Synchronous Granulocytic Sarcoma of the Gallbladder and Stomach as the Initial Presentation of Chronic Myeloid Leukemia: A Case Report and Review of the Literature

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Abstract

Granulocytic Sarcoma (GS) is a rare extramedullary tumor composed of myeloid progenitor cells. GS usually arises with a diagnosis of acute myeloid leukemia, although it also infrequently occurs during the accelerated or blast crisis phases of Chronic Myeloid Leukemia (CML). Involvement of gastrointestinal or gallbladder is rare. We report the first case of synchronous GS of gallbladder and stomach as the initial presentation of CML in the blast crisis in a patient who presented with acute upper abdominal discomfort and hematemesis. Emergency gastroscopy and exploratory laparotomy revealed two gastric masses and one lesion on the surface of gallbladder, which were suspected of mesenchymoma. Combining with the result of complete blood count, the patient was initially diagnosed with CML with other neoplasm. However, the results of pathological examination, immune histochemistry and in situ hybridization test of specimens did not support a diagnosis of mesenchymoma. Finally, with Bone Marrow (BM) aspiration, flow cytometry of the BM aspirate, and fluorescence in situ hybridization test for **bcr-abl** oncogene, we made the diagnosis of CML with GS. It is very difficult to differentiate between CML with GS or CML with other malignancies. A careful work-up using immune histochemistry and cytogenetic/molecular testing is critical to reach a correct diagnosis.

Keywords: Granulocytic sarcoma; Chronic myeloid leukemia; Stomach; Gallbladder

Introduction

Granulocytic Sarcoma (GS), or myeloid sarcoma, is a rare extramedullary tumor that is composed of immature myeloid cells [1]. GS usually arises during the course of Acute Myeloid Leukemia (AML), although it also infrequently occurs during the accelerated or blast crisis phases of Chronic Myeloid Leukemia (CML) and Myelodysplastic Syndrome (MDS), or as an isolated event without bone marrow involvement [2-4]. The most common sites of involvement are the skin, soft tissues, lymph nodes, and bone, while Gastrointestinal (GI) involvement is rare. Thus, we report what is, to the best of our knowledge, the first case of synchronous GS of the gallbladder and stomach in a patient with CML in the blast crisis phase.

Case Presentation

A 53-year-old woman presented to our emergency room complaining of a 12-h history of upper abdominal discomfort and nausea, which was followed by three episodes of hematemesis as well as dizziness, fatigue, chills, abdominal distension, acid reflux, and melena. We did not detect any evidence of headache, hemoptysis, chest pain, hematochezia, or neurological deficits. The patient’s health was generally good, with no history of abdominal surgery, night sweats, anorexia, or family history of malignancy. A physical examination revealed a mildly distended abdomen with mild upper abdominal tenderness, but without rebound tenderness, and her spleen was palpable at 6 cm...
below the left rib. A Complete Blood Count (CBC) revealed a White Blood Cell (WBC) count of 266.96 × 10^9/L, Hemoglobin (Hb) levels of 51 g/L, and a Platelet (PLT) count of 312 × 10^9/L. We also detected Blood Cell (WBC) count of 266.96 × 10^9/L, Hemoglobin (Hb) levels below the left rib. A Complete Blood Count (CBC) revealed a White Blood Cell (WBC) count of 266.96 × 10^9/L, Hemoglobin (Hb) levels of 51 g/L, and a Platelet (PLT) count of 312 × 10^9/L. We also detected Hepatitis C Virus (HCV) RNA levels of 2.6 × 10^6 IU/mL. Chest radiography revealed bilateral pleural effusion, and we diagnosed the patient with gastrointestinal hemorrhage and suspected CML, which we treated using transfusion (2 units of packed red blood cells) and the administration of sandostatin, nexium, and antibiotics.

