Review Article

Review on gall bladder myeloid sarcoma: a great masquerader

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Abstract: Pain in abdomen has wide differentials and narrowing down the clinical possibilities depends on type of pain, location, characterization which is usually assisted by imaging studies. Cholecystitis and cholelithiasis are amongst the common causes of acute abdomen. This study reviews the literature for the clinical characteristics, differential diagnosis, treatment and prognosis of reported cases of gallbladder myeloid sarcoma (GB-MS) who presented with abdominal symptoms. A total of 17 cases of GB-MS were studied. The median age was 52 years with age range of 23 to 84 years. All except 1 patient presented with abdominal symptoms. Based on imaging or pathological studies, 3 cases were initially confused with gallbladder lymphoma or cancer. Only 5 patients were treated with AML like chemotherapy. Treatment given included combinations of surgery, chemotherapy, and radiotherapy. None of the cases underwent HSCT for GB-MS. Seven patients were alive till the time of last F/U, 9 succumbed to death while F/U of 1 patient was not available. Irrespective of treatment protocol followed suggesting the poor prognosis in GB-MS cases. In conclusion, acute abdomen complicating blood malignancies is life threatening and can be devastating if not detected and treated in a timely fashion.

Keywords: Acute abdomen; myeloid sarcoma (MS); acute myeloid leukaemia (AML); chemotherapy; gallbladder

Introduction

Acute abdomen is one of the frequently encountered scenario in emergency room. Cholecystitis and cholelithiasis are amongst the common causes of acute abdomen. Approximately 5% of patients with acute leukemia can have acute abdomen due to variety of reasons (1). Term “Granulocytic sarcoma (GS)” was coined by Rappaport et al. in 1966, also commonly known as myeloid sarcoma (MS) and referred to as extramedullary solid deposits, found either in isolation or in association with leukemias. Most commonly, it has been reported to be associated with acute myeloid leukemia (AML). Other hematological conditions like myelodysplastic syndrome (MDS), chronic myelogenous leukemia (CML), acute lymphoblastic leukemia (ALL), and myelofibrosis (MF) are also reported to have leukemic deposits. MS commonly involves lymph nodes, skin, head and neck region, and orbit although almost any site may be involved (2-13). Gastrointestinal involvement is very rare site of MS. Gallbladder is even more rare to involve and often confused with other common gallbladder pathologies like cholecystitis, gallbladder cancer etc.

Clinically, depending on the time of occurrence, MS is categorized in three different groups as follows: (I) concurrent, when primary hematological disease and MS is diagnosed at the same time; (II) isolated, when MS is the sole finding without any evidence of leukemia/MPN etc.; (III) secondary, when MS develops in a known case of leukemia/MPN signifying either as a relapse or extramedullary blast crisis.
Methodology

A comprehensive search strategy was devised by two independent researchers. By using a combination of the medical subject heading (MeSH) terms “gallbladder and myeloid sarcoma”, “gallbladder and Chloroma”, “gallbladder and granulocytic sarcoma”, we searched the Ovid MEDLINE and Ovid Embase along with relevant citations between 1946 and 2019. English as a language restriction was applied and abstract and title of the all the citations were screened. Ultimately, the search showed in total 17 cases of myeloid leukemic infiltration of gallbladder.

Results

Patient characteristics

In total, we included 17 cases in our study cohort. Patient's age, sex, clinical presentations, and laboratory data are shown in Table 1. Of the 17 total patients, the median age was 52 years old with age range of 23 to 84 years.

Diagnostic challenges

Based on imaging or pathological studies, 3 cases were initially confused with gallbladder lymphoma or cancer. Later, review of the case confirmed them as gallbladder myeloid sarcoma (GB-MS) (14-16).

Other sites of involvement by leukemic infiltrates

We also reviewed other sites of involvement by leukemic infiltrates apart from gallbladder. We found MS involvement in pancreas, stomach, common bile duct, omental bursa, liver, cystic duct, lymph node and so on (Table S1).

Categorizations of TMS

By analyzing the clinical data, we divided the patients to either concurrent GB-MS cases (4 cases), isolated GB-MS cases (5 cases) and secondary GB-MS cases (8 cases). In patients with secondary and concurrent GB-MS, the underlying diseases were AML (5 cases), MF (4 cases), 2 CML (2 cases) and MDS (1 case).

