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CASE REPORT

One Case of Abnormal Elevation of PIVKA-II

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SUMMARY

Background: **Protein Induced by Vitamin K Absence or Antagonist II (PIVKA-II) is a serum biomarker that is specifically elevated in hepatocellular carcinoma (HCC) and has important value in early diagnosis, prognosis evaluation, and recurrence prediction of liver cancer.**
Methods: **We report a case of extreme elevation of serum PIVKA-II due to the use of warfarin.**
Results: **The patient's abdominal ultrasound and enhanced CT examinations showed no significant abnormalities. The patient has been taking warfarin for atrial fibrillation, and after supplementing with vitamin K, the PIVKA-II level significantly decreased. Therefore, the PIVKA-II results were extremely elevated, which is believed to be caused by taking warfarin.**
Conclusions: **When patients take warfarin anticoagulant therapy, it may cause an extreme increase in PIVKA-II results. Laboratory staff and clinical doctors should consider the existence of this situation and avoid unnecessary examinations and treatments for patients.**
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KEYWORDS

PIVKA-II, warfarin, vitamin K

INTRODUCTION

PIVKA-II, also known as des gamma carboxy prothrombin (DCP), is a protein synthesized in the liver. Under normal circumstances, when prothrombin is synthesized in the liver, it relies on vitamin K for gamma carboxylation, forming prothrombin with coagulation activity. However, in patients with hepatocellular carcinoma (HCC) or vitamin K deficiency, an abnormal form of prothrombin PIVKA-II is synthesized due to obstruction of the gamma carboxylation process. PIVKA-II is commonly used to evaluate the occurrence, development, and recurrence of HCC and is an important prognostic indicator for HCC [1]. We found one case without evidence of hepatocellular carcinoma, where serum PIVKA-II was extremely elevated due to the use of warfarin. The specific situation is as follows:

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CASE PRESENTATION

The patient is an 85-year-old female. She was admitted on October 11, 2024, due to the discovery of gallstones for over 10 years and abdominal pain for 1 week. Patient admission examination: Serum tumor markers showed extreme elevation of PIVKA-II (50,496 mAU/mL), while no significant abnormalities were observed in other tumor markers (Table 1). At the same time, routine biochemical coagulation tests were performed, which showed abnormal liver function (Table 1). The patient underwent abdominal ultrasound, which showed gallstones and sediment accumulation in the gallbladder. B-ultrasound did not find any evidence related to hepatocellular carcinoma. Considering such a high level of PIVKA-II, the doctor performed abdominal enhanced CT on the patient to screen for hepatocellular carcinoma, and the results also showed gallstones with gallbladder inflammation, with no significant abnormalities observed in the rest.

The imaging test result of the patient's hepatocellular carcinoma is negative and the AFP level is normal. PIVKA-II levels were more than 100 times higher than the reference range. Considering the clinical diagnosis of gallstones in the patient, laboratory staff had doubts about the results. The laboratory staff first retested the sample, and the results were consistent with the previous ones. At the same time, it was discovered that the internal quality control (IQC) of PIVKA-II was under control on that day. The status of instruments and reagents was also normal. Therefore, we believed that the results were reliable. We reviewed the patient's medical records and found that the elderly patient has a history of atrial fibrillation and had been taking warfarin anticoagulant therapy for a long time. Warfarin is an antagonist of vitamin K, causing abnormal synthesis of vitamin K-dependent coagulation factors (including coagulation factors II, VII, IX, and X). At the same time, the accumulation of gallstones in the patient for more than ten years resulted in poor absorption of vitamin K and vitamin K deficiency, further exacerbating the abnormal synthesis of coagulation factors dependent on vitamin K, indirectly promoting the production of PIVKA-II. So we tested the sample for vitamin K and the result was 0.09 ng/mL, which is below the normal range. So we contacted the clinical doctor and suggested that the patient stop using warfarin for a period of time before undergoing further testing. Considering the severity of the patient's gallstones and the risk of atrial fibrillation, the clinical doctor evaluated status and decided to continue using warfarin while supplementing with vitamin K and to perform surgery at an appropriate time. Starting on October 15th, daily intramuscular injections of vitamin K 10 mg were administered. On October 16th, vitamin K and PIVKA-II were tested again. With the increase of serum vitamin K levels, PIVKA-II significantly decreased (Table 2). Therefore, we believe that the patient's PIVKA-II is extremely elevated due to the combination of taking warfarin and vitamin K deficiency. So, on October 17th, the doctor performed laparoscopic cholecystectomy on the patient as scheduled. On the second day after surgery, vitamin K and PIVKA-II were retested, and PIVKA-II (9,104.63 mAU/mL) levels further decreased significantly (Table 2). On October 21st, the patient's condition improved, and there was no obvious abdominal pain, so the patient was discharged.