Unfortunately, the patient’s symptoms did not significantly improve and we performed emergency gastroscopy, which revealed a bleeding mass in the interface between the gastric antrum and gastric body (Figure 1A) and another mass in the interface between gastric fundus and gastric body (Figure 1B). Endoscopic hemostasis using titanium clips did not provide satisfactory results, and the patient was transferred to our Department of Gastrointestinal Surgery for further treatment. Despite the shock, hemostasis, and antacid treatments, the patient experienced two episodes of hematemesis, her blood pressure decreased to 75/36 mmHg, and she began to feel drowsy. Thus, emergency exploratory laparotomy was performed, and the surgeons found two sub mucous eminent lesions: one in the interface between the gastric antrum and gastric body (1.5 cm × 1.5 cm) and the other in the interface between the gastric fundus and gastric body (1.0 cm × 0.8 cm) (Figure 1C). Based on a visual inspection, the masses were initially suspected to be mesenchymoma, although the surgeons also detected a similar nodule (0.8 cm × 0.6 cm) on the gallbladder surface during the intraoperative exploration (Figure 1C). A careful examination did not detect any other masses in the duodenum, small intestine, colon, and rectum. Approximately 500 mL of canary yellow ascites were detected in the peritoneal cavity, and the liver was swollen with dull margins and tough surface nodules. The spleen was also enlarged and could be extended to the umbilicus. Based on these findings, the operative diagnoses were a bleeding mass in the interface between the gastric body and gastric antrum, hemorrhagic shock, a mass in the interface between the gastric fundus and gastric body, a lesion on the gallbladder surface, CML with splenomegaly, and HCV infection with cirrhosis. The three lesions and gallbladder were removed and sent for pathological examination, as well as immune histochemistry and in situ hybridization testing (Figure 2). The histological examinations of the gastric and gallbladder masses revealed infiltrative grown and diffuse distributed neoplastic cells with large irregular nuclei and small nucleoli, as well as clear mitotic figures and dominant atypia figures. The immune histochemistry results were positive for CD43 and CD99, partly positive for CD163, CD68, CD117, and Cyclin D1; individually positive for LCA; 80% positive for Ki-67; and negative for CD20, CD79a, CD2, CD3, CD4, PAX-5, CD30, ALK, CD34, MPO, CD61, SOX-11, CD21, CD10, Bcl-6, MUM-1, TdT, CD56, S-100, HMB-45, CK, DOG-1, CD30, EMA, and CD123. In situ hybridization testing revealed negative results for Epstein–Barr encoding regions and IgH rearrangement. As the pathological results did not support a diagnosis of mesenchymoma or lymphoma, the masses etiology remained unclear, and the possibility of comorbid CML required further verification.

Table 1: Cases of granulocytic sarcoma as the extramedullary blast crisis of CML in the literature review.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age (years)</th>
<th>CML phase at diagnosis</th>
<th>Bone marrow status at extramedullary blast crisis</th>
<th>Location of granulocytic sarcoma</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ai DI, et al. [14]</td>
<td>23</td>
<td>Chronic</td>
<td>Complete molecular response</td>
<td>Right inguinal lymph nodes</td>
<td>Imatinib-based combined chemotherapy, allogeneic hematopoietic stem cell transplantation, donor lymphocyte infusions and dasatinib treatment</td>
</tr>
<tr>
<td>Simpson E, et al. [12]</td>
<td>62</td>
<td>Chronic</td>
<td>Major molecular response, complete cytogenetic response</td>
<td>Small bowel, brain</td>
<td>Imatinib</td>
</tr>
<tr>
<td>Jabbour E, et al. [10]</td>
<td>54</td>
<td>Chronic</td>
<td>Complete cytogenetic response</td>
<td>Skin</td>
<td>Interferon, Imatinib</td>
</tr>
<tr>
<td>Maloula M, et al. [9]</td>
<td>17</td>
<td>Chronic</td>
<td>Complete cytogenetic response</td>
<td>Central nervous system</td>
<td>Imatinib</td>
</tr>
</tbody>
</table>

Table 2: Cases of granulocytic sarcoma in the gallbladder in the literature review.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age (years)</th>
<th>Bone marrow involvement</th>
<th>Manifestation</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bartley AN, et al. [20]</td>
<td>63</td>
<td>No</td>
<td>Jaundice</td>
<td>Surgery (hepatopancreatoduodenectomy) + chemotherapy</td>
<td>Did not develop acute leukemia during the follow up of 4 years</td>
</tr>
<tr>
<td>Ojima H, et al. [21]</td>
<td>33</td>
<td>No</td>
<td>Back pain and sweating</td>
<td>Surgery (open cholecystectomy)</td>
<td>Death from dissemination of myeloid neoplasm</td>
</tr>
</tbody>
</table>
To make a definite diagnosis, the patient underwent Bone Marrow (BM) aspiration, flow cytometry of the BM aspirate, and Fluorescence In Situ Hybridization (FISH) testing for the \textit{bcr-abl} oncogene. The BM smear results revealed blasts (1%), progranulocytes (1%), myelocytes (13%), metamyelocytes (19%), granulocytes (24%), eosinophils (4%), basophils (2%), lymphocytes (6%), normoblasts (6%), and no plasma cells or monocytes (Figure 3). Flow cytometry of the BM aspirate revealed a significant increase in granulocytes (92.2%) and relative decreases in the lymphocyte populations (1.2%), with 63.6%, 24.6%, and 9.0% for the T-cell, B-cell, and NK-cell populations, respectively. We did not detect a significant increase in the proportions of blasts or abnormal cells. The FISH test results were positive for \textit{bcr-abl1} rearrangement (160/200). Based on these findings, and the low proportion of blasts in the BM aspirate (<5%), we reached a final diagnosis of CML with synchronous GS of the gallbladder and stomach. Therefore, we administered hydroxyurea and benzbramaron to reduce the patient’s WBC count and increase the pH of her urine, respectively. The patient’s WBC count reached 11.33 × 10^9/L after 8 days of treatment using hydroxyurea. A second-generation tyrosine kinase inhibitor was recommended to the patient for treating her CML, although she selected first-generation imatinib (400 mg/day) based on the drugs’ costs.

