The Spectrum of Hematologic Malignancies Involving the Pancreas

Potential Clinical Mimics of Pancreatic Adenocarcinoma

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Key Words: Pancreas; Hematologic malignancy; Lymphoma; Leukemia; Primary pancreatic lymphoma; Pancreatic adenocarcinoma

Abstract

Hematologic malignancies often involve the pancreas, causing potential diagnostic pitfalls and, rarely, potentially avoidable surgical resection. We review the spectrum of hematologic malignancies involving the pancreas and describe features useful in preoperative distinction from adenocarcinoma.

Archived clinical, pathologic, and radiologic data (1965 to present) for hematologic malignancies involving the pancreas were reviewed and compared with the data for 157 surgically resected pancreatic adenocarcinomas. Of 42 cases, 27 (64%) were clinically “suspicious” for hematologic malignancies. Of the remaining 15 cases, 4 patients underwent resection for presumed pancreatic adenocarcinoma. Isolated pancreatic masses proved most difficult to identify clinically. Significant factors in distinguishing hematologic malignancies from adenocarcinoma included history of hematologic malignancy, young age, large tumor size, low CA19-9 level, B symptoms, and lack of jaundice or diabetes mellitus.

Various hematologic malignancies involve the pancreas, most commonly diffuse large B-cell lymphoma. Pancreatic masses are usually correctly identified clinically. Preoperative and operative sampling is strongly recommended when hematologic malignancies cannot be excluded.

Masses of the pancreas can create unique diagnostic pitfalls. It is not unusual for a pancreatic mass to reach large proportions or for a tumor to be widely disseminated before the first clinical symptoms are identified. Clinical and radiologic data can often be used to characterize these lesions and determine the most appropriate intervention. Most malignant neoplasms of the pancreas are adenocarcinoma, and, as such, it is not unusual for a pancreatic mass deemed radiologically and clinically malignant to undergo subsequent surgical resection without the aid of tissue diagnosis. In fact, with false-negative rates of preoperative pancreatic sampling historically approaching 15%, pancreatic adenocarcinomas will occasionally be resected despite negative biopsy, bile duct brushing, fine-needle aspiration (FNA), or endoscopic ultrasound–guided (EUS)-FNA.1,2

Hematologic malignancies, particularly non-Hodgkin lymphomas (NHL), can often manifest in an extranodal location, including the pancreas. A substantial percentage of these extranodal NHLs arise within the gastrointestinal tract, particularly the stomach and small intestine, accounting for 10% to 30% of all NHLs.3-7 In addition, the retroperitoneal and peripancreatic lymph nodes are common sites of involvement by systemic lymphomas. Whether from the surrounding lymph nodes or adjacent organs, it is not surprising that secondary involvement of the pancreas by lymphoma is a well-documented entity, reported to occur in 5% to 30% of all lymphomas.4,8 Rarely, hematologic malignancies involving the pancreas manifest as an isolated mass. When the hematologic malignancy is NHL, the term primary pancreatic lymphoma is used. Primary pancreatic lymphoma accounts

Upon completion of this activity you will be able to:

• describe the types and frequency of hematologic malignancies involving the pancreas.
• discuss the criteria and potential pitfalls associated with the diagnosis of primary pancreatic lymphoma.
• compare the clinical, radiographic, and laboratory findings of a hematologic malignancy of the pancreas to those of a pancreatic adenocarcinoma.
• apply clinical, radiographic, and laboratory findings in patients with pancreatic masses to identify those suspicious for hematologic malignancy requiring pancreatic sampling prior to resection.

