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Warfarin-Induced Hepatotoxicity: A Case Report

Warfarine Sekonder Gelişen Hepatotoksisite: Olgu Sunumu

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Abstract

A 30-year-old male patient with no comorbidities was admitted to hospital after developing a pulmonary embolism and was started on warfarin treatment. His hepatic enzymes increased progressively. In the early period after warfarin, an elevated liver function test was observed on the 4th day. Hepatotoxicity was thought to have developed secondary to warfarin, and the enzymes decreased gradually after the warfarin treatment was discontinued. We present this case as evidence of the possible development of hepatotoxicity secondary to warfarin treatment, even in the early period of treatment, and to discuss the management and follow-up outcomes of such patients.

Keywords: *Hepatotoxicity, pulmonary embolism, warfarin.*

Öz

Otuz yaşında, bilinen ek hastalığı olmayan erkek hasta pulmoner emboli tanısı ile kliniğimize yatırıldı. Takibinde varfarin tedavisi başlanan hastada tedavinin dördüncü gününde karaciğer fonksiyon testlerinde yükseklik izlendi. Diğer nedenler dışlanarak varfarine sekonder hepatotoksisite tanısı konulan hastanın varfarin kesildikten sonra değerlerinde kademeli düşüş izlendi. Bu olgu sunumunun amacı, varfarin tedavisine sekonder görülen hepatotoksisitenin, tedavinin erken döneminde de gelişebileceğini hatırlatmak, bu hastaların yönetimi ve takibinin tartışılmasıdır.

Anahtar Kelimeler: *Hepatotoksisite, pulmoner emboli, varfarin.*

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Thromboembolic conditions are responsible for one in four deaths worldwide, among which pulmonary embolism (PE), one of the major thromboembolic conditions, has an incidence ranging from 39 to 115 per 100,000 population/year (1). Acute PE ranks third on the list of the most prevalent cardiovascular diseases, following coronary artery disease and stroke (2).

Warfarin therapy, despite its narrow therapeutic index and wide range of responses, continues to be a common approach to the treatment of thromboembolic disease in various clinical settings. Oral anticoagulants such as vitamin K antagonists (VKAs) which include warfarin (Coumadin), acenocoumarol and phenprocoumon, are considered safe options to the point that they have for many years been considered the optimum treatment (3) The most preferred and widely used of the VKAs is "warfarin sodium", which acts mainly by inhibiting the synthesis of the coagulation factors of prothrombin (factor II), factor VII, factor IX and factor X, in the liver, thus intervening into the vitamin K cycle (4).

As the response to warfarin therapy is extremely volatile among patients, optimal dosing is key. One serious adverse effect of warfarin is excessive bleeding, while other side effects include nausea, vomiting, abdominal pain, bloating, flatulence and changes to the sense of taste. Rarer side effects include purple finger syndrome, skin necrosis and calciphylaxis (5,6). Warfarin requires cautious monitoring as it elevates transaminases levels in 0.8–1.2 of cases%. Once hepatotoxicity develops close monitoring is simply required and clinical management may be difficult. There are reports of cases developing fulminant liver failure secondary to warfarin treatment, but most frequently in older adults (7,8).

We present here the case of a young male patient who developed warfarin-related hepatotoxicity in the early treatment period.

CASE

A 30-year-old male patient was admitted to our emergency department with complaints of increasing left-sided back pain for four days and hemoptysis. The patient had undergone a lumbar disc herniation operation in the previous month. He was employed as a long-distance driver and had an ongoing smoking history of 23 pack/years.

Physical examination, respiratory sounds and vital signs were normal. Among the laboratory parameters at admission, C-reactive protein (CRP) was 19.8 mg/L (N: 0-5) and leukocyte was 10.6 103/µl (N: 7-10 103), while all other hemogram and biochemistry parameters were within the normal range. No abnormal findings were observed on postero-anterior chest radiography (Figure 1).

