

Isolated Biliary Granulocytic Sarcoma Followed by Acute Myelogenous Leukemia with Multilineage Dysplasia : A Case Report and Literature Review

Granulocytic sarcoma is a rare extramedullary tumor composed of myeloid progenitor cells. Primary involvement of the biliary tract without evidence of leukemia is exceedingly rare. Here, we report an isolated biliary granulocytic sarcoma in a 30-yr-old man who presented with jaundice, fever, and chill without any evidence of leukemia. However, five months after the diagnosis, he developed acute myelogenous leukemia with multilineage dysplasia and chromosomal abnormality. A rare possibility of biliary granulocytic sarcoma should be considered as a differential diagnosis in patients with obstructive jaundice. A histologic evaluation by aggressive diagnostic intervention is important and may improve prognosis.

Key Words : *Sarcoma, Granulocytic; Leukemia; Jaundice, Obstructive; Bile Ducts*

Chang Ohk Sung, Young Hyeoh Ko,
Cheol Keun Park, Kee Taek Jang,
Jin Seok Heo*

Departments of Pathology and Surgery*, Samsung
Medical Center, Sungkyunkwan University School of
Medicine, Seoul, Korea

Received : 28 February 2005
Accepted : 7 June 2005

Address for correspondence

Young Hyeoh Ko, M.D.
Department of Pathology, Samsung Medical Center,
Sungkyunkwan University School of Medicine, 50
Irwon-dong, Gangnam-gu, Seoul 135-710, Korea
Tel : +82.2-3410-2762, Fax : +82.2-3410-0025
E-mail : yhko@smc.samsung.co.kr

INTRODUCTION

Granulocytic sarcoma is an extramedullary collection of myeloblasts. It was first described by Burns (1) in 1811, and named "chloroma" by King (2) in 1853 because of its green color, which is due to the presence of myeloperoxidase enzymes in the immature myeloid cells. Rappaport first used the term "granulocytic sarcoma" in 1966 (3). This disease usually arises during the course of acute myelogenous leukemia, although it also occurs infrequently in chronic myelogenous leukemia and other myeloproliferative disorders. The most common sites of involvement are the periosteum, soft tissue, bone, lymph nodes, and skin, but almost any site may be involved, e.g., the brain, breasts, urinary bladder, and gastrointestinal tract, and multiple organ involvement is also common (4). However, isolated granulocytic sarcoma in the biliary tract without evidence of leukemia is exceedingly rare.

Here, we describe a case of granulocytic sarcoma of the proximal common bile duct, and right and left hepatic ducts causing obstructive jaundice in a patient without evidence of bone marrow disease; this was followed by acute myelogenous leukemia with multilineage dysplasia.

CASE REPORT

A 30-yr-old man was admitted to our hospital because of

jaundice and mild fever with a chill. The patient had been well until 3 months earlier, when he began to develop right upper quadrant pain. One month before admission, the pain worsened and at times radiated into his back. On admission, a physical examination was unremarkable except for icteric sclera. An abdominal examination revealed right upper quadrant tenderness but did not disclose hepatosplenomegaly or a palpable mass. Laboratory tests on admission showed elevated total bilirubin (6.9 mg/dL; normal range 0-0.5), serum aspartate aminotransferase (201 μ /L; normal range 0-40), serum alanine aminotransferase (814 mg/dL; normal range 0-40), and alkaline phosphatase (158 μ /L; normal range 53-128). Complete blood cell counts were within normal limits, with no blast cells. Ultrasonography (US) revealed thickening of the gallbladder wall and multiple tiny stones with some sludge in the gallbladder. Endoscopic retrograde cholangiopancreatography (ERCP) revealed bile duct strictures (Fig. 1). Endoscopic nasobiliary drainage (ENBD) was performed using a 5-Fr. plastic stent. Abdominal computed tomography after ENBD disclosed a low density rim around the ENBD tube, but no definitive abnormal enhancing lesion of the wall or mass was recognized (Fig. 2). The jaundice was temporally relieved after ENBD and the patient received open cholecystectomy under the impression of cholelithiasis with bile duct stricture. The histologic diagnosis of the gallbladder was chronic cholecystitis with cholelithiasis. Because jaundice had not resolved after cholecystectomy, right lobectomy with hepatic



Fig. 1. Endoscopic retrograde cholangiopancreatography (ERCP) reveals the common bile duct stricture.