Treatment strategies and outcome

Different authors treated their patients with different regimens including various combinations of cholecystectomy, chemotherapy and radiotherapy. Table S1 mentions different regimens used for treatment of GB-MS which clearly points to the fact that there is no unifying protocol driven treatment guidelines till now. Table S1 also mentions in detail the follow up details about the patients. Analysis also showed that 56.25% patients died during the same hospitalization or at follow up. Reasons were variable, sepsis, multiorgan failure, DIC, or disease progression.

Discussion

The available literature with regards to leukemic involvement of gastrointestinal tract has been known since long (16). The gastrointestinal tract is otherwise a rare site of MS involvement. Due to rarity, the exact frequency is relatively unknown. However, few autopsy series evaluating patients dying during acute phase of acute leukemia (both lymphocytic and myelocytic) have reported gastrointestinal tract involvement to be variable and anywhere ranging from 13% to 63% (17).

Diagnostic dilemma for ER physicians

As depicted in our study, GB-MS can be easily confused with benign conditions like cholecystitis, cholangitis or malignant conditions like adenocarcinoma. Though GB-MS is a rare entity, but ER physicians should always keep it in mind while evaluating any case of right upper quadrant pain or obstructive jaundice especially with a background history of myeloid leukemia or abnormal cells in peripheral circulation. Menasce et al. reported that almost in 75–86% nonleukemic patients, MS were initially misdiagnosed. Our review also shows the similar results which underscores the importance of educating ER physicians about this rare entity (18).

Other malignant differential diagnosis for acute abdomen/cholecystitis

There are various close differentials to GB-MS like: non-Hodgkin’s lymphoma (NHL), Ewing’s sarcoma, primitive neuroectodermal tumors, high risk small cell type stromal tumors, eosinophilic granuloma, and undifferentiated small cell lung cancer (18). Microscopically, MS cells can be easily confused with lymphoma cells. MS blast cells have acidophilic cytoplasm and are positive for CD 117, MPO and CD 43. Cytogenetic abnormalities like inv chromosome 16, t (8:21), lack of Auer rods, FAB M2, M4, M5 and
Table 1 Demographics of patients, symptomatology and laboratory parameters