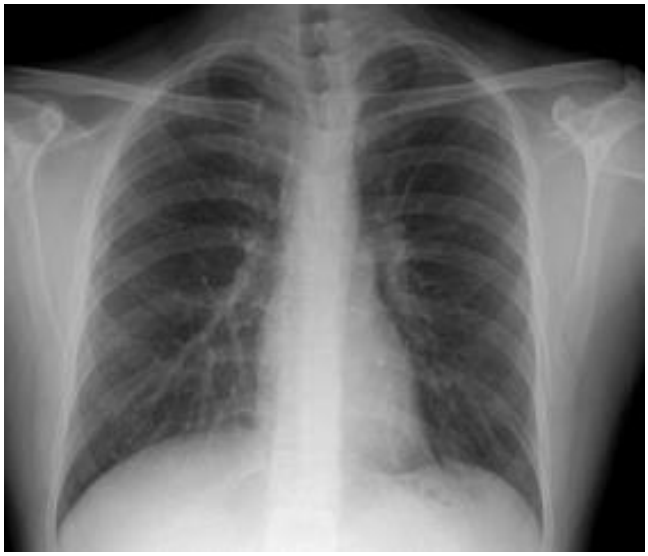

Figure 1: *Chest X-ray at admission*

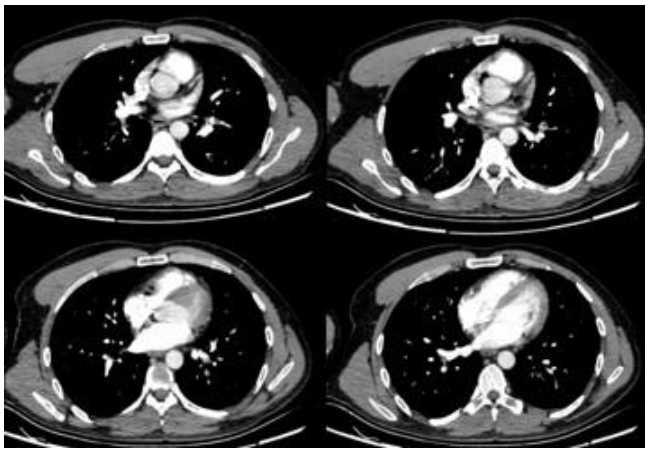

Figure 2: *Thorax computed tomography at admission showing thrombus in the left lower lobe pulmonary artery*

Our patient's troponin level was 5.09 ng/l and pro-brain natriuretic protein level was 17 pg/ml and was within the normal range. The patient's Wells Score indicated a medium clinical probability of pulmonary embolism.

Despite the normality of the patient's findings, PE was considered due to the patient's recent surgery, and his employment as a long-distance driver, hemoptysis history and D-dimer of 2.54 µg/ml (0–0.5). A thoracic computed tomography angiography (CTA) requested for further examination revealed a filling defect consistent with thrombus in the left lower lobe pulmonary artery (Figure 2).

The patient was admitted to our clinic and started on enoxaparin 8000 iu/0.8 ml 2*1, cefuroxime 500 mg 2*1 po and symptomatic treatments. Electrocardiography (ECG) revealed an incomplete right bundle branch block, but no evidence of right heart failure on 108/min echocardiography. A Doppler ultrasonography of the lower extremities revealed no deep vein thrombosis in the acute phase. No hemoptysis was noted during follow-up at that point, and 5 mg warfarin was added to the therapy on

