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

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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.

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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

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Table 1 Demographics of patients, symptomatology and laboratory parameters

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

N/V/D, nausea, vomiting, diarrhea; LFT, liver function tests; Hb, hemoglobin; WBC, white blood cell; NA, not available.

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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

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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/cco-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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Supplementary

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

Author *et al.*	Basic disease/background	Radiographic findings	Surgery performed	I/S/C	Primary disease	Other MS sites	Blast cell % in BM Bx at the time of diagnosis of MS	Chemotherapy for MS	HSCT	Outcome
Huang *et al.*	No cancer	CT: pancreatitis and intrahepatic and extrahepatic bile duct dilation	No, UGIE showed gastric MS	I	Not applicable	Pancreas, stomach, common bile duct, RPLN, omental bursa, skeleton	0	Induction (IDA + ARA-C) followed by consolidation	No	Alive, till 1-year f/u, patient alive and disease in remission
Azin *et al.*	CML with myeloid blast crisis, received induction chemotherapy (Ara-C, IDA) → relapsed → re-induction NOVE-HiDAC → achieved remission and was waiting for HSCT	Gallbladder distension and thickening consistent with cholecystitis	Cholecystectomy	S	CML with myeloid blast crisis in remission (BM-no blast cells)	None	Yes, details NA	None	No	Alive, patient denied any further chemotherapy and was in remission till 5 months of follow up
Lee et al.	No cancer	Hepatosplenomegaly, mild dilatation of intrahepatic bile ducts and mild distension of the gallbladder	None	C	AML	No	75.60	Induction chemotherapy (cytarabine and idarubicin)	No	Alive, patient continued to receive consolidation till last follow up
Trenker *et al.*	AML, M5	USG: enlarged, wall-accented gallbladder with intraluminal echogenic sludge and small nodules in the wall	Cholecystectomy and percutaneous biliary drainage	S	AML, M5	Cystic duct	No	NA	NA	NA
Yu *et al.*	No evidence of cancer	CT: mass in the gastric antrum area, 5.2 cm × 6.2 cm in size, with possible infiltration of the duodenum, gallbladder and head of the pancreas, and possible retroperitoneal lymph node metastasis	Percutaneous transhepatic cholangial drainage and gastric mucosal biopsy	I	Not applicable	Stomach, duodenum, gallbladder and head of the pancreas, and possible retroperitoneal lymph node metastasis	0	Radiotherapy (total dose 2,450 cGy)	No	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 DLI but died due to disease progression
Bloom *et al.*	No evidence of cancer	HIDA scan: revealed impaired gall bladder emptying	Cholecystectomy	C	AML, M4	Mesenteric LN, sacral root infiltrates and pancreatic mass	No	Two sessions of leukaphereses and Induction therapy (idarubicin and cytarabine) followed by 3 consolidation cycles. Till 19 months f/u, patient is in remission	None	Alive and in remission for 19 months after the induction therapy till last F/U
Fleming *et al.*	CML, post HSCT with post-transplant complications-GVHD, CMV pneumonia	CT scan: revealed distended gall bladder and HIDA scan revealed ductal obstruction	Cholecystectomy	S	Yes	Cystic duct	30	Immunosuppression withdrawn, cyclosporine discontinued, and prednisone tapered	No	Died due to respiratory failure on 59th day after HSCT
Geddy *et al.*	No evidence of cancer	USG: small gallstone in gall bladder	Cholecystectomy	C	MF	No	Yes (blast cells not mentioned)	No	No	Died. After 2 months, patient developed frank AML and died due to progression of disease
Sahasrabudhe *et al.*	Myelofibrosis for last 4 years	USG: gallstones; ERCP: dilated bile duct	ERCP and removal of stones	S	MF	No	No	No	No	Alive, at follow-up after 7 months, patient underwent cholecystectomy and doing well
Holzwanger *et al.*	No evidence of cancer	USG: cholelithiasis and thickened gall bladder; ERCP: stone in common bile duct	Cholecystectomy	I	None	None	None	No	No	Died. Family requested for comfort measures only as patient continued to deteriorate due to sepsis and died soon
Lillicrap *et al.*	Was evaluated for anemia and thrombocytopenia, and was diagnosed as AML M2 for which she received induction chemotherapy (Ara-C, TG, DNR) f/b maintenance chemotherapy (BCNU and cyclophosphamide) when she developed jaundice	CT scan: large mass in head of pancreas with no gallstones	Cholecystectomy	S	AML-M2, active disease (BM-70% blast cells)	Cystic duct and RPLN	70	Yes, initiated details NA	No	Died within 2.5 weeks due to acute hemorrhagic pneumonia
Matsueda *et al.*	She was evaluated 18 months ago for right inguinal lymphadenopathy-biopsied and diagnosed as chronic lymphadenitis	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 dilatation of the intrahepatic bile ducts	Conservative with stent placement and antibiotics	C	AML-M0, active disease (BM-blast cell)	Confirmed post-mortem: porta hepatis, liver, spleen, lymph node, heart, lungs, kidney, testis, brainstem	88.40	No, as diagnosed at postmortem	No	Died. ERCP + stent placement. Initial diagnosis was suspected as gallbladder carcinoma and family opted for supportive care. After 1 month, he was diagnosed with AML-M0 and he died due to DIC. Diagnosis of GMS was made during postmortem period
Ojima *et al.*	No evidence of cancer	Abdominal computed tomography imaging showed partial infiltration of the tumor into the GB wall	Hepatopancreatoduodenectomy	I	No	Cystic duct, CBD, portal vein, liver, hepatoduodenal ligament, omentum, transverse colon and duodenum	0%	Yes, regimen not available	No	Alive 4 years later, in remission
Shimizu T 2006	MDS	USG and CT scan: GB wall thickening, gall stone, intrahepatic bile duct dilation	Open cholecystectomy	S	MDS	No	No	No	No	Died. Within 2 weeks of surgery, disease progressed to frank leukemia for which chemotherapy (details not available) was started but patient died due to sever pneumonia, DIC and multiorgan failure
Bartley *et al.*	No evidence of cancer	CT: e/o cholangitis	Cholecystectomy	I	No	Confirmed post-mortem: myocardium, lungs, kidney, pancreas, thyroid, parathyroid, adrenal gland	0% in BM examination at postmortem	No, patient died after cholecystectomy during post-operative period	No	Died. Postoperatively, the patient experienced respiratory distress requiring intubation and died of multiorgan failure
Payan *et al.*	Recently diagnosed myelofibrosis	USG: thickened GB wall	Laproscopic cholecystectomy	S	MF	Liver, cystic duct, lymph node	Distress requiring intubation and died of multiorgan failure			Died, within 6 weeks due to leukemic conversion
Thorns *et al.*	Myelofibrosis	USG: gallstones	Cholecystectomy	S	MF	No	0	No	No	Alive, 11 months F/U, no leukemic transformation, disease stable

MS, myeloid sarcoma; USG, ultrasonography; MF, myelofibrosis; GB, gallbladder; CT, computed tomography; Ara-C, cytarabine; UGIE, upper GI endoscopy; ERCP, endoscopic retrograde cholangiopancreatography; I, isolated; C, concurrent; S, secondary; RPLN, retroperitoneal lymphadenopathy; BM, bone marrow; MS, myeloid sarcoma; CML, chronic myeloid sarcoma; DIC, disseminated intravascular coagulation; BCNU, bis-chloroethyl nitrosourea; IDA, idarubicin; Ara-C, cytosine arabinoside; HSCT, hematopoietic stem cell transplantation; HAG, high-dose cytosine arabinoside and mitoxantrone; DLI, donor leukocyte infusion.