Histiocytic Sarcoma of the Bile Duct

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Abstract

An 80-year-old man was admitted with anorexia, a high fever and general icterus. Laboratory examinations revealed remarkable inflammation and elevation of liver/biliary enzymes. Computed tomography (CT) showed a high-density lesion in the bile duct, and endoscopic retrograde cholangiopancreatography (ERCP) disclosed an oval filling defect mimicking choledocholithiasis. Plastic stents were inserted to treat the acute cholangitis; however, the patient’s symptoms recurred. An erythematous hypervascular mass obtained with a balloon catheter contained numerous pleomorphic histiocytic cells with eosinophilic cytoplasm, remarkable anisonucleosis and occasional mitoses. A diagnosis of histiocytic sarcoma (HS) was made based on the results of intensive immunohistochemistry. Monoclonal rearrangement of the IGH and TCRG genes, IGH split and IGH/BCL2 fusion was negative, although polysomy 8, 14, and 18 was detected. The patient was treated conservatively and died of the disease 20 months after the initial diagnosis. To the best of our knowledge, this is the first case of bile duct HS. This case, which involved numerical alterations of chromosomes, presented with CT and ERCP findings similar to those of choledocholithiasis.

Key words: histiocytic sarcoma, bile duct, fluorescence in situ hybridization, polysomy, choledocholithiasis

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Introduction

Histiocytic sarcoma (HS), also formerly known as “true” histiocytic lymphoma, is a rare malignant proliferation of cells exhibiting the morphological and immunophenotypic features of mature tissue histiocytes (1). The diagnosis of histiocytic sarcoma relies predominantly on the confirmation of a histiocytic lineage and the exclusion of other poorly differentiated tumors, such as lymphoma, carcinoma, sarcoma and melanoma (2). Prior to the development and widespread use of immunohistochemistry and the availability of molecular genetic tools, HS was not an uncommon diagnosis (3). However, only limited numbers of bona fide HS cases have been reported since the WHO classification of hematopoietic and lymphoid tissue tumors was issued in 2001 (4). The most common primary sites of HS are the lymph nodes, skin and gastrointestinal tract (5, 6), with other reported primary sites including the spleen, central nervous system, bone marrow, nasal cavity, lungs and thyroid (3, 5). Interestingly, some cases of HS arise during or after the appearance of B-cell lymphoma (particularly follicular lymphoma) and precursor B-cell acute lymphoblastic leukemia (7-9) and involve the monoclonal rearrangement of the immunoglobulin heavy chain gene (IGH) and T-cell receptor-gamma gene (TCRG) (8, 10) in addition to IgH/BCL2 gene fusion (7). We herein describe a case of HS of the bile duct. To the best of our knowledge, there have been no such previous case reports in the literature.

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Case Report

An 80-year-old man with senile dementia presented to the emergency room with complaints of anorexia, a high fever and general icterus. His past medical history included a lumbar compression fracture one year earlier. In addition, he had been admitted our hospital two years before the present illness due to megaloblastic anemia, which had resolved with appropriate treatment. He denied abdominal pain, and neither hepatosplenomegaly nor abdominal tenderness were noted on abdominal palpation. The laboratory examinations revealed remarkable inflammation and elevation of liver/biliary enzymes in the serum: white blood cell count, 10,900/μL (normal range, 3,600-9,600); red blood cell count, 397×10^10/μL (400-552×10^10); hemoglobin, 12.3 g/dL (13.2-17.2); total protein, 5.9 g/dL (6.7-8.3); albumin, 3.1 g/dL (4.0-5.0); total bilirubin, 5.9 mg/dL (0.3-1.2); aspartate aminotransferase, 106 IU/L (13-33); alanine aminotransferase, 196 IU/L (6-30); lactate dehydrogenase, 133 IU/L (119-359); alkaline phosphatase, 1,365 U/L (100-340); and C-reactive protein, 14.49 mg/dL (≤0.30). Computed tomography (CT) revealed bile duct dilatation starting from the upper common bile duct and extending to the intrahepatic bile duct with a high-density lesion in the lower bile duct and gallstones in the gallbladder. No other mass lesions were detected on the chest or abdominal CT images. The patient was diagnosed as having acute obstructive suppurative cholangitis (AOSC) and admitted for emergency endoscopic biliary drainage. Endoscopic retrograde cholangiopancreatography (ERCP) revealed an oval filling defect measuring 2.5 cm in diameter, indicating impaction in the common bile duct mimicking choledocholithiasis (Fig. 1a). The patient was diagnosed with AOSC, and, considering the difficulty of removing the stones at such an advanced age, endoscopic sphincterectomy was performed and two plastic straight stents were inserted into the common bile duct with good drainage. He recovered rapidly with resolution of all signs and symptoms and was discharged home nine days post-ERCP.

