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A case of early gastric cancer with bone metastases : are bone marrow micrometastases significant ?

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Abstract

Gastric adenocarcinoma is currently the 14th cause of death worldwide. Early gastric cancer, defined as cancer not penetrating deeper than the submucosa, is considered to carry an excellent prognosis with 5-year survival rates reaching more than 90%. Cases of bone metastases due to intramucosal gastric cancer are very rarely described. A case of a 70-year old male presenting with confirmed bone metastases 7 years after a curative resection for a mucosal gastric carcinoma is discussed. The patient was investigated with bone marrow biopsy and bone scan and showed no other signs of disease. The clinicopathologic features included poor differentiation, signet ring cells presence, no lymph node involvement and a negative second laparotomy two years after the initial surgery. Studies concerning the presence of residual disease in the form of bone marrow micrometastases are briefly reviewed emphasizing that intramucosal gastric cancer still carries the possibility for metastasis, many years after a curative resection, mandating long term alertness from the attending physician. (Acta gastroenterol. belg., **2006**, 69, **231-234**).

Key words : early gastric cancer, bone metastases, bone marrow micrometastases.

Introduction

Gastric adenocarcinoma is currently the 14th cause of death worldwide (1). Early gastric cancer, defined as cancer not penetrating deeper than the submucosa, is considered to carry an excellent prognosis with 5-year survival rates reaching more than 90% (2,3). Cases of bone metastases due to early gastric cancer are rarely described and almost exclusively derive from the Japanese literature (4,5). Early gastric cancer rarely metastasizes, but when it does, bones and in particular bone marrow seem to constitute a large proportion of those metastases (6). Interest in bone marrow micrometastases in gastric cancer is not new and various efforts have been made to relate the detection of tumor cells in the bone marrow of affected individuals with prognosis (7). It is proposed to serve as a useful tool but awaits validation in large trials such as those conducted in breast cancer patients.

Case report

A seventy-year old male was referred to our department because of a 20 fold elevation of alkaline phosphatase and mild normocytic anemia. He had undergone subtotal gastrectomy for carcinoma at our hospital 8 years previously. The primary tumor was located in the antrum along the great curvature. Histological examination had revealed poorly differentiated signet-ring cell adenocarcinoma confined to the mucosa with all 24 lymph nodes examined free of metastasis, no venous or lymphatic invasion and clear surgical margins : T1N0M0m3l0v0. Two years after the initial operation a second surgery was conducted because of symptomatic choledocholithiasis. It also served as a second-look laparotomy with no signs of residual disease, and cholecystectomy and choledochoduodenal anastomosis were performed. No other serious illness, drug ingestion or inherited conditions were mentioned at his medical history. Regular visits as part of his follow up these years had included physical examination, gastroscopy, abdominal CT and tumor markers. His present evaluation included bone scintigraphy, which demonstrated a so called super bone scan picture with diffuse abnormal uptake (Fig. 1). No other abnormal findings resulted

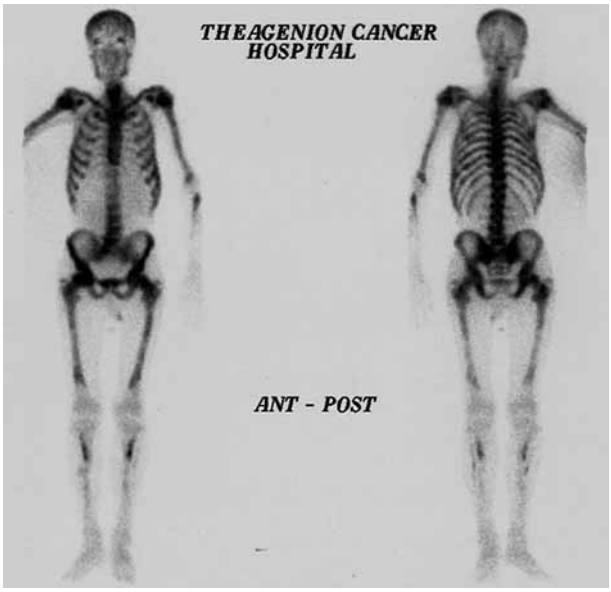

Fig. 1. — Bone scintigramm demonstrating diffuse skeletal uptake : “superscan”.

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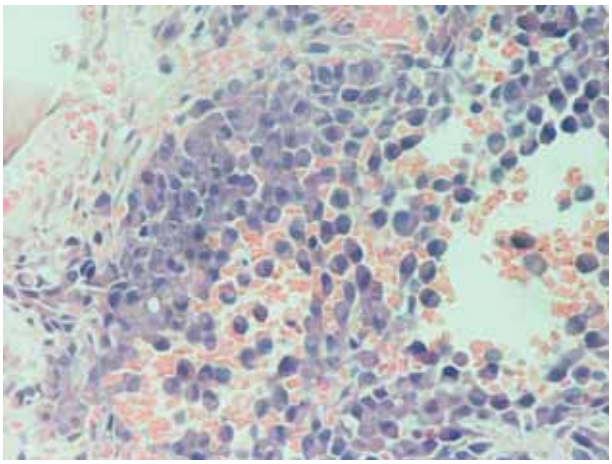

Fig. 2a. — Bone marrow histology showing obvious infiltration with signet-ring cancer cells, whose characteristics when compared were similar with the known resected gastric adenocarcinoma. Immunohistopathology with CEA which was performed showed positivity in both specimens.