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for fewer than 0.5% of all pancreatic malignancies and 1% of extranodal lymphomas.\textsuperscript{9-13} It may be difficult or impossible to distinguish primary pancreatic lymphoma from secondary involvement of the pancreas by direct extension from peripancreatic lymph nodes, leaving the true number of primary pancreatic lymphomas in question. Diagnostic criteria for primary pancreatic lymphoma include lymphomatous spread limited to the pancreas and peripancreatic lymph nodes, lack of splenic and hepatic involvement, no involvement of superficial or mediastinal lymph nodes, and a normal leukocyte count in the peripheral blood.\textsuperscript{14} The vast majority of cases described in the literature are B-cell type,\textsuperscript{5,7,15} with a strong propensity toward diffuse large B-cell lymphoma (DLBCL). Rare cases of T-cell primary pancreatic lymphoma have been described.\textsuperscript{16,17}

Although the histologic distinction between hematologic malignancies and pancreatic adenocarcinoma is usually straightforward, surgical resections may occur based on clinical and radiologic suspicion without preoperative tissue diagnosis. We identified and reviewed cases of all hematologic malignancies involving the pancreas to determine their spectrum and determined clinical features useful in distinguishing hematologic malignancies of the pancreas from pancreatic adenocarcinoma.

Materials and Methods

Tissue and cytology archives from 1965 to the present at The Ohio State University, Columbus, were searched to identify hematologic malignancies involving the pancreas. Available autopsy reports (1990 to the present) with any hematologic malignancy were also reviewed. Clinical and radiologic data from each case were reviewed, including diagnostic, treatment, and follow-up information. Staging was performed using the Ann Arbor staging system for NHL for cases in which adequate applicable data were available. The diagnostic information from each case, including H&E-stained sections, immunohistochemical stains, and flow cytometry reports, was reviewed and, when necessary, updated terminology was substituted. Follow-up data were collected by review of patients’ medical records and review of obituary materials. For comparison, clinicopathologic data from 157 cases of surgically resected pancreatic adenocarcinoma with adequate preoperative and postoperative information were reviewed from 1997 to 2007. Statistical comparison of variables was performed by using a 2-tailed Student t test and Fisher exact test.

Results

We found 42 cases of hematologic malignancies involving the pancreas in surgical and cytology archives. Most (29/42 [69%]) of these were high-grade B-cell lymphomas including DLBCL (n = 28) and grade 3 follicular lymphoma (n = 1). The remaining cases included 6 low-grade B-cell lymphomas, including grade 1 or 2 follicular lymphomas (n = 4), small lymphocytic lymphoma (CLL/SLL; n = 1), and marginal zone lymphoma (n = 1), and granulocytic/myeloid sarcomas (acute myeloid leukemia [AML], n = 2), Epstein-Barr virus–related posttransplant B-cell lymphoproliferative disorders (n = 2), plasma cell myeloma (n = 1), chronic myelomonocytic leukemia (n = 1), and nodular sclerosing Hodgkin lymphoma (n = 1) \textbf{Table 1} and \textbf{Image 1}.

The diagnosis of a hematologic malignancy was made using FNA in 4 cases, core needle biopsy in 26, and surgical resection in 12. In 2 of the 4 cases in which an FNA was read as a hematologic malignancy, a subsequent surgical biopsy was performed to further classify the lymphoma. In 1 additional case, the FNA from an outside facility had been read as “suspicious for carcinoma,” but owing to the patient’s history of lymphoma was correctly identified by core biopsy, precluding a surgical resection. In 3 cases resulting in surgical resection, sampling was preoperatively attempted, but results were benign in 2 cases (1 FNA, 1 core biopsy), and necrotic in 1 case (core biopsy). In 1 of these cases, a subsequent

\textbf{Table 1}  

\textbf{Clinicopathologic Features of Hematologic Malignancies Involving the Pancreas in Surgical and Cytologic Material}\textsuperscript{a}

