

Undifferentiated Gallbladder Carcinoma with Osteoclast-like Giant Cells – A Case Report –

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Undifferentiated carcinoma with osteoclast-like giant cells (OGCs) is the least common type of gallbladder carcinoma. Here, the author presents a case of undifferentiated gallbladder carcinoma with OGCs in an 81-year-old male patient. Grossly, the tumor was a 10 × 7 cm sized, polypoid, lumen-filling mass with extensive hemorrhage and necrosis. Microscopically, the tumor was composed of pleomorphic ovoid to spindle cells admixed with numerous OGCs. There was a minute focus of mucosal dysplasia and carcinoma *in situ*. Immunohistochemically, the mononuclear cells were positive for cytokeratin, p53 and Ki-67, while the OGCs were negative for these markers but positive for CD68. These findings support an epithelial origin for the ovoid to spindle cells and the nonneoplastic reactive histiocytic lineage of the OGCs.

Key Words : Carcinoma, Undifferentiated; Gallbladder; Osteoclast; Giant cells

Undifferentiated carcinoma of the gallbladder is an uncommon neoplasm and includes four morphologic variants: spindle and giant cell type, small cell type, lobular type and osteoclast-like giant cell type.¹ Undifferentiated carcinoma with osteoclast-like giant cells (OGCs) is the least common but most distinctive type. It comprises of sheets of round and ovoid cells, and fascicles of spindle cells admixed with numerous OGCs, thereby mimicking a giant cell tumor of the bone. Identical cases occur in the pancreas, where it is referred to as osteoclast-like giant cell tumor.² The author presents a case of undifferentiated carcinoma of the gallbladder with OGCs and discusses the pathogenesis of this tumor with a review of the literature.

CASE REPORT

An 81-year-old man presented with fatigue, general weakness and weight loss. He was referred to our institution after visiting a local health care center where he was found to have a gallbladder mass. Physical examination showed no remarkable findings except for high blood pressure. Laboratory examination revealed mild anemia (hemoglobin of 9.0 g/dL and hematocrit of 29),

and a normal serum levels of carcinoembryonic antigen (CEA), CA19-9, and α -fetoprotein. Ultrasonographic examination and computerized tomography of the abdomen showed a distended gallbladder with diffuse irregular wall thickening and luminal bile sludge, suggestive of an infiltrative type of cancer (Fig. 1). The presence of several gallstones was also noted, and there was no regional lymph node enlargement. The patient underwent cholecystectomy and hepatic resection of the gallbladder bed.

Grossly, the gallbladder, including cystic duct, measured 12 cm in length and 8 cm in the greatest diameter. Patchy areas of hemorrhage and irregularity were observed on the outer peritoneal surface. On opening, the lumen was almost entirely filled with hemorrhagic and necrotic mass, measuring 10 × 7 cm (Fig. 2). The surrounding mucosa was hemorrhagic and erosive, and the gallbladder wall revealed irregular thickening. The resected hepatic tissue was adhered to the nearby gallbladder wall. Three pigmented gallstones were found and measured up to 1.5 cm in size.

Microscopically, the tumor was composed of mononuclear ovoid to spindle cells showing considerable variation in size and degree of atypia. The majority of tumor cells revealed marked nuclear pleomorphism, while some mononuclear cells had bland-

looking nuclei with little atypia. Those cells displayed frequent mitotic figures up to 8/10 high power fields, including abnormal ones (Fig. 3A). Multinucleated giant cells that morphologically resembled osteoclasts were evenly dispersed throughout the tumor. These cells contained variable numbers of nuclei, ranging from 2 to 50, and each nucleus often had vesicular chromatin and a small discrete nucleolus (Fig. 3B). These giant cells dis-



Fig. 1. An abdominal computerized tomography reveals a distended, stone containing gallbladder with diffuse irregular wall thickening, lobulated internal border and luminal bile sludge.

played plenty amount of eosinophilic cytoplasm with occasional intracytoplasmic vacuoles and phagocytosis of nuclear debris. Mitotic figures were not found in these giant cells. At several foci, the giant cells showed a wreath of nuclei surrounded by foamy cytoplasm, mimicking Touton giant cells that intermingled with xanthoma cells and lymphocytes. Neither glandular differentiation nor mucin-containing cells were observed with-



Fig. 2. The resected gallbladder shows a huge, friable, luminal hematoma-like mass. Three pigmented stones are noted.