cojejunostomy was performed. During the operation a diffuse stricture from the middle common bile duct extending to right and left hepatic ducts with wall thickening was observed. A pathologic examination showed a monomorphous and discohesive infiltration of tumor cells along the bile duct wall (Fig. 3A, B). Tumor cells were of medium size with large nuclei showing dispersed chromatin, and one or more distinct but not prominent nucleoli. The cytoplasm was deeply eosinophilic and granular reminiscent of metamyelocytes, and indicative of myeloid differentiation (Fig. 3B). Immunohistochemistry showed positivity for myeloperoxidase (1:20,000, Dako, Denmark) (Fig. 3C), CD34 (1:100, Dako, Denmark), and lysozyme (1:100, Zymed, New Zealand) but negativity for CD3 (1:200, Novocastra, U.K.) and CD20 (1:500, Novocastra, U.K.). The liver was not involved by the tumor. The histologic diagnosis was granulocytic sarcoma involving the right and left hepatic ducts, superior bile duct, and cystic duct. A bone marrow biopsy taken at the time was normal, and the patient had no symptoms or signs of leukemia. The patient was then followed without other therapies such as chemotherapy or radiotherapy. Five months after the initial diagnosis of granulocytic sarcoma, peripheral blood smear showed normochromic normocytic anemia (Hb 11.4 g/dL, Hct 33.1%) with aniso- and poikilocytosis, neutropenia (3,700/ μ L) with 10% blasts, and thrombocytopenia (73,000/ μ L) with giant forms. Bone marrow aspiration and biopsy showed leukemic blasts with abnormal nuclear folding, and cytoplasmic blebs which were counted up to 40.1% of all nucleated cells and infiltrated between normal and dyshematopoietic erythroid and myeloid cells (Fig. 4). Those blasts were positive for myeloperoxidase, Sudan-black B, and per-



Fig. 2. Computed tomogram discloses a low density rim around the ENBD tube, but no definitive abnormal enhancing lesion or mass is recognized.

oxidase in cytochemical stain and expressed CD13, CD33, myeloperoxidase, and CD34 in flow cytometric analysis. Megakaryocytes with dysplasia were hardly observed in aspiration smear but increased in number in biopsy. A diagnosis of acute myelogenous leukemia with multilineage dysplasia was made according to the WHO classification or M2 by the French-American-British (FAB) classification. A chromosomal study showed 45,XY,del(3)(q21q27),-16,add(21)(q22)[18]/46,XY[2]. The patient received induction chemotherapy with idarubicin and cytarabine. A follow up bone marrow examination 21 days after the induction chemotherapy showed persistent acute myelogenous leukemia (AML) with multilineage dysplasia (Blasts: up to 4.3% of all nucleated cells).

DISCUSSION

Granulocytic sarcoma usually occurs in one of the following three clinical settings. The first is in patients with previous or current AML, and the second in patients as a sign of blast transformation of CML or of some other chronic myeloproliferative disorder. Third setting is in patients with no other clinical evidence of hematologic disease at the time of diagnosis. Neiman et al. (5) reported 61 patients with granulocytic sarcoma, in which 48% of the cases were associated with myeloproliferative disorder, 30% presented with no overt leukemia, and 22% occurred as the initial presentation or during the course of AML. The most common sites of involvement were the periosteum, soft tissue and bone followed by the lymph nodes and skin, however it may be

