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# Case Report of Warfarin Induced Hemoperitoneum

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**Abstract**: Although spontaneous hemoperitoneum is a rare condition, it has the potential to be devastating. A common coumarin anti-coagulant used for therapeutic and preventive anticoagulation is warfarin. Despite being a drug that can save lives, it is linked to severe side effects, mainly bleeding. The aim and objective of the study include the unusual occurrence of Hemoperitoneum that an Anti-Coagulant Drug Warfarin induces. Although reports of spontaneous hemoperitoneum in anticoagulant-using individuals have been published