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Protein induced by vitamin K absence or antagonist Ⅱ-producing gastric cancer

Yoshihisa Takahashi, Tohru Inoue, Toshio Fukusato

Yoshihisa Takahashi, Toshio Fukusato, Department of Pathology, Teikyo University School of Medicine, Tokyo 173-8605, Japan
Tohru Inoue, Department of Pathology, Tokyo Kousei-Nenkin Hospital, Tokyo 162-8543, Japan
Author contributions: Takahashi Y wrote the manuscript; Inoue T diagnosed a case that we previously reported, and provided the computed tomography images of the case; and Fukusato T checked and revised the manuscript.
Correspondence to: Yoshihisa Takahashi, MD, Department of Pathology, Teikyo University School of Medicine, Tokyo 173-8605, Japan. ytakaha-tky@umin.ac.jp
Telephone: +81-3-39641211 Fax: +81-3-39649622
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Abstract

Protein induced by vitamin K absence or antagonist Ⅱ (PIVKA-Ⅱ) is a putative specific marker of hepatocellular carcinoma (HCC), but it may also be produced by a small number of gastric cancers. To date, 16 cases of PIVKA-Ⅱ-producing gastric cancer have been reported, 2 of which were reported by us and all of which were identified in Japan. There are no symptoms specific to PIVKA-Ⅱ-producing gastric cancer, and the represen tative clinical symptoms are general fatigue, appetite loss, and upper abdominal pain. Serum alpha-fetoprotein (AFP) levels are also increased in almost all cases. Liver metastasis is observed in approximately 80% of cases and portal vein tumor thrombus is observed in approximately 20% of cases. Differential diagnosis between metastatic liver tumor and HCC is often difficult. Grossly, almost all cases appear as advanced gastric cancer. Histologically, a hepatoid pattern is observed in many cases, in addition to a moderately to poorly differentiated adenocarcinoma component. The production of PIVKA-Ⅱ and AFP is usually confirmed using immunohistochemical staining. Treatment and prognosis largely depends on the existence of liver metastasis, and the prognosis of patients with liver metastasis is very poor. PIVKA-Ⅱ may be produced during the hepatocellular metaplasia of the tumor cells.

Key words: Protein induced by vitamin K absence or antagonist Ⅱ; Gastric cancer; Alpha-fetoprotein; Hepatocellular carcinoma; Hepatoid carcinoma

Peer reviewer: Tsutomu Nishida, MD, Department of Gastroenterology and Hepatology, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita 565-0871, Japan

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INTRODUCTION

Since Liebman *et al*[1] reported the increase of protein induced by vitamin K absence or antagonist Ⅱ (PIVKA-Ⅱ) in the serum of hepatocellular carcinoma (HCC) patients, PIVKA-Ⅱ has been regarded as a tumor marker of HCC. PIVKA-Ⅱ has been reported to be a more specific marker than alpha-fetoprotein (AFP), another tumor marker of HCC[2,3]. The production of AFP and PIVKA-Ⅱ by HCC cells has been elucidated morphologically[4]. However, serum AFP or PIVKA-Ⅱ levels may increase in patients with tumors other than HCC, and if such tumors metastasize to the liver, it may be difficult to clinically differentiate them from HCC. Although the number of reported cases of AFP-producing gastric cancer has been gradually increasing[5-9], only 16 cases of PIVKA-Ⅱ-producing gastric cancer have been reported

Table 1 Clinicopathological data of protein induced by vitamin K absence or antagonist Ⅱ producing gastric cancer

