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【 CASE REPORT 】

Helicobacter pylori-negative Advanced Gastric Cancer with Massive Eosinophilia

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Abstract:

The incidence of *Helicobacter pylori*-negative gastric cancer is very low. A 60-year-old man was referred to Tokai University Hospital from a local clinic because of eosinophilia. The laboratory data revealed prominent eosinophilia, with a white blood cell count of 7,900/μL and increased eosinophil granulocyte level of 1,659/μL. After an examination for secondary eosinophilia, esophagogastroduodenoscopy showed an enlarged gastric fold in the corpus, suggesting type 4 gastric cancer. Repeated esophagogastroduodenoscopy (EGD) and a re-biopsy demonstrated poorly differentiated adenocarcinoma and signet ring cell carcinoma. The patient was negative for *Helicobacter pylori* infection according to the serum anti-*Helicobacter pylori* antibody, culture and histopathological findings.

Key words: *Helicobacter pylori*-negative gastric cancer, eosinophilia, poorly differentiated adenocarcinoma, signet ring cell carcinoma

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Introduction

The incidence of *Helicobacter*-negative gastric cancer is estimated to be 0.42-0.66% (1, 2). Regarding the characteristics of *Helicobacter*-negative gastric cancer, the undifferentiated type is more frequent than the differentiated type (3). Furthermore, the marked eosinophilia occurs in several important disorders, such as allergic diseases, parasitic infection, and collagen diseases and malignancy (4). There are some eosinophil-derived malignancies (acute and chronic eosinophilic leukemia) as well as malignancies in which eosinophils are increased as part of the overall cellular response.

We herein report a case of *Helicobacter pylori*-negative gastric carcinoma with peripheral eosinophilia. The patient received chemotherapy with S-1 and cisplatin. After the first course of chemotherapy, the eosinophilia was resolved, with values in the normal range.

Case Report

A 60-year-old man was referred to Tokai University Hospital from a local clinic because of eosinophilia. At the local clinic, stool testing results for ova and parasites were negative, and he had no history of allergic disorder. He had taken no medication that could have caused eosinophilia. At the consultation, the laboratory data revealed prominent eosinophilia, with a white blood cell count of 7,900/μL and increased eosinophil granulocyte level of 1,659/μL.

A physical examination on consultation demonstrated no wheezing, rhinitis, or eczema, and a review of the patient's history revealed no abnormalities, or the presence of a pet dog. After the first visit, he lost 1 kg of body weight and developed anorexia within 2 months. Laboratory tests showed elevated CA 19-9 of 179.7 U/mL (normal range, <30 U/mL), and slight elevation of interleukin (IL)-2R was observed (Table 1).

To determine the cause of eosinophilia, computed tomography (CT) was performed (Fig. 1). The findings were

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Table 1. Laboratory Data on Initial Admission.

Hematology			
WBC	7,400 /μL	Ca	8.8 mg/dL
RBC	514×10⁴ /μL	T.bil	0.4 mg/dL
Hb	17.0 g/dL	AST	12 U/L
Ht	50.8 %	ALT	10 U/L
Plt	25.1×10⁴	ALP	186 U/L
		γ-GTP	32 U/L
Neu	51.0 %	LDH	171 U/L
Lym	22.0 %	Glu	114 mg/dL
Mono	2.0 %	CRP	0.15 mg/dL
Eos	23.0 %	IgE	253 IU/mL
Baso	1 %	antiPR2-ANCA	<1.0 U/mL
Chemistry		antiMPO-ANCA	<1.0 U/mL
TP	6.8 g/dL	ANA	-
Alb	3.5 g/dL	CEA	4.5 ng/mL
UN	7 mg/dL	CA19-9	179.7 U/mL
Cre	0.73 mg/dL	IL-2R	695 U mL
UA	5.1 mg/dL	IL-3	<31 pg/mL
Na	142 mEq/L	IL-5	<3.9 pg/mL
K	4.1 mEq/L	GM-CSF	<8 pg/mL
Cl	105 mEq/L	*H. pylori* antibody	<3 U/mL

