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Case Report

Persistent Elevation of Serum Prothrombin Induced by Vitamin K Deficiency or Antagonist Despite Discontinuation of Warfarin Administration in Alcoholic Cirrhosis in The Absence of Hepatocellular Carcinoma: A Case Report

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1. Abstract

Whereas serum prothrombin induced vitamin K deficiency or antagonist II (PIVKA-II) is a diagnostic and prognostic marker of hepatocellular carcinoma (HCC), the serum PIVKA-II level rarely increases in chronic liver diseases in the absence of HCC. Although warfarin administration induces marked elevation of PIVKA-II, warfarin discontinuation may lead to swift normalization of PIVKA-II, usually within several weeks, although the elimination half-time of warfarin varies greatly among individuals. The case of a 65-year-old man with alcoholic cirrhosis showing persistently elevated PIVKA-II for four years after warfarin discontinuation is presented. The patient started receiving warfarin orally (1.0-1.5 mg /day) for atrial fibrillation. A marked elevation of the serum PIVKA-II level (24,822 mAU /mL) was noted a year later when he developed a hemorrhagic gastric ulcer and overt hepatic encephalopathy with hyperammonemia, necessitating warfarin discontinuation. Interestingly, serum PIVKA-II levels remained abnormal (maximum level: 2863 mAU /mL) for four years after warfarin discontinuation, before finally returning to the normal range (<40 mAU/mL). During this period, serum parameters of liver function, such as total bilirubin, aminotransferases, and γ-glutamyltranspeptidase, continued to be within normal ranges, and imaging examinations never suggested the existence of HCC. Factors potentially affecting the vitamin K dynamics, such as long-term administration of antibiotics and hidden alcohol intake, were not observed despite vigorous investigations. Serum PIVKA-II levels can be increased in cirrhosis without HCC for a long period following discontinuation of warfarin administration. Potential reasons for PIVKA-II elevation in the present case are discussed.

2. Keywords: Prothrombin induced vitamin K deficiency or antagonist II; Warfarin; Liver cirrhosis; Hepatocellular carcinoma

3. Introduction

Patients with chronic liver diseases (CLDs), in particular liver cirrhosis (LC), often develop hepatocellular carcinoma (HCC) [1,2]. To detect early HCC, regular examinations of serum tumor markers and imaging examinations have been recommended in patients with LC [3,4]. As specific serum tumor markers for HCC detection, α-fetoprotein (AFP), AFP-lectin-bound type 3, and prothrombin induced vitamin K deficiency or antagonist II (PIVKA-II) are currently used [5-7]. The appropriate cut-off value of serum PIVKA-II for the detection of HCC using an enzyme immunoassay is 40 mAU/mL. However, serum PIVKA-II levels can be elevated in CLDs, including LC, in the absence of HCC [8-10].

Warfarin administration induces prolongation of the prothrombin time (PT) due to inhibition of the bioactivity of vitamin K-dependent coagulation factors (II, VII, IX, and X) in the liver, resulting in the marked elevation of PIVKA-II [11-13]. Warfarin discontinuation leads to swift normalization

of PIVKA-II usually within one week after warfarin discontinuation, because the half-times of vitamin K-dependent coagulation factors are only several days [14,15]. The case of a 65-year-old man with alcoholic LC who showed persistently elevated serum PIVKA-II levels for four years after discontinuation of warfarin administration is presented.

4. Case Presentation

A 65-year-old man with LC has been treated at the Yasumi clinic since 2009 because of hypertension, atrial fibrillation (AF), and CLD. The etiology of his CLD was considered to be alcoholic, because serum hepatitis B virus antigen, hepatitis C antibody, antinuclear antibody, and anti-mitochondrial antibody were all negative. His estimated mean ethanol intake had been over 100 g /day for the past 35 years. Anti-hepatitis B core antibody was not measured. Warfarin administration was started orally at a daily dose of 1 mg in February, 2015 for the prevention of thrombosis due to AF because the liver function tests were stable, and the severity of liver dysfunction based on the Child-Pugh classification was grade A (Child-Pugh score 5). The warfarin was increased to 1.5 mg /day in June, 2015, and it was then maintained at 1.0 mg /day since September, 2015, based on the results of the PT international ratio (PT-INR) (Figure 1). The patient developed tarry stools and abdominal distension in January, 2016, and was admitted to our hospital. Laboratory tests showed the following results: total bilirubin (T-Bil.) 1.66 (normal range [NR]: 0.1-1.0) mg /dL, aspartate aminotransferase (AST) 30 (NR: 8-38) IU /L, alanine aminotransferase (ALT) 16 (NR: 4-44) IU /L, γ-glutamyltranspeptidase (γ-GTP) 23 (NR: 9-32) IU /L, blood urea nitrogen 24.3 (NR: 7-18) mg /dL, white blood cell count 10,900 /μL, red blood cell count 301 x 104 /μL, hemoglobin 9.1 g /dL, platelet count 15.6 x 104 /μL, albumin (Alb) 2.7 (NR: 3.7-5.0) g /dL, and C-reactive protein 0.94 (NR: 0-0.3) mg /dL. Serum PIVAKA-II, measured by a commercially available PIVKA-II assay kit (ARCHITECT PIVKA-II, Abbott Laboratories, Tokyo, Japan) was markedly elevated (24,822 mAU /mL). Because PT-INR was prolonged at 2.28, warfarin administration was discontinued at this point. AFP was 3.7 (NR: <10) ng /mL, and computed tomography showed no mass lesions suggesting HCC in the liver, although bilateral hydrothorax, diffuse ascites, and atrophic liver were present. Since the hepatic encephalopathy progressed, he was transferred to the Iwate Prefectural Central Hospital the next month. Upper gastrointestinal endoscopy showed an active gastric ulcer with mild portal hypertensive gastropathy and esophageal varices. He was successfully treated with a proton pump inhibitor, diuretics, lactulose, and a branched-chain amino acid formula for two weeks and then discharged from the hospital.