Case	Age	Sex	Serum AFP (ng/mL)	Serum PIVKA-Ⅱ (AU/mL)	Macroscopic type	Tumor size (cm)	Histological type	Liver metastasis	Treatment	Prognosis	Ref.
1	56	M	2810	2.45	0-Ⅱc	6.5 × 4.5	por + tub1 + hepatoid	(-)	subtotal gastrectomy	Alive without tumor (17 mo)	[10]
2	43	M	483380	134	Borrmann 3	7.5 × 7.0	por	(+)	best supportive care	Died of disease (3 mo)	[11]
3	42	F	190	2.9	Borrmann 3	ND	por	(+)	TACE + systemic chemotherapy	Died of disease (3 mo)	[12]
4	63	M	120000	> 8	Borrmann 1	ND	por + hepatoid	(+)	systemic chemotherapy	Died of disease (2 mo)	[13]
5	72	M	14500	32.8	Borrmann 1	ND	por	(+)	best supportive care	Died of disease (1mo)	[14]
6	71	M	73	5.15	Borrmann 2	About 2	tub2	(+)	subtotal gastrectomy + enucleation of liver metastasis + HAIC	Alive (2 mo)	[15]
7	71	M	1230	28.5	Borrmann 2	About 4	por	(+)	best supportive care	Died of disease (3 mo)	[16]
8	55	M	247000	320	Borrmann 1	ND	por	(+)	systemic chemotherapy	Died of disease (4 mo)	[17]
9	71	M	18551.7	1.08	Borrmann 3	ND	tub2	(+)	systemic chemotherapy	Died of disease (5 mo)	[18]
10	87	F	490200	2.284	Borrmann 2	3.8 × 2.3/4.5 × 3.2	por + tub2 + hepatoid	(+)	best supportive care	Died of disease (1 mo)	[19]
11	49	M	21552.9	3.7	Borrmann 2	5 × 5	tub2 + hepatoid	(+)	HAIC	Died of disease (5 mo)	[20]
12	68	M	4	15.6	Borrmann 3	about 15	por + tub2	(-)	preoperative chemotherapy + pancreatico-spleno total gastrectomy	Alive without tumor (15 mo)	[21]
13	45	M	13827	0.405	Borrmann 2	ND	tub2	(+)	systemic chemotherapy	Died of disease (6 mo)	[22]
14	61	M	495.2	0.635	Borrmann 3	8.0 × 7.0/9.5 × 8.5	tub2 + pap + por + hepatoid	(+)	total gastrectomy + postoperative adjuvant chemotherapy	Died of disease (6 mo)	[23]
15	61	M	9630	0.091	Borrmann 2	4.5 × 4.0	por + hepatoid	(-)	distal gastrectomy with resection of the extra-gastric tumor	Alive without tumor (9 mo)	[24]
16	71	M	296838	56.387	Borrmann 1	ND	por + hepatoid	(+)	systemic chemotherapy	Died of disease (6 mo)	[25]

HAIC: hepatic arterial infusion chemotherapy; ND: no data; pap: papillary adenocarcinoma; por: poorly differentiated adenocarcinoma; TACE: transcatheter arterial chemoembolization; tub1: well differentiated tubular adenocarcinoma; tub2: moderately differentiated tubular adenocarcinoma; Ref: references; PIVKA-Ⅱ: Protein induced by vitamin K absence or antagonist Ⅱ.

to date[10-25], 2 of which were reported by us[19,23]. The exact definition of PIVKA-Ⅱ-producing gastric cancer has not been established yet. However, we propose to make a diagnosis of PIVKA-Ⅱ-producing gastric cancer when a patient with gastric cancer has high serum level of PIVKA-Ⅱ and PIVKA-Ⅱ production by gastric cancer cells is confirmed by immunohistochemistry, or when in a patient with gastric cancer and high serum level of PIVKA-Ⅱ, the other sources of PIVKA-Ⅱ production, such as HCC and vitamin K deficiency, are ruled out. In this paper, we review the clinicopathological features of PIVKA-Ⅱ-producing gastric cancer; furthermore, we discuss the differential diagnosis between HCC and liver metastasis of PIVKA-Ⅱ-producing gastric cancer, and the mechanism of PIVKA-Ⅱ production by gastric cancer cells. In addition, we compare PIVKA-Ⅱ- and AFP-producing gastric cancers.

