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MINI REVIEW

Pancreatic small cell cancer

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Summary Small cell carcinoma (SCC) is most commonly associated with lung cancer. Extra-pulmonary SCC can originate in virtually any organ system, with the gastrointestinal tract being the most common site of involvement. We review the clinical presentation, pathogenesis, histology, imaging modalities and optimal therapeutic management of PSCC in light of available evidence.

Introduction and overview

Generally, small cell carcinoma (SCC) is known to affect the lungs, but extra-pulmonary SCC can originate in virtually any organ system, particularly the gastrointestinal and the genitourinary tracts [1,2]. In pancreatic cancer, in particular, the presence of tumoral disease usually underlines pancreatic adenocarcinoma (PA) because, until 1951, it was the only histologic subtype of pancreatic cancer identified. Miller et al. reported the presence of other subtypes, including squamous cell carcinoma, acinar cell carcinoma, mucinous cystadenocarcinoma and SCC [3]. Of particular interest to this paper is the neuroendocrine variant of pancreatic cancer because of its poor prognosis. Although rarely reported in the literature, different interchangeable terms describe this entity as follows: small cell carcinoma, oat cell carcinoma, high-grade neuroendocrine carcinoma and poorly differentiated neuroendocrine carcinoma [3].

There have been very few publications regarding pancreatic SCC (PSCC) in the past 20 years. Most data indicate that PSCC accounts for approximately 1% of all pancreatic cancers [4]. Despite having names similar to those of well-differentiated neuroendocrine tumors, PSCC and pulmonary SCC differ significantly from these tumors in terms of their proliferative rates, aggressivity, therapeutic approaches and paraendocrine/paraneoplastic secretions. It is also uncertain whether these poorly differentiated cancerous cells arise de novo or derive from well-differentiated neuroendocrine cells or normal ductal precursor cells [5].

Clinical presentation and diagnosis

The first case series relating to PSCC described weight loss, jaundice, cachexia, hepatomegaly, abdominal pain,

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ascites, and disorientation at presentation. In this series, two patients presented with liver metastasis, and one patient presented with lymph node metastasis. Ectopic hormone production was not described in this paper [6]. To date, analyzed data from PSCC publications have presented the tumor in a single pancreatic location in 85% of cases, including 56% in the head, 20% in the tail, and 10% in the body, and in multiple pancreatic locations in 15% of cases [5,7—11].

Clinically, the initial presentation of PSCC is dictated by the location of the disease. Tumors of the head of the pancreas often present with painless jaundice (33%) and weight loss (52%). Other common frequent symptoms encountered at diagnosis are abdominal pain (62%), weight loss (52%), loss of appetite (14%), slight fever (14%), peripheral adenopathy (14%), hepatomegaly (10%), and ascites (10%) [7]. Acute pancreatitis is uncommon [9]. Other possible presentations for PSCC are paraneoplastic syndromes. Unlike pulmonary SCC, in which paraneoplastic syndromes are frequent at presentation, reports of extrapulmonary associated paraendocrine syndromes are sparse. Only two published papers have reported elevated hormone levels in these tumors. The first paper presented a case of increased adrenocorticotrophic hormone (ACTH) secretion, and the second paper presented a case of paraneoplastic hypercalcemia [12,13].

To date, 89% of patients with PSCC have extensive disease at the time of their initial diagnosis, which is attributed to the high proliferative rate of PSCC. In a review by Vos et al. (2008), metastasis predominantly occurred in peripancreatic lymph nodes (62%), the liver (38%), the lungs (14%), the bone marrow (14%), the bone (10%), the colon (10%), and the adrenal glands (10%) [7]. Other reported metastatic sites included the spleen, gallbladder, kidney, skin, brain, and soft tissue [7,11]. Clinically, extrapulmonary SCC and metastatic primary pulmonary SCC are not always distinguishable through histology. Consequently, exclusion of pulmonary SCC is a prerequisite for the diagnosis of extrapulmonary SCC [8].

