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Case Report:

Gastric carcinoma with osteoclast-like giant cells: a case report and review of the literature*

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Abstract: Gastric carcinoma with osteoclast-like giant cells (OGCs) is an extremely rare tumor. So far, only six cases have been reported in the literature. Here we report an additional case of this tumor in a Chinese 78-year-old man presented with abdominal pain, vomiting, and hematemesis. Physical examination and gastroscopy revealed a tumor in the gastric antrum. The biopsy and pathological findings indicated a gastric adenocarcinoma with OGCs, which were present in both the tumor and the metastatic lymph nodes. Further immunohistochemical staining indicated that OGCs were reactive with CD68, CD45, and vimentin protein, but not with pancytokeratin, carcinoembryonic antigen, or epithelial membrane antigen, suggesting the monocytic/histiocytic derivation of these OGCs. In situ hybridization for Epstein-Barr virus showed no nuclear positivity in either adenocarcinoma or OGCs. Postoperative follow-up showed that the patient had survived for at least 6 months without recurrence. Further investigation is warranted to clearly define the prognostic significance of OGCs in gastric carcinoma.

Key words: Gastric carcinoma, Adenocarcinoma, Osteoclast-like giant cell (OGC)
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INTRODUCTION

Benign multinucleated giant cells have been reported in neoplasms of various organs, such as the breast, pancreas, thyroid, liver, gallbladder and lung (Gjerdrum *et al*., 2001; Tezuka *et al*., 2006; Mehdi *et al*., 2007; Ahaouche *et al*., 2005; Akatsu *et al*., 2006; Bocklage *et al*., 1998). Because these giant cells present similar morphology with those in giant cell tumors of bones, they are named as osteoclast-like giant cells (OGCs) (Gjerdrum *et al*., 2001). Recently, some authors have suggested that the OGCs originate from monocytes/histiocytes, and probably represent an unusual host response to the accompanying neoplasm (Al-Brahim and Salama, 2005). However, the clinical importance of this phenomenon remains unclear, owing to the rarity of such cases. So far, only six cases of gastric carcinoma with OGCs have been reported (Baschinsky *et al*., 1999; Stracca-Pansa *et al*., 1995; Willems *et al*., 2005). Although the significance of OGCs still remains unclear, these authors believed that gastric carcinoma with OGCs may represent a distinct pathological entity (Baschinsky *et al*., 1999; Stracca-Pansa *et al*., 1995; Willems *et al*., 2005). Here, we report an additional case of gastric carcinoma with OGCs and review the literature.

CASE REPORT

A 78-year-old male patient was admitted because of abdominal pain, vomiting, and hematemesis in the preceding 12-month period. There was no

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history of hematochezia, melena, clay-colored stools, jaundice, or hepatitis. Physical examination revealed mild tenderness in the epigastric and right upper quadrant regions of abdomen. A 6 cm×5 cm solid mass with obscure boundary was palpable in the middle abdomen around the navel. During the gastroscopical examination, an 8 cm×6 cm tumor mass was clearly observed in the antrum and posterior wall of the stomach. Since the mass biopsy indicated an adenocarcinoma, an exploratory laparotomy was undertaken for the patient with resection of the whole stomach. Postoperative follow-up showed that the patient had survived for at least 6 months without recurrence.

Pathological findings

The initial gastroscopic biopsy showed that some tissue fragments of the initial gastroscopic biopsy contained necrosis of ulceration, whereas others contained infiltrating signet ring cell cancer. The OGCs were not identified under a microscope. The specimens of laparotomy included the whole stomach, and parts of the proximal duodenum and omentum. In the stomach body and antrum, a 10 cm×8 cm lump area was observed. There were 25 lymph nodes within the connective tissue around the stomach. Representative tumor specimens were collected, fixed in 0.1 g/ml neutral formalin, embedded in paraffin, sliced at thickness of 3~4 μm, and stained with hematoxylin and eosin. Under a microscopy, the peripheral tumor specimens showed a poorly differentiated adenocarcinoma with glandular spaces. The central part of ulceration was characterized by a poorly differentiated adenocarcinoma with focal signet ring cells. There was no prominent vascularity throughout the tumor. OGCs, small round lymphocytes and plasma cells were present at the periphery of tumor and sprinkled among the tumor cells (Fig.1). The giant cells contained 3~20 regular and round nuclei with evenly dispersed chromatin. The tumor invaded into the muscular layer and through seromuscular layer. There was no carcinoma at the surgical resection margins. However, the gastric mucosa represented chronic gastritis and focal intestinal metaplasia. Metastatic adenocarcinoma was observed in 13 of the 25 lymph nodes. Within all of the metastatic lymph nodes, there were a lot of OGCs intermixed with the tumor cells.