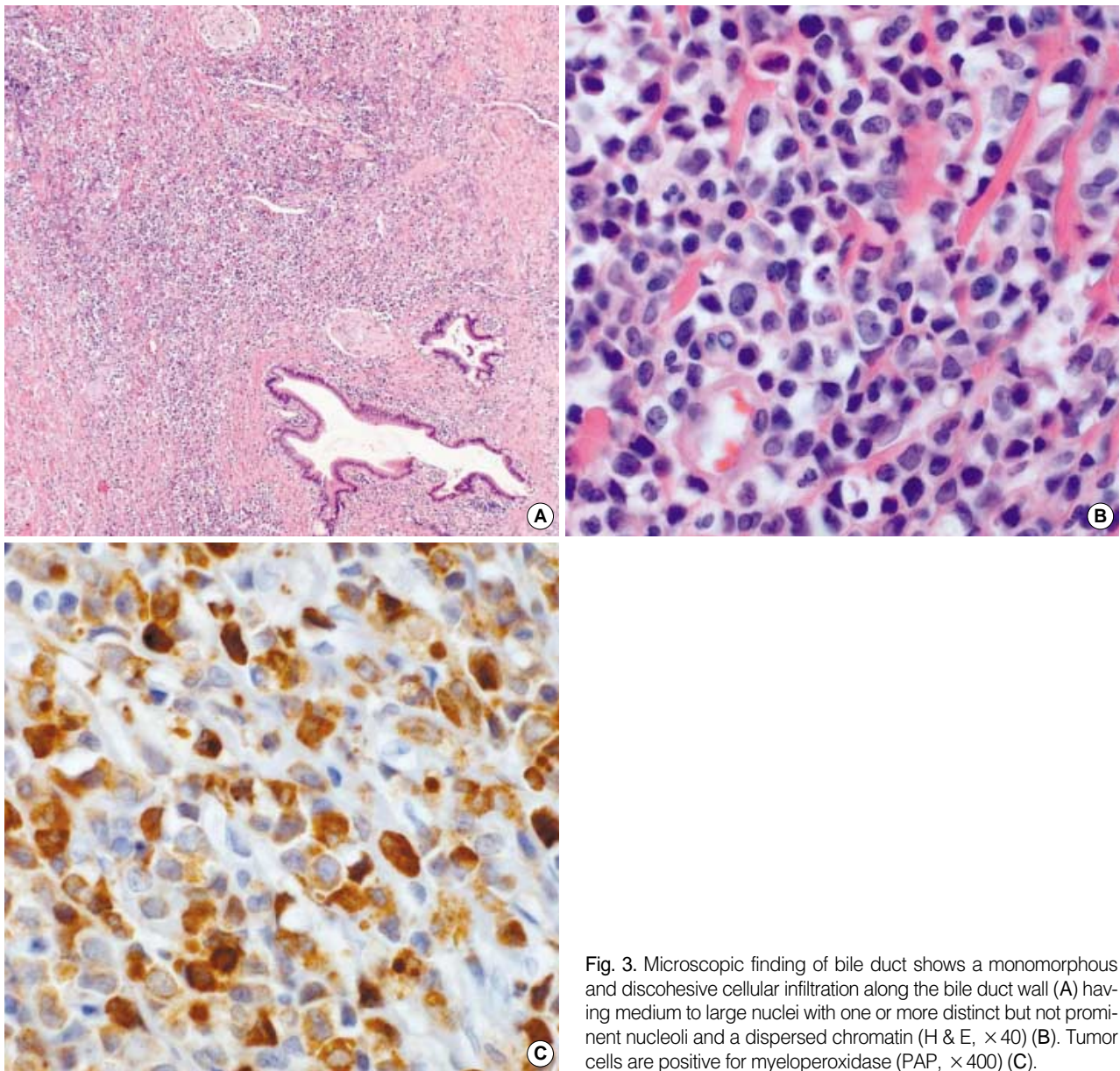


Fig. 3. Microscopic finding of bile duct shows a monomorphic and discohesive cellular infiltration along the bile duct wall (A) having medium to large nuclei with one or more distinct but not prominent nucleoli and a dispersed chromatin (H & E, $\times 40$) (B). Tumor cells are positive for myeloperoxidase (PAP, $\times 400$) (C).

found in any location including gingiva, pancreas, breast, testis, spinal cord, or ovary (5-13).

Isolated biliary involvement by granulocytic sarcoma is extremely rare. Only four cases of biliary granulocytic sarcoma have been reported in the English literature (Table 1). The first case (14) was presented with a sign of AML relapse. The patient received chemotherapy because of AML M2 and reached complete remission. However, 29 months later, the patient developed jaundice and abdominal pain, and was diagnosed as having a granulocytic sarcoma in the common bile duct. The second case (15) was of a 45-yr-old man who underwent allogeneic bone marrow transplantation (BMT) because of chronic myelogenous leukemia in blast crisis. On day 69 after BMT, he presented with anorexia and jaundice and was diagnosed as having a granulocytic sarcoma by open

biopsy. Third case (16) was of an 84-yr-old man presented with jaundice. A CT scan showed a low-density mass at the porta hepatis, and thickening of the gallbladder wall which suggests gallbladder carcinoma. Endoscopic retrograde biliary drainage was performed. Other therapies, such as laparotomy, chemotherapy, and radiotherapy were not performed because of old age. Fifty-one days after first admission, a peripheral blood examination showed a white cell count of $16,400/\mu\text{L}$ with 60% blast cells. A bone marrow examination revealed AML (FAB type M0), and he died 1 month after diagnosis. At autopsy, the suspected gallbladder carcinoma turned out to be granulocytic sarcoma associated with AML. The fourth case (17) was of a 75-yr-old woman who presented with severe obstructive jaundice. A bile duct carcinoma arising in the hilum of the liver (a so-called Klatskin tumor) was clinically