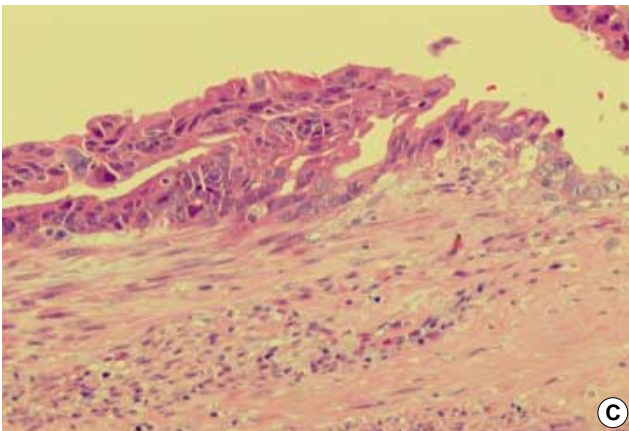
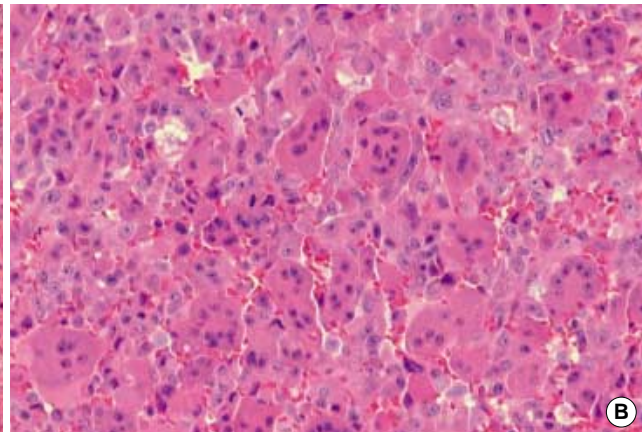
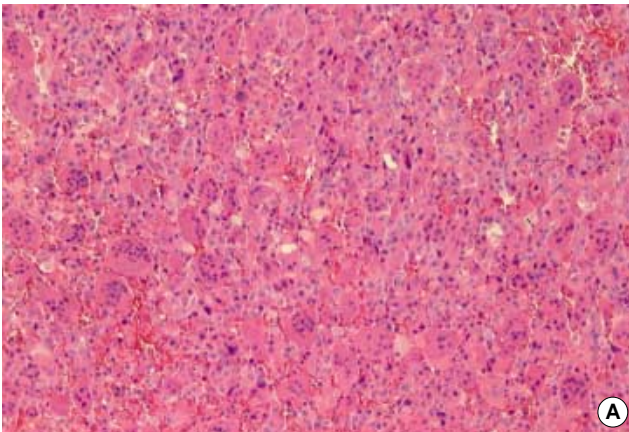


Fig. 3. (A) Osteoclast-like multinucleated giant cells (OGCs) are evenly intermixed within the tumor. (B) Tumor cells have ovoid or elongated nuclei, showing variable pleomorphism and frequent mitosis. OGCs have abundant eosinophilic cytoplasm with multiple, benign-appearing nuclei. (C) A minute focus of mucosal carcinoma *in situ* lesion is noted.

in the main tumor. Twenty-five histological sections were made throughout the gallbladder, and only one showed a minute area of epithelial dysplasia and *in situ* carcinoma in the surrounding

Table 1. Primary antibodies used in the immunohistochemical stainings and their expression pattern

Antibody	Type (clone)	Source	Expression		
			Pleomorphic cells	OGCs	Carcinoma <i>in situ</i>
CK	M (MNF116)	Dako	focal +	--	+
Vimentin	M (V9)	Dako	+	+	--
CD68	M (KP1)	Dako	--	+	--
CEA	M (II-7)	Dako	--	--	+
p53	M (DO-7)	Dako	focal +	--	NE
Ki-67	M (7B11)	Zymed	15%	--	NE

CK, cytokeratin; CEA, carcinoembryonic antigen; M, monoclonal; OGCs, osteoclast-like giant cells; NE, not evaluated.

flat, erosive mucosa (Fig. 3C). Many parts of the tumor revealed extensive necrosis and fresh or old hemorrhage. The tumor infiltrated into full thickness of the gallbladder wall and focally penetrated the serosa. At the gallbladder bed, the tumor provoked a desmoplastic stromal reaction but did not invade the hepatic parenchyma. A few lymphatic tumor emboli were noted. The cystic duct resection margin and a lymph node around the cystic duct were both tumor negative.