CLINICAL FEATURES

Epidemiology

PIVKA-Ⅱ-producing gastric cancer is very rare, with only 16 cases reported to date[10-25], and its precise prevalence has not been elucidated. Table 1 summarizes the clinicopathological features of the reported cases of PIVKA-Ⅱ-producing gastric cancer. Interestingly, all of the reported cases were identified in Japan. The reason for this is unclear, but the following possibilities are conceivable: (1) PIVKA-Ⅱ-producing gastric cancer is especially prevalent in the Japanese; and (2) in Japan, PIVKA-Ⅱ-producing gastric cancer is correctly diagnosed because of sufficient endoscopic, laboratory, radiological, and pathological examinations. The serum AFP levels were increased in all but one case and liver metastasis was detected in all but three of the reported PIVKA-Ⅱ-producing gastric cancer

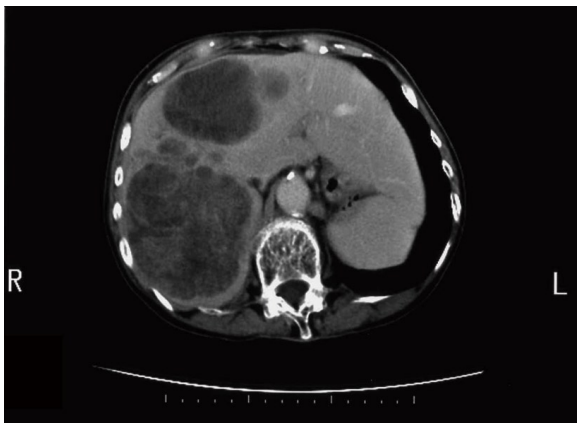

Figure 1 Contrast-enhanced computed tomography image of liver metastasis of protein induced by vitamin K absence or antagonist Ⅱ-producing gastric cancer. Multiple low density nodules, which are poorly enhanced, are observed in the liver.

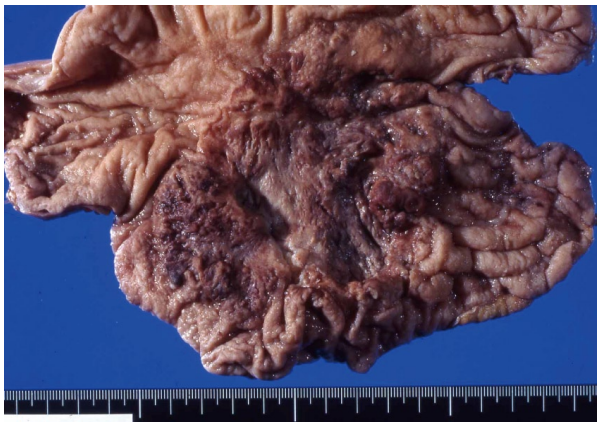

Figure 2 Gross appearance of a case of protein induced by vitamin K absence or antagonist Ⅱ-producing gastric cancer. A large Borrmann type 3 tumor occupies the gastric body.

cases. PIVKA-Ⅱ-producing gastric cancer predominantly occurs in elderly men. The patients' ages ranged from 42-87 years (mean, 62 years). Fourteen cases were male and 2 cases were female; thus, the male-to-female ratio is 7:1.

Symptoms and signs

There are no symptoms specific to PIVKA-Ⅱ-producing gastric cancer, and the representative clinical symptoms are general fatigue, appetite loss, and upper abdominal pain. A mass in the abdomen or right hypochondrium and abdominal distention or discomfort are also occasionally seen. These symptoms are considered to be related to the gastric tumor or metastatic liver tumor. Tarry stool, back pain, edema in the lower leg, and pyrexia were observed in a small number of cases.