the fifth day. The enoxaparin was discontinued on the third day of treatment after the INR (international normalized ratio) was noted to have risen to 2.2. Liver function tests were also conducted revealing alanine aminotransferase (ALT): 163 (N: 0-40) U/L; aspartate aminotransferase (AST): 109 (N: 0-40) U/L; and bilirubin values within normal limits. Antibiotics and other symptomatic treatments were discontinued and intravenous hydration therapy was started, and the treatment was discontinued the following day after the patient's liver function values increased the following day. The probability of secondary hepatic toxicity from warfarin was almost certain by that time, and so enoxaparin treatment was considered the first choice (Figure 3). The patient's physical examination and abdominal ultrasonography were normal. Contrast-enhanced abdomen CT, and hepatitis and autoimmune hepatitis marker tests [anti-nuclear antibody, anti-double strand-DNA, anti-liver-kidney microsomal antibody tests (anti-LKM), and anti-mitochondrial antibody (AMA)] amylase and lipase tests were requested by the internal medicine specialist, along with treatment with hepatamine, N-acetyl cysteine and hydration support containing vitamins. The liver function test results started to decrease after the third day of follow up. Radiological imaging was unremarkable other than the identification of a hiatal hernia. The internal medicine physician recommended no further treatment, and so the patient was discharged upon their own request on the condition that he would return for a check-up 2 days later while his liver enzymes were AST 116 U/L and ALT 492 U/L, planning to continue treatment with low molecular weight heparin treatment until his LFT returned to normal range.

Liver enzymes, which usually start to decrease 11 days after the discontinuation of warfarin treatment, started to increase again on the 11th day after discontinuation, the cause of which was unknown, and the patient's liver enzymes were observed to have decreased again by the time of the next control.

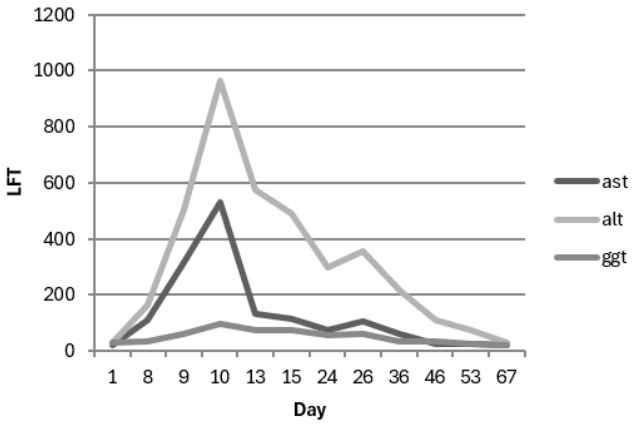

Figure 3: Follow-up results of liver function tests after the initiation of warfarin treatment

The patient's LFT values were recorded to be within the normal range during outpatient clinic follow-ups. There is no clear suggestion of how long it takes for the liver enzymes to return to normal in cases of hepatotoxicity secondary to warfarin.

The patient declined subcutaneous treatment, and so treatment with dabigatran 150 mg twice daily was initiated, with no side effects or laboratory abnormalities noted on follow up.

A thrombophilia panel in the third and fourth month of follow-up revealed a decrease in protein S activity to 45% and 33% (77–143) and a total protein S antigen of 55.7% (60-130). Consultation with the hematology department led to the continuation of oral anticoagulants. The patient remains stable under dabigatran treatment in the second year of treatment.

DISCUSSION

Warfarin is a widely used oral anticoagulant that exerts its influence through an anti-vitamin K activity mechanism. Acute liver injury typically occurs within 3–8 weeks of starting warfarin therapy. Though rare, cases of liver injury occurring after months or years of treatment have also been reported (9).

Similar to our case, a 79-year-old female patient who developed hepatotoxicity in the first week of warfarin treatment has been reported in the literature. In this case, LFTs were normal prior to treatment, and started to increase 6 days after the initiation of warfarin treatment for deep vein thrombosis (DVT) (10). This case has similarities with our presented case, as in both cases the patient suffered liver damage within a week of starting warfarin treatment, which is a notably rare occurrence. In the example above, the patient's LFTs returned to within the normal range 3 days after the discontinuation of warfarin, compared to approximately 2 months in the presented case, despite the young age profile of the patient. This wide discrepancy, we believe, merits attention.

While the exact cause of liver injury in cases undergoing oral anticoagulant therapy remains unknown, it is safe to assume that the fundamental causation is mainly immunological (9). A recent study in mice identified four primary mechanisms with the potential to explain the hepatotoxicity in oral warfarin administration: i) CYP2C9 regulation affecting the amount of bleeding, depending on nuclear factor erythroid 2-related factor 2 (NRf2) and P450 levels, ii) a fall in NRf2 leaving the system open to oxidative stress, increasing the likelihood of bleeding, iii) decreased hemoglobin, albumin and antitrypsin levels leading to apoptosis liver hemorrhage, apoptosis and fibrosis by activating cleaved caspase-3, and 4) warfarin elevating transferrin levels and lipid peroxidation with pro-fibrogenic stimuli, leading to fibrosis and acute liver damage with higher iron level and hemosiderin (11).