Histology

In most reports, biopsy specimens show sheets of small or oat-like cells that are spindle-shaped with scant cytoplasm and hyperchromatic nuclei.

PSCC are immunoreactive for epithelial membrane antigen and keratin, which is a reflection of their epithelial origin. In all reported cases, positive immunoreactivity to chromogranin A or synaptophysin, in addition to CD56 expression, confirms the diagnosis. Neuron-specific enolase (NSE) is another valuable marker of neuroendocrine differentiation showing positive immunoreactivity in biopsy specimens. Biopsy specimens should be tested for CD99 receptor status, which is positive in primitive neuroectodermal tumors of the pancreas [14,15].

Just as immunohistochemistry identifies the neuroendocrine origins of tumors, it may also help localize sites of origin. Thyroid transcription factor-1 is expressed in most poorly differentiated neuroendocrine carcinomas and some well-differentiated NETs of pulmonary origin [16].

In reference to the accepted definition of PSCC, these tumors are usually high grade and poorly differentiated. Consequently, PSCC are defined by a mitotic index of more than 20 mitoses per high power field and a Ki67 labeling index of more than 20% [17]. In one series of 107 pancreatic resections initially diagnosed as poorly differentiated neuroendocrine carcinoma, fifty-eight percent were reclassified as well differentiated neuroendocrine carcinoma or acinar cell carcinoma. The amplitude of misdiagnosis illustrated by this series demonstrates the importance of following strict criteria to ensure an adequate diagnosis [5].

Alterations in the cellular checkpoints Rb/p16 and p53 abrogate cell cycle control and promote, among other activities, the emergence of pancreatic malignancies. The loss of these proteins is an essential genetic anomaly of poorly differentiated NET. These inactivations are much less common in well-differentiated tumors and PA. Bcl-2 protein, a central apoptotic inhibitor, also plays an essential role in the pathogenesis of PSCC. Bcl-2 appears to be ubiquitously overexpressed in PSCC, which contrasts with its expression in well-differentiated NET and PA. Its overexpression accounts for the high proliferative rate and aggressive malignant phenotype of PSCC [18].

Biomarkers

NSE is a biomarker found in neuroendocrine cells and is known for its close correlations with the extent of the disease and response to therapy [4,8,14,19]. With the exception of one published case, all other patients demonstrated increases in serum NSE levels in SCC of the pancreas. Gastrin related peptide (GRP) and Pro-GRP are also possible markers that have been shown to be more sensitive and specific than NSE for extrapulmonary SCC [20]. Pro-GRP is more sensitive than GRP and is a possible marker for the diagnosis of and the assessment of responsiveness to therapy in PSCC [4]. Serum carcinoembryonic antigen (CEA) is another possible marker that may be used for the assessment of treatment response despite its lower specificity [14]. Similar to PA, Ca19-9 is almost constantly elevated in patients with PSSC but is not reported as a valuable marker for follow-up in these patients [8—11].

Imaging features

Initial imaging studies should include cross-sectional studies of chest, abdomen, pelvis, and brain (if symptomatic) using computed tomography or magnetic resonance imaging (MRI). Unlike well-differentiated NET, somatostatin receptor scintigraphy holds no value in the workup of PSCC. On the other hand, fluorodeoxyglucose (FDG)-PET scanning is very sensitive in this context due to the high metabolic rate of PSCC [21]. Patients presenting with localized PSCC will not have their disease readily distinguished from PA by imaging studies alone. The distinction of pancreatic islet cell tumors from localized PSCC is challenging because the imaging features displayed by this tumor subtype are almost indistinguishable from those of PSCC [22]. However, some imaging features may be useful in diagnosing PSCC. In several reports, computed tomography and MRI have demonstrated hypervascularized homogenous mass patterns different from the characteristic hypovascular lesions encountered in adenocarcinomas [23]. However, it is