However, the patient was readmitted twice for two months for a recurrence of AOSC due to stent occlusion. On the third admission, emergency ERCP revealed multiple de-
Effects throughout the bile duct, which suggested a diagnosis of cholangiocarcinoma with hemobilia or mucobilia (Fig. 1b). As we attempted to remove these defects using a 15-mm wire-guided balloon catheter, an erythematous, hypervascular tumor was obtained (Fig. 1c). Plastic stents were inserted into the common bile duct for drainage, and thereafter the patient recovered rapidly.

Immunostaining was performed using an autostainer (Bond-Max, Leica Microsystems, Wetzler, Germany). The immunohistochemical stains were interpreted as positive if at least 50% of the neoplastic cells showed immunoreactivity, focally positive if 5-50% of the tumor cells showed immunoreactivity and negative if less than 5% of the tumor cells showed immunoreactivity. A histological examination of the mass in the bile duct demonstrated dense collections of pleomorphic histiocytes with eosinophilic cytoplasm, remarkable anisonucleosis, an irregular nuclear shape and occasional mitoses (Fig. 1d). The immunohistochemical analysis revealed that the tumor cells were positive for CD68 (clones KP1 and PG-M1), focally positive for CD163, lysozyme and S100 and negative for CD1a, CD3e, CD4, CD15, CD20, CD21, CD30, CD31, CD35, CD45, CD45RO, CD56, CD79a, cytokeratins (clones AE1/3 and CAM5.2), neuron-specific enolase, alpha-fetoprotein, hepatocyte, chromogranin, synaptophysin, neurofilament, factor VIII, HMB45 and Melan-A (Fig. 2a-d). Ki67 labeled approximately 20% of the tumor cells. These histological and immunohistochemical characteristics were consistent with a diagnosis of HS.

In order to explore a possible association with B-cell or T-cell lymphoma in this case, polymerase chain reaction (PCR) procedures were performed to analyze IGHI and TCRG rearrangement using the paraffin-embedded tumor specimen. The DNA extraction and PCR protocols were based on previous reports (11, 12). The PCR analyses, however, showed rearrangement of neither clonal IgH nor TCRG in this case.

Furthermore, the tissue fluorescence in situ hybridization (FISH) procedures were performed using the paraffin-embedded biopsy specimen employing a previously described method (12). The cut-off value for each FISH probe was set as the mean+3 SDs by counting the number of signals or fusions in more than 100 cells obtained from ten reactive lymph nodes. The FISH probes were as follows: IGHI (14q32) Break-Apart Rearrangement Probe (Kreatech Diagnostics, Amsterdam, Netherland, cut-off value, 9%), BCL2 (18q21)/IGH (14q32) Fusion Probe (Kreatech Diagnostics, 10%) and Satellite Enumeration Probe (Kreatech Diagnostics, cut-off value, 9%). The FISH analyses revealed neither IGHI gene split nor IGHI/BCL2 gene fusion (Fig. 3a, b).
However, the number of FISH signals in the tumor cells apparently increased; 33% of the tumor cells had an increased number of \textit{IGH} signals (cut-off value, 11%) and 55% possessed an increased number of \textit{BCL2} signals (12%). This finding strongly suggested the presence of polysomy 14 and 18. The presence of polysomy 8 and 18 was further confirmed by FISH using a Satellite Enumeration Probe for the centrometric region of chromosomes 8 and 18, which showed an increased number of FISH signals (25% and 31%, respectively; Fig. 3c, d). No FISH probe for the centrometric region of chromosome 14 was commercially available.

After obtaining the final diagnosis, contrast-enhanced CT performed to examine HS progression detected neither metastasis nor local invasion in the liver parenchyma. The patient was treated with best supportive care due to his generally poor condition and advanced age. CT images obtained six months after the initial diagnosis revealed tumor progression and invasion in the liver parenchyma, and recurrent cholangitis due to stent occlusion occurred four times before the patient was transferred to another hospital 19 months after the initial diagnosis. He died of general debility one month after the transfer. An autopsy was refused by his family.