Laboratory data

Serum PIVKA-II levels (normal value < 0.04 AU/mL) in the reported cases ranged from 0.091-320 AU/mL (median, 4.4 AU/mL). Serum AFP levels (normal value < 20 ng/mL) were abnormally high in all but one case (range, 4-490200 ng/mL; median, 14164 ng/mL). AFP can be fractionated into 3 isoforms: L1 is produced in non-neoplastic liver disease, L2 is produced in yolk sac tumors, and L3 is produced in HCC and hepatoblastoma[26]. The AFP fractions were examined in 3 PIVKA-Ⅱ-producing gastric cancer cases, and the L3 fraction was increased in all of those cases[18,23,25]. With regard to other tumor markers, serum carcinoembryonic antigen (CEA) levels are often increased.

Anemia is often observed because of malnutrition and/or bleeding from the tumor. Thrombocytosis and hypoproteinemia are occasionally observed. Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), and gamma-glutamyl transpeptidase (gamma-GTP) levels are often increased because of frequent liver metastasis, and total and direct bilirubin levels are also occasionally increased. Serum C-reactive protein (CRP), white blood cell count, and erythrocyte sedimentation rate (ESR) are increased if the tumor is complicated by inflammation.

Endoscopy

The most important test in the clinical diagnosis of gastric cancer is upper digestive tract endoscopy. The features describing the gross appearance of PIVKA-Ⅱ-producing gastric cancer are presented in the PATHOLOGICAL FEATURES section.

Clinical imaging findings

Liver metastasis was observed in 13 (81%) of the 16 reported cases of PIVKA-Ⅱ-producing gastric cancer, and there were multiple metastatic foci in the majority of those cases. Metastatic tumors were commonly observed in most parts of the liver. Portal vein tumor thrombus was observed in 3 (19%) of the 16 cases; furthermore, lymph node metastasis was often observed.

By abdominal ultrasonography, metastatic liver foci usually present as an intermingled pattern of hyperechoic and hypoechoic areas. By abdominal computed tomography (CT), metastatic liver tumors are generally observed as low density areas. By contrast-enhanced CT, the marginal zone of metastatic liver tumors may be enhanced, but the internal portion is poorly enhanced (Figure 1). By angiography, arterial blood flow in the metastatic liver tumors is scarce. In patients with portal vein tumor thrombus, a filling defect is observed on portography.

PATHOLOGICAL FEATURES

Gross appearance

PIVKA-Ⅱ-producing gastric cancer occupies the gastric body and the pyloric antrum with almost the same frequency. One reported case presented with a 0-Ⅱc-type early cancer, and the remaining 15 cases presented with advanced cancer (Borrmann type 1, 4 cases; Borrmann type 2, 6 cases; and Borrmann type 3, 5 cases) (Figure 2). There were no Borrmann type 4 cases. The diameter of

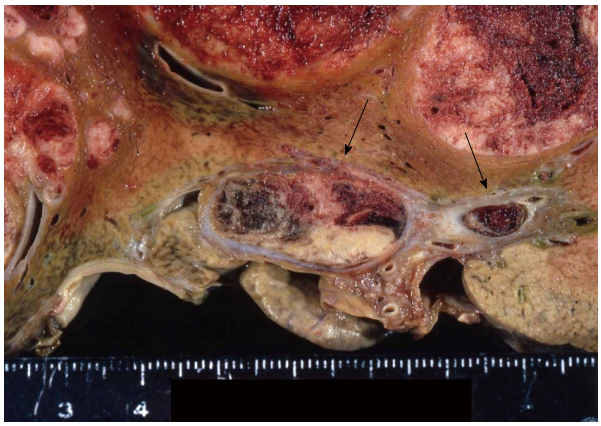

Figure 3 Gross appearance of liver metastasis of protein induced by vitamin K absence or antagonist Ⅱ-producing gastric cancer. Multiple nodular tumors and portal vein tumor thrombi (arrows) are observed.

the tumor ranged from 2-15 cm (mean, 6.5 cm). As mentioned above, multiple liver metastases are frequently detected in PIVKA-Ⅱ-producing gastric cancer, and the presence of portal vein tumor thrombus is not rare (Figure 3).