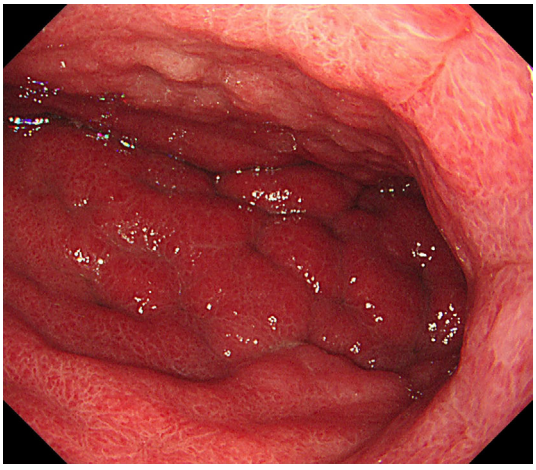

Figure 2. EGD demonstrated an enlarged gastric fold in the corpus, suggesting type 4 gastric cancer.

circumferential thickening of the gastric wall and thickening of the transverse colon, as well as ascites, suggesting gastric carcinoma with colonic invasion. Esophagogastroduodenoscopy (EGD) revealed an enlarged gastric fold in the corpus, suggesting type 4 gastric cancer (Fig. 2). The histopathological results were not neoplastic. Furthermore, ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) demonstrated no uptake anywhere in the body, including the stomach (Fig. 3). These findings suggested that the biopsy was a false-negative and that the gastric lesion was type 4 advanced gastric cancer. *H. pylori* culture, serum anti-*H. pylori* antibody (E-plate Eiken *H. pylori* II, Tokyo, Japan), and a histological examination were negative. Repeated EGD and a re-biopsy showed poorly differentiated adenocarcinoma and signet ring cell carcinoma (Fig. 4). Immunohistochemistry for carcinoembryonic antigen (CEA) and CA19-9 showed positive staining in the tumor cells. Periodic acid-Schiff (PAS)/alcian blue staining showed mucin in the signet ring cells. The patient was diagnosed with an inoperable stage of advanced gastric carcinoma and received chemotherapy with S-1 and cisplatin. After the first course of chemotherapy, the eosinophil count returned to a normal range (Table 2).

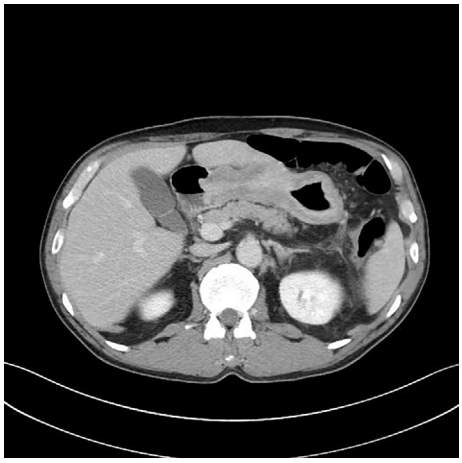

Figure 1. Abdominal CT showed circumferential wall thickening of the whole stomach.

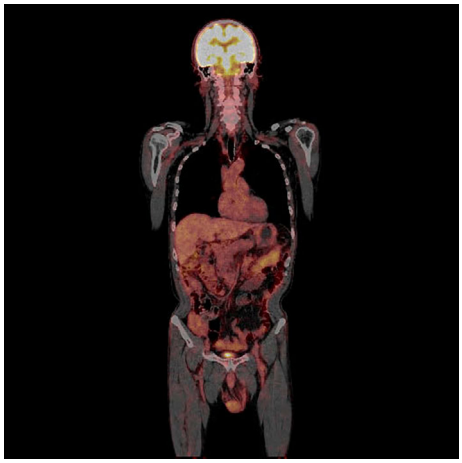

Figure 3. FDG-PET showed no uptake anywhere in the body, including the stomach.

