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Primary colon cancer with a high serum PIVKA-II level

Kazuya Kato[a,*], Yoshiaki Iwasaki[b], Masahiko Taniguchi[c], Kazuhiko Onodera[d], Minoru Matsuda[e], Takako Kawakami[a], Mineko Higuchi[a], Kimitaka Kato[a], Yurina Kato[a], Hiroyuki Furukawa[c]

[a] Department of Surgery, Pippu Clinic, 2-10, 1 cyome Nakamachi, Pippu Town Kamikawa-gun, Hokkaido 078-0343, Japan
[b] Department of Gastroenterology and Hepatology, Okayama University, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558,Japan
[c] Department of Surgery, Asahikawa Medical University, 1-1, 2-1 Midorigaoka, Asahikawa City 078-8510, Japan
[d] Department of Surgery, Sapporo Hokuyu Hospital, 5-1, 6-6Higashi- Sappro, Shiroishi-ku Sapporo City 003-0006, Japan
[e] Department of Surgery, Nihon University, 1-8-13 Surugadai Kanda, Chiyoda-ku, Tokyo 010-8309, Japan

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ABSTRACT

INTRODUCTION: Protein induced by vitamin K absence/antagonist-II (PIVKA-II) is an abnormal protein, and several reports have demonstrated the efficacy of PIVKA-II in the diagnosis of hepatocellular carcinoma (HCC). We report an extremely rare case of adenocarcinoma of the colon with a high serum PIVKA-II level.

PRESENTATION OF CASE: A 95-year-old woman presented with right lower quadrant pain and appetite loss. An abdominal computed tomography scan and ultrasonography showed an ascending colon tumor and multiple metastatic tumors in the liver. The serum level of PIVKA-II was extremely high, 11,900 ng/mL. Colonoscopic examination revealed a tumor accompanied by an ulcer in the ascending colon, which was highly suspicious for malignancy. Multiple biopsies showed well-differentiated adenocarcinoma of the colon, which was evaluated as colon cancer, stage IV. PIVKA-II-productive colon cancer was confirmed. Chemotherapy with TS-1 was administered. The patient died 3 months after initial admission.

DISCUSSION: The expression of PIVKA-II was detected in non-cancer areas, with non-specific expression observed in plasma cells in our case. There might be some possibility that hepatoid differentiation exists in other regions of the colon tumor or in the liver tumor, parenchymal cells or lung metastases, which were composed of PIVKA-II-positive and AFP-negative cells.

CONCLUSION: To the best of our knowledge, high serum levels of PIVKA-II resulting from colon adenocarcinoma have not been reported previously. We report this rare case together with a review of the literature.

1. Introduction

Protein induced by vitamin K absence or antagonist II (PIVKA-II) is a newly recognized tumor marker for hepatocellular carcinoma (HCC) [1]. PIVKA-II has been shown to be a useful and specific marker for the diagnosis of HCC. However, PIVKA-II levels may increase in patients with tumors other than HCC [2]. PIVKA-II-producing gastric cancer and embryonal carcinoma have been reported recently [3]. Here, we report a rare case of advanced colon cancer in a patient with a high serum PIVKA-II level. To the best of our knowledge, a high serum level of PIVKA-II resulting from colon adenocarcinoma has not been reported previously.

2. Presentation of case

A 95-year-old Japanese woman presented with a 3-week history of upper abdominal discomfort, dysphagia, and loss of appetite. Upon physical examination, a smooth mass measuring 20 cm in its largest dimension was palpated in the right upper abdomen. She did not drink and took no medications including warfarin or antibiotics. At admission, laboratory findings revealed leukocytosis of 13,200 /mm^3; 233 U/L aspartate aminotransferase (AST); 32 U/L alanine aminotransferase (ALT); 791 U/L alkaline phosphates (ALP); 440 U/L g-glutamyl transferase (GGT); 6.4 g/dl total protein; and 1.2 mg/dL total bilirubin. The level of C-reactive protein (CRP) was 9.3 mg/mL (normal range, 0.5–0.8 mg/mL). The serum level of carcinoembryonic antigen (CEA) was extremely high, 1270 ng/mL (cutoff, 2.5 ng/mL); the α-fetoprotein (AFP) level was 2 ng/mL (cutoff of 10 ng/mL); and the level of CA 19–9 was extremely high,

* Corresponding author. Tel.: +81 166 85 2222; fax: +81 166 58 9008.
E-mail address: pippuclinickato@gold.ocn.ne.jp (K. Kato).