<table>
<thead>
<tr>
<th>Hematologic Malignancy</th>
<th>M/F Ratio</th>
<th>Mean Age (y)</th>
<th>Mean Tumor Size (cm)</th>
<th>Localized to Pancreas</th>
<th>History</th>
<th>Suspected</th>
<th>No. Resected</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGBCL (n = 29)</td>
<td>0.8:1</td>
<td>58</td>
<td>6.5</td>
<td>6</td>
<td>5</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>LGBCL (n = 6)</td>
<td>2:1</td>
<td>58</td>
<td>3.9</td>
<td>0</td>
<td>3</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Myeloid sarcoma (n = 2)</td>
<td>2:0</td>
<td>70</td>
<td>0.9</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Transplant (n = 2)</td>
<td>2:0</td>
<td>40</td>
<td>12.3</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Other (n = 3)\textsuperscript{a}</td>
<td>2:1</td>
<td>62</td>
<td>3.1</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Total (n=42)</td>
<td>1.2:1</td>
<td>58</td>
<td>7.3</td>
<td>9 (21)</td>
<td>12 (29)</td>
<td>27 (64)</td>
<td>14 (33)</td>
</tr>
</tbody>
</table>

HGBCL, high-grade B-cell lymphoma; LGBCL, low-grade B-cell lymphoma.

\textsuperscript{a} Data are given as number of cases or number (percentage) of cases unless otherwise indicated.

\textsuperscript{a} Includes plasma cell myeloma, chronic myelomonocytic leukemia, and nodular sclerosing Hodgkin lymphoma.
intraoperative frozen section was performed and read as lymphoma; the resection was completed for symptomatic relief.

Clinical and radiologic data led to the suspicion of a hematologic malignancy in 27 cases (64%), including all but 1 of 12 patients (29%) with a medical history of a hematologic malignancy. Pancreatic adenocarcinoma was the second most commonly suspected diagnosis based on the clinical and radiologic findings in 22 cases (52%). Other clinically suspected differential diagnoses included gastric cancer ($n = 2$), pancreatitis ($n = 2$), pseudocyst ($n = 1$), peritonitis ($n = 1$), and metastases from ovarian and breast cancer (1 each). Of the 14 patients with hematologic malignancies who underwent resection, 10 had a clinically suspected diagnosis of a hematologic malignancy but were thought to still require resection, most commonly for splenic involvement by lymphoma with local extension into the distal pancreas ($n = 5$). Of these 10, 2 had a tissue-confirmed diagnosis of a hematologic malignancy before surgery with an additional 2 cases confirmed intraoperatively with frozen sections. Four patients with a hematologic malignancy of the pancreas underwent resection for presumed pancreatic adenocarcinoma. Two of them did not have preoperative tissue sampling. One had an FNA read as benign, and the other had a core needle biopsy read as necrotic tissue (both previously mentioned).

**Image 1** Hematologic malignancies involving the pancreas. A. Diffuse large B-cell lymphoma involving the pancreas (H&E, ×200). B. Follicular lymphoma infiltrating the pancreatic parenchyma (H&E, ×200). C. Granulocytic (myeloid) sarcoma surrounding the bile duct in the pancreas (H&E, ×100). D. Endoscopic ultrasound–guided fine-needle aspiration showing the cytologic features of this high-grade B-cell lymphoma that was found with molecular analysis to be a “double-hit” lymphoma (rapid Romanowsky, ×600).
Three cases were identified with pancreatic involvement by a hematologic malignancy and another pancreatic tumor and were not included in data comparisons. One contained a small adenocarcinoma with widespread pancreatic involvement by CLL/SLL, accounting for the mass seen radiographically. This case, not surprisingly, was associated with the highest CA19-9 level of all hematologic malignancies involving the pancreas (453.1 U/mL). Two other cases had peripancreatic lymph node involvement by a low-grade B-cell lymphoma in pancreas removed for another neoplasm (poorly differentiated carcinoma and solid pseudopapillary tumor).