Immunohistochemical stainings for cytokeratin, vimentin, CEA, CD68, Ki-67 and p53 were performed. The mononuclear pleomorphic cells were diffusely positive for vimentin and focally positive for cytokeratin and p53. Both the OGCs and bland-looking mononuclear cells were positive for CD68 and vimentin. CEA was positive only in the mucosal carcinoma *in situ*. Ki-67 stained the nuclei of the mononuclear pleomorphic

Table 2. Clinicopathological findings of the reported cases* of gallbladder tumor with OGCs

	Case 1	Case 2	Case 3	Case 4	Case 5
Age, Sex	74, M	74, F	72, F	45, F	81, M
Presentation	RUQ mass RUQ pain	Weight loss	Abdominal pain	Abdominal pain	Weakness Weight loss
Size (cm)	7 × 4	5 × 3	6	4	10 × 7
Gross	Hematoma-like	Hemorrhagic	Nodular	Polypoid	Hemorrhagic
Stone	+	+	--	+	+
Carcinoma ¹	Adenoca	Adenosq	Adenosq	none	<i>In situ</i> Ca
PMC	+	--	--	--	+
Invasion	Liver	Liver Colon	Liver LN	Subserosa ²	Serosa
Follow up	?	DOD (2 mo)	DOAC (6 yr)	Alive, DF	Death (7 mo)
References	9	10	11	12	Present case

*Only the reported cases with thorough clinicopathological informations were included. All of the cases were carcinoma while case 4 was a benign giant cell tumor, ¹Coexisting differentiated carcinoma, ²The giant cell tumor extended through the muscle coat into the subserosal fat.

OGCs, osteoclast-like giant cells; RUQ, right upper quadrant; Adenoca, adenocarcinoma; Adenosq, adenosquamous carcinoma; Ca, carcinoma; PMC, pleomorphic mononuclear cells; LN, lymph node; DOD, died of disease; DOAC, died of another cause; DF, disease free; mo, months; yr, years.

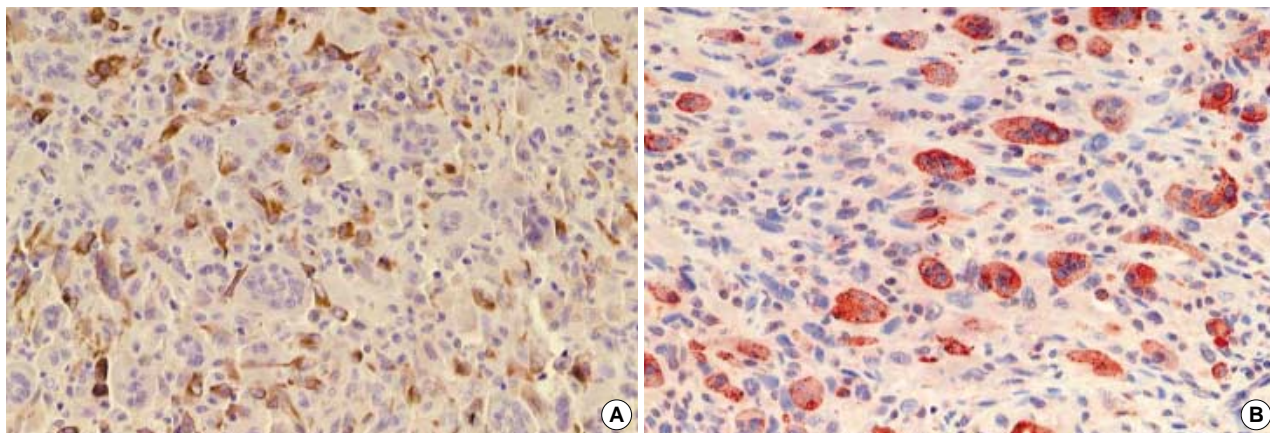


Fig. 4. The immunohistochemical stainings demonstrate cytokeratin positivity in pleomorphic cells (A) and CD68 expression in osteoclast-like giant cells (B).

cells in which the labeling index was 15%, but it did not stain the OGCs. The results of the immunohistochemical stainings are shown in Fig. 4 and summarized in Table 1.