At 2 months after the diagnosis of CML, the patient re-visited the emergency room complaining of a fever, chills, and dizziness. However, the patient did not have gastrointestinal symptoms, melena, hematochezia, or hematemesis. A physical examination revealed unremarkable findings, with the exception of an elevated body temperature (38.5°C). A CBC revealed a WBC count of 1.19 × 10^9/L, a red blood cell count of 3.04 × 10^12/L, Hb levels of 92 g/L, and a PLT count of 32 × 10^9/L. Chest computed tomography suggested a bilateral inflammatory lung disease, with scattered patches of low-density areas and bilateral loculated pleural effusion. We also observed pericardial and peritoneal effusion. The granulocytopenia was very likely related to imatinib-induced bone marrow depression, and the patient’s refusal of a second-generation tyrosine kinase inhibitor and irregular hemogram monitoring likely contributed to this granulocytopenia. Thus, we stopped the imatinib based on her granulocytopenia and pulmonary infection, and started anti-infection therapy. The patient’s hemogram and temperature values subsequently normalized, and she was discharged from the hospital. Unfortunately, she developed a serious systemic infection within 2 weeks after her discharge, rapidly progressed to septic shock, and subsequently died.

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Discussion

GS is usually associated with AML, is less frequently observed in cases of CML or other myeloproliferative disorders, and is even rarer as isolated GS without BM involvement [4,5], as the initial manifestation of CML in the blast crisis phase [6], and as extramedullary blast crisis occurring after CML remission [7,8]. Among the 32 GS cases that were reviewed by Paydas et al., 11 cases were associated with CML, including 6 cases in patients with chronic-phase CML. 3 cases in patients with accelerated-phase CML, and 2 cases in patients with CML in the blast crisis phase [3]. Given the rarity of GS as the initial manifestation of CML, only a few reports have described GS as the first presentation of CML (in the thigh, groin, nose, kidney, iliac bone, and larynx) [4,7,9-13]. To the best of our knowledge, ours is the first report of synchronous GS in the gallbladder and stomach as the initial presentation of the extramedullary blast crisis in chronic-phase CML.

The existing literature only includes one case of extramedullary blast crisis as the initial manifestation of CML (enlarged right inguinal lymph nodes) and four cases of GS as the extramedullary blast crisis during complete cytogenetic response achieved using imatinib therapy (Table 1) [9,10,12,14,15]. In addition, it can be very difficult to morphologically diagnose GS as the initial manifestation in patients without a concurrent/previous myeloid neoplasm [16]. In the present case, the GS was initially suspected of being mesenchymoma based on the masses’ endoscopic and intraoperative findings. Unfortunately, the morphological features of GS can mimic those of other malignancies, and misdiagnoses of lymphoma or other malignancies are common [3,16-18]. Furthermore, even if a diagnosis of CML can be made when the masses are detected, it can be very difficult to differentiate between CML with GS or CML with other malignancies, because CML can coexist with other malignancies (e.g., gastric cancer). Involvement of the GI tract usually occurs in the advanced stages of different hematological malignancies, or as a complication of chemotherapy and radiotherapy, and leukemia-related GI complications have recently become relatively common. Therefore, similar to our process in the present case, a careful work-up using immune histochemistry and cyogenetic/molecular testing is critical to reach a correct diagnosis.

Although GI involvement in GS is very rare, infiltration of the GI tract can produce polypoid masses, plaque-like thickening, ulcers, and diffuse masses that may cause obstruction, hemorrhage, perforation, or intussusception. Thus, the diagnosis of GS in the GI tract is poor, given the high rate of the previously mentioned early complications. Other manifestations include abdominal pain, liver infarction, pancreatitis, and bile duct obstruction. Neiman et al. reported that 4 of 61 GS cases presented with GI lesions, and presumed that involvement of the biliary tract would be extremely rare [19], and our literature review only identified two reported cases of GS in the gallbladder, which did not exhibit evidence of BM involvement (unlike our patient) (Table 2) [20,21]. Gastric GS is relatively more common (Table 3) [22-35], compared to GS in the gallbladder. Furthermore, GS lesions can present as either isolated or multiple lesions (synchronous or metachronous), and our case is, to the best of our knowledge, the first reported case with synchronous involvement of the gallbladder and stomach.

Conclusion

In conclusion, GS as the initial presentation of the extramedullary blast crisis in chronic-phase CML is an extremely rare disease, and synchronous GS in the gallbladder and stomach is even rarer. In addition, GS poses diagnostic challenges when it is the initial manifestation of CML, and can very easily be misdiagnosed. Thus, careful and comprehensive work-ups are needed to achieve an early and accurate diagnosis, and these work-ups should include morphological evaluation, immune histochemistry, flowcytometry, and cyogenetic and molecular testing. In cases of gastrointestinal GS in CML with emergent complications, local systemic therapies may be needed to treat the CML and avoid a grim prognosis.

References