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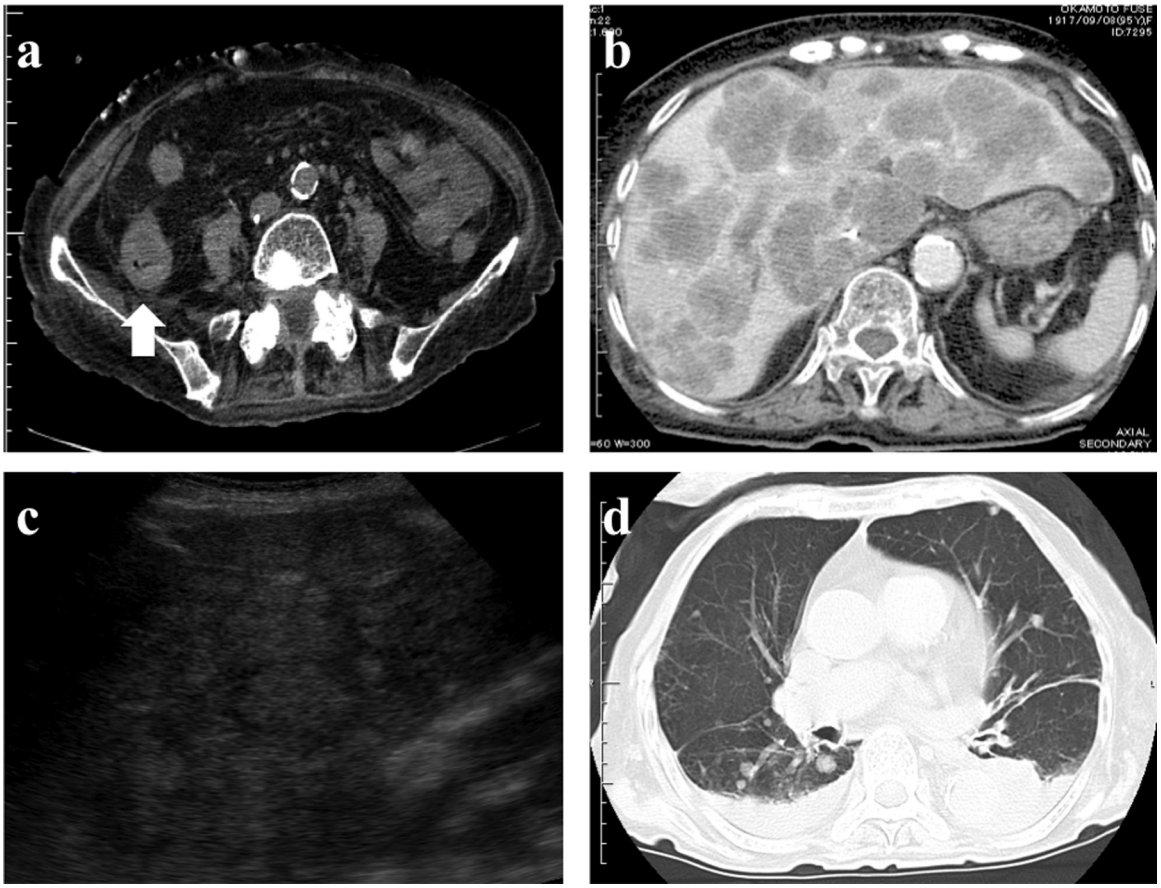

Fig. 1. **a** and **b**: An abdominal computed tomography (CT) study showed a tumor with a diameter of 6 cm occupying the right upper abdominal quadrant together with multiple liver lesions (arrow). **c:** Ultrasonography showed well-defined hypoechoic liver tumors. **d:** Chest CT scan showed multiple lung lesions.

3070 U/mL (cutoff of 37 U/mL). The level of PIVKA-II was also extremely high, 11,900 AU/mL(cutoff, 40 AU/mL). An abdominal computed tomography (CT) scan and ultrasonography showed multiple liver lesions, ascites, and a tumor with a diameter of 6 cm occupying the right upper abdominal quadrant, but no lymph node enlargement was identified (Fig. 1a–c). A chest CT scan showed multiple lung lesions (Fig. 1d). The colonoscopic examination revealed a tumor accompanied by a giant ulcer on the ascending colon (Fig. 2a). Multiple biopsies showed well-differentiated tubular adenocarcinoma of the colon at stage IV (Fig. 2b). Hepatoid-differentiated cells were not detected in the biopsy specimens. Monoclonal antibody raised against PIVKA-II (Eisai, Chiba, Japan) was used for immunohistochemical analysis, but cancer cells were not positive for PIVKA-II (Fig. 2c). Non-cancer cells (mainly plasma cells) were non-specifically positive (Fig. 2d). An immunohistochemical study showed that CEA- and CA19–9-positive and AFP- and glypican-3 (GP-3)-negative cells were present in the tumor (Fig. 3a–d). The patient was administered palliative chemotherapy with TS-1. The patient died of liver failure 3 months after the initial admission. An autopsy was not performed.

