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Des-γ-carboxy Prothrombin (PIVKA-II)-producing Mediastinal Embryonal Carcinoma with Features of Hepatoid Differentiation

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Abstract. *The case of a 48-year-old man with primary nonseminomatous embryonal carcinoma at the posterior mediastinum is described. The patient displayed extremely high plasma levels of Des-γ-carboxy prothrombin (PIVKA-II) (4040 mAU/ml). Ultrasonography and dynamic computed tomography ruled out hepatocellular carcinoma (HCC) or liver metastasis. After preoperative systemic chemotherapy, total tumor resection was performed. Postoperatively, the plasma levels of PIVKA-II returned to within the normal range (24 mAU/ml). An immnohistochemical study using anti-PIVKA-II monoclonal antibody revealed the cytoplasmic expression of PIVKA-II in the carcinoma cells. These results indicate that tumor cells, which are manifested as hepatoid differentiation, may produce PIVKA-II. This case seems to be the first case reported in which PIVKA-II was produced by nonseminomatous mediastinal embryonal carcinoma without HCC or liver metastasis.*

Des-γ-carboxy prothrombin (PIVKA-II), a protein induced by vitamin K absence or antagonist-II, is a newly recognized tumor marker for hepatocellular carcinoma (HCC) (1). Generally, it has been shown to be a useful and specific marker for the diagnosis of HCC. It has been reported that PIVKA-II is produced from gastric cancer (2-4), but the production of PIVKA-II by nonseminomatous mediastinal embryonal carcinoma has not yet been reported. A case of primary nonseminomatous mediastinal embryonal carcinoma is described with high plasma levels of PIVKA-II, the localization of which was noted in tumor cells with hepatoid differentiation by immunohistochemical staining.

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Case Report

A 48-year-male was admitted to our hospital for treatment of a posterior mediastinal tumor. The tumor was visualized by chest radiography 3 months prior to admission, and grew gradually. On admission, laboratory tests, including blood cell counts, liver function tests and blood coagulation tests with tests of prothrombin time, were normal, except for high serum levels of α-fetoprotein (AFP) (9367 ng/ml; normal values < 20 ng/ml) and plasma PIVKA-II (4040 mAU/ml; normal value < 6 mAU/ml). No hepatic tumors were observed with ultrasonography, enhanced computed tomography (CT), or whole-body gallium scintigraphy. The chest CT revealed a heterogeneous solid tumor located in the posterior mediastinum (Figure 1). Examination by CT-guided percutaneous needle biopsy revealed an embryonal carcinoma. Intensive chemotherapy was begun with the BEP regimen including cisplatin (20 mg/m^2, days 1-5), etoposide (100 mg/m^2, days 1-5) and bleomycin (30 mg/body, days 1, 8, 15). After five administrations of systemic chemotherapy, the tumor was removed.

In postoperative macroscopic observation, the resected mediastinal tumor (7 x 5 x 3 cm) was found to have directly invaded the lung. It had a tan-white, homogeneous cut surface with scattered areas of hemorrhage. The histology was consistent with germ cell carcinoma, particularly embryonal carcinoma (H-E staining, X 200, Figure 2A). Carcinoma cells proliferated with remarkable hepatoid differentiations. There was change in the plasma PIVKA-II levels during the clinical course. The tumor was removed completely, and the serum levels of AFP and plasma levels of PIVKA-II declined rapidly after surgery, reaching normal values within 1 month postoperatively (Figure 3). To confirm whether or not the tumor cells produced PIVKA-II, an immunohistochemical study of this tumor specimen,

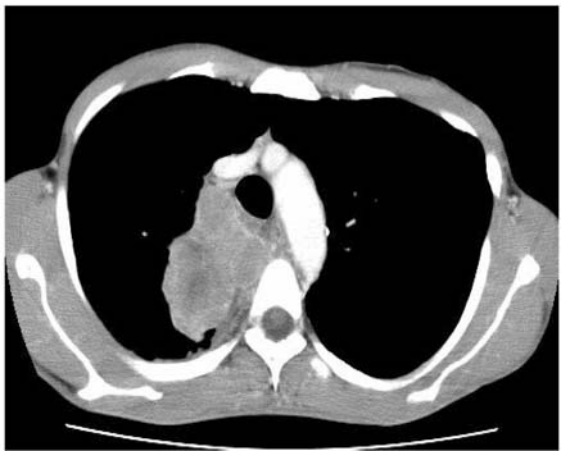

Figure 1. *Chest computed tomography showing the giant solid tumor in the posterior mediastinum.*