Discussion

We encountered a case of *H. pylori*-negative gastric cancer with eosinophilia. The incidence of *H. pylori*-negative gastric cancer is very low. It is reported to be 0.42-0.66% (1, 2). Regarding the characteristics of *Helicobacter* negative-gastric cancer, the undifferentiated type is more frequent than the differentiated type (3). Repeated EGD and a re-biopsy showed poorly differentiated adenocarcinoma and signet ring cell carcinoma. Immunohistochemistry for CEA and CA19-9 showed positive staining in the tumor cells, and

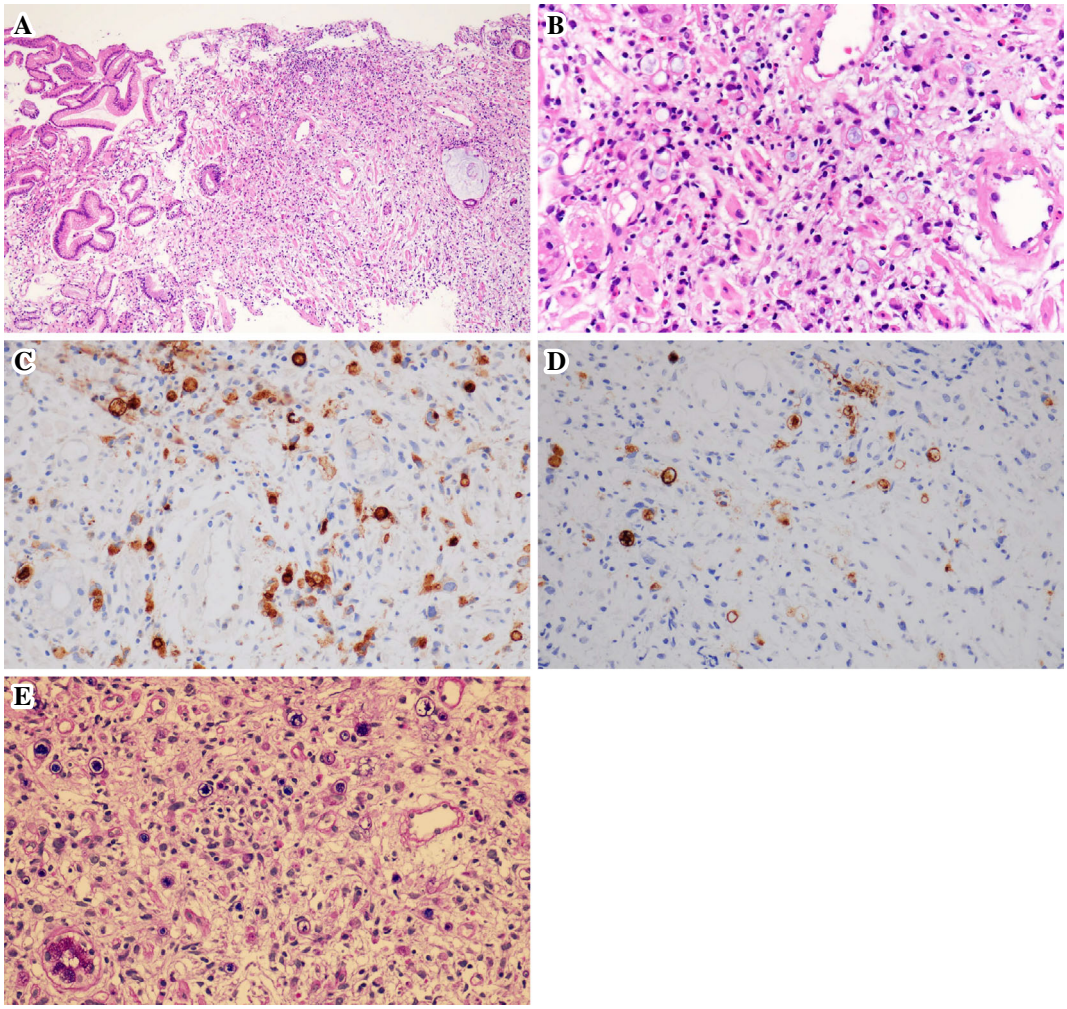

Figure 4. **A: A biopsy of the gastric specimens revealed poorly differentiated adenocarcinoma with signet cell carcinoma. Low-power view (original magnification ×40). Proliferation of adenocarcinoma occupies the right side of the figure. B: The adenocarcinoma comprises signet ring cells and poorly differentiated cells with a high N/C ratio. About 10 eosinophils can be seen in the adenocarcinoma lesion in the high-power view. C: Immunohistochemistry for CEA showed positive staining in the tumor cells. D: Immunohistochemistry for CA19-9 showed positive staining in 10% of the tumor cells. E: PAS/alcian blue staining showed mucin in the signet ring cells.**

