Surg Today (2002) 32:81–85

SURGERY TODAY

Inflammatory Malignant Fibrous Histiocytoma of the Gallbladder: Report of a Case

TATSUYA KATO[1,2], TETSUFUMI KOJIMA[2], TETSUYA SHIMIZU[2], HARUKI SASAKI[3], MASAKAZU ABE[3], SHUNICHI OKUSHIBA[1], SATOSHI KONDO[1], HIROYUKI KATO[1], and HIDETOSHI SATO[4]

[1] Cancer Medicine, Surgical Oncology, Division of Cancer Medicine, Hokkaido University Graduate School of Medicine, N15, W7 Kita-ku, Sapporo 060-8638, Japan
[2] Department of Surgery and [3] Department of Internal Medicine, Hakodate Central General Hospital, Hakodate, Japan
[4] Department of Pathology, Sapporo City Hospital, Sapporo, Japan

Abstract We describe herein a case of inflammatory malignant fibrous histiocytoma (IMFH) of the gallbladder that subsequently metastasized to the ascending colon and later to the stomach. A 70-year-old Japanese man with a palpable mass in the right upper quadrant of the abdomen was referred to our hospital for investigation and treatment. Laboratory data showed severe leukocytosis and elevated serum granulocyte colony-stimulating factor (G-CSF) concentrations. A laparotomy was performed, and the tumor was excised en bloc with the gallbladder and part of the liver bed. Histopathologically, the tumor was composed of ordinary malignant fibrous histiocytoma (MFH) components characterized by pleomorphic tumor cells, bizarre giant cells, and conventional spindle cells in a storiform growth pattern, as well as a xanthogranulomatous component, including inflammatory cells, foamy histiocytes, and plasma cells. Immunohistochemical study revealed that the pleomorphic tumor cells and bizarre giant cells were positive for antibodies against α_1-antitrypsin and α_1-antichymotrypsin. The final pathologic diagnosis was IMFH. The tumor cells were diffusely positive for anti-G-CSF monoclonal antibody, and the inflammatory reaction subsided immediately after tumor resection, strongly suggesting that the primary tumor cells produced G-CSF. This patient is still alive with no signs of recurrence more than 3 years after his primary operation, which to our knowledge is the longest survival period ever reported. Therefore, visceral IMFH is manageable in some cases by resecting the primary and isolated metastatic lesions.

Key words Inflammatory malignant fibrous histiocytoma · Gallbladder · Granulocyte colony-stimulating factor

Reprint requests to: T. Kato
Received: October 11, 2000 / Accepted: May 15, 2001

Introduction

Malignant fibrous histiocytoma (MFH) is a soft-tissue sarcoma that most commonly develops in the extremities or the retroperitoneum. Visceral involvement is rare, and only a few cases of primary MFH of the gallbladder have been reported.[1–7] MFH is classified into four types: storiform-pleomorphic, myxoid, giant cell, inflammatory.[8] The inflammatory type of MFH (IMFH) is particularly rare, accounting for only 0.7%–3.0% of all soft-tissue MFHs.[9,10] Moreover, a review of the world literature failed to reveal any reports of IMFH that developed primarily in the gallbladder. IMFH is frequently associated with leukocytosis, leukemoid reaction, and paraneoplastic syndromes, such as fever and general fatigue, which has led to the suggestion that certain cytokines are produced by the tumor cells.[8,11,12] This report describes the first documented case of IMFH of the gallbladder with subsequent metastasis to the ascending colon and later to the stomach. Immunohistochemical studies confirmed that this tumor produced granulocyte colony-stimulating factor (G-CSF).