Review of all autopsy cases from 1990 to present identified 153 cases of hematologic malignancy. Of these, 20 had pancreatic involvement (13.1%). The majority were B-cell lymphomas (15/20 [75%]) and included 7 DLBCL, 5 CLL/SLL, 2 Burkitt lymphomas, and 1 mantle zone lymphoma. The remaining cases were AML (n = 2) and T-cell lymphoma (n = 3). Of 85 NHLs identified at autopsy, 15 (18%) involved the pancreas. Although several cases showed distinct pancreatic masses, all cases showed widespread disease with involvement of regional lymph nodes and other organs. None of the patients had primary pancreatic lymphoma.

In contrast with the autopsy findings, 6 (14%) of 42 cases identified in surgical or cytology specimens met criteria to be classified as primary pancreatic lymphoma. All tumors were DLBCL and were in the head of the pancreas. One case was subsequently found with molecular testing to have translocations for c-myc and bcl-2, and it was reclassified as a “double-hit lymphoma.” Not surprisingly, in each case, pancreatic adenocarcinoma was considered before pathologic diagnosis of lymphoma. Of these cases, 5 patients had no history of a lymphoproliferative disorder, and 1 patient had a history of DLBCL but had been disease-free for 7 years. Of the 4 surgical resections for presumed adenocarcinoma, 2 occurred in these primary pancreatic lymphomas Table 2.

Of 42 cases of hematologic malignancy, 17 (40%) manifested with a potentially deceptive clinical picture of a predominant pancreatic mass. These cases included the 6 primary pancreatic lymphomas and 11 with similar clinical features that did not meet criteria for primary pancreatic lymphoma. Three cases are not considered primary pancreatic lymphoma owing to the type of the hematologic malignancy. These included 2 Epstein-Barr virus–related posttransplant B-cell lymphoproliferative disorders following combined renal and pancreatic transplantation and a myeloid/granulocytic sarcoma, the first recurrence of AML in remission for 4 years. One case of DLBCL (5.3 cm) in a patient who was disease-free 6 years after follicular lymphoma did not meet criteria owing to concurrent bone marrow involvement. The final 7 cases not meeting criteria were new occurrences of B-cell lymphoma that manifested as a predominant pancreatic mass (≥6 cm; mean, 9.4 cm) but had regional lymph node spread in the abdomen. Of the 7, 6 were DLBCL, and 1 was a c-myc– and bcl-2–positive double-hit lymphoma.

Hematologic malignancies are most likely to be confused with pancreatic adenocarcinoma when spread is limited to the pancreas and surrounding peripancreatic lymph nodes. To identify features clinically useful in this distinction, findings from resected cases of pancreatic adenocarcinoma were compared to cases with hematologic malignancies involving the pancreas. Clinical history, demographics, preoperative laboratory data, and symptoms at diagnosis were helpful in distinguishing pancreatic involvement by a hematologic malignancy from pancreatic adenocarcinoma. Features seen significantly more often in patients with hematologic malignancies than in patients with pancreatic adenocarcinoma included young age, large tumor size (seen in all categories with the exception of granulocytic sarcomas), low preoperative CA19-9 level, history of a hematologic malignancy (regardless of disease-free interval), presence of B symptoms, and a lack of jaundice or diabetes mellitus.

Lactate dehydrogenase (LD) and serum β2-microglobulin (β2M) levels were prominently elevated in patients with hematologic malignancies; however, values from a sufficient number of patients with pancreatic adenocarcinoma were not available for comparison. Although patients with hematologic malignancies were significantly younger than patients with adenocarcinoma, there was a large degree of overlap. Abdominal pain and male/female ratio were similar in the groups Table 3 and Table 4. In the 4 cases of hematologic malignancies involving the pancreas in which surgical resection was performed for a presumed diagnosis of pancreatic involvement, CA19-9 values of 90.2, 243, 49, and 51 were recorded. The highest CA19-9 level of all hematologic malignancies was recorded in this study was 1425 U/mL, which was in the c-myc– and bcl-2–positive double-hit lymphoma.