3. Discussion

PIVKA-II is a circulating precursor of prothrombin, which is found in the blood of patients who are deficient in vitamin K [4]. In 1984, Leibman et al [1]. reported PIVKA-II levels to be significantly elevated in HCC patients. The clinical usefulness of PIVKA-II in the detection of HCC has been demonstrated in many studies [5,6]. PIVKA-II has been reported to predict the progression of HCC patients because those with higher PIVKA-II levels had a significantly higher frequency of intrahepatic metastasis, portal or hepatic vein tumor thrombosis and capsular infiltration [7,8]. It is proposed that PIVKA-II may be useful primarily as a prognostic biomarker, predicting rapid tumor progression and poorer prognosis [7]. These findings may be explained by an in vitro study showing that PIVKA-II stimulates cell proliferation and cell migration of vascular endothelial cells by binding to the kinase insert domain receptor, alternatively referred to as vascular endothelial growth factor receptor-2 [9]. The increased production of the prothrombin precursor in tumor cells, abnormalities in vitamin K-dependent carboxylation, and vitamin K deficiency in tumor tissues have been speculated to be the underlying mechanisms of PIVKA-II production in HCC [10]. PIVKA-II-producing gastric cancers occur initially as common gastric adenocarcinoma and the hepatoid component arises during tumor progression. The stomach is one of the most common sites in which hepatoid adenocarcinomas have been described, the reason for which is unknown. Almost all cases were with advanced cancers and the hepatoid pattern is observed in the invasive portion. It has been indicated that the hepatoid-differentiated foci of the gastric adenocarcinoma may produce the prothrombin precursor in addition to both AFP and PIVKA-II [2]. It seems to that the clinicopathological features of PIVKA II-producing gastric cancer resemble those of AFP-producing gastric cancer, especially AFP-producing hepatoid adenocarcinoma [11]. The hepatoid pattern is often detected histologically, and the production of PIVKA-II by tumor cells usually is confirmed immunohistochemi-