Table 2. **Time Course of Laboratory Data after Chemotherapy.**

		TS-1							TS-1		
		Cis							Cis		
Day		1	8	10	12	21	28	35	41	43	45
WBC	(μL)	6,400	6,600	9,400	7,800		4,000		5,400	10,200	8,900
eosinophil	(μL)	1,376	1,518	94	0		172		507	0	0
RBC	(μL)	468×10^4	430×10^4	395×10^4	407×10^4		405×10^4		380×10^4	363×10^4	376×10^4
Hb	(g/dL)	14.9	13.9	12.7	13.2		13.4		12.9	12.3	12.7
Ht	(%)	45.7	41.7	38.2	39.4		40.4		38.3	36.5	36.8
PLT	(μL)	23.2×10^4	22.5×10^4	21.1×10^4	20.4×10^4		16.4×10^4		19.4×10^4	20×10^4	22.2×10^4
CEA	(ng/dL)	4.1					4.9				
CA19-9	(U/mL)	45.3					24.7				

PAS/alcian blue staining showed mucin in the signet ring cells.

The mechanisms underlying *H. pylori*-negative gastric cancer are not fully understood, although it has been reported that the Epstein-Barr (EB) virus is associated with gastric cancer (5). In the current case, *H. pylori* culture, se-

rum anti-*H. pylori* antibody, and the findings of a histological examination were all negative.

Peripheral eosinophilia is associated with a broad range of allergic, infectious, neoplastic, hematological, collagen and idiopathic diseases (4). Among these conditions, malignancy is a well-recognized albeit unusual cause of hypereosinophilia. In the current case, blood and feces examinations ruled out the possibility of allergic diseases, collagen disease, and parasitic infection. A relationship between gastric cancer and hypereosinophilia has been reported (6-8), although the mechanism by which gastric cancer induces hypereosinophilia is not clear. The major growth factors for eosinophils are IL-5, granulocyte-macrophage colony-stimulating factors, and IL-3 (4). Hong et al. suggested that gastric cancer cells produce IL-2, IL-5, and granulocyte-macrophage colony-stimulating factors (9). We detected no elevations in these cytokines in the serum; however, after the first course of chemotherapy, the eosinophilia was resolved, suggesting a relationship between the gastric cancer and eosinophilia.

No previous case studies have analyzed the relationship between *H. pylori* infection and eosinophilia. Indeed, some reports predate the discovery of *H. pylori* or recognition of the relationship between *H. pylori* and gastric cancer (6, 7). Interestingly, *H. pylori* colonization is inversely correlated with asthma and allergy (10, 11). Furthermore, *H. pylori* infection is reported to be associated with a reduced risk of developing eosinophilic esophagitis (12). Although the effects of *H. pylori* on eosinophilia are unclear, it is possible that, in the current case, the suppression of eosinophilia did not occur without *H. pylori* infection.

FDG-PET has recently been used in clinical oncology (10). The diagnosis of gastric cancer is made by endoscopy and biopsies. The sensitivity of FDG-PET for the detection locally advanced gastric carcinoma is dependent on the microscopic growth type of the tumor, as an increased uptake of FDG is more commonly seen in the intestinal growth type than non-intestinal types (13). Interestingly, all previously reported cases of gastric cancer with eosinophilia were poorly differentiated carcinoma. This finding suggests that, in the differential diagnosis of eosinophilia, the FDG-PET findings and the presence of negative *H. pylori* antibodies are considered to be insufficient diagnostic information to rule out gastric cancer.

The authors state that they have no Conflict of Interest (COI).

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