Microscopic findings

In many cases, gastric biopsy specimens have the histological appearance of poorly or moderately differentiated adenocarcinoma; however, a hepatoid pattern is also fre quently detected by the examination of operation or autopsy materials. Careful examination is required because it may be difficult to differentiate between the hepatoid pattern and poorly differentiated solid-type adeno carcinoma. The tumor generally shows a medullary growth pattern, and there have been no reports of the scirrhous type. Lymphatic and venous invasion is frequently observed, and venous invasion may be very conspicuous. The histological appearance of liver metastasis basically resembles that of a primary gastric tumor, but the hepatoid pattern may be more conspicuous. In a case that we reported[19], a gastric tumor in an area other than the venous invasion primarily demonstrated the histological appearance of a moderately to poorly differentiated adenocarcinoma (Figure 4A), while almost the entire intravenous part of the tumor and liver metastases showed the hepatoid pattern (Figure 4B, C). This finding may suggest that the hepatoid component is especially prone to venous invasion and metastasis to the liver.

Immunohistochemical staining

The primary gastric tumor and metastatic liver tumor show positive immunohistochemical staining for PIVKA-Ⅱ in the majority of the cases, and positive staining is most frequently observed in the area of the hepatoid structure. However, in a case that we reported, positive staining for PIVKA-Ⅱ was primarily observed in the area of the tubular structure[23] (Figure 5A). Cases with very few[19] or no[13,14] PIVKA-Ⅱ-positive tumor cells have also been reported. In both cases with no PIVKA-Ⅱ-positive tumor cells, a biopsy specimen was used for immunohistochemical staining, and the size of the sample may be the cause for the negative staining.

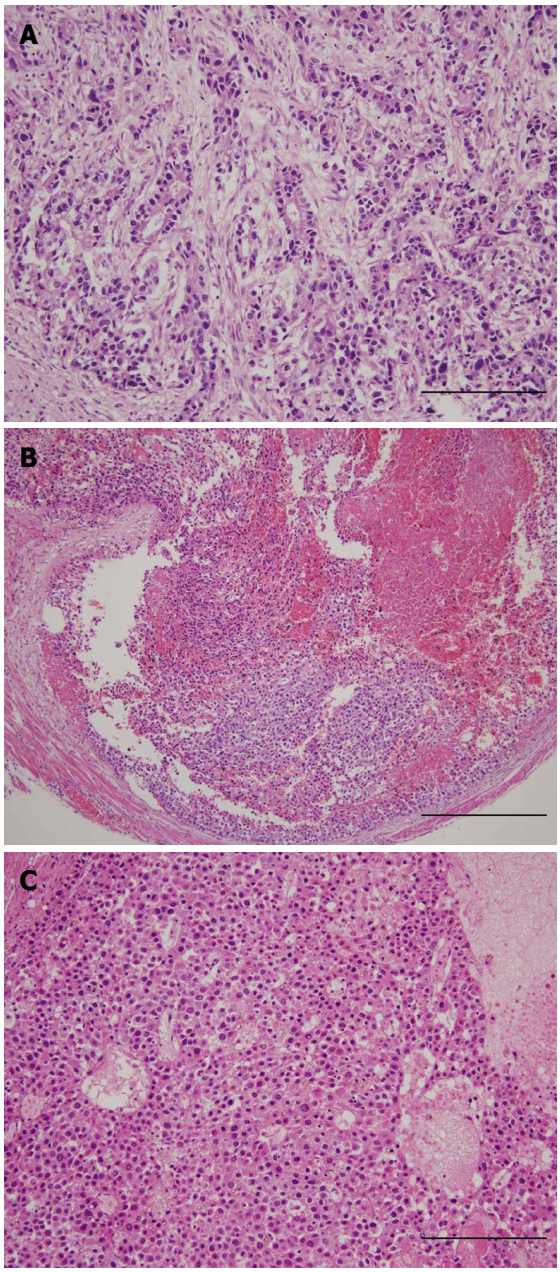

Figure 4 Microscopic appearance of protein induced by vitamin K absence or antagonist Ⅱ-producing gastric cancer. A: Gastric tumor with the appearance of a moderately to poorly differentiated adenocarcinoma (HE stain; the scale bar indicates 50 μm); B: Intravenous tumor with a hepatoid pattern (HE stain; the scale bar indicates 100 μm); C: Metastatic liver tumor with a hepatoid pattern (HE stain; the scale bar indicates 50 μm).