Discussion

Since the WHO classification of hematopoietic and lymphoid tissue tumors was issued in 2001, approximately one hundred HS cases have been reported (4). Immunostaining is essential for making a definitive diagnosis and distinguishing HS from other neoplasms, such as large cell lymphoma, melanoma and carcinoma (1). The International Lymphoma Study Group has suggested four categories for the immunophenotypic classification of histiocytic and dendritic cell neoplasms: histiocytic sarcoma (CD68+, lysozyme−, CD1a−, S100−, CD21 or CD35), Langerhans cell tumor/sarcoma (CD68−, lysozyme−, CD1a+, S100+, CD21 or CD35), interdigitating cell sarcoma/tumor (CD68−, lysozyme+, CD1a+, S100−, CD21 or CD35) and follicular
dendritic cell tumor (CD68⁺, lysozyme, CD1a, S100⁺, CD21⁺ or 35⁺) (5). In addition, CD163, a hemoglobin scavenger receptor, has been shown to identify histiocytic cells with a high degree of specificity and has become a useful marker for diagnosing histiocytic sarcoma (10). The immunohistochemical findings in the present case (positive for CD68 (clones KP1 and PG-M1), focally positive for CD163, lysozyme and S100 and negative for other markers, including CD21, CD35 and CD1a) strongly supported the diagnosis of HS. An association between HS and various types of lymphoma has been reported (7-9), and some HS cases have been reported to involve monoclonal IGH or TCRG rearrangement (8, 10) and IgH/BCL2 gene fusion (7), providing evidence for a common clonal origin of HS and a variety of hematopoietic neoplasms. Our patient did not exhibit monoclonal IgH and TCRG rearrangement, IGH gene split or IGH/BCL2 gene fusion. However, the FISH analysis strongly suggested the presence of polysomy 8, 14, and 18, which may be associated with HS tumorigenesis. Chromosomal alterations in HS have rarely been described, and only one case of polysomy 8 has been reported (13); this abnormality was also observed in our case. Although the reason for the gain in chromosome 8 in that case was unknown, this feature has been described in a series of myeloid malignancies corresponding predominantly to neoplasms with monocytic differentiation (14, 15), and its detection in HS supports the myelomonocytic origin of the disease and sheds light on the genetic alterations underlying this uncommon neoplasm (13).

Several factors, including the clinical stage of the disease, are associated with the prognosis of HS, and patients with clinically localized disease reportedly have a good prognosis (3). Primary treatment consists of surgery, radiotherapy and systemic chemotherapy (3, 5). Recently, allogeneic hematopoietic stem cell transplantation with the administration of thalidomide has been performed, albeit with limited efficacy (16). Since the tumor was localized and the size of the lesion was relatively small in our case, the use of aggressive therapy may have been associated with longer patient survival. However, due to the patient’s advanced age and comorbidities, we treated him with best supportive care.

To date, 15 HS cases (including the present case) involving the gastrointestinal tract have been reported, and, to the best of our knowledge, the present case is the first case of HS in the bile duct (Table). The 15 cases included seven men and eight women with an age at diagnosis ranging from 20 to 89 years (mean: 51 years, median: 55). This indicates that gastrointestinal HS can occur in both young and old individuals, and there seems to be no sex predilection. The tumors were located in the digestive tract, with sizes ranging from 2 to 20 cm (mean: 7.8 cm). The survival time, excluding cases with unknown courses, ranged from 2 to 120 months (one-year survival rate: 70% and median survival time: 21 months). The prognosis of the disease is unlikely to be governed by the status at the primary site. We initially misinterpreted the patient’s bile duct tumor to be choledocholithiasis. Other differential diagnoses included