Case Report

A 70-year-old man was referred to our hospital in May 1997. On admission his temperature was 37.1°C, and a large, elastic hard mass was palpable in the right upper quadrant of the abdomen. Laboratory findings showed severe inflammatory reactions, with a leukocyte count of 50700/mm^3 (80% segmented neutrophils, 8% stab neutrophils, 1% myelocytes, 2% eosinophils, 0% basophils, 3% monocytes, and 6% lymphocytes) and an elevated serum C-reactive protein (CRP) level (9.9 mg/dl). The serum concentrations of alkaline phosphatase (ALP) and fibrinogen were increased to 503 U/l and 1066 mg/dl, respectively. Tumor markers, including carcinoembryonic antigen (CEA), α-fetoprotein (AFP),

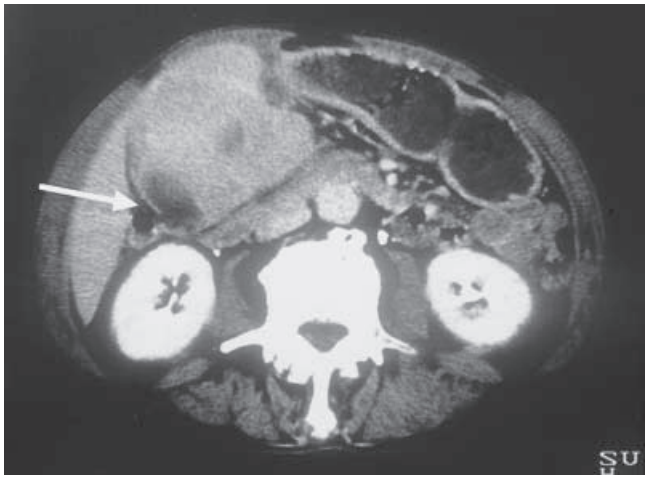

Fig. 1. Abdominal computed tomography (CT) scan showed a large well-defined, well-enhanced heterogeneous mass involving the gallbladder (*arrow*), extending from the hepatic hilum to the liver bed

and CA19-9, were within normal limits. The serum cytokine values were assessed by enzyme immunoassay, which showed an elevated G-CSF of 133 pg/ml (normal 2.2–30.9 pg/ml). Enhanced computed tomography (CT) of the abdomen revealed a relatively well-defined mass, 12 × 10 cm, that was slightly enhanced and heterogeneous, extending from the hepatic hilum to the liver bed and appearing to involve the gallbladder (Fig. 1). Endoscopic retrograde cholangiography (ERC) showed an enlarged gallbladder, about 13 × 7 cm, which contained a round shadow defect 4 cm in diameter in the body. Angiography revealed that the tumor was supplied by a highly developed cystic artery and was hypovascular without tumor vessel growth (Fig. 2). Echo-guided needle biopsy of the tumor showed fibrous granulation tissue consisting of foamy histiocytes with infiltration of neutrophils, lymphocytes, and plasma cells. The tumor was diagnosed as a xanthogranuloma.

The initial operation was performed on July 31, 1997 with a presumptive diagnosis of xanthogranulomatous cholecystitis. At laparotomy a large mass, approximately 14 cm in diameter, was found adjacent to the transverse colon and duodenum, extending from the hepatic hilum to the liver bed. No peritoneal dissemination or enlargement of regional lymph nodes was observed. The mass was excised completely en bloc with the gallbladder and part of the liver bed. Macroscopically, the cut surface of the tumor showed a lobular pattern and was grayish-white or pale yellow (Fig. 3). The tumor was 5 × 6 cm, lay in the lumen of the gallbladder body, and had invaded the liver bed through the gallbladder wall.

Histopathologically, the tumor was composed of bimorphic components, one being typical MFH histol-