### Table 2

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (y)</th>
<th>Diagnostic Procedure</th>
<th>Diagnosis</th>
<th>Stage</th>
<th>Survival (mo)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72</td>
<td>Biopsy</td>
<td>DLBCL</td>
<td>IEA</td>
<td>59</td>
<td>DFOD</td>
</tr>
<tr>
<td>2</td>
<td>78</td>
<td>Biopsy</td>
<td>DLBCL</td>
<td>IEA</td>
<td>7</td>
<td>DOD</td>
</tr>
<tr>
<td>3</td>
<td>76</td>
<td>Biopsy</td>
<td>DLBCL</td>
<td>IEA</td>
<td>6</td>
<td>DOD</td>
</tr>
<tr>
<td>4</td>
<td>69</td>
<td>Whipple</td>
<td>DHL</td>
<td>IIEB</td>
<td>30</td>
<td>FOD</td>
</tr>
<tr>
<td>5</td>
<td>26</td>
<td>FNA/Whipple</td>
<td>DHL</td>
<td>IIIEB</td>
<td>6</td>
<td>DOD</td>
</tr>
<tr>
<td>6</td>
<td>85</td>
<td>Biopsy</td>
<td>DLBCL</td>
<td>IEA</td>
<td>4</td>
<td>DOD</td>
</tr>
</tbody>
</table>

DFOD, died, free of disease; DHL, double-hit lymphoma; DLBCL, diffuse large B-cell lymphoma; DOD, died of disease; FOD, free of disease.
adenocarcinoma, we found that in 3 of the 4 cases at least 1 of the aforementioned findings (those found significantly more commonly in hematologic malignancies than in pancreatic adenocarcinoma) was present, including large tumor, B symptoms, low CA19-9 level, and young age. Two of the patients (cases 2 and 4) had sampling attempted before surgical resection Table 5.

In resected cases of pancreatic adenocarcinoma, 29 (18.5%) of 157 had preoperative sampling, of which 11 (38%) had a preoperative diagnosis of adenocarcinoma or atypical. The 29 cases with preoperative sampling included 5 FNA (3/5 diagnostic), 7 bile duct brushings (3/7 diagnostic), and 17 core needle biopsies (5/17 diagnostic). An additional 36 (22.9%) of 157 resections had an attempted intraoperative frozen section for diagnosis, of which 21 (58%) of 36 were correctly identified as adenocarcinoma. This included 7 intraoperative frozen sections for which preoperative sampling had been previously performed and called negative (4/7 positive on frozen section). In total, 14 resections were performed based on clinical suspicion despite negative cytology, biopsy, or intraoperative frozen section. Cases of hematologic malignancies that were resected also showed a relatively low rate of preoperative or intraoperative pathologic confirmation, with 5 (36%) of 14 cases preoperatively sampled (2/5 diagnostic) and another 2 diagnosed on intraoperative frozen section Table 6.

Patient follow-up was available in 39 of 42 surgical pathology and cytology cases of hematologic malignancies involving the pancreas and all 157 of the surgically resected pancreatic adenocarcinomas. Patients with hematologic malignancies involving the pancreas had a complete remission rate of 62%, with overall survival rates of 55% at 12 months and 38% at 5 years. For patients with DLBCL, the complete remission rate was 61% and survival rates were 56% at 12 months and 32% at 5 years. In primary pancreatic lymphoma, a relatively poor complete remission rate and 12-month survival of 33% (2/6) was noted, despite low Ann Arbor stage at diagnosis. None of the 3 patients with 5 years of follow-up were alive. The patients with pancreatic adenocarcinoma