Immunohistochemical staining for AFP is also positive in the primary gastric tumor and metastatic liver tumor in the majority of cases (Figure 5B), and positive staining is most frequently observed in the area of the hepatoid structure. However, in a case in which a biopsy specimen was used for immunohistochemical staining, no AFP-positive tumor cells were detected[12].

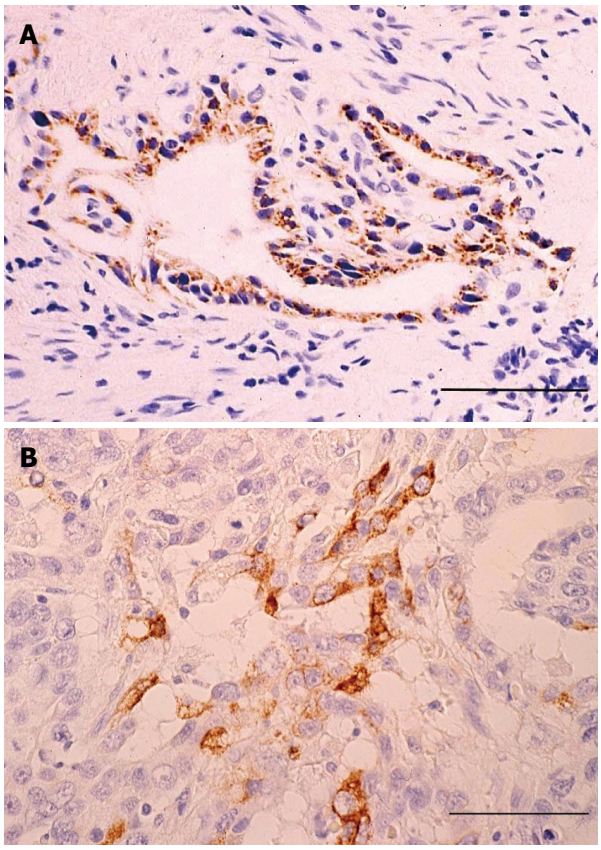

Figure 5 The results of immunohistochemical staining. A: The tumor cells forming glandular structure are positive for protein induced by vitamin K absence or antagonist Ⅱ; B: The tumor cells are also positive for alpha-fetoprotein. All scale bars indicate 25 μm.

DIFFERENTIAL DIAGNOSIS BETWEEN HCC AND LIVER METASTASIS OF PIVKA-Ⅱ-PRODUCING GASTRIC CANCER

It is often difficult to differentiate between HCC and liver metastasis of PIVKA-Ⅱ-producing gastric cancer because PIVKA-Ⅱ is a putative specific marker of HCC and PIVKA-Ⅱ-producing gastric cancer frequently metastasizes to the liver. HCC usually occurs in patients who are infected with the hepatitis virus and have liver cirrhosis or chronic hepatitis. Accordingly, when multiple liver tumors are found in a patient without an underlying liver disease, the possibility of metastatic liver tumor should be considered even if the serum PIVKA-Ⅱ levels are abnormally high, and systemic examination, including upper digestive tract endoscopy, should be performed. If gastric cancer is found in such a patient, histological examination by biopsy and immunohistochemical staining for AFP and PIVKA-Ⅱ is necessary. If a hepatoid pattern is found in the gastric tumor and the tumor cells are positive for AFP and PIVKA-Ⅱ, it is probable that the liver tumor is a result of the metastasis of PIVKA-Ⅱ-producing gastric cancer. However, it is noteworthy that a hepatoid pattern and positive staining for AFP and PIVKA-Ⅱ may not be confirmed in a biopsy specimen because of the limited size of the sample. It was recently reported that immunohistochemical staining for SALL4, a stem cell marker, was positive in all cases of AFP-producing gastric carcinoma and completely negative in HCC[27]. This marker may also be useful to differentiate between PIVKA-Ⅱ-producing gastric cancer and HCC, although further examination is required to confirm this. In addition to the above-mentioned histopathological examination, radiographic examination such as contrast-enhanced CT is also useful for differential diagnosis.