<table>
<thead>
<tr>
<th>No.</th>
<th>Author et al.</th>
<th>Age</th>
<th>Sex</th>
<th>Presenting symptoms</th>
<th>Hb (gm/dL)</th>
<th>Platelet count (/µliter)</th>
<th>WBC count (/µliter)</th>
<th>Blast cells % in PB</th>
<th>AST (IU/L)</th>
<th>ALT (IU/L)</th>
<th>ALP (IU/L)</th>
<th>T. Bil (mg/dL)</th>
<th>D. Bil (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Huang et al.</td>
<td>38</td>
<td>1</td>
<td>Abdominal pain</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>Azin et al.</td>
<td>50</td>
<td>1</td>
<td>N/V/D, abdominal pain</td>
<td>9.8</td>
<td>17,000</td>
<td>1,100</td>
<td>0</td>
<td>NA</td>
<td>218</td>
<td>2.8</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>3</td>
<td>Lee et al.</td>
<td>23</td>
<td>1</td>
<td>Jaundice, weight loss</td>
<td>6.1</td>
<td>124,000</td>
<td>30,880</td>
<td>72</td>
<td>113</td>
<td>234</td>
<td>558</td>
<td>4.9</td>
<td>3.5</td>
</tr>
<tr>
<td>4</td>
<td>Trenker et al.</td>
<td>64</td>
<td>NA</td>
<td>Abnormal LFTs, asymptomatic</td>
<td>7</td>
<td>20,000</td>
<td>1,000</td>
<td>NA</td>
<td>105</td>
<td>172</td>
<td>428</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>5</td>
<td>Yu et al.</td>
<td>31</td>
<td>2</td>
<td>Abdominal pain, melena, vomiting and jaundice</td>
<td>13.8</td>
<td>202,000</td>
<td>9,500</td>
<td>0</td>
<td>596</td>
<td>761</td>
<td>1,092</td>
<td>18</td>
<td>14.7</td>
</tr>
<tr>
<td>6</td>
<td>Bloom et al.</td>
<td>49</td>
<td>1</td>
<td>Abdominal pain</td>
<td>12.4</td>
<td>66,000</td>
<td>105,000</td>
<td>78</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>7</td>
<td>Fleming et al.</td>
<td>57</td>
<td>1</td>
<td>Abdominal distension, palpable mass on day +52, post HSCT period</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>10–20</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>4</td>
<td>NA</td>
</tr>
<tr>
<td>8</td>
<td>Geddy et al.</td>
<td>61</td>
<td>1</td>
<td>Abdominal pain</td>
<td>9.4</td>
<td>95,000</td>
<td>1,700</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>9</td>
<td>Sahasrabudhe</td>
<td>59</td>
<td>1</td>
<td>Abdominal pain, jaundice</td>
<td>11</td>
<td>299,000</td>
<td>15,200</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1,741</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>10</td>
<td>Holzwanger et al.</td>
<td>74</td>
<td>2</td>
<td>Abdominal pain</td>
<td>9</td>
<td>10,000</td>
<td>17,300</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>800</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>11</td>
<td>Lillcrap et al.</td>
<td>51</td>
<td>2</td>
<td>Jaundice</td>
<td>11.2</td>
<td>NA</td>
<td>3,100</td>
<td>4</td>
<td>NA</td>
<td>NA</td>
<td>568</td>
<td>14</td>
<td>NA</td>
</tr>
<tr>
<td>12</td>
<td>Matsueda et al.</td>
<td>84</td>
<td>1</td>
<td>Anorexia, abdominal pain, jaundice</td>
<td>13</td>
<td>112,000</td>
<td>6,600</td>
<td>0</td>
<td>102</td>
<td>137</td>
<td>1,082</td>
<td>9.5</td>
<td>8.4</td>
</tr>
<tr>
<td>13</td>
<td>Ojima et al.</td>
<td>33</td>
<td>1</td>
<td>Jaundice</td>
<td>NA</td>
<td>NA</td>
<td>9,600</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>688</td>
<td>5.1</td>
<td>3.7</td>
</tr>
<tr>
<td>14</td>
<td>Shimizu T 2006</td>
<td>59</td>
<td>1</td>
<td>Fever, malaise</td>
<td>5.4</td>
<td>36,000</td>
<td>2,900</td>
<td>14</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>15</td>
<td>Bartley et al.</td>
<td>63</td>
<td>2</td>
<td>Back pain</td>
<td>9.2</td>
<td>32,000</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>16</td>
<td>Payan et al.</td>
<td>71</td>
<td>2</td>
<td>Fever, abdominal pain</td>
<td>7.5</td>
<td>2,800</td>
<td>6,900</td>
<td>0</td>
<td>NA</td>
<td>305</td>
<td>368</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>17</td>
<td>Thorns et al.</td>
<td>69</td>
<td>1</td>
<td>Abdominal pain</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>482</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

N/V/D, nausea, vomiting, diarrhea; LFT, liver function tests; Hb, hemoglobin; WBC, white blood cell; NA, not available.
CBFB/MYH 11 fusion gene have been associated with high incidence of MS (19).

**Clinical presentation**

Basically, the symptomatology in GI based MS is variable and depends on the site of location. As evident in our study, in all cases, GB-MS presented with non-specific symptoms of cholecystitis. It is almost impossible to diagnose GB-MS without histopathological evaluation in naïve cases except in conditions when there is already a known history of hematological malignancy or presence of frank circulating blast cells to lead the physicians. This fact emphasizes the need for ER physicians to quickly scan patient’s history for hematological malignancy which will help start evaluating the patient from day 1 itself for GB-MS which will save previous time.

Ultrasound of abdomen (USG) and CT abdomen are two major supplementary diagnostic modalities. Best specimen to diagnose GB-MS would be histopathological study of the resected gall bladder. In case of simultaneous biliary tract involvement, ERCP and cytology of exfoliated cells may assist in diagnosing additional sites of MS involvement. Recently, Matsueda et al. reviewed MS cases presenting with obstructive jaundice (15). In all cases, the site of infiltration was reported as biliary tract or head of pancreas. Azin et al.’s case had multiple hospitalizations for recurrent cholecystitis (20). After approximately 7 weeks of the initial presentation, patient underwent elective cholecystectomy and was diagnosed with GB-MS. Although, the course of therapy did not change as patient denied any further chemotherapy however an early diagnosis and surgical interventions could have at least improved the quality of life of the patient (20). Hunter et al. studied gastrointestinal complications of leukemia (142 patients) while undergoing chemotherapy and reported that 9% had abdominal symptoms with only 1 case of MS involving common bile duct (21).