### Table 3
Comparison of HM with Adenocarcinoma: Demographics, Clinical History, and Symptoms*

<table>
<thead>
<tr>
<th>M/F Ratio</th>
<th>Mean ± SD</th>
<th>History of DM</th>
<th>History of HM</th>
<th>Abdominal Pain</th>
<th>B Symptoms</th>
<th>Jaundice</th>
</tr>
</thead>
<tbody>
<tr>
<td>HM (n = 37)</td>
<td>1.2:1</td>
<td>Age (y)</td>
<td>(5)</td>
<td>(11)</td>
<td>(21)</td>
<td>(21)</td>
</tr>
<tr>
<td>Pancreatic adenocarcinoma</td>
<td>1.3:1</td>
<td>65 ± 11</td>
<td>49 (31.4)</td>
<td>2 (1.3)</td>
<td>96 (60.9)</td>
<td>51 (32.7)</td>
</tr>
<tr>
<td>P</td>
<td>.68</td>
<td>.01</td>
<td>.048</td>
<td>&lt;.001</td>
<td>.7773</td>
<td>.0113</td>
</tr>
</tbody>
</table>

DM, diabetes mellitus; HM, hematologic malignancy.

* Data are given as number (percentage) unless otherwise indicated.

### Table 4
Comparison of Hematologic Malignancies With Adenocarcinoma: Radiographic and Laboratory Findings*

<table>
<thead>
<tr>
<th>Size (cm)</th>
<th>CA19-9 (U/mL)</th>
<th>LD (U/L)</th>
<th>β2M (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic malignancy</td>
<td>7.3 ± 3.8</td>
<td>118 ± 158</td>
<td>503.0 ± 505.5</td>
</tr>
<tr>
<td>Pancreatic adenocarcinoma</td>
<td>3.9 ± 1.6</td>
<td>1,162 ± 3,426</td>
<td>—</td>
</tr>
<tr>
<td>P</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

CA19-9, carbohydrate antigen 19-9 (reference range, 0-37.0 U/mL); LD, lactate dehydrogenase (reference range, 0-190 U/L); β2M, β2-microglobulin (reference range, 0.60-1.11 mg/L).

* Data are given as mean ± SD.

### Table 5
Resections for Presumed Pancreatic Adenocarcinoma

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Procedure</th>
<th>Age (y)</th>
<th>Tumor Size (cm)</th>
<th>CA19-9 (U/mL)</th>
<th>B Symptoms</th>
<th>Jaundice</th>
<th>History of DM</th>
<th>Outcome (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Whipple</td>
<td>73</td>
<td>1.8</td>
<td>327.5</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>DOD (33)</td>
</tr>
<tr>
<td>2</td>
<td>Distal pancreatectomy</td>
<td>61</td>
<td>8.1</td>
<td>—</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>FOD (18)</td>
</tr>
<tr>
<td>3</td>
<td>Whipple</td>
<td>69</td>
<td>7.1</td>
<td>15</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>FOD (30)</td>
</tr>
<tr>
<td>4</td>
<td>Whipple</td>
<td>26</td>
<td>4</td>
<td>—</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>DOD (6)</td>
</tr>
</tbody>
</table>

CA19-9, carbohydrate antigen 19-9 (reference range, 0-37.0 U/mL); DM, diabetes mellitus; DOD, died of disease; FOD, free of disease.
had survival rates of 38% and 6% at 12 months and 5 years, respectively. As expected, the patients with hematologic malignancies had longer survival than patients with pancreatic adenocarcinoma.

**Discussion**

The majority of solid masses in the pancreas are ductal adenocarcinomas, and, if deemed resectable in a patient healthy enough to undergo resection, they are treated by resection. By using radiologic, laboratory, and clinical data, surgeons are able to correctly identify operable lesions in the vast majority of cases, even without tissue diagnosis. Core biopsies and ultrasound-guided FNA are used in many cases, but benign findings may not preclude operative management because chronic pancreatitis frequently surrounds adenocarcinoma. Therefore, experienced surgeons take many patients with clinical and radiologic features suggestive of pancreatic carcinoma to the operating room without preoperative tissue diagnosis. A variety of hematologic malignancies can involve the pancreas, and, on rare occasion, manifest as an isolated mass. This manifestation can rarely result in resections that are likely not indicated because hematologic malignancies are generally treated medically with surgical management limited to cases necessitating secondary symptom control.