TREATMENT AND PROGNOSIS

Operations were performed on 3 cases without liver metastasis[10,21,24]. In one of those 3 cases, preoperative chemotherapy [low-dose cisplatin (CDDP) and continuous 5-fluorouracil (5-FU) i.v.] was administered[21]. The operative surgical procedures used were subtotal gastrectomy, pancreatico-spleno total gastrectomy, and distal gastrectomy with resection of the extra-gastric tumor according to the spread of the tumor.

Chemotherapy is the main treatment option for patients with liver metastasis, although gastrectomy was also performed in two cases[15,23]. Only best supportive care was performed in four cases with liver metastasis[11,14,16,19]. Systemic chemotherapy or hepatic arterial infusion chemotherapy, and usually, several anti-cancer drugs such as CDDP, 5-FU, and mitomycin C are used in combination; however, the effect is generally poor. Although the efficacy of TS-1, a novel oral derivative of 5-FU, has been reported for several cases of AFP-producing gastric cancer[28,29], long-term survival with TS-1 therapy has not been reported for PIVKA-Ⅱ-producing gastric cancer[22,25].

The prognosis largely depends on the existence of liver metastasis. All 3 patients without liver metastasis are alive without tumor at 9, 15, and 17 mo after surgery. Twelve of the 13 patients with liver metastasis died from their disease and the longest survival period of those patients was 6 mo. The cause of death in the majority of those cases was hepatic failure. The follow-up period for the only patient who was still alive with liver metastasis was only 2 mo[15].

MECHANISM OF PIVKA-Ⅱ PRODUCTION IN GASTRIC CANCER

Glutamic acid, located near the N-terminal of the prothrombin precursor is converted to gamma-carboxyl glutamic acid by vitamin K-dependent carboxylase, and PIVKA-Ⅱ is produced when this mechanism is disturbed. PIVKA-Ⅱ had been known to be produced in the absence of vitamin K or when a vitamin K antagonist is used, and PIVKA-Ⅱ has been regarded as a specific tumor marker of HCC since 1984 when Liebman *et al*[1] reported that it was increased in HCC patients. The increased production of the prothrombin precursor in tumor cells, abnormalities in vitamin K-dependent carboxylation, and vitamin K deficiency in tumor tissue have been spe-

culated to be the underlying mechanisms of PIVKA-Ⅱ production in HCC[30]. We speculate that gastric cancer produces PIVKA-Ⅱ *via* hepatocellular metaplasia because an HCC-like histological pattern is observed in many PIVKA-Ⅱ-producing gastric cancer cases, almost all PIVKA-Ⅱ-producing gastric cancer cases have increased serum AFP levels, and the L3 fraction of AFP was increased (HCC-like pattern) in all cases in which the AFP fractions were examined. The liver is derived from an outpouching of the foregut, as is the stomach, so it is not particularly surprising that the neoplastic gastric mucosa may sometimes differentiate into hepatic-type cells.

In addition, we speculate that many PIVKA-Ⅱ-producing gastric cancers occur initially as common gastric adenocarcinomas and that the hepatoid component arises during tumor progression, given that almost all cases are advanced cancers and the hepatoid pattern is most frequently observed in the deep invasive portion. Fujii *et al*[31] performed loss of heterozygosity analysis on AFP-producing gastric cancer using a panel of microsatellite markers, and concluded that AFP-producing carcinoma foci may evolve through genetic progression and/or genetic divergence. They also described that the silencing of a crucial gene on 13q may be involved in the acquisition of the AFP-producing phenotype. Further examination is required with regard to the genetic evolution of PIVKA-Ⅱ-producing gastric cancer.