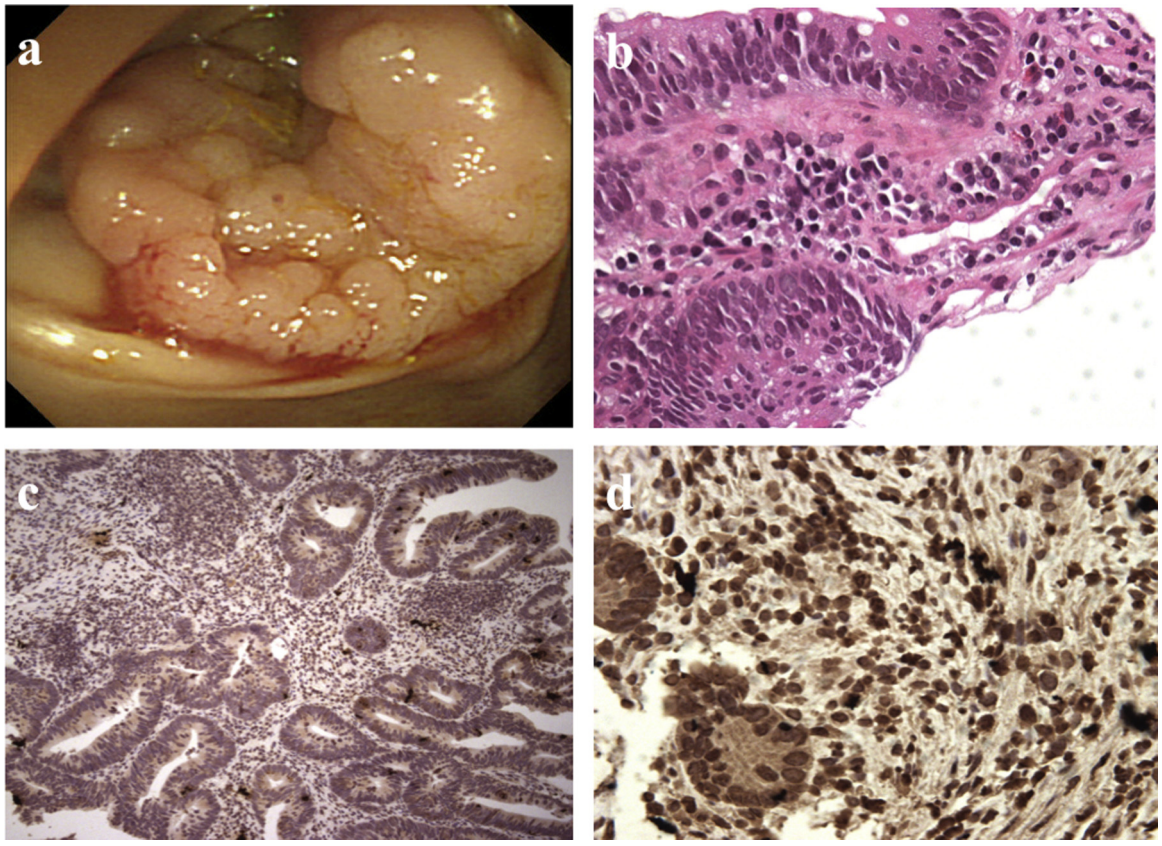

Fig. 2. **a**: The colonoscopic examination revealed a tumor accompanied by a giant ulcer on the ascending colon. **b**: Multiple biopsies showed a well-differentiated tubular adenocarcinoma (X 400). **c**: Immunohistochemical determination of PIVKA-II expression in the area of the adenocarcinoma was negative (X 100). **d:** Immunohistochemical determination of PIVKA-II expression in the non-cancer area of plasma cells was non-specifically positive (X 400).

cally [11]. Hepatoid-differentiated cells are derived from germ cell tumors located close to the embryonic association of the foregut endoderm and yolk sac [12]; the foregut derivation of both liver and stomach and their embryologic proximity likely have a role. Hepatocellular metaplasia of tumor cells is suggested to be the mechanism of PIVKA-II production. Carcinomas that histologically resemble hepatocellular carcinoma (hepatoid adenocarcinomas) have been described at various sites, including the colon [13].

By contrast, PIVKA-II has been reported to be positive in 26% of non-cancer tissues adjacent to HCC. The expression of PIVKA-II in non-cancer tissue adjacent to the HCC is stronger than the expression in the tumor. The explanation for this phenomenon might be that accelerated production of the prothrombin precursor in HCC causes a deficiency of vitamin K in the local region surrounding the HCC [14]. It is suggested that non-cancer tissue including liver parenchyma adjacent to the HCC may produce PIVKA-II [14]. The expression of PIVKA-II was detected in non-cancer areas, with non-specific expression observed in plasma cells in our case. Most hepatoid adenocarcinomas are associated with the production of alpha-fetoprotein (AFP), but not all AFP-producing carcinomas show hepatoid features histologically [15,16]. In our case, serum AFP level was not high, and hepatoid cells were not detected in the biopsy specimen. In many gastric cancer cases, biopsy specimens show only the histological appearance of poorly or moderately differentiated adenocarcinoma, but hepatoid cells are detected by the examination of surgical or autopsy materials [11]. There might be some possibility that hepatoid differentiation exists in other regions of the colon tumor or in the liver tumor, parenchymal cells or lung metastases, which were composed of PIVKA-II-positive and AFP-negative cells.

CA 19–9 has been developed for the diagnosis of digestive tract malignancies. Recent reports indicated that serum CA19–9 is frequently elevated in subjects with various gastrointestinal malignancies, such as pancreatic, colorectal, gastric and hepatic carcinomas [17] The antibody has been obtained by immunizing mice with a human colorectal cell line [18]. The epitope is expressed on the cell surface as glycolipids and glycoproteins. In patients with digestive malignancies, the antigen is found in serum, where it is associated with a high molecular weight carbohydrate-rich mucin fraction. Serum CA19–9 concentration was most increased in a patient with pancreatic cancer or cholangiocarcinoma. CA 19–9 resembles carcinoembryonic antigen in colorectal carcinoma and various different gastrointestinal adenocarcinomas. Expression of CA19–9 has been studied in normal and malignant gastrointestinal tissues. The antigen was found by immunoperoxidase staining in 40% to 80% of carcinomas from gallbladder, stomach, pancreas, and colon [19].

The oncofetal antigen glypican 3 (GP 3) is a heparin sulfate proteoglycan that is expressed in more than 70% of HCCs. They are the first transcripts to appear during malignant hepatocyte transformation [20]. An immunohistochemical analysis showed that the cells present in the colonic lesion were GP3 negative in our case.