We identified 42 cases of hematologic malignancies involving the pancreas from surgical and cytologic material during a 45-year period and an additional 20 cases from autopsies performed during 20 years, encompassing a diverse spectrum. DLBCL accounted for the majority (~67% surgical/autopsy cases; ~75% autopsy cases) of hematologic malignancies manifesting as pancreatic masses and those showing secondary involvement of the pancreas. These included 2 cases of c-myc- and bcl-2-negative double-hit lymphoma. Low-grade B-cell lymphomas made up a sizable proportion of the remaining cases. Our findings were similar to those previously reported that show the majority of patients with pancreatic involvement by hematologic malignancies have DLBCL, with low-grade B-cell lymphomas the next most frequently encountered.

Pancreatic involvement by non-B-cell hematologic malignancies, including but not limited to Hodgkin lymphoma, myeloid (granulocytic) sarcoma, plasmacytoma, T-cell lymphoma, and anaplastic large cell lymphoma, consists predominantly of individual case reports and small case series.

Of our 42 cases, 10 were primarily isolated to the pancreas with an additional 7 limited to the peripancreatic zone (by clinical and radiologic findings). This percentage of cases localized to the pancreas and peripancreatic region (17/42 [40%]) seems greater than expected given the generally systemic nature of hematologic malignancies and much lower reported percentage of primary pancreatic lymphoma. This finding, however, is not entirely surprising because patients with widespread hematologic malignancies rarely undergo pancreas biopsy. Pancreatic sampling is essentially performed only in patients without a more easily accessible mass. In fact, in only 9 of the 42 pancreatic hematologic malignancies sampled in our patients was a diagnosis of a hematologic malignancy strongly favored over all other possible diagnoses.

Given the nonspecific nature of clinical symptoms associated with pancreatic lesions, it is possible that many patients with known widespread hematologic malignancies have concurrent involvement of the pancreas. In an attempt to determine how often the pancreas is involved in patients with widespread hematologic malignancies, we searched autopsy records for all decedents with existing or treated hematologic malignancies at the time of death. We identified 153 with hematologic malignancies present at the time of death, of which 13.1% (20/153) had some degree of pancreatic involvement. Furthermore, we found that 18% (15/85) of NHLs involved the pancreas. The percentage of cases we found with pancreatic involvement is within the 5% to 30% reported with gastrointestinal involvement in the literature.

Pancreatic involvement by NHL is more commonly the result of local extension or secondary involvement by widespread disease as opposed to development of a primary lesion. Despite this fact, much of the literature on pancreatic involvement by a hematologic malignancy focuses on primary pancreatic lymphoma, likely owing to its propensity to be clinically and radiologically mistaken for pancreatic adenocarcinoma. We identified 6 cases of primary pancreatic lymphoma in our study (14%), with each case manifesting as a pancreatic head mass. This finding is similar to that...
described in the literature, although cases manifesting in the body, tail, and diffusely throughout the pancreas have been reported. There were no cases of primary pancreatic lymphoma in our autopsies, similar to the literature in which the majority of reported cases were from surgical specimens with only rare reports at autopsy. It is unclear if this is due to the rarity of primary pancreatic lymphoma or whether some tumors extended beyond the pancreas by the time of death. It is interesting to note that the number of cases of primary pancreatic lymphoma reported has ballooned since the early 1990s, likely owing to the improvement in radiologic and biopsy techniques during that period. However, it has been suggested that up to 55% of all cases reported in the literature do not represent true primary pancreatic lymphoma, but rather extension from peripancreatic lymph nodes or more widespread involvement.