COMPARISON BETWEEN AFP- AND PIVKA-Ⅱ-PRODUCING GASTRIC CANCERS

It has been reported that AFP-producing gastric cancer comprises 2.7%-5.4% of all gastric cancer[7,32]. According to a review of 270 cases of AFP-producing gastric cancer by Adachi *et al*[33], AFP-producing gastric cancer shows a male predominance (73%), predominant tumor location in the gastric antrum (57%), lymph node metastasis (83%), and liver metastasis (33%). Histologically, AFP-producing gastric cancer is classified as hepatoid adenocarcinoma-type or non-hepatoid adenocarcinoma-type, with the latter including fetal gastrointestinal tube-type and yolk sac-type[24]. Hepatoid adenocarcinomas are more invasive, especially to the small veins, than the non-hepatoid adenocarcinoma-type[24]. The prognosis for AFP-producing gastric cancer is worse than for conventional gastric cancer, and the 5-year survival rates for hepatoid and non-hepatoid AFP-producing carcinomas are 21.4% and 38.2%, respectively[8]. Thus, it seems that the clinicopathological features of PIVKA-Ⅱ-producing gastric cancer resemble those of AFP-producing gastric cancer, especially AFP-producing hepatoid adenocarcinoma, although the frequency of liver metastasis and portal vein tumor thrombus is higher and the prognosis is worse in PIVKA-Ⅱ-producing gastric cancer than in AFP-producing gastric cancer. The possibility that PIVKA-Ⅱ production is related to a worse prognosis has also been observed in HCC[34].

The mechanisms responsible for the production of AFP and PIVKA-Ⅱ in HCC appear to be independent[30,35], and HCCs produce either or both of AFP and PIVKA-Ⅱ. However, as mentioned above, PIVKA-Ⅱ-producing gastric cancer is far rarer than AFP-producing gastric cancer, and almost all PIVKA-Ⅱ-producing gastric cancers also produce AFP. The reason for this is unclear, but the following possibilities are conceivable: (1) AFP can be produced not only via hepatocellular metaplasia but also via retrodifferentiation to fetal gastrointestinal tract or yolk sac in gastric cancer; (2) hepatoid carcinoma of the stomach may possess different cytological characteristics from those of HCC; and (3) gastric cancer producing only PIVKA-Ⅱ might be overlooked because PIVKA-Ⅱ is not measured so frequently as AFP.

PIVKA-Ⅱ-producing cancers other than HCC and gastric cancer

Malignant tumors other than HCC and gastric cancer that produce PIVKA-Ⅱ have been reported although the frequency is extremely low. To date, PIVKA-Ⅱ-producing cancers in the lung[36,37], colon[38], adrenal cortex[39], ovary[40], and pancreas[41] have been reported. Serum AFP levels were increased in all of those cases. Immunohistochemically, all of those cases were positive for PIVKA-Ⅱ and all but one case were positive for AFP. Histologically, hepatoid structure was observed in all but one case. Liver metastasis was observed in 2 (33%) of the 6 cases. Four patients died and the median survival period was 14.5 mo. Two patients were alive for 4 and 48 mo respectively and liver metastasis was not present in either of those cases.

CONCLUSION

PIVKA-Ⅱ-producing gastric cancer is a very rare subtype of gastric cancer, and AFP is also produced in almost all cases. The hepatoid pattern is often detected histologically, and the production of PIVKA-Ⅱ by tumor cells is usually confirmed immunohistochemically. Liver metastasis and portal vein tumor thrombus are frequently observed, and almost all patients with liver metastasis die within 6 mo. Hepatocellular metaplasia of tumor cells is suggested to be the mechanism of PIVKA-Ⅱ production. Analysis of a larger number of cases is needed to clarify the clinicopathological features of this very rare subtype of gastric cancer.

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