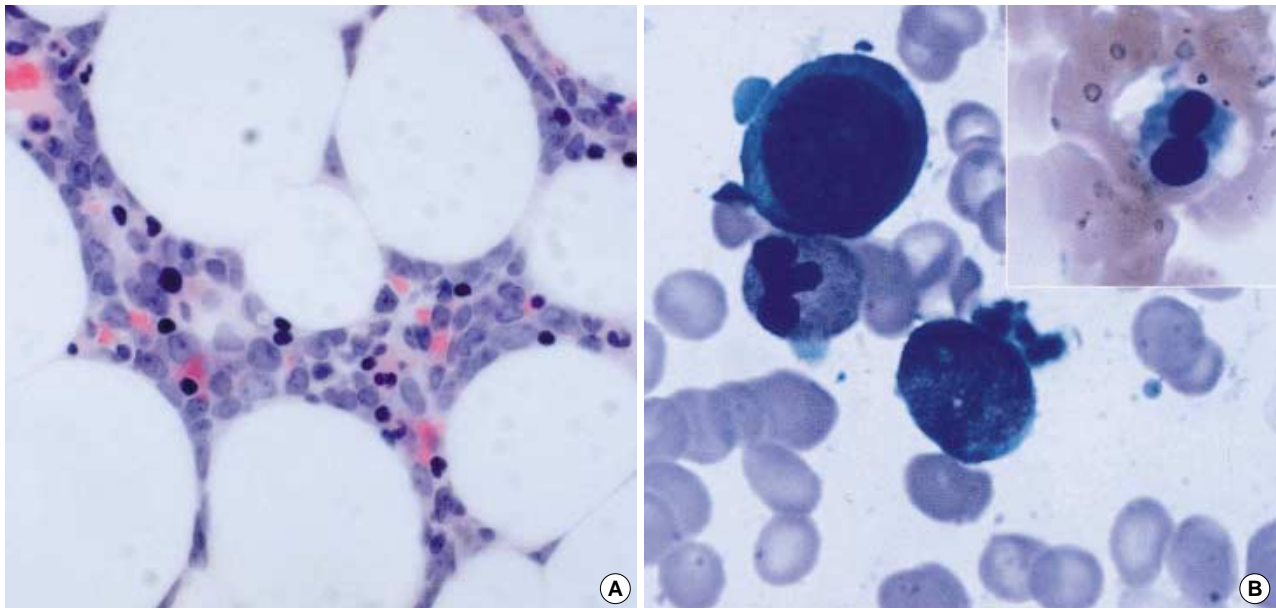


Fig. 4. Bone marrow findings. Monomorphic myeloblasts in trephine biopsy (H & E, $\times 400$) (A). Myeloblasts with cytoplasmic blebs and dysmature erythroid cell (inset) (Wright stain, $\times 1,000$) (B).

Table 1. Summary of biliary granulocytic sarcomas reported

Reference (year)	Age (yr)	Sex	Associated leukemia	Involvement site	Clinical feature
N Engl J Med (1988) [14]	47	M	AML (FAB M2)	Common bile duct	Presentation as first sign of AML relapse
Rotter et al. (1992) [15]	45	M	CML	Hepatic duct	Presentation as a sign of CML relapse after bone marrow transplantation
Matsueda et al. (1998) [16]	84	M	AML (FAB M0)	Porta hepatis	Isolated granulocytic sarcoma without evidence of leukemia
Ascani et al. (2003) [17]	75	W	AML (FAB M4)	Hepatic duct	Granulocytic sarcoma with current leukemia
Our patient	30	M	AML with multilineage dysplasia (FAB M2)	Superior bile duct and hepatic duct	Isolated granulocytic sarcoma without evidence of leukemia

suspected. A right hepatectomy was performed and revealed a granulocytic sarcoma. Subsequently, a bone marrow biopsy showed acute myelomonocytic leukaemia. The patient died of disease 1 month after surgery.

The present case also presented with abdominal pain and jaundice. Likewise to the case reported by Matsueda et al. (16), the patient had no preceding leukemia. Neiman et al. (5) reported that among 15 patients of granulocytic sarcoma without leukemia, 13 patients developed AML between 1 and 49 months (mean: 10.5 months) after diagnosis. Most non-leukemic granulocytic sarcomas left untreated will progress to acute nonlymphoblastic leukemia (ANLL), and patients initially administered chemotherapy for ANLL showed longer disease free intervals and overall survival (18-20). The present patient did not receive chemotherapy until development of leukemia, which may have caused the early development of acute leukemia.

Granulocytic sarcoma occurs in only 2 to 8% of AML cases,

which are mainly of the M2 morphology, although the disease has also been associated with M3, M4, M5, and M7 morphologies (21). A patient having AML type M2 with t(8;21) showed a greater tendency to develop granulocytic sarcoma than others, as demonstrated by a study which found that 4.5 to 38% of patients with t(8;21)(q22;q22) developed granulocytic sarcoma (22, 23). The acute leukemia that developed in the current patient was FAB type M2 with chromosomal abnormality affecting chromosome 21(q22).

A diagnosis of biliary granulocytic sarcoma is difficult to make by radiographic examination only, and is virtually impossible in a nonleukemic patient. Biliary granulocytic sarcoma may be misdiagnosed as inflammatory lesion such as cholangitis or cholecystitis or as a malignancy. Biliary granulocytic sarcoma reported previously, and the current case commonly presented with obstructive jaundice with extrinsic bile duct compression. Therefore, biliary granulocytic sarcoma should be included in the differential diagnosis of

patients with obstructive jaundice. Early diagnostic intervention with histologic evaluation is important, and may lead to a better prognosis.

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