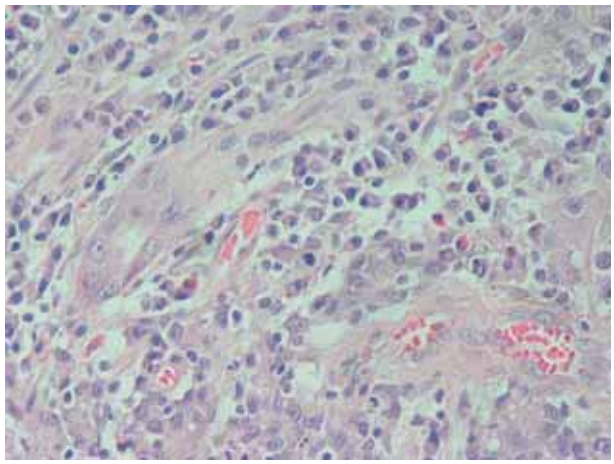

Fig. 2b. — The original histologic slides from the gastrectomy specimen were thoroughly reviewed, again showing no penetration of the lamina propria and no lymphovascular invasion.

from physical examination and routine laboratory tests including chest X-ray and tumor markers. A thorough search for another primary malignant lesion (prostate, lung, and colon) was inconclusive and endoscopy or abdominal imaging failed to prove local recurrence. Ultimately, bone marrow specimen from the sacrum disclosed infiltration with cancer cells identical to those of the previous gastric cancer with presence of signet ring cells in both specimens and compatible immunohistochemistry (Figs. 2a, 2b). The patient was treated successfully with chemotherapy consisting of oxaliplatin, fluoracil and leucovorine (FOLFOX-4 regimen) for a period of 1 year while receiving support with transfusions and haematopoetic growth factors at the initial cycles. No serious side effects were observed and the patient remained in excellent condition. Serum alkaline phosphatase was normalized after 4 months and the need for transfusion stopped after two months. He eventually developed symptoms of intense skeletal pain and laboratory deterioration and denied any further medical intervention. He died 15 months after the initial diagnosis.

Discussion

Gastric cancer is the 2nd most common cause of cancer-related mortality in the world (8). Those involved in the treatment of this disease often have to deal with the disappointment of watching their patients develop metastases, and early gastric cancer remains the only hope for definite cure. Unfortunately, it represents only a small percentage of gastric cancers detected in western industrialized societies as opposed to Japan. Recurrence in early gastric cancer is rare as stated by reports from Matsusaka and Kodama (9,10). Studies by Furusawa (11) and Sano (12) that observed hundreds of patients showed that haematogenous metastases constitute a large part of those recurrences (48% and 59% respectively), in particular bone metastases. In a review of the cases of bone metastases resulting from early gastric cancer, Kobayashi concluded that poor differentiation along with the existence of signet ring cells were among the most common histological features predicting an unfavorable outcome. Kobayashi had speculated that cancer cells invade the small venule in the mucosa during the operation (13).

Our patient is the first case of early gastric cancer with diffuse bone metastases reported outside Japan. He exhibits some of the clinicopathologic features described earlier, without lymph node involvement or submucosal invasion. Moreover the resection was clearly a curative one, as evidenced by a laparotomy conducted two years later. During his follow up endoscopies all these years pathology had revealed a seriously inflamed mucosa with foci of moderate dysplasia, but no attempts of Helicobacter pylori eradication were made. A detailed investigation showed no signs of disease outside the bones.

Micrometastases are defined as microscopic (smaller than 2 mm) deposits of malignant cells. Extensive research in the last decade has shown the existence of cancer cells and micrometastases in bone marrow specimens of patients with gastric cancer, with varying rates according to methodology used (14,15,16,17). Usually monoclonal antibodies against cytoceratins are used as means of detection. With the exception of one study by de Manzoni and colleagues (18), researchers in this field conclude that the detection of cancer cells in bone marrow is associated with a poor prognosis. Some even propose that the detection of bone marrow micrometastases should be integrated in the established TNM staging system (19). O'Sullivan and coworkers have repeatedly

demonstrated that the majority of curatively resected gastric cancers have micrometastases usually in rib marrow, a fact that seems irrelevant to intraoperative tumor manipulation, since specimens were also obtained preoperatively (20,21). Kageji and Maehara studied 45 patients with early gastric cancer and found cytoceratin-positive cells in the bone marrows of 20% of the patients. They also found no correlation between these positive findings and features like vascular or lymphatic invasion (22,23).

The presence of microscopic residual disease after total resection of an early stage cancer is suggested but not fully explained by the- admittedly short numbered-studies above. Furthermore it is difficult to explain the progression from latent residual disease to clinically overt metastasis in the bone marrow after such a long period of time. This recurrence pattern seems quite similar to that observed in breast cancer patients. In breast cancer immunocytochemical detection and prognostic value of bone marrow micrometastases have been studied vigorously in large scale studies (24,25). It is suggested for example that metastatic potential is acquired early, but is manifested after a series of mutations. Disseminated and primary cancer cells possibly constitute a rather heterogeneous group of cancer cells with different characteristics and biologic behaviour (26). In this context primary tumor size is not as important as for example cases of metastatic cancer of unknown primary indicate.

We think that the case reported herein should be seen in the light of these interesting observations. First of all early intramucosal gastric cancer still carries the possibility for metastasis, surprisingly many years after a curative resection, mandating long term alertness from the attending physician. According to Kobayashi's most recent review in 2005, signet ring cells, also present in this case, were present in 23 out of all 48 cases of early gastric cancer with bone metastases (27). Macroscopic appearance or depth of invasion were not that significant. Recent experimental studies, like the bone marrow-derived stem cell theory by Houghton and Wang, point to the systemic nature of gastric cancer (28,29). Our case along with the Japanese experience does not underestimate the well established role of resections or even mucosectomies (30,32) but does question their efficacy as exclusive treatments in specific circumstances. Better understanding of gastric carcinogenesis may help in selecting patient subpopulations that might benefit from other ways of treatment or follow up, and treat the individual patient, instead of the disease altogether.

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