DISCUSSION

PIVKA-II is an effective and specific biomarker for hepatocellular carcinoma (HCC), and its level is closely related to the occurrence and development of HCC tumors. It is a necessary supplement to AFP and imaging examinations [2,3]. However, for those who appear normal on imaging tests, high levels of PIVKA-II may be associated with vitamin K deficiency and warfarin use, and further screening may be necessary for this population in clinical practice [4].

There are studies showing that liver cancer, cirrhosis, hepatitis, and gallstones can all cause varying degrees of elevation in PIVKA-II levels. The median PIVKA-II level in liver cancer patients reaches 1,245.0 mAU/mL, while the median PIVKA-II level in gallstones patients is only 85.0 mAU/mL [1]. The PIVKA-II of this patient with gallstones was as high as 50,496 mAU/mL, and imaging did not show any evidence of liver cancer. Therefore, the laboratory suspects that there may be other factors causing the extreme increase in PIVKA-II levels in the patient. Upon reviewing the patient's medical records, it was discovered that the patient had been taking warfarin for a long time due to atrial fibrillation. Warfarin is an oral anticoagulant drug that is an antagonist of vitamin K. Long term use of Warfarin can lead to a deficiency of vitamin K [5]. The mechanism of action of warfarin is to inhibit vitamin K epoxide reductase, thereby preventing the recycling of vitamin K and inhibiting the gamma carboxylation of vitamin K-dependent coagulation factors, indirectly leading to an abnormal increase in PIVKA-II [6]. At the same time, the patient is an 85-year-old elderly patient who has been suffering from gallstones for more than ten years, with insufficient nutrient intake and poor fat absorption. Vitamin K is a lipophilic vitamin stored in the liver, and malnutrition or insufficient fat intake can easily lead to vitamin K deficiency [7,8]. We detected the patient's vitamin K level using liquid chromatography tandem mass spectrometry, and the result was 0.09 ng/mL, indicating that the patient does indeed have vitamin K deficiency. Under normal circumstances, liver cells synthesize clotting factors that depend on vitamin K. When vitamin K is deficient, liver cells cannot synthesize these normal coagulation factors and can only synthesize PIVKA-II without coagulation activity. The combination of two factors leads to an extreme increase in PIVKA-II levels in patients. The anticoagulant effect of warfarin may last for a period of time after discontinuation, and when rapid reversal of coagulation factor

Table 1. The results of the patient's serum biochemistry and tumor markers.

Test items	Results	Reference value
Alanine aminotransferase (ALT)	177.4	7 - 40 U/L
Aspartate transaminase (AST)	93.3	13 - 35 U/L
Carbohydrate antigen 19-9 (CA19-9)	< 2.00	≤ 37.00 U/mL
Carbohydrate antigen 242 (CA242)	< 0.50	≤ 20 IU/mL
Carbohydrate antigen 50 (CA50)	< 1.00	≤ 25 IU/mL
Alpha fetoprotein (AFP)	2.16	≤ 13.4 ng/mL
Carcino-embryonic antigen (CEA)	2.0	≤ 5 ng/mL
PIVKA-II	50,496	≤ 40.00 mAU/mL

Table 2. The serum PIVKA-II levels of patients before and after vitamin K treatment.

	PIVKA-II	Vitamin K
October 12, 2024	50,496.00	0.09
October 16, 2024	16,876.45	3.13
October 18, 2024	9,104.63	3.25
Reference value	≤ 40.00 mAU/mL	0.1 - 2.2 ng/mL

activity is required, vitamin K can be administered to restore coagulation factor activity [9]. So we suggested that clinical doctors supplement the patient with vitamin K. Two days later, the results showed a significant increase in the patient's vitamin K level, while PIVKA-II showed a significant decrease. Warfarin is one of the most commonly used anticoagulant drugs. If PIVKA-II levels are significantly elevated in clinical practice and there are no obvious abnormalities on imaging, patients should be asked about their recent medication history in detail. For patients taking warfarin, especially elderly patients with gallstones, after supplementing with vitamin K, PIVKA-II can be dynamically monitored to screen for and correct vitamin K deficiency or abnormal increase in PIVKA-II caused by warfarin use.

In summary, this case emphasizes that laboratory staff should fully understand that warfarin and vitamin K deficiency can lead to abnormal PIVKA-II elevation in patients and should take corresponding screening and corrective measures to avoid unnecessary examinations and psychological burden on patients.

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Declaration of Interest:
All authors declare that they have no competing interests.

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