Hence for a comprehensive and timely diagnosis, a combined diagnosed strategy including imaging studies, ERCP, histopathology, and immunohistochemistry are the necessary requirements. Accurate diagnosis becomes more daunting in post HSCT patients due to other concomitant complexities like graft versus host disease (GVHD), immunosuppressive drug related adversities like cholestasis, opportunistic infections, sinusoidal obstruction syndrome (SOS), acalculous cholecystitis and so on (22). Approximately 5% of patient’s undergoing chemotherapy for leukemia developed cholecystitis in one series (23).

Background information can play a crucial role especially in emergency room. In our review, there were 12 cases (70.58% of study cohort) who had associated hematological malignancy (5 AML, 4 MF, 2 CML and 1 MDS case). It is expected to have a higher probability of having GB-MS with cancer background when compared to those without cancer history. Scully et al.’s case was challenging as the 47-year-old had history of both colon cancer and AML thereby keeping both differentials as the possibility during evaluation of the abdominal pain and obstructive jaundice in their case (24). Microscopic evaluation of the surgical specimen confirmed it to be leukemic infiltration of common bile duct (24). Hence, sometimes despite the best clinical judgement, only the specimen examination confirms the diagnosis. Our review showed 5 cases out of 17 to have isolated GB-MS without any bone marrow involvement (14,25-28). Bartley et reported an interesting case of disseminated extramedullary myeloid tumor of the gallbladder but without involvement of the bone marrow (28).

**Management and prognosis**

Conventionally the prognosis of MS is extremely poor. Untreated MS cases usually transform to frank leukemia within 6–12 months (29). With regards to the treatment, surgical resection like cholecystectomy serves purpose for not only immediate relief to the patient but also provides specimen for definitive diagnosis. However, cholecystectomy is not a definitive treatment for GB-MS and cannot delay the transformation to leukemia or prevent the progression of disease unless chemotherapy is initiated soon (30). This is based on the expert opinion that suggests treating primary or isolated GB-MS just like any systemic AML disease. Hence, hematology opinion should be sorted for the patient care as soon as the diagnosis is established. Also, important to note that in general any surgery in patients with leukemia are associated with high mortality rates (31). Although, there has been significant improvement in survival in last few decades, most of the non-cancer related deaths are reported to result from uncontrolled sepsis (32-34). The current literature supports the use of systemic anti-leukemic therapy followed by HSCT as soon as possible in order to control the progression and improve the prognosis (26,35,36).

**Conclusions**

In conclusion, MS involving gallbladder and nearby organs
is extremely rare and tends to be misdiagnosed. Awareness of this entity amongst the ER physicians, surgeons and hospitalists is of utmost importance. Despite the exponential advancement in the management, prognosis is still dismal and further RCTs are need of hour to improve survival of patients.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/cc-19-250). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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References

Table S1: Shows background information, type of GB-MS, treatment regimen received with F/U data