Immunohistochemical staining and in situ hybridization

To better define the nature of OGCs, immunohistochemical staining was applied. As shown in Fig.2, OGCs were immuno-reactive with antibodies against CD68 (Dako, Glostrup, Denmark), CD45 (Dako), and vimentin protein (Dako), but not reactive with antibodies against pancytokeratin (AE1/AE3; Dako), carcinoembryonic antigen (CEA; Dako), or epithelial membrane antigen (Dako). The tumor cells were reactive with pancytokeratin and CEA, but no reactive with CD68, CD45, vimentin protein, or epithelial membrane antigen. In addition, neither the adenocarcinoma nor OGCs were reactive with antibodies (Dako) against the muscle-specific actin (clone HHF-35), smooth muscle antigen, S-100 protein, and latent membrane protein (LMP) of the Epstein-Barr virus (EBV). Moreover, in situ hybridization showed no nuclear positivity of EBV in either the adenocarcinoma or OGCs.

DISCUSSION

Extraskeletal tumors containing OGCs are frequently reported in the breast and pancreas (Krishnan and Longacre, 2006; Molberg *et al*., 1998). So far, only six cases of gastric carcinoma with OGCs have been reported in the literature (Baschinsky *et al*., 1999; Stracca-Pansa *et al*., 1995; Willems *et al*., 2005). All these cases were poorly differentiated adenocarcinoma characterized by the presence of OGCs sprinkled among the tumor cells (Baschinsky *et al*., 1999; Stracca-Pansa *et al*., 1995; Willems *et al*., 2005). Gastric carcinomas with OGCs should be distinguished from giant cell carcinomas, which have the following distinctive features. Firstly, they are composed of pleomorphic and undifferentiated giant cells with bizarre nuclei (Alasio *et al*., 2007). Secondly, giant cell carcinomas show immunohistochemical evidences of epithelial characteristics (Alasio *et al*., 2007). Thirdly, these tumors represent a transition between adenocarcinoma and giant cells since these components have the same origin (Alasio *et al*., 2007). The OGCs found in our patient had none of these characteristics. Similar to the reported cases of gastric carcinoma with OGCs (Baschinsky *et al*., 1999; Stracca-Pansa *et al*., 1995; Willems *et al*., 2005),

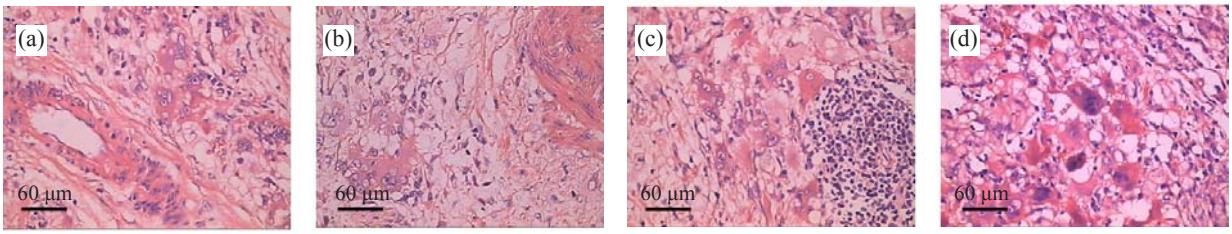

Fig.1 Pathological characteristics of gastric carcinoma with OGCs (hematoxylin and eosin staining). (a) Within the gastric lesions, poorly formed neoplastic glands were surrounded by numerous OGCs, with remaining of some normal stomach mucous membrane; (b) OGCs were sprinkled among the tumor cells in cancer tissues; (c) Cancer cells metastasized to the lymph nodes, with the remaining of lymph follicle; (d) Within the involved lymph nodes, OGCs were sprinkled among the tumor cells as part of formed cancer nests

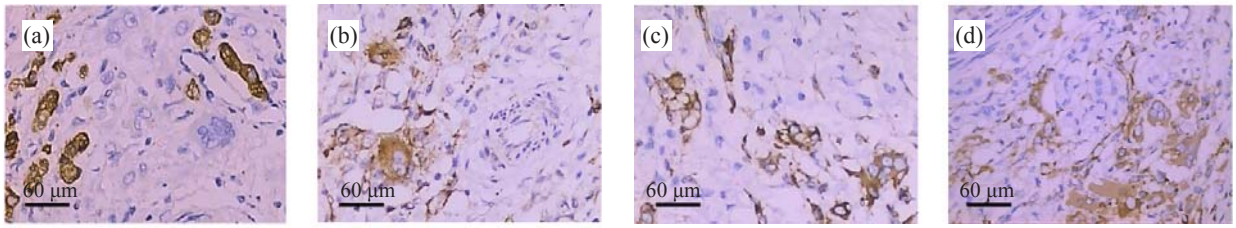

Fig.2 Immunohistochemical staining for gastric carcinoma with OGCs (avidin-biotin immunoperoxidase method). (a) Strong pancytokeratin staining of the cancer cells, but a complete lack of staining in OGCs; (b) Positive staining of CD45 in OGCs, but not in cancer cells; (c) Positive staining of CD68 in OGCs, but not in cancer cells; (d) Positive staining of vimentin in OGCs and vessels, but not in cancer cells