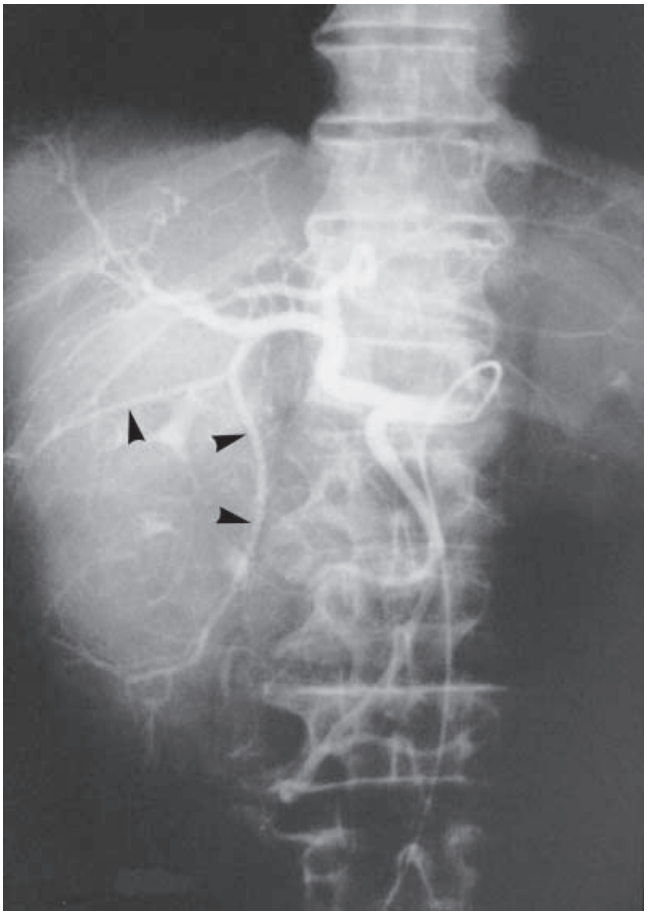

Fig. 2. Common hepatic angiography revealed encasement of a highly developed cystic artery (*arrowheads*). The tumor was hypovascular without tumor stain

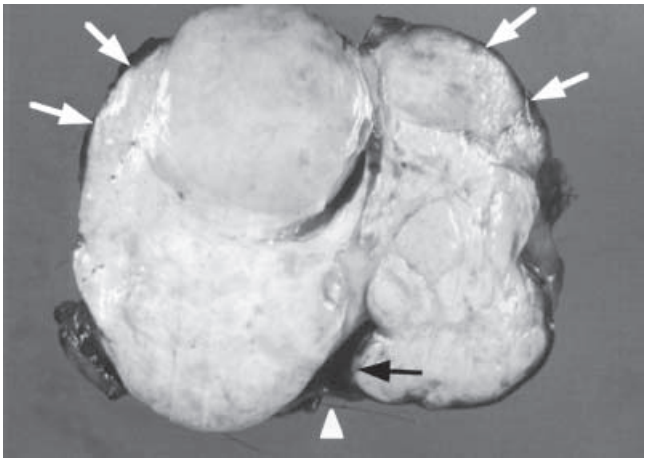

Fig. 3. Macroscopic appearance of the tumors. The resected edge was lobulated and grayish-white, pale yellow, or both. *White arrowhead* indicates the gallbladder; *white arrows* indicate the liver bed tissue; *black arrow* indicates the tumor protruding into the gallbladder lumen