As shown in Figure 1, despite warfarin discontinuation, PIVKA-II levels remained elevated for four years, with the highest level at 2863 mAU /mL. However, PIVKA-II finally became normal (i.e., 40 mAU /mL) in January, 2020. During this four-year period, although a one-week course of amoxicillin hydrate, clarithromycin, and vonoprazon fumarate was given for Helicobacter pylori eradication in April, 2016, no factors possibly affecting the vitamin K dynamics were observed. PT-INR recovered rapidly after warfarin discontinuation, and it has been well maintained without apparent fluctuations. Liver function tests (serum T-Bil., AST, ALT, and γ-GTP) have been within normal ranges, and imaging examinations never suggested the presence of HCC. The serum AFP level continued to be normal.

Figure 1.

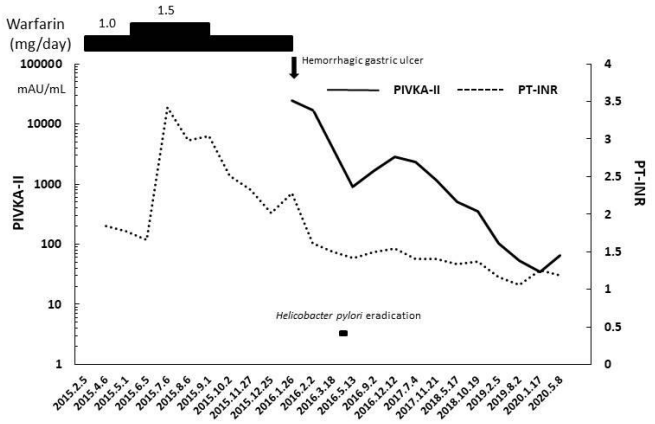

Figure 1: Serial changes of prothrombin induced vitamin K deficiency or antagonist II and the prothrombin time-international ratio during the clinical course.

PIVKA-II, prothrombin induced vitamin K deficiency or antagonist II; PT-INR, prothrombin time-international ratio.

5. Discussion

AF is associated with increased mortality and an increased risk of stroke worldwide [17]. A large-scale study showed that the prevalence of AF in LC patients was about 6.6% in the United States, and LC patients with AF showed higher mortality than those without AF [18]. Therefore, anticoagulants including warfarin have been recommended to decrease mortality even in LC patients [19,20]. Moreover, a more recent study showed that treatment using novel non-vitamin K anticoagulants in LC patients with AF could be used safely [21]. Among the anticoagulants, warfarin remains the most commonly prescribed oral anticoagulant worldwide because of its low cost, although careful adjustment of warfarin dosage based on PT-INR measurement is necessary, because the half-time of warfarin varies greatly among individuals [12]. Prothrombin is produced by converting a precursor having 10 glutamic acid (Glu) residues to γ-carboxyglutamic acid (Gla) via the action of γ-glutamylcarboxylase in the liver [16,17]. PIVKA-II, des-gamma-carboxy prothrombin, is an abnormal, immature prothrombin that is found in the serum of patients with vitamin K deficiency or with the administration of vitamin K antagonists such as warfarin [12,16,17]. Moreover, in patients with HCC, PIVKA-II is formed instead of prothrombin because γ-carboxylation of prothrombin is impaired [6-10].