the tumor invaded beyond the muscular layers in this case. There were 13 metastatic lymph nodes, and one of them was 3.5 cm in diameter. We suspected that the gastric carcinoma may represent a metastasis from other organs. However, we did not find any other mass during the exploratory laparotomy, which indicated a primary carcinoma of gastric origin. In addition, a previous report indicated that increased vascularity was associated with tumor with OGCs (Min and Gillies, 1996); however, we did not find the abnormality of vascularity (such as hemorrhage) in this case.

The nature and origin of OGCs still remain largely unknown. Some authors suggest that OGCs derive from epithelial, histiocytic, or mesenchymal metaplasia (Gjerdrum *et al*., 2001; Tezuka *et al*., 2006; Krishnan and Longacre, 2006; Molberg *et al*., 1998). Consistent with previous cases of gastric carcinoma, OGCs were present in both the tumor tissues and the metastasic lymph nodes in this case. These evidences suggest that OGCs may be one part of the systemic response to tumor, but not a local reaction to tumor tissue damage and invasion. In accordance with the previous reports (Baschinsky *et al*., 1999; Stracca-Pansa *et al*., 1995; Willems *et al*., 2005), OGCs present in this case showed immunohistochemical evidence of monocytic/histiocytic origin, but not of epithelial derivation. The cancer cells were strongly and exclusively immuno-reactive with pancytokeratin, while the OGCs represented strong CD68 staining in cytoplasm. These findings indicate that OGCs are a specialized form of macrophage. The detailed mechanism of this peculiar reaction still remains speculative. The formation of OGCs may result from fusion of mononuclear histiocytes/macrophages, which were attracted to the tumor tissues by cancer cell-released growth or chemotactic factors (Newbould *et al*., 1992). Further investigations are needed to confirm this hypothesis.

Since the presence of a marked lymphocytic infiltrate in this case, the possibility of a lymphoepithelioma-like carcinoma (LELC), which can occur in the stomach, was raised. The LELCs are undifferentiated adenocarcinomas characterized by a strong lymphoid reaction and shortage of OGCs (Willems *et al*., 2005). In a previous report, the EBV sequences were found in seven of eight gastric carcinomas with LELC morphology, which indicated a potential linkage between EBV and lymphoid infiltrate within tumors (Shibata *et al*., 1991). In six reported cases of

gastric carcinoma with OGCs (Baschinsky *et al*., 1999; Stracca-Pansa *et al*., 1995; Willems *et al*., 2005), one case was immunohistochemical positive for LMP of the EBV (EBV-LMP) (Stracca-Pansa *et al*., 1995), while another case showed intense nuclear positivity for EBV measured by in situ hybridization (Willems *et al*., 2005). However, in this case, the immunohistochemical staining for EBV-LMP and in situ hybridization for EBV were non-reactive.

Although the OGCs are a characteristic feature of tumors, its significance is unknown. Recently, some authors have suggested that gastric carcinoma with OGCs is associated with a more favorable prognosis (Baschinsky *et al*., 1999). As shown in Table 1, males appear to be affected in a higher rate than females. In these cases, the tumor was at an advanced stage with metastasis of lymph nodes. Postoperatively, the patient had survived for at least 6 months without evidence of recurrence. Follow-up data in the literature (Table 1) have shown that 50% of patients with gastric carcinoma containing OGCs were still alive after surgery, and that one patient was alive for 10 years (Stracca-Pansa *et al*., 1995). However, further investigation is warranted to clearly define the prognostic significance of OGCs in gastric carcinoma.

Table 1 Summary of reported cases of gastric carcinoma with OGCs

Cases	References	Patient's age (year)	Gender	Tumor stage	Postoperative follow-up
1	Stracca-Pansa *et al*., 1995	63	Male	T2 N1 M0	Alive and well for 120 months
2	Stracca-Pansa *et al*., 1995	53	Male	T2 N2 M0	Dead of disease after 24 months
3	Stracca-Pansa *et al*., 1995	61	Male	T2 N1 M0	Dead of disease after 15 months
4	Stracca-Pansa *et al*., 1995	76	Male	T2 N1 M0	Dead of disease after 13 months
5	Baschinsky *et al*., 1999	64	Female	T1 N2 M0	Alive and well for 12 months
6	Willems *et al*., 2005	50	Male	T3 N0 M0	Alive for 3 months
7	Current case	78	Male	T3 N2 M1	Alive for 6 months so far

