HER2-positive Gastric Cancer with Paraaortic Nodal Metastasis Successfully Resected After Chemotherapy with Trastuzumab: A Case Report

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Abstract. *We report on a case of human epidermal growth factor receptor-2 (HER2)-positive gastric cancer with paraaortic lymph node metastasis. The patient (a 49-year-old female) received chemotherapy (capecitabine and cisplatin) plus molecular-targeted therapy (trastuzumab), followed by curative resection. Interestingly, the resected residual cancer was HER2-negative. Intra-tumor heterogeneity hinders molecular-targeted therapy for gastric cancer. In our case, continued trastuzumab administration presented few benefits since the residual cancer cells were HER2-negative. No consensus exists regarding the appropriate therapy for unresectable gastric cancers whose non-curative factors disappear following trastuzumab chemotherapy. The principal options are treatment with surgery or continued chemotherapy with trastuzumab. In our case, resection treated the HER2-negative residual cancer effectively, resulting in curative therapy. This is the first case of positive-to-negative change in the HER2 expression of residual tumor cells following trastuzumab therapy. It suggests that, due to intra-tumor heterogeneity, the risks presented by remnant HER2-negative cancer cells persist despite trastuzumab therapy.*

Case Report

In May 2011, a 49-year-old woman with epigastralgia underwent upper-gastrointestinal (GI) endoscopy, during which an irregular lesion at the posterior wall of the antrum was noted. In June 2011, she was referred to our hospital for further examination. The upper GI endoscopy showed a centrally-ulcerating tumor that was indistinctly delineated from its surroundings at the antrum. Stenosis of the pylorus was also evident. Examination of a biopsy specimen led to the diagnosis of a moderately-differentiated adenocarcinoma, and immunohistochemistry (IHC) showed a tumor cell cluster with strong complete basolateral membranous reactivity (Figure 1), the presence of which identified the case as IHC3+ according to the IHC scoring system that was used in the ToGA trial (1). Barium meal radiography showed a circumscribed crater with irregular borders and a surrounding radiolucent defect. Computed tomography (CT) showed two swollen paraaortic lymph nodes that were 17 mm and 14 mm in diameter (Figure 2). Coincidentally, the tumor was considered unresectable.

In June 2011, we first performed a stomach-partitioning gastrojejunostomy, because of the stenosis. There was no peritoneal metastasis. Further, cytological examination indicated that the peritoneal washings were negative for carcinoma. After palliative surgery, the patient received three courses of trastuzumab (as a molecular-targeted therapy), which were initiated in August 2011 in combination with chemotherapy with capecitabine and cisplatin. This combination was similar to the combination used in the ToGA trial (1). Capecitabine (1,000 mg/m^2) was administered orally twice a day for 14 days, followed by a 1-week interval. An intravenous infusion of cisplatin (80 mg/m^2) was given on day 1. Trastuzumab was administered by intravenous infusion at a dose of 8 mg/kg on day 1 of the first course, followed by 6 mg/kg every 3 weeks. This treatment resulted in a partial response. However, our patient experienced incremental nausea following cisplatin therapy and, despite the use of anti-emetic agents, she was unable to even drink water during the fourth course of chemotherapy. Subsequently, she was administered a combination of capecitabine and trastuzumab. During the therapy, she suffered from mild but tolerable weakness, and was able to continue treatment.

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After completion of the 12th course of chemotherapy, the swollen paraaortic lymph nodes disappeared (Figure 3). This indicated that the patient was clinically cured; however, because of concerns regarding progression of the disease with time and age, we decided to perform a surgical resection of any residual tumor (after obtaining informed consent from the patient). We then successfully performed distal gastrectomy (D2) as curative surgery in November 2012. We found no peritoneal metastasis, and cytological examination of the peritoneal washings indicated that they were negative for carcinoma. No cancer cells were found in the paraaortic lymph node tissue that was sampled during surgery. In the resected gastric tissue, residual cancer was found in the sub-serosa, measuring 0.5 mm in diameter (Figure 4). No cancer cells were identified in the dissected lymph nodes. The residual cancer in the resected specimen was diagnosed as a moderately-differentiated adenocarcinoma. Interestingly, the specimen showed no reactivity or membranous reactivity in any of its tumor cells, thereby establishing that it was HER2-negative (0) (Figure 5). Postoperatively, in the 10 months of follow-up, the patient remains in good health with no recurrence and without adjuvant chemotherapy.