The final diagnosis of the tumor was undifferentiated carcinoma with OGCs, and the pathological stage was determined to be IIA (T3, N0, M0) according to the AJCC cancer staging system.³ The patient did not receive any additional therapy and died seven months after the surgery.

DISCUSSION

Carcinomas with OGCs have been infrequently described in a variety of anatomic sites, including the breast, pancreas, stomach, small intestine, and liver.⁴⁻⁸ The terminology, histogenesis, and biologic behavior of these tumors remain controversial, although some authors have suggested that they might represent a distinct neoplasm with a more favorable prognosis.^{4,6} Several cases of gallbladder tumor with a prominent OGC component have been reported (Table 2).⁹⁻¹² However, no such case has been reported in Korea based on a search of the KoreaMed database.

Undifferentiated carcinoma of the gallbladder includes four heterogeneous variants and the OGC type is the fourth morphologic variant. It is the most uncommon type and accounted for just 2% of the reported undifferentiated carcinomas according to one of the previous studies.¹³ Microscopically, OGC type undifferentiated carcinoma shows two major components admixed throughout the mass: mononuclear ovoid to spindle cells and multinuclear OGCs. The mononuclear cells, which show varying degrees of nuclear atypia, are the neoplastic component of the tumor, and they are immunoreactive for epithelial markers. The OGCs have bland nuclear features and are positive for histiocytic markers, thus indicating that they are the reactive component of the tumor. The present case had mononuclear cells showing variable nuclear atypia and reactivity for cytokeratin, p53 and Ki-67. The mononuclear cells often showed marked nuclear pleomorphism. The OGCs in the present case displayed bland-looking nuclei, a lack of reactivity for epithelial or proliferative markers and were positive for CD68. The OGCs also showed occasional phagocytotic activity, and they were evenly distributed throughout the tumor. These microscopic findings fulfilled the diagnostic criteria for OGC type undifferentiated carcinoma.¹

The previously reported gallbladder carcinomas with OGCs were heterogeneous and associated with or frequently contained foci of conventional differentiated carcinoma.⁹⁻¹¹ The present

case did not show any glandular differentiation within the main tumor and only a minute focus of *in situ* carcinoma was observed in the tumor-adjacent mucosa. Although the transition between the two components was not obvious, it might reflect the dedifferentiation from *in situ* carcinoma to undifferentiated carcinoma.

No unified gross feature has been defined for the carcinomas with OGCs in the gallbladder, however, they usually showed hemorrhage, cystic changes, and necrosis when occurring in the pancreas and periampullary region.⁵ In most of the previously reported cases, gallstones coexisted with the carcinoma, as was the case in our patient.^{9,10,12}

The clinical and prognostic significance of OGCs in gallbladder carcinoma remains unclear. According to the previously reported cases, gallbladder carcinoma with OGCs tends to present after the 7th decade of life and is typically associated with a poor prognosis.⁹⁻¹¹ The present case did not have regional lymph node metastasis, which was quite unusual considering the large primary tumor mass. However, he died seven months after the surgery.

Recently Arbores-Saavedra *et al.* reported a true benign osteoclast-like giant cell tumor of the extrahepatic biliary tree, including the gallbladder, which should be distinguished from the undifferentiated carcinoma with OGCs.¹² They also mentioned that a small portion of spindle and giant cell type undifferentiated carcinomas may contain a few OGCs. Therefore, it should be aware that neoplasms with reactive OGCs show a wide range of clinicopathological variants, from benign osteoclastoma to highly aggressive undifferentiated carcinoma.

The majority of previous reports were in agreement on the histiocytic nature of the OGCs.^{4-7,9-12} It was also suggested that the formation of OGCs may result from the fusion of mononuclear histiocytes attracted to the tumor by growth or chemotactic factors elaborated by the neoplastic cells.⁵ The presence of benign-looking mononuclear histiocytic cells around OGCs in the present case is consistent with this hypothesis.

In summary, the author described a case of undifferentiated gallbladder carcinoma with numerous OGCs. It is expected that this case may provide additional relevant clinicopathological information on this rare but distinct neoplasm.

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