly when the tumor is diagnosed within the first year of diabetes. Pancreatic cancer may alter glucose metabolism not only by tumor infiltration and islet cell destruction, but also because of remote effects of the tumor that induces peripheral resistance to insulin [21,22]. Diabetes has also been reported as a risk factor for pancreatic malignancy [7,8]; although this association has not always been found to be significant [23]. In a recent meta-analysis [7] the relative risk for developing pancreatic cancer in diabetics has been assessed to be of 2.0, even for diabetes of longer than 5 years duration. The same meta-analysis points out the poor characterization of diabetes in the majority of published studies, suggesting that the modest increased risk may be related to non-insulin-dependent diabetes, or even glucose intolerance.

Table 1. Presenting symptoms of patients with adenocarcinoma of the pancreas

<table>
<thead>
<tr>
<th>Authors</th>
<th>No.</th>
<th>Tumor size</th>
<th>Location in head</th>
<th>Abdominal Pain</th>
<th>Jaundice</th>
<th>Weight loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaiser et al [11], 1985</td>
<td>393</td>
<td>Any</td>
<td>266 (70%)</td>
<td>307 (79%)</td>
<td>184 (48%)</td>
<td>-</td>
</tr>
<tr>
<td>Mannell et al [17], 1986</td>
<td>79</td>
<td>Any</td>
<td>76 (96%)</td>
<td>62 (79%)</td>
<td>67 (85%)</td>
<td>65 (82%)</td>
</tr>
<tr>
<td>Manabe et al [19], 1988</td>
<td>17</td>
<td>&lt;2 cm</td>
<td>17 (100%)</td>
<td>7 (42%)</td>
<td>10 (59%)</td>
<td>-</td>
</tr>
<tr>
<td>Alvarez et al [12], 1993</td>
<td>126</td>
<td>Any</td>
<td>87 (69%)</td>
<td>63 (50%)</td>
<td>54 (43%)</td>
<td>-</td>
</tr>
<tr>
<td>Furukawa et al [13], 1996</td>
<td>31</td>
<td>&lt;2 cm</td>
<td>18 (58%)</td>
<td>10 (32%)</td>
<td>5 (16%)</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

Rarely, pain may develop very acutely as a result of an episode of acute pancreatitis, due to tumoral Wirsung occlusion. Another uncommon cause of pain is that secondary to giant splenomegaly. An exceptional cause of pain in the right costal margin may be secondary to gallbladder distension.

Diabetes

Diabetes mellitus and glucose intolerance have been recognized as clinical signs of pancreatic cancer, particularly when the tumor is diagnosed within the first year of diabetes. Pancreatic cancer may alter glucose metabolism not only by tumor infiltration and islet cell destruction, but also because of remote effects of the tumor that induces peripheral resistance to insulin [21,22]. Diabetes has also been reported as a risk factor for pancreatic malignancy [7,8]; although this association has not always been found to be significant [23]. In a recent meta-analysis [7] the relative risk for developing pancreatic cancer in diabetics has been assessed to be of 2.0, even for diabetes of longer than 5 years duration. The same meta-analysis points out the poor characterization of diabetes in the majority of published studies, suggesting that the modest increased risk may be related to non-insulin-dependent diabetes, or even glucose intolerance.

Acute pancreatitis

A typical episode of acute pancreatitis may be the initial clinical feature of pancreatic cancer, corresponding to approximately 3% of consecutive cases of pancreatic carcinoma in two series of 255 and 302 patients respectively [24,25]. In the last series, these cases of cancer represented only 1.3% of the 754 patients admitted in the same period with an acute pancreatitis. Nevertheless, it is relevant to note that when pancreatitis is defined by histological rather than clinical criteria, the incidence is higher. Thus, in the first series [24], significant inflammation diagnosed by histologic evidence was present in 26 of the 255 patients, whereas only 8 referred attacks of pain and elevation of amylases suggestive of an acute pancreatitis episode. This phenomenon may be relevant in the interpretation of a cytological needle aspiration for diagnostic purposes. The acute inflammation of the pancreatic gland may be due to Wirsung obstruction, invasion of parenchyma, tumor induction of vascular thrombosis, or even induction of intraductal activation of trypsinogen [26]. In fact, the incidence of acute pancreatitis and/or hyperamylasemia is

Weight loss

Weight loss occurs in most patients, being usually the sign present for longer duration [17,20]. Weight loss is a common finding in patients with cancer, being generally the result of decreased food intake due to anorexia, vomiting, and the catabolic metabolism induced by the tumor. Nevertheless, in pancreatic and biliary carcinomas, it may also arise to some extent from malabsorption. In fact, when the contributing factors leading to weight loss in pancreatic cancer (decreased caloric consumption, abnormal metabolism, and malabsorption) are assessed; the fundamental mechanism responsible is malabsorption [19].
highest when the papilla of Vater or head of pancreas are involved [27].

**Malabsorption**

Malabsorption is an uncommon presenting sign of pancreatic cancer. It is, nevertheless, a frequent mechanism of weight loss in patients with pancreatic and biliary carcinoma, as stated above. In fact, a decrease of pancreatic enzyme and bicarbonate output is a common finding. Secretory deficiency seems to be secondary to an obstruction of the pancreatic duct rather than due to diffuse pancreatic insufficiency. The site of obstruction of the main pancreatic duct is a primary determinant for significant malabsorption secondary to decreased secretion. Only head tumors occluding the main duct near the papilla will reduce enough pancreatic enzyme output as to produce steatorrhea [28]. Characteristically, fat malabsorption is more severe than protein malabsorption [29], as not only pancreatic, but biliary secretion may be compromised. Thus, patients with moderate or severe fat or protein malabsorption may improve with pancreatic enzyme replacement therapy [29].

**Other manifestations**

It is well known that pancreatic cancer may be found in a patient admitted with an episode of peripheral venous thrombosis or with a recurring, migrating thrombophlebitis in any vascular territory. This phenomenon has been described in association with cancer in various organs. Of particular importance in pancreatic cancer is a mesenteric venous thrombosis [30]. Thromboembolic complications occur more commonly in highly differentiated adenocarcinomas, and in those arising from the body and tail of the pancreas [31].

Another rare presenting sign of pancreatic and biliary carcinoma is a gastrointestinal hemorrhage, except in the carcinoma arising from the papilla of Vater. These ampullary tumors may bleed intermittently. Bleeding may also occur secondarily to stomach or duodenal tumor infiltration or metastases, or even secondarily to esophageal varices in the context of portal thrombosis. In this regard, splenic antigen is not an uncommon finding in a patient with an advanced carcinoma, due to liver of spleen metastases, or venous splenic thrombosis.

Skin manifestations are also known to occur in some patients with carcinoma of the pancreas. Particularly, both cicatricial and bullous pemphigoid are well characterized, even as a first sign of the disease [32]. It is worth to point out that the three reported cases of pemphigoid associated-pancreatic carcinoma were complicated by venous thrombosis.

Finally, mental disturbances may occur in the context of a pancreatic carcinoma. Emotional and personality changes may attend the somatic symptoms of pancreatic carcinoma, or may even occur as a prodrome of the disease [33]; being chiefly depression frequently diagnosed in association to pancreatic neoplasias [34].