This is the first report of a male patient with LC showing persistent elevation of PIVKA-II for four years after warfarin discontinuation. Since the present patient had no HCC, and there have been no similar reports of serum PIVKA-II levels remaining elevated for a long time following the discontinuation of warfarin, we cannot fully explain the causes of the elevated serum PIVKA-II levels following warfarin discontinuation for up to four years. However, understanding of this unusual phenomenon occurring in the present patient may be useful to elucidate the different mechanisms of PIVKA-II elevation in benign CLD patients in the absence of HCC. First, the method of measuring the serum PIVKA-II level might be associated with the persistent elevation of the PIVKA-II level. Liebman et al. showed that the serum PIVKA-II levels were significantly elevated in patients with HCC by competitive radio immunoassay using a polyclonal antibody [5]. Afterwards, enzyme-linked immunosorbent assays (ELISAs) using two types of monoclonal antibodies (MU-3 and 19B7) were developed [6-10,22]. However, several clinical studies have used the ELISA with the monoclonal antibody MU-3 [7-11]. More recently, an automated chemiluminescent immunoassay using a new monoclonal antibody (3C10) as a primary antibody and a monoclonal antibody as a secondary antibody has been developed (ARCHITECT PIVKA-II assay and Lumipulse Presto PIVKA-II Eisai, respectively) [23,24]. The values of serum PIVKA-II obtained using these methods showed positive correlations [24]. In the present case, since serum PIVKA-II levels were measured by the ARCHITECT PIVKA-II assay using the monoclonal antibody 3C10, a different result may have been obtained than had measurement been done using the monoclonal antibody MU-3. Second, the existence of variant types of PIVKA-II in benign CLD in the absence of HCC may affect this phenomenon [16,26,27]. Naraki et al. suggested that HCC exhibits PIVKA-II variants with less than four Gla residues, whereas CLD without HCC showed PIVKA-II with more than five Gla residues, affecting the reaction of MU-3 antibody [27]. Indeed, it was reported that measurement of serum PIVKA-II using antibodies more sensitive to PIVKA-II with fewer-Glu residues was effective for distinguishing serum PIVKA-II elevation in HCC patients from that in non-HCC patients with warfarin administration [28]. Although it was not possible to evaluate the heterogeneity of PIVKA-II in the present patient, it may be necessary to clarify the characteristics of variant types of PIVKA-II after warfarin administration in the future.

Numerous causes are associated with serum PIVKA-II elevation in benign CLD without HCC. In particular, alcohol abuse and use of antibiotics such as cephalosporin are important. In addition, commonly used drugs, malnutrition including an imbalanced diet, herbal medicines, digestive diseases with malabsorption such as ulcerative colitis, and cholestasis such as primary biliary cholangitis are important [29-32]. Of these, alcohol abuse, antibiotic use, cholestasis, and malnutrition that induce vitamin K deficiency are the most frequent cause of PIVKA-II elevation. In the present case, initial marked elevation of serum PIVKA-II (>20,000 mAU /mL) was apparently associated with the administration of warfarin, although the serum PIVKA-II level was not measured prior to the administration of warfarin. Ohhira et al. reported that alcoholic LC tends to show an increase in serum PIVKA-II levels compared to LC of viral origin and that a case with alcoholic LC shows serum PIVKA-II level fluctuations in parallel with ethanol intake [9]. However, there appeared to be no evidence of alcoholic intake by the present patient during the period of serum PIVKA-II elevation, although the patient and family were repeatedly asked if he were not hiding his drinking. The antibiotics that could affect gut microbiota leading to impaired vitamin K production were not used except for only one week for Helicobacter pylori eradication (this period was before re-elevation of serum PIVKA-II levels). Cholestasis is also an important factor in the elevation of serum PIVKA-II levels, because vitamin K deficiency is common in cholestatic liver diseases [29,30]. However, the serum vitamin K levels were not measured in the present case, because vitamin K measurement is not approved by Japanese health insurance. With respect to malnutrition, although a detailed analysis of body composition was not performed, the patient constantly had a low body mass index (< 20 kg /m^2) and transient hypoalbuminemia (serum albumin concentration <3.5 g /dL) during the early period of illness after admission. Among foods and herbal medicines, grapefruit, chamomile, mango, ginkgo biloba, and cranberry can affect the synthesis of vitamin K and induce PT-INR prolongation [31,32]. However, intake of these foods and herbal medicines could not be confirmed based on careful interviews of the patient and his family.

Finally, the true reason for PIVKA-II elevations following warfarin discontinuation remains an enigma. Recently, a novel liquid chromatography-tandem mass spectrometry assay was developed for quantification of PIVKA-II and characterization of warfarin-induced changes [33]. Analysis using this method may be expected to solve the enigmatic phenomenon in this case.

In conclusion, a patient with alcoholic LC showing persistently elevated serum PIVKA-II levels for over four years after warfarin discontinuation was presented. Further study will be needed to examine the relationship between serum PIVKA-II levels and vitamin K deficiency in CLD in the absence of HCC.

6. Conflict of Interest: The authors declare that they have no conflicts of interest.

7. Human /Animal Rights: All procedures followed were in accordance with the ethical standards of the Iwate Medical University on human experimentation (institutional and national) and with the 1975 Declaration of Helsinki.

8. Informed Consent: Informed consent was obtained from the patient included in this study.

9. Author Contributions: Suzuki K was a chief physician and mainly wrote this article. Yasumi Y and Konishi Y summarized the clinical data and wrote part of this article. Abe M and Takahashi K actually participated in the examinations and treatment of this patient during the illness. Takikawa Y advised on coagulopathy in liver disease for writing this article. All authors carefully read this article and appropriately advised Suzuki K before the submission of this article.

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