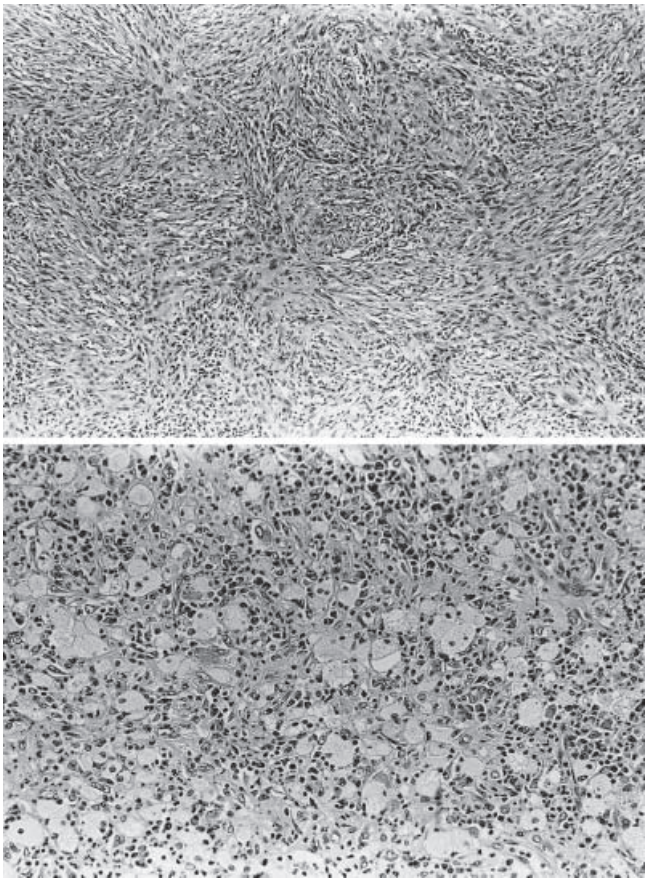

Fig. 4. Photomicrographs of the tumors. Primary tumor was composed of bimorphic components. The malignant fibrous histiocytoma (MFH) component was characterized by pleomorphic tumor cells and bizarre giant cells as well as **(a)** spindle cells with features of a storiform growth pattern. (H&E, ×25). **(b)** Xanthogranulomatous component was comprised of inflammatory cells, foamy histiocytes, and plasma cells. (H&E, ×100)

ogy characterized by pleomorphic tumor cells with bizarre giant cells and conventional spindle cells in a fascicular or storiform growth pattern (Fig. 4a) and the other a xanthogranulomatous component comprised of inflammatory cells, foamy histiocytes, and plasma cells (Fig. 4b). The pleomorphic tumor cells and bizarre giant cells stained positively for the antibody against α_1-antitrypsin and α_1-antichymotrypsin (Nichirei, Tokyo, Japan), which established its histiocytic origin. Immunoreactivity for vimentin (Dako, Kyoto, Japan) was demonstrated in both the giant cells and spindle cells; however, none of the tumor cells stained positively for desmin (Nichirei), CD34 (Nichirei), sm-actin (Dako), or S-100 protein (Dako). Based on these findings, the final pathologic diagnosis was inflammatory MFH. An immunohistochemical study using an anti-G-CSF monoclonal antibody (Calbiochem, La Jolla, CA, USA) suggested the production of G-CSF by the tumor be-

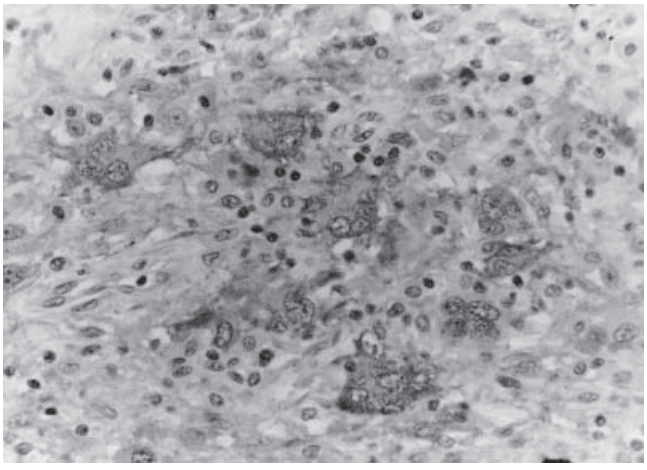

Fig. 5. Immunohistochemical study shows a diffusely positive reaction for granulocyte colony-stimulating factor antibody in the cytoplasm of the bizarre giant cells. (×200)

cause the cytoplasm was diffusely positive (Fig. 5). The patient's systemic inflammatory response resolved immediately after resection of the tumor.

A follow-up CT scan done 4 months later revealed a large, well-enhanced 6.5 × 5.5 cm tumor in the ascending colon. Colonoscopy disclosed an exophytic tumor with an irregular surface in the ascending colon, resembling a submucosal tumor. Endoscopic biopsy results indicated that the tumor was an MFH, and metastasis of MFH to the colon was diagnosed. The preoperative serum G-CSF concentration was 89.0 pg/ml, but leukocytosis was absent. Right hemicolectomy and dissection of regional lymph nodes were performed on February 3, 1998. Grossly, the resected specimen was an oval tumor, 8.0 × 5.5 × 4.5 cm, arising from the colonic wall and protruding intraluminally, consistent with metastasis. Histological examination revealed virtually the same features as had been seen in the primary tumor. The final pathological diagnosis was IMFH with no evidence of metastasis to the regional lymph nodes.