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**Table. Histiocytic Sarcoma Cases of the Gastrointestinal Tract Reported since 2001**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/ Sex</th>
<th>Site</th>
<th>Initial symptoms</th>
<th>Presenting signs or findings</th>
<th>Tumor size (cm)</th>
<th>Stage at presentation</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Follow-up (months)</th>
<th>Reference†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>62/F</td>
<td>Stomach</td>
<td>Abdominal pain</td>
<td>Large ulcer within the stomach</td>
<td>20</td>
<td>NA</td>
<td>Surgery</td>
<td>DOD</td>
<td>7</td>
<td>[9]</td>
</tr>
<tr>
<td>2</td>
<td>28/F</td>
<td>Stomach/Jejunum</td>
<td>Abdominal pain</td>
<td>Wall thickness</td>
<td>5, 7</td>
<td>NA</td>
<td>Surgery/ Chemotherapy</td>
<td>AW</td>
<td>36</td>
<td>[2]</td>
</tr>
<tr>
<td>3</td>
<td>56/M</td>
<td>Small intestine</td>
<td>NA</td>
<td>Mass lesion</td>
<td>NA</td>
<td>I</td>
<td>Surgery/ Chemotherapy</td>
<td>DOD</td>
<td>60</td>
<td>[5]</td>
</tr>
<tr>
<td>4</td>
<td>46/F</td>
<td>Small intestine</td>
<td>NA</td>
<td>Mass lesion</td>
<td>NA</td>
<td>I</td>
<td>Surgery</td>
<td>NA</td>
<td>NA</td>
<td>[5]</td>
</tr>
<tr>
<td>5</td>
<td>NA/M</td>
<td>Small intestine</td>
<td>NA</td>
<td>Mass lesion</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>[5]</td>
</tr>
<tr>
<td>6</td>
<td>NA/M</td>
<td>Small intestine</td>
<td>NA</td>
<td>Mass lesion</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>[5]</td>
</tr>
<tr>
<td>7</td>
<td>68/F</td>
<td>Small intestine</td>
<td>Nausea, and vomiting</td>
<td>Mass lesion</td>
<td>5</td>
<td>II</td>
<td>Surgery</td>
<td>NA</td>
<td>NA</td>
<td>[6]</td>
</tr>
<tr>
<td>8</td>
<td>58/M</td>
<td>Terminal ileum</td>
<td>Abdominal pain</td>
<td>Intestinal obstruction and mass lesion</td>
<td>8</td>
<td>IV</td>
<td>BSC</td>
<td>AW</td>
<td>12</td>
<td>[3]</td>
</tr>
<tr>
<td>9</td>
<td>89/M</td>
<td>Colon/Stomach</td>
<td>Abdominal pain with bloody diarrhea</td>
<td>NA</td>
<td>12</td>
<td>II</td>
<td>BSC</td>
<td>DOD</td>
<td>5</td>
<td>[3]</td>
</tr>
<tr>
<td>10</td>
<td>20/F</td>
<td>Colon</td>
<td>Abdominal pain</td>
<td>Ulcerating mass</td>
<td>6</td>
<td>IV</td>
<td>Chemotherapy</td>
<td>DOD</td>
<td>15</td>
<td>[10]</td>
</tr>
<tr>
<td>11</td>
<td>55/M</td>
<td>Colon</td>
<td>NA</td>
<td>Mass lesion with intussusception</td>
<td>9.5</td>
<td>IV</td>
<td>Surgery</td>
<td>DOD</td>
<td>2</td>
<td>[10]</td>
</tr>
<tr>
<td>12</td>
<td>40/F</td>
<td>Rectum</td>
<td>Hematochezia, abdominal pain, and weight loss Hematochezia and abdominal pain</td>
<td>NA</td>
<td>7</td>
<td>II</td>
<td>BSC</td>
<td>AW</td>
<td>21</td>
<td>[3]</td>
</tr>
<tr>
<td>13</td>
<td>27/F</td>
<td>Rectum</td>
<td>NA</td>
<td>Mass lesion</td>
<td>9</td>
<td>I</td>
<td>Chemotherapy</td>
<td>AW</td>
<td>120</td>
<td>[3]</td>
</tr>
<tr>
<td>14</td>
<td>40/F</td>
<td>Anus</td>
<td>NA</td>
<td>Mass lesion</td>
<td>2</td>
<td>I</td>
<td>BSC</td>
<td>NA</td>
<td>NA</td>
<td>[3]</td>
</tr>
<tr>
<td>15</td>
<td>80/M</td>
<td>Bile duct</td>
<td>NA</td>
<td>Mass lesion</td>
<td>2.5</td>
<td>I</td>
<td>BSC</td>
<td>DOD</td>
<td>20</td>
<td>Present case</td>
</tr>
</tbody>
</table>

NA: not available, BSC: best supportive care, AW: alive and well, DOD: dead of disease, *: synchronous with diffuse large B cell lymphoma, and †: references of the text
cholangiocarcinoma and extranodal non-Hodgkin’s lymphoma of the bile duct. These tumors usually appear on CT or MRI as well-defined mass lesions, as in our case, or the presence of diffuse wall thickening of the bile duct (17). Therefore, it is difficult to distinguish HS from non-Hodgkin’s lymphoma and cholangiocarcinoma employing solely radiographic imaging. Hence, obtaining a pathological diagnosis of the tumor specimen is very important for determining the differential diagnosis. Most bile duct tumors are diagnosed intra- or postoperatively based on histopathology. This case was particularly informative because the HS diagnosis was made using the specimen obtained preoperatively with ERCP.

In summary, we herein presented the first case report of HS in the bile duct with the onset of obstructive jaundice and CT and ERCP findings resembling choledocholithiasis. We were able to diagnose this case based on the analysis of the biopsy specimen without performing surgery. This case draws our attention to the fact that hematopoietic tumors can occur in cases of obstructive jaundice.

The authors state that they have no Conflict of Interest (COI).

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KM and AM contributed equally to this work.

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