<table>
<thead>
<tr>
<th>Author et al.</th>
<th>Basic disease/background</th>
<th>Radiologic findings</th>
<th>Surgery performed</th>
<th>VS/C</th>
<th>Primary disease</th>
<th>Other MS sites</th>
<th>Blast cell % in BM Dx at the time of diagnosis of MS</th>
<th>Chemotherapy for MS</th>
<th>HSCT</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang et al.</td>
<td>No cancer</td>
<td>CT: pancreatitis and intrahepatic and extrahepatic bile duct dilation</td>
<td>No, UGIE showed gastric MIS</td>
<td>I</td>
<td>Not applicable</td>
<td>Pancreas, stomach, common bile duct, RPLN, omental bursa, skeleton</td>
<td>0</td>
<td>Induction (IDA + Ara-C) followed by consolidation</td>
<td>No</td>
<td>Alive, till 1-year F/U, patient alive and disease in remission</td>
</tr>
<tr>
<td>Lin et al.</td>
<td>CMML with myeloid blast crisis, received induction chemotherapy (Ara-C, IDA) relapsed → re-induction NOVE-HDAC → achieved remission and was waiting for HSCT</td>
<td>Gallbladder distension and thickening consistent with cholecystitis</td>
<td>Cholecystectomy</td>
<td>S</td>
<td>CML with myeloid blast crisis in remission (BM: no blast cells)</td>
<td>None</td>
<td>None, yes, details NA</td>
<td>None</td>
<td>No</td>
<td>Alive, patient continued to receive consolidation till last follow up</td>
</tr>
<tr>
<td>Lee et al.</td>
<td>No cancer</td>
<td>Hepatomegaly, mild dilation of intrahepatic bile ducts and mild distension of the gallbladder</td>
<td>None</td>
<td>C</td>
<td>AML</td>
<td>No</td>
<td>75.60 Induction chemotherapy (cytarabine and idarubicin)</td>
<td>No</td>
<td>Alive, 11 months F/U, no leukemic transformation, disease stable</td>
<td></td>
</tr>
<tr>
<td>Tenker et al.</td>
<td>AML, MS</td>
<td>USG: enlarged, wall-adjacent gallbladder with intraluminal echogenic sludge and small nodules in the wall</td>
<td>Cholecystectomy and percutaneous biliary drainage</td>
<td>S, AML, MIS</td>
<td>Cystic duct</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Yu et al.</td>
<td>No evidence of cancer</td>
<td>CT: mass in the gastric antrum area, 5.2 cm x 6.2 cm in size, with possible infiltration of the duodenum, gallbladder and head of the pancreas, and possible retroperitoneal lymph node metastasis</td>
<td>Percutaneous transhepatic cholangio-digestive drainage</td>
<td>I</td>
<td>Not applicable</td>
<td>Stomach, duodenum, gallbladder and head of the pancreas, and possible retroperitoneal lymph node metastasis</td>
<td>0</td>
<td>Radiotherapy (total dose 2,400 cGy)</td>
<td>No</td>
<td>Died, Disease progression with new MS lesions involving breast and orbits. Subsequently, patient received induction (IDA, Ara-C), followed by consolidation and HSCT. In 5 months, disease relapsed, for which he received HAG regimen and DL but died due to disease progression</td>
</tr>
<tr>
<td>Bloom et al.</td>
<td>No evidence of cancer</td>
<td>HIDA scan: revealed impalpable gall bladder and pancreatic mass</td>
<td>Cholecystectomy</td>
<td>C, AML, MIS</td>
<td>Mesenteric LN, sacral root infiltrates</td>
<td>No</td>
<td>Two sessions of leukapheresis and induction therapy (idarubicine and cytarabine) followed by 3 consolidation cycles. Till 19-months F/U, patient is in remission</td>
<td>None</td>
<td>Alive and in remission till 19 months after the induction therapy till last F/U</td>
<td></td>
</tr>
<tr>
<td>Fleming et al.</td>
<td>CMML, post HSCT with post-transplant complications-GAHD, CMV pneumonia</td>
<td>CT scan: revealed distended gall bladder and HIDA scan revealed ductal obstruction</td>
<td>Cholecystectomy</td>
<td>S</td>
<td>Yes</td>
<td>Cystic duct</td>
<td>30</td>
<td>Immunosuppression withdrawal, cyclosporine discontinued, and prednisone tapered</td>
<td>No</td>
<td>Died due to respiratory failure on 53th day after HSCT</td>
</tr>
<tr>
<td>Gaddy et al.</td>
<td>No evidence of cancer</td>
<td>USG: small gallstone in gallbladder</td>
<td>Cholecystectomy</td>
<td>C</td>
<td>MF</td>
<td>No</td>
<td>Yes (blast cells not mentioned)</td>
<td>No</td>
<td>Died, After 3 months, patient developed frank AML and died due to progression of disease</td>
<td></td>
</tr>
<tr>
<td>Saharabandi et al.</td>
<td>Myelofibrosis for last 4 years</td>
<td>USG: gallstones; ERCP: dilated bile duct</td>
<td>ERCP and removal of stones</td>
<td>S</td>
<td>MF</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Died, Alive, at follow-up after 7 months, patient underwent cholecystectomy and dying wall</td>