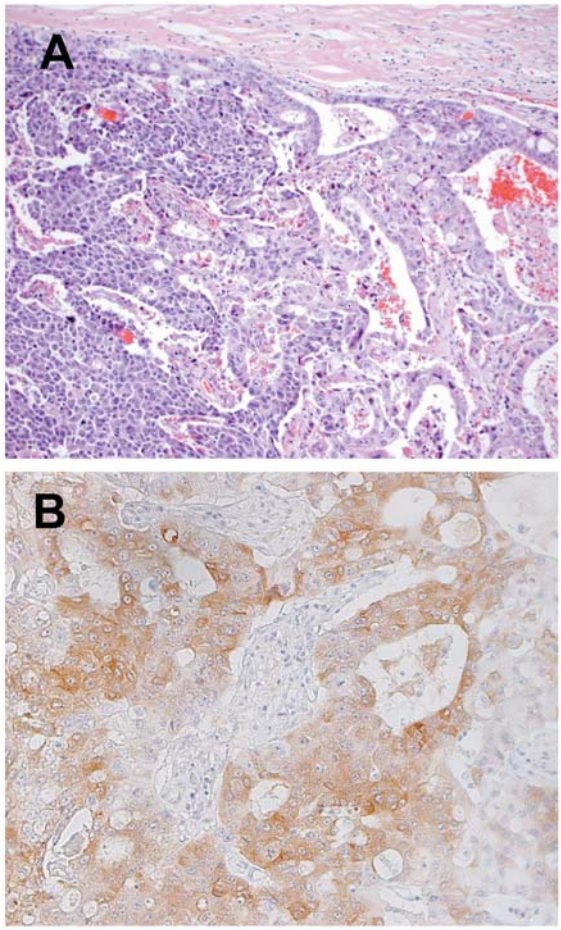

Figure 2. *Histological findings in the post-operative embryonal carcinoma. A: Histology was consistent with germ cell carcinoma, particularly embryonal carcinoma (H-E staining, X 200). Carcinoma cells proliferated with remarkable hepatoid differentiations. B: Immnohistochemical staining for the PIVKA-II was performed by using the streptavidin-biotin-peroxidase complex technique. A monoclonal antibody for PIVKA-II was used in this staining. The cytoplasmic expression of PIVKA-II was remarkably seen in carcinoma cells with hepatoid differentiations (X 200).*

using a monoclonal antibody for PIVKA-II (Eisai, Tokyo, Japan), was performed. The immunoreaction was visualized by the streptavidin-biotin-peroxidase complex technique. The cytoplasmic expression of PIVKA-II was remarkably seen in carcinoma cells with hepatoid differentiations (Figure 2B). The patient underwent two courses of postoperative chemotherapy with the VIP regimen including cisplatin (20 mg/m^2, days 1-5), ifosfamide (1.2 g/m^2 days 1-5), and vinblastine (0.11 mg/kg, days 1, 2) because a small number of viable cells were histopathologically recognized in the embryonal cells component (Figure 3). At the time of writing, the patient remains alive without any evidence of recurrence.

Discussion

PIVKA-II is a circulating precursor of prothrombin, that is found in the blood of patients who are deficient in vitamin K or who are receiving a vitamin K antagonist (5). In many cases, the high plasma levels of PIVKA-II in HCC are attributed to an increased production of prothrombin precursors by HCC itself (6, 7). In the present case, there was no evidence of HCC or hepatic failure that could explain the increased plasma PIVKA-II levels. In this clinical course, the plasma PIVKA-II levels declined gradually following systemic chemotherapy, reaching a normal value after total resection. We were able to make a pathological diagnosis of PIVKA-II-producing embryonal carcinoma through immunohistochemical staining for PIVKA-II, by using the anti-PIVKA-II monoclonal antibody. In a PIVKA-II-producing tumor, such as in the present case, the plasma PIVKA-II levels may be useful for diagnosis and as a marker in evaluating recurrent disease and therapeutic response.

The mechanism by which embryonal carcinoma acquires the ability to produce PIVKA-II is unknown. It has been reported that some cases of gastric cancer have produced PIVKA-II (2-4, 8, 9). It has also been indicated that the hepatoid-differentiated foci of the gastric adenocarcinoma may produce the prothrombin precursor, and that gastric adenocarcinoma, which shows a differentiation similar to HCC (hepatoid differentiation), produces both AFP and PIVKA-II (2). Hepatoid differentiation may be classified into two broad categories, the first of which is derived from germ cell tumors, the histogenetic basis of which is believed to be related to the close embryonic association of the foregut endoderm and the primary yolk sac (10). It has been reported that hepatoid differentiation can be observed in

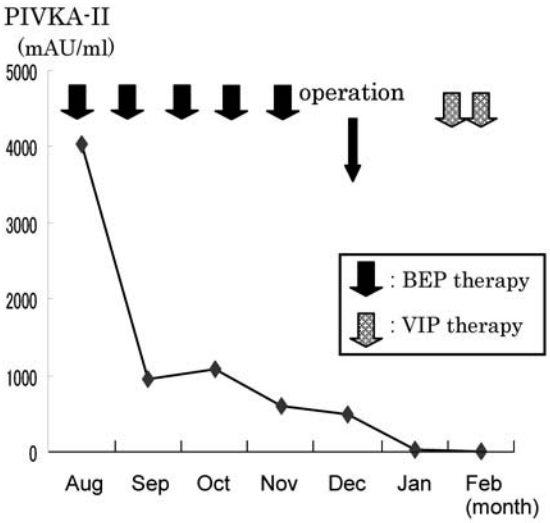

Figure 3. *Change in plasma PIVKA-II levels during the clinical course. The abbreviations used are: BEP, cisplatin + etoposide + bleomycin; VIP, vinblastine + ifosfamide + cisplatin.*

9.3% of extragonadal germ cell tumors (11). The second category involves the true hepatoid adenocarcinomas of a variety of organs in the stomach that fulfill the strict morphological criteria of hepatoid differentiation (12, 13). Most of these resected tumors histologically reveal striking hepatocellular carcinoma-like differentiation. The present immunohistochemical study revealed that the signal of PIVKA-II increased remarkably in the hepatoid area, suggesting that PIVKA-II production in embryonal carcinoma is derived from hepatoid differentiation in the carcinoma cells.

In summary, the case presented herein seems to be the first in which PIVKA-II was observed to be produced by an embryonal carcinoma, as confirmed by immunohistochemical staining. This finding appears to support the hepatoid differentiation of embryonal carcinomas as one of the mechanisms of production of PIVKA-II.

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