Since our hospital is not a multidisciplinary center and no liver biopsy was performed, the mechanism of hepatotoxicity could not be ascertained.

Patient liver enzyme elevation patterns are typically cholestatic, although hepatocellular and mixed patterns have also been reported. Eosinophilia may also be encountered, while other immunoallergic manifestations and autoantibodies are less common.

Elevated ALT or AST in patients using anticoagulants make differential diagnosis challenging. The optimum diagnostic approach is liver biopsy, however, its invasiveness bears high risk potential (12). The first step in the evaluation of elevated ALT or AST levels a repeat of laboratory tests, and if the results are still abnormal, conditions such as alcohol use, hepatotoxic drugs, chronic hepatitis B and C, autoimmune hepatitis, nonalcoholic fatty liver disease, hemochromatosis, Wilson disease, alpha-1 antitrypsin deficiency and celiac sprue should be considered (13). If the increasing trend is still not stemmed, switching to another class of anticoagulant agent is supported in the literature. The immediate termination of anticoagulant therapy may also be considered, especially if bilirubin levels are higher than twice the normal range. Fulminant liver failure may develop within two weeks of the onset of hepatocellular damage (12).

One noteworthy feature in our patient profile was the protein S deficiency, which has been reported to have potential links to hepatotoxicity (14). As our case confirmed this relationship, we believe that more detailed research is warranted as elucidating the mechanisms of hepatotoxicity will clarify if any relationship exists with the toxic mechanism of the drug, or whether the relationship is purely coincidental.

Dabigatran has been shown to be as effective as warfarin in patients with thrombophilia (15,16), while apixaban and rivaroxaban have been reported to be safe in small case series (17). No bleeding or recurrent thrombosis was identified in our patient while under dabigatran treatment for 1 year, leading us to consider dabigatran to be another safe option in such cases.

In contrast, apixaban should be avoided in patients with warfarin-induced cholestasis, although existing research is not unambiguous, and further studies are needed to determine the optimum agents for anticoagulant-induced hepatotoxicity (10). Our case was continued on low molecular weight heparin until the liver enzymes returned to normal, after which he was switched to dabigatran treatment with close monitoring. Independent of warfarin hepatotoxicity, hepatotoxicity under dabigatran treatment was reported in an 84-year-old patient, although the mechanism was thought to have other bases and interactions since the drug has no effect on the cytochrome P450 enzyme (18). Since our patient was young and declined subcutaneous treatment, we opted for dabigatran treatment with close clinical and laboratory follow-up, and he has remained stable throughout his 1-year follow-up.

There are limited resources in the literature reporting on protein C and protein S deficiencies. An article published in China in 2024 reported on a patient who presented with acute liver failure due to protein C deficiency (19).

The mechanism of liver damage attributable to warfarin could not be further determined since no liver biopsy could be performed.

In conclusion, hepatotoxicity secondary to warfarin may develop rapidly while laboratory recovery may catch up lately. Although our patient's condition was rendered stable with dabigatran treatment, more case reports and clinical studies are needed to better understand the mechanisms of hepatotoxicity to identify safer and more appropriate treatment choices.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - Ç.S., S.G., H.A., F.T.A., A.T.I.; Planning and Design - Ç.S., S.G., H.A., F.T.A., A.T.I.; Supervision - Ç.S., S.G., H.A., F.T.A., A.T.I.; Funding - Ç.S.; Materials - Ç.S.; Data Collection and/or Processing - Ç.S.; Analysis and/or Interpretation - Ç.S.; Literature Review - Ç.S.; Writing - Ç.S., F.T.A.; Critical Review Ç.S., F.T.A.

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