</tr>
<tr>
<td>Holzene et al.</td>
<td>No evidence of cancer</td>
<td>USG: cholelithiasis and thickened gall bladder; ERCP: stone in common bile duct</td>
<td>Cholecystectomy</td>
<td>I</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Died, Family requested for comfort measures only as patient continued to deteriorate due to sepsis and died soon</td>
</tr>
<tr>
<td>Lillo et al.</td>
<td>No evidence of cancer</td>
<td>CT scan: large mass in head of pancreas with no gallstones</td>
<td>Cholecystectomy</td>
<td>S</td>
<td>AML-AML, active disease (BM-70% blast cells)</td>
<td>Cystic duct and RPLN</td>
<td>70</td>
<td>Yes, initiated details NA</td>
<td>No</td>
<td>Died within 2.5 weeks due to acute hemorrhagic pneumonia</td>
</tr>
<tr>
<td>Matsuda et al.</td>
<td>She was evaluated 18 months ago for right inguinal lymphadenopathy-biopsied and diagnosed as chronic lymphadenitis</td>
<td>USG: GB thickening and mass; CT scan: low density mass at the porta hepatis and thickening of the gall bladder; ERCP: stricture common hepatic ducts and dilation of the intrahepatic bile ducts</td>
<td>Conservative with arterial placement and antibiotics</td>
<td>C</td>
<td>AML-AML, active disease (BM-blast cell)</td>
<td>Confirmed post-mortem: porta hepatitis, liver, spleen, lymph node, heart, lung, kidney, testis, brainstem</td>
<td>86.40</td>
<td>No, as diagnosed at postmortem</td>
<td>No</td>
<td>Died, ERCP = stent placement, abdominal examination was suspected as gallbladder carcinoma and family opted for supportive care. After 1 month, he was diagnosed with AML-AML and he died due to DIC. Diagnosis of GNAS was made during postmortem period</td>
</tr>
<tr>
<td>Ojima et al.</td>
<td>No evidence of cancer</td>
<td>Abdominal computed tomography imaging showed partial infiltration of the tumor into the GB wall</td>
<td>Hepatopancreaticoduodenectomy</td>
<td>I</td>
<td>No</td>
<td>Cystic duct, CBD, portal vein, liver, hepatoduodenal ligament, omentum, transverse colon and duodenum</td>
<td>0%</td>
<td>Yes, regimen not available</td>
<td>No</td>
<td>Alive 4 years later, in remission</td>
</tr>
<tr>
<td>Shimizu T</td>
<td>MDS</td>
<td>USG and CT scan: GB wall thickening, gall stone, intrahepatic bile duct dilation</td>
<td>Open cholecystectomy</td>
<td>S</td>
<td>MDS</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Died, Within 2 weeks of surgery, disease progressed to frank leukemia which chemotherapy (details not available) was started but patient died due to severe pneumonia, DIC and multorgan failure</td>
</tr>
<tr>
<td>Barthet et al.</td>
<td>No evidence of cancer</td>
<td>CT: s/o cholangitis</td>
<td>Cholecystectomy</td>
<td>I</td>
<td>No</td>
<td>Confirmed post-mortem: myoccardium, lungs, kidney, pancreas, thyroid, parathyroid, adrenal gland</td>
<td>30% in BM examination at postmortem</td>
<td>No, patient died after cholecystectomy</td>
<td>No</td>
<td>Died, Postoperatively, the patient experienced respiratory distress requiring intubation and died of multorgan failure</td>
</tr>
<tr>
<td>Payen et al.</td>
<td>Recently diagnosed myelofibrosis</td>
<td>USG: thickened GB wall</td>
<td>Laparoscopic cholecystectomy</td>
<td>S</td>
<td>MF</td>
<td>Liver, cystic duct, lymph node</td>
<td>Disease requiring intubation and died of multorgan failure</td>
<td>No</td>
<td>Died, within 8 days due to leukemic conversion</td>
<td></td>
</tr>
<tr>
<td>Thorne et al.</td>
<td>Myelofibrosis</td>
<td>USG: gallstones</td>
<td>Cholecystectomy</td>
<td>S</td>
<td>MF</td>
<td>No</td>
<td>0</td>
<td>No</td>
<td>No</td>
<td>Died, At 11 months F/U, no leukemic transformation, disease stable</td>
</tr>
</tbody>
</table>

MB, myeloid sarcoma; USG, ultrasoundography; SM, myelofibrosis; GB, gallbladder; CT, computed tomography; Ara-C, cytarabine; USG, upper GI endoscopy; ERCP, endoscopic retrograde cholangiopancreatography; I, resistant; G, concurrent; S, secondary; RPLN, retroperitoneal lymphadenopathy; BM, bone marrow; PB, myeloid sarcoma; CMML, chronic myeloid leukaemia; DIC, disseminated intravascular coagulation; BONJ, bis-chloroethyl nitrosourea; IDA, idarubicin; Ara-C, cytosine arabinoside; HSCT, hematopoietic stem cell transplantation; HAG, high-dose cytosine arabinoside and mitoxantrone; DL, donor leukocyte infusion. 

**Supplementary Author et al.:**

1. Bartley et al.
2. Bloom et al.
3. Fleming et al.
4. Gaddy et al.
5. Lillicrap et al.
7. Ojima et al.
8. Shimizu T
9. Thorne et al.