References

Ahaouche, M., Cazals-Hatem, D., Sommacale, D., Cadranel, J.F., Belghiti, J., Degott, C., 2005. A malignant hepatic tumour with osteoclast-like giant cells. *Histopathology*, **46**(5):590-592. [doi:10.1111/j.1365-2559.2005.02018.x]

Akatsu, T., Kameyama, K., Kawachi, S., Tanabe, M., Aiura, K., Wakabayashi, G., Ueda, M., Shimazu, M., Kitajima, M., 2006. Gallbladder carcinoma with osteoclast-like giant cells. *J. Gastroenterol.*, **41**(1):83-87. [doi:10.1007/s00535-005-1726-5]

Alasio, T.M., Sun, W., Yang, G.C., 2007. Giant cell carcinoma of the lung impact of diagnosis and review of cytological features. *Diagn. Cytopathol.*, **35**(9):555-559. [doi:10.1002/dc. 20701]

Al-Brahim, N., Salama, S., 2005. Malignant melanoma with osteoclast-like giant cells: an unusual host response: immunohistochemical and ultrastructural study of three cases and literature review. *Am. J. Dermatopathol.*, **27**(2):126-129. [doi:10.1097/00000372-200504000-00007]

Baschinsky, D.Y., Frankel, W.L., Niemann, T.H., 1999. Gastric carcinoma with osteoclast-like giant cells. *Am. J. Gastroenterol.*, **94**(6):1678-1681. [doi:10.1111/j.1572-0241.1999.01162.x]

Bocklage, T.J., Dail, D., Colby, T.V., 1998. Primary lung tumors infiltrated by osteoclast-like giant cells. *Ann. Diagn. Pathol.*, **2**(4):229-240. [doi:10.1016/S1092-9134(98)80012-9]

Gjerdrum, L.M., Lauridsen, M.C., Sorensen, F.B., 2001. Breast carcinoma with osteoclast-like giant cells: morphological and ultrastructural studies of a case with review of the literature. *Breast*, **10**(3):231-236. [doi:10.1054/brst.2000.0244]

Krishnan, C., Longacre, T.A., 2006. Ductal carcinoma in situ of the breast with osteoclast-like giant cells. *Hum. Pathol.*, **37**(3):369-372. [doi:10.1016/j.humpath.2005.11.012]

Mehdi, G., Ansari, H.A., Siddiqui, S.A., 2007. Cytology of anaplastic giant cell carcinoma of the thyroid with osteoclast-like giant cells—a case report. *Diagn. Cytopathol.*, **35**(2):111-112. [doi:10.1002/dc.20595]

Min, K.W., Gillies, E., 1996. Multinucleated giant stromal tumor of the omentum: report of a case with immunohistochemical and ultrastructural investigation. *Ultrastruct. Pathol.*, **20**(1):89-99. [doi:10.3109/01913129609023243]

Molberg, K.H., Heffess, C., Delgado, R., Albores-Saavedra, J., 1998. Undifferentiated carcinoma with osteoclast-like giant cells of the pancreas and periampullary region. *Cancer*, **82**(7):1279-1287. [doi:10.1002/(SICI)1097-0142(19980401)82:7<1279::AID-CNCR10>3.0.CO; 2-3]

Newbould, M.J., Benbow, E.W., Sene, A., Young, M., Taylor, T.V., 1992. Adenocarcinoma of the pancreas with osteoclast-like giant cells: a case report with immunocytochemistry. *Pancreas*, **7**(5):611-615. [doi:10.1097/0000

6676-199209000-00015]

Shibata, D., Tokunaga, M., Uemura, Y., Sato, E., Tanaka, S., Weiss, L.M., 1991. Association of Epstein-Barr virus with undifferentiated gastric carcinomas with intense lymphoid infiltration. Lymphoepithelioma-like carcinoma. *Am. J. Pathol.*, **139**(3):469-474.

Stracca-Pansa, V., Menegon, A., Donisi, P.M., Bozzola, L., Fedeli, F., Quarto, F., Nappi, O., Pettinato, G., 1995. Gastric carcinoma with osteoclast-like giant cells. Report of four cases. *Am. J. Clin. Pathol.*, **103**(4):453-459.

Tezuka, K., Yamakawa, M., Jingu, A., Ikeda, Y., Kimura, W., 2006. An unusual case of undifferentiated carcinoma in situ with osteoclast-like giant cells of the pancreas. *Pancreas*, **33**(3):304-310. [doi:10.1097/01.mpa.0000235303.11734.2a]

Willems, S., Carneiro, F., Geboes, K., 2005. Gastric carcinoma with osteoclast-like giant cells and lymphoepithelioma-like carcinoma of the stomach: two of a kind? *Histopathology*, **47**(3):331-333. [doi:10.1111/j.1365-2559.2005.02135.x]