A subsequent CT scan 29 months after the initial operation showed a well-enhanced image of a tumor, 4 cm in diameter, in the antrum of the gastric wall. Barium gastrography revealed extrinsic compression by a 6.0 × 4.5 cm lesion along the greater curvature of the antrum. Endoscopy showed a submucosal tumor in this region. Laboratory findings showed a mild inflammatory response with a leukocyte count of 11 000/mm^3 and a CRP of 2.6 mg/dl. The serum G-CSF concentration was 34.7 pg/ml. A distal partial gastrectomy with regional lymph node dissection was performed on April 3, 2000. Grossly, the resected specimen was an oval-shaped tumor, 5.3 × 5.2 × 4.2 cm, that was submucosal but protruded into the gastric lumen. The histopathologic diagnosis was metastasis from IMFH of the gall-

bladder. No lymph node metastasis was found. The postoperative course was uneventful, and the patient is currently alive and tumor-free but being followed closely.

Discussion

The IMFH was first described by Kyriakos and Kempson[13] in 1976 as "inflammatory fibrous histiocytoma." Unlike other types of MFH, IMFH is more likely to develop in the retroperitoneum than in the extremities, and diseases previously called "malignant xanthogranuloma"[14] or "xanthosarcoma"[15] are in fact IMFH. Histopathologically, IMFH is characterized by: (1) bland and anaplastic histiocytes; (2) diffuse, intense infiltration of neutrophils; and (3) no tissue necrosis. Characteristically, it often causes hematologic disorders, which can be neoplastic or reactive, and paraneoplastic syndromes such as fever and general fatigue.[13] In 1979 Roques et al.[11] reported a case of abdominal MFH accompanied by a leukemoid reaction and suggested the possible production of hematopoietic growth factors by IMFH tumor cells. Since then, it has been speculated that certain cytokines are produced by IMFH tumor cells.[8,12] Melhem et al.[12] detected cytokines in the sera from IMFH patients and demonstrated their production by malignant histiocytes. In our patient the leukocyte count prior to the initial surgery was extremely high, and the serum G-CSF concentration was elevated. Moreover, the cytoplasm of the tumor cells stained diffusely for G-CSF, and the inflammatory reaction subsided immediately after tumor resection. Hence, it is highly likely that the tumor cells produced G-CSF.

Benign inflammatory lesions, such as xanthogranulomatous cholecystitis (XGC) should be included in the differential diagnosis of IMFH of the gallbladder. The gallbladder is more vulnerable to inflammation and infection than soft tissues, and it can be difficult to distinguish IMFH from inflammatory pseudotumors (IPTs). Histologically, XGC is characterized by predominant foamy histiocytes (xanthoma cells) with acute and chronic inflammatory cells.[16] The preoperative needle biopsy from the tumor in our patient revealed dense foamy histiocytes and fibrous granulation tissue with the infiltration of neutrophils, lymphocytes, and plasma cells, leading to a presumptive diagnosis of XGC. The difference between XGC and IMFH depends on the documentation of atypia and mitotic activity in the xanthoma cells or fibroblastic area resembling the usual form of MFH.[8] Because of this, it is difficult to make a correct diagnosis preoperatively using scant biopsy material. The major part of the tumor had xanthogranulomatous histology, and only a small portion consisted of classic MFH in this case. Therefore, biopsies should be performed at multiple sites when MFH is suspected.

Since Kristofferson et al.[1] first reported primary MFH in the gallbladder in 1983, only nine cases (eight reports), including the present one, have been documented,[2–7] six (66.7%) of which were accompanied by gallstones. In most cases, ultrasonography and computed tomography of the gallbladder reveal irregular wall thickness or an ill-defined mass with areas of low or heterogeneous echogenicity that represent necrosis or hemorrhage. Angiography usually shows hypovascular areas with no evidence of tumor vessel growth, although hypervascularity with a faint tumor stain has been reported.[2–4,6,7] In summary, the absence of distinctly characteristic features makes establishing a preoperative diagnosis of MFH of the gallbladder exceedingly difficult.