When hematologic malignancies are primarily limited to the pancreas, there is an increased likelihood of mistaking the tumor for pancreatic adenocarcinoma. We found that in 15 cases (36%) of 42, a hematologic malignancy was not suspected before tissue diagnosis, resulting in 4 resections for presumed pancreatic adenocarcinoma. In comparing clinical and radiologic characteristics of patients with hematologic malignancies with the characteristics of patients with adenocarcinoma, we determined that some preoperative features are useful to raise suspicion for a hematologic malignancy, even when a tumor is localized to the pancreas. Patients with a hematologic malignancy of the pancreas were statistically more likely than patients with pancreatic adenocarcinoma to have younger age, larger tumors, lower CA19-9 level, increased incidence of B symptoms, a history of hematologic malignancy (regardless of disease-free interval), and a lack of jaundice or diabetes mellitus. B symptoms encountered in patients with hematologic malignancies of the pancreas included a combination of weight loss, fever, and night sweats, while only weight loss was noted in patients with pancreatic adenocarcinoma. Additional findings seen in association with a hematologic malignancy of the pancreas included elevated LD and serum β₂M levels and demonstration of a mass showing contiguous involvement of the spleen. Unfortunately, we were not able to compare LD and β₂M levels with those in cases of adenocarcinoma because the laboratory values were not frequently checked in these cases.

Our findings are in agreement with other studies examining clinical symptoms seen in patients with hematologic malignancies. Clinical symptoms reported to be diagnostically useful in the literature include isolated abdominal pain, increased presence of B symptoms, and a palpable mass without jaundice. We reevaluated features that we found to be significantly different between groups (young age, large tumor, low CA19-9 level, B symptoms, history of hematologic malignancy, and lack of jaundice or diabetes mellitus) in the 4 patients who underwent a potentially avoidable pancreatic resection for presumed pancreatic adenocarcinoma. Three patients had 1 or more of these features and could have been identified for more aggressive attempts at preoperative or intraoperative sampling.

The most commonly used methods for the preoperative tissue evaluation of pancreatic lesions are EUS-FNA and core needle biopsies. EUS-FNA of the pancreas has been shown to be a safe and reliable technique for diagnosis of pancreatic masses that has evolved during the past 20 years and is now one of the most commonly used diagnostic modalities at many centers. During the last 5 years, EUS-FNA has become much more widely available at the Ohio State University Medical Center. In our patients, 27 of 42 hematologic malignancies were diagnosed before this time. It is likely that more patients would have undergone EUS-FNA rather than core biopsy had it been more readily available. Even though only 5 patients in our series had an EUS-FNA for diagnosis of a hematologic malignancy, 4 were diagnostic. Core needle biopsy was very useful in correctly diagnosing hematologic malignancies, with 26 (93%) of 28 biopsy specimens accurately identified. In the remaining 2 biopsy specimens, one was nondiagnostic (owing to necrosis) and the other was called benign (slide unavailable for review). Both cases resulted in surgical resection. Despite the diagnostic usefulness of these techniques, the majority of resected pancreatic adenocarcinomas at our institution were correctly identified without preoperative pathologic sampling.

It is unclear how the increased use of EUS-FNA will change this practice pattern. Because chronic pancreatitis frequently surrounds adenocarcinoma, resection is still typically indicated in patients with suspicious clinical and radiographic findings, even with benign biopsy or FNA findings. In patients with a clear history of a hematologic malignancy or widespread disease, pancreatic sampling was also not performed. In patients with no history and/or disease limited to the pancreas, preoperative sampling was vital to ensure correct treatment. We found most cases of hematologic malignancies were correctly identified for sampling by radiologic and clinical findings, with only 4 resections performed that were not necessarily indicated.

A wide variety of hematologic malignancies can involve the pancreas and, on rare occasion, may manifest as an isolated pancreatic mass. Our results suggest that patients with younger age, larger tumors, B symptoms, low CA19-9 level, and lack of jaundice or diabetes mellitus should be extensively worked up before resection by rebiopsy or frozen section analysis if diagnostic material is not obtained on initial evaluation. Although routine preoperative sampling is not considered necessary in every case, in the setting of the aforementioned findings, the suspicion for a hematologic malignancy...
involving the pancreas should be raised and preoperative or, if necessary, intraoperative diagnosis is vital.

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