Discussion

Human epidermal growth factor receptor-2 (HER2) was first identified in 1985 (2). Trastuzumab was developed as a recombinant DNA-derived humanized monoclonal antibody against HER2 (3), and its efficacy for treating patients with HER2-overexpressing breast cancer was demonstrated in clinical trials after 1992 (4). The first phase-3 trial for gastric cancer that involved the administration of a molecular-targeted agent was ToGA, which demonstrated the benefit of including trastuzumab in the chemotherapy regimen for patients with HER2-positive gastric cancer (1). In a subset analysis of patients whose tumors had high levels of HER2 protein (IHC2+ and FISH+, IHC3+), median overall survival was observed to extend to 16 months following trastuzumab therapy, compared to 11.8 months among controls.

Some case reports have described a pathologically-complete response following chemotherapy with use of trastuzumab (5, 6). In our case, we observed remarkable effects of trastuzumab therapy. In particular, completion of trastuzumab therapy and a chemotherapeutic regimen allowed a patient with a previously unresectable tumor to undergo curative operation.

There is no consensus regarding the appropriate therapy for cases where factors that indicate non-curative status disappear following the use of trastuzumab therapy (as in the present case). The principal options are surgical resection or continuation of trastuzumab therapy. In the ToGA trial, trastuzumab was used every 3 weeks with chemotherapy for 6 cycles. Afterwards, trastuzumab was used alone until disease progression, unacceptable toxicity, or withdrawal of consent, in which case surgical resection was not performed. Although the rate of complete response was 5%, the median progression-free survival (PFS) among patients who received trastuzumab was 6.7 months (1).

Acquired resistance to anticancer agents is one of the factors assumed to limit the PFS of patients with gastric cancer. Acquired resistance to trastuzumab is considered to be related to the impaired access of trastuzumab to HER2, which can arise from various causes: truncated HER2 (7, 8); masked HER2 (9); alternative signaling from other receptor tyrosine kinases, such as insulin-like growth factor-1 receptor (10-12) and Met receptor (13); aberrant downstream signaling caused by alterations in downstream signaling molecules, such as PTEN deficiency (14); and gain-of-function mutations in *PIK3CA* (15).

Intra-tumor heterogeneity is another factor that specifically affects PFS in cases of gastric cancer. This is a pathognostic problem involving HER2-overexpression. Unlike the IHC scoring system for HER2 in breast cancer, the IHC scoring system for HER2 in gastric cancer differentiates between whole-tissue sections and biopsy specimens, because of intra-tumor heterogeneity (1, 16). An IHC score of 3+ for whole-tissue sections is defined as strong complete, basolateral, or lateral membranous reactivity in ≥10% of tumor cells (1). On the other hand, an IHC score of 3+ for biopsy specimens is defined by the presence of a tumor cell cluster with a strong complete, basolateral, or lateral membranous reactivity, irrespective of the percentage of tumor cells that are stained (1). Nonetheless, in a study that compared whole-tissue sections with 5 tissue micro-arrays serving as biopsy procedures, Warneke *et al*. (17) reported a false-negative rate of 24% and a false-positive rate of 3% for HER2 expression. For gastric cancer, HER2 expression (3+) is the highest score, which is indicative of HER2-positivity, similar to that for breast cancer. However, this score only requires ≥10% of tumor cells to show immunohistochemical reactivity. However, as recommended by American Society of Clinical Oncology/College of American Pathologists, the definition of IHC3+ in breast cancer is uniform intense membrane staining in >30% of tumor cells (16). These facts suggest the possibility that treatment with trastuzumab for HER2-positive gastric cancer may have different effects in different cancer cells from the same patient, owing to intra-tumor heterogeneity. In other words, despite the effectiveness of trastuzumab therapy, there is a risk that remnant HER2-negative cancer cells may persist, as a result of tumor heterogeneity. In the present case, only the HER2-negative cells remained viable and, therefore, there appeared to be no further benefits of continuing trastuzumab therapy. A previous case report registered to the ToGA trial revealed a clinically complete response after the 10th cycle of continued