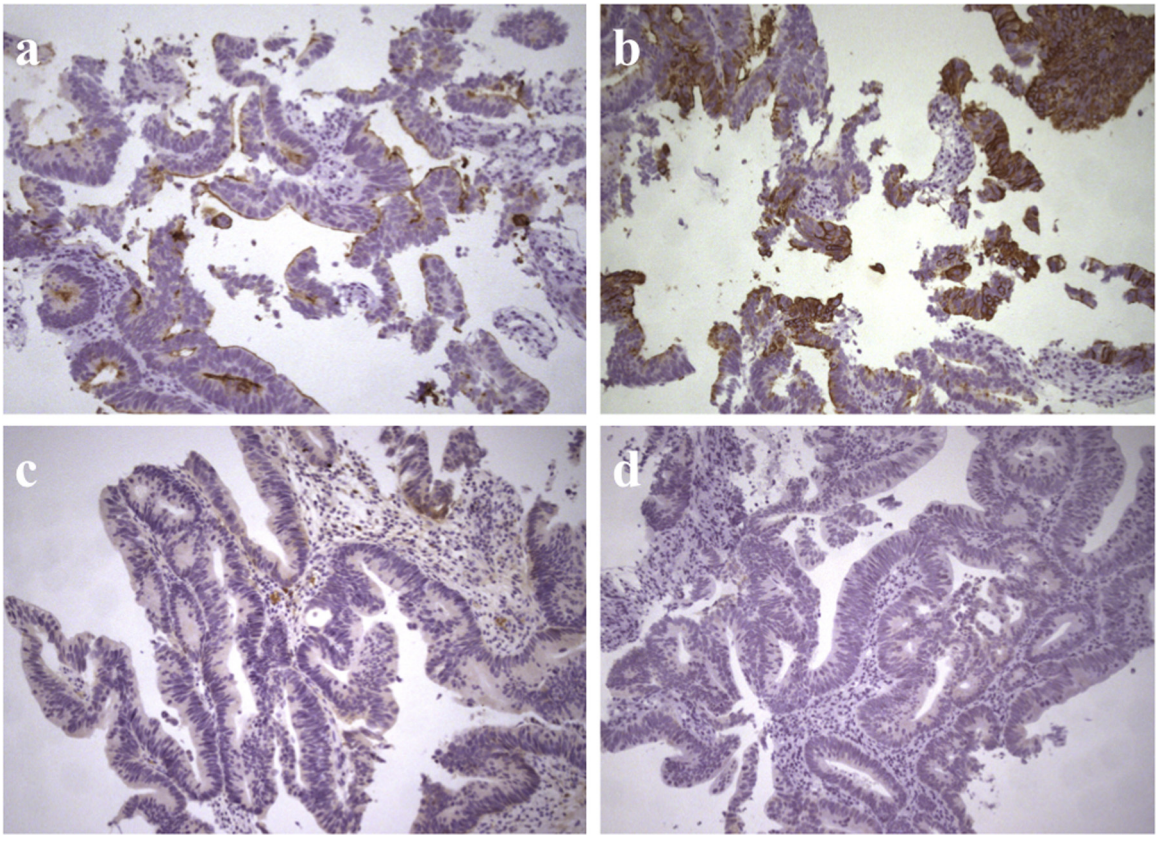

Fig. 3. **a** and **b**: Immunohistochemical determination of CEA and CA 19–9 expression in the area of the adenocarcinoma was positive (X 100). **c** and **d**: Immunohistochemical determination of AFP and GP-3 expression in the area of the adenocarcinoma was negative (X 100).

4. Conclusion

We have reported a rare colon cancer in a patient with high serum levels of multiple serum tumor markers. PIVKA-II-producing colon cancer is an extremely rare subtype of colon cancer.

Conflict of interest

The authors declare that they have no competing interests.

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Written consent was obtained from the patient's relatives for publication of the study. No funds supported this study.

Consent

Written informed consent was obtained from the patient's relatives for publication of this case report and any accompanying images. Copies of the written consent are available for review by the Editor-in-Chief of this journal.

Authors' contributions

KK, TK, and KO conceived and designed the study, analyzed all the reports and drafted the manuscript. MH, YI, YK and KiK drafted the manuscript and searched the literature. MM performed colonoscopy on the patient and participated in designing the study. MT, KK and HF participated in designing the study. All authors read and approved the final manuscript.

Key Learning Points

- PIVKA-II-producing colon cancer is an extremely rare subtype of colon cancer.

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