Our patient has survived more than 3 years. It is generally agreed that the inflammatory type of MFH has a relatively better prognosis than other types of MFH. Enzinger and Weiss[8] hypothesized that the prominent inflammatory component is responsible for the better prognosis. The tumor spread in this case almost certainly was hematogenous rather than lymphogenous because no lymph node metastases were identified. Based on our experience with this case, we believe that multiple surgical procedures to resect primary and metastatic lesions of IMFH of the gallbladder are appropriate when each tumor is solitary and well circumscribed.

References

1. Kristofferson AO, Domellof L, Emdin SO, Kullenberg K (1983) Malignant fibrous histiocytoma of the gallbladder: a case report. J Surg Oncol 23:56–59
2. Sasada A, Yanagawa M, Hayashi S, Kita Y, Yoshimura M (1988) Primary malignant fibrous histiocytoma of the gallbladder: a case report (in Japanese with English abstract). Nippon Geka Gakkai Zasshi (J Jpn Surg Soc) 89:1306–1309
3. Kakutani H, Yamada T, Ikeda H, Harada Y, Saito T, Ashizawa S, Koyanagi Y, Kimura K (1989) A case report: primary sarcoma of the gallbladder: malignant fibrous histiocytoma (in Japanese with English abstract). Fukubu Gazo Shindan (Diagnostic Imaging of the Abdomen) 9:649–653
4. Miyakawa R, Anbe R, Miyazaki K, Kawa I, Hamano K (1992) A case report: primary sarcoma of the gallbladder: malignant fibrous histiocytoma (in Japanese with English abstract). Nippon Rinsyo Geka Igakkai Zasshi (J Jpn Soc Clin Surg) 53:955–959
5. Sreekantaiah C, Rao UNM, Karakousis CP, Sandberg AA (1992) Cytogenetic findings in a malignant fibrous histiocytoma of the gallbladder. Cancer Genet Cytogenet 59:30–34
6. Sakamoto K, Yukimoto K, Hayashibe A, Tanaka H, Kitou H, Taruya E, Yanagi Z, Tokura K, Asada K, Takebayashi J (1996) A case of primary malignant fibrous histiocytoma of the gallbladder (in Japanese with English abstract). Nippon Syokaki Geka Gakkai Zasshi (Jpn J Gastroenterol Surg) 29:746–750
7. Tomono H, Fujioka S, Kato K, Yoshida K, Nimura Y (1998) Malignant fibrous histiocytoma of the gallbladder. Hepatogastroenterology 45:1468–1472

8. Enzinger FM, Weiss SW (1995) Soft tissue tumors, 3rd edn. Mosby, St. Louis, pp 351–380
9. Enjoji M, Hashimoto H, Tsuneyoshi M, Iwasaki H (1980) Malignant fibrous histiocytoma: a clinicopathological study of 130 cases. Act Pathol Jpn 30:727–741
10. Rooser B, Willen H, Gustafson P (1991) Malignant fibrous histiocytoma of soft tissue: a population-based epidemiologic and prognostic study of 137 patients. Cancer 67:499–505
11. Roques AWW, Horton LWL, Leslie J, Buxton-Thomas MS (1979) Inflammatory fibrous histiocytoma in the left upper abdomen with a leukemoid blood picture. Cancer 43:1800–1804
12. Melhem MF, Meisler AI, Saito R, Finley GG, Hockman HR, Koski RA (1993) Cytokines in inflammatory malignant fibrous histiocytoma presenting with leukemoid reaction. Blood 82:2038–2044
13. Kyriakos M, Kempson RL (1976) Inflammatory fibrous histiocytoma: an aggressive and lethal lesion. Cancer 37:1584–1606
14. Stout AP, Lattes R (1967) Tumors of the soft tissues. In: Atlas of tumor pathology, second series, fascicle 1. Armed Forces Institute of Pathology, Washington, DC, p 107
15. Kahn LB (1973) Retroperitoneal xanthogranuloma and xanthosarcoma (malignant fibrous xanthoma). Cancer 31: 411–422
16. Dao AH, Wong SW, Adkins RB (1989) Xanthogranulomatous cholecystitis: a clinical and pathologic study of twelve cases. Am Surg 55:32–35