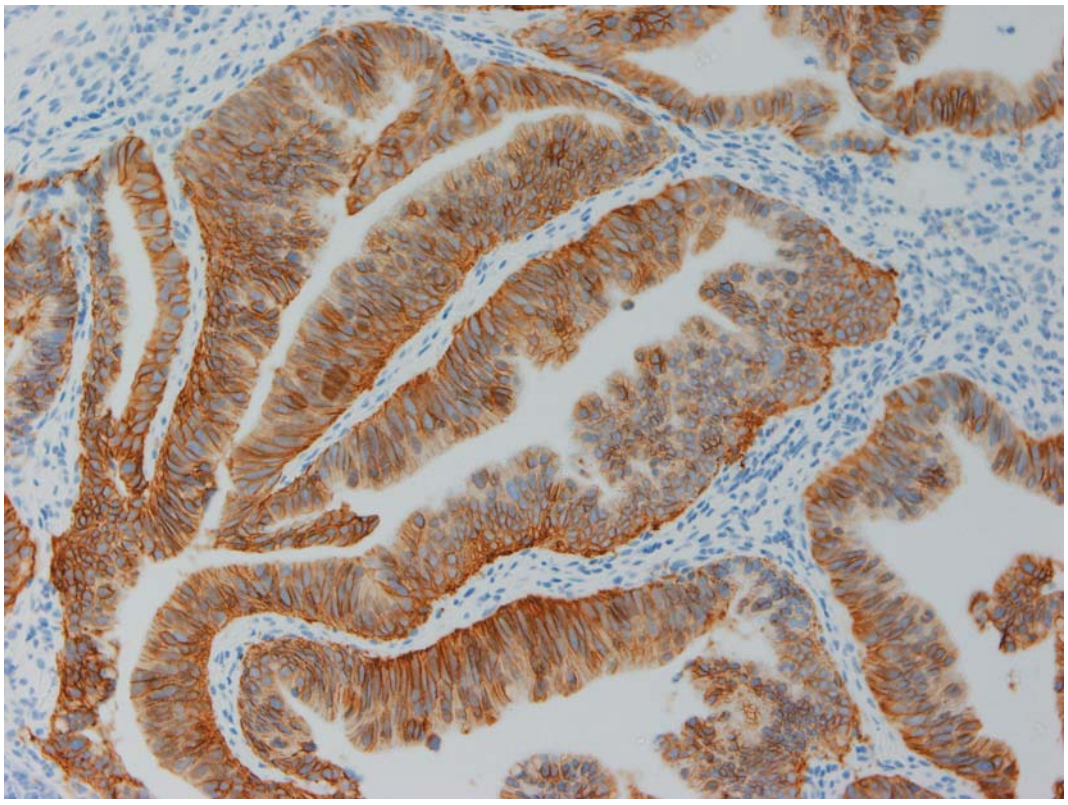

Figure 1. *HER2 immunohistochemical staining in the biopsy specimen before chemotherapy-plus-trastuzumab. A tumor cell cluster with strong basolateral membranous reactivity can be observed (original magnification, ×200).*

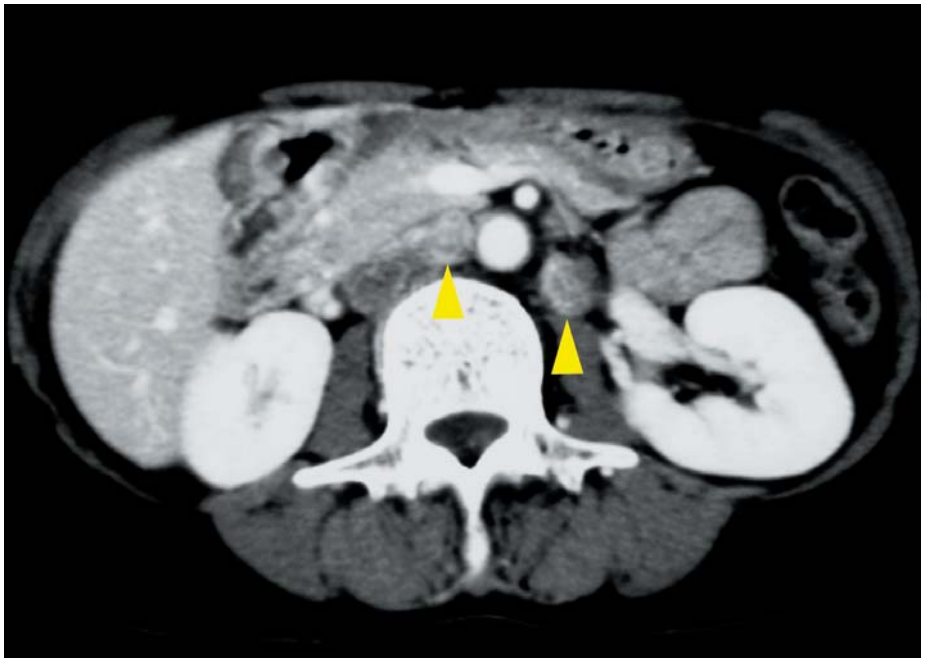

Figure 2. *CT before chemotherapy-plus-trastuzumab. Swollen paraaortic lymph nodes were located just below the left renal vein, measuring 17 mm and 14 mm in diameter (arrowheads).*

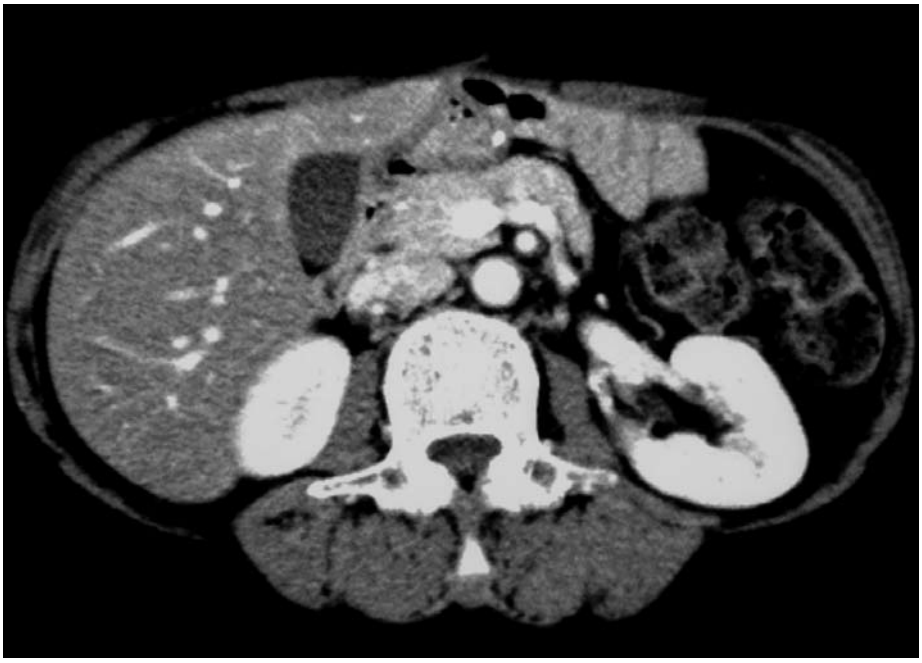

Figure 3. *CT after chemotherapy-plus-trastuzumab. The swollen paraaortic lymph nodes had disappeared.*

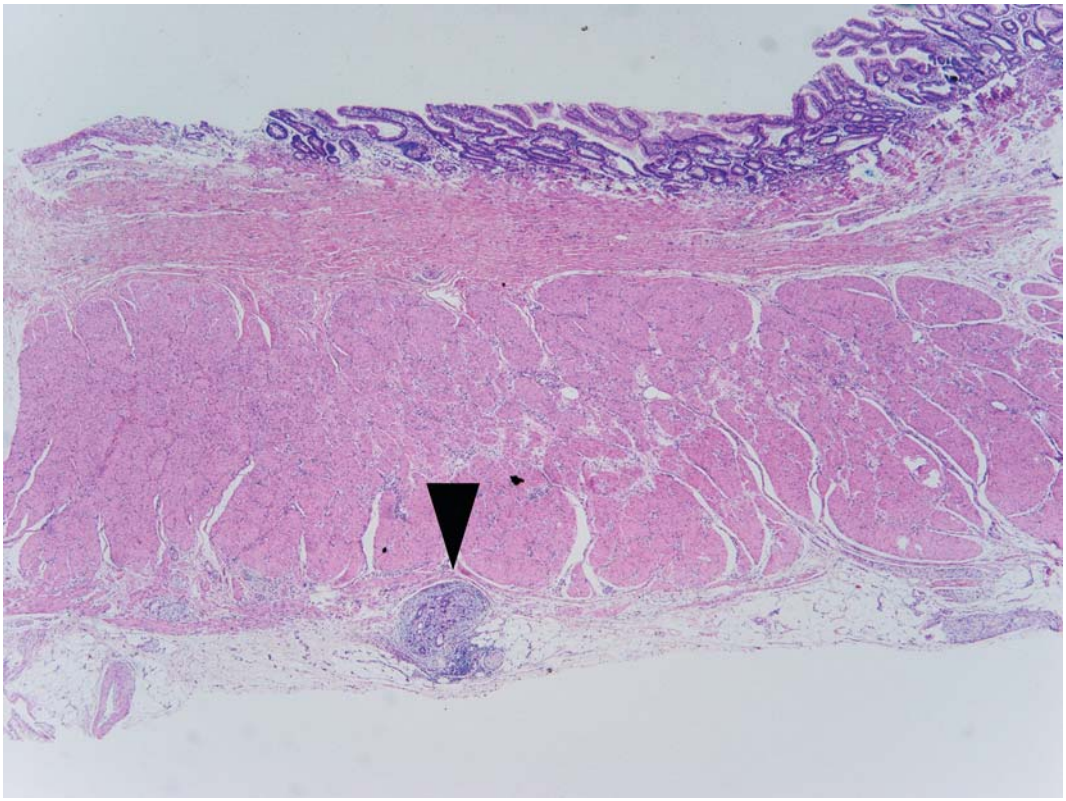

Figure 4. *Hematoxylin-eosin staining of the resected specimen after chemotherapy-plus-trastuzumab. Residual cancer was located in the sub-serosa, measuring 0.5 mm in diameter (original magnification, ×40, arrowhead).*

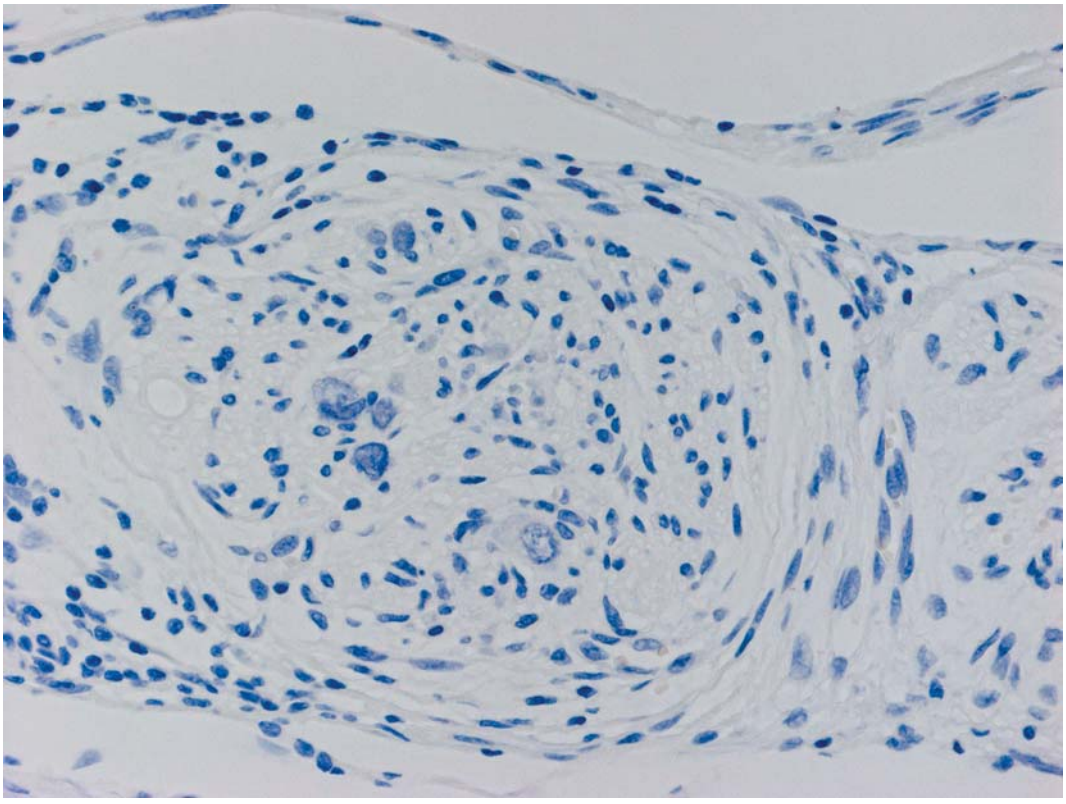

Figure 5. *HER2 immunohistochemical staining in the resected specimen after chemotherapy-plus-trastuzumab. No reactivity of the tumor cells was observed (original magnification, ×400).*

trastuzumab therapy; however, dissemination was noted before the 23rd cycle, and the patient died 28 months after initial therapy commencement (18).

Because of intra-tumor heterogeneity and the limited PFS associated to trastuzumab therapy, the combination of surgical resection and trastuzumab therapy may have curative potential for certain gastric cancer patients. Trastuzumab could potentially be used as a neoadjuvant therapy for down-staging unresectable HER2-positive gastric cancer.

In cases where chemotherapy is used in combination with trastuzumab to preoperatively down-stage unresectable cases, whether and how to perform adjuvant therapy remains controversial. In contrast with the regimens of the MAGIC trial (three 21-day preoperative cycles) (19), the ACCORD-07 study (4 weeks to or three 28-day preoperative cycles) (20), the EORTC-40954 trial (two 48-day preoperative cycles) (21), and other trials for resectable gastric cancer, our case required 13 months of chemotherapy before the swollen paraaortic lymph nodes disappeared and surgical resection became feasible. For capecitabine-alone, however, the median time-to-progression and time-to-treatment failure are reported to be 4.7 and 4.3 months, respectively (22). In our patient, the resected residual cancer cells were HER2-negative; therefore, we did not administer postoperative adjuvant chemotherapy or molecular-targeted therapy. The period of preoperative therapy should be considered individually when selecting for an optimal postoperative strategy. Indeed, the appropriate time for converting to surgical resection will generally differ for each patient with primarily unresectable gastric cancer.

In conclusion, trastuzumab has been effective for the treatment of gastric cancer in many cases. However, for cases in which trastuzumab is used to treat unresectable gastric cancer, one should consider the heterogeneity of each patient's cancer cells; all of the cells may not be HER2-positive. In such cases, surgical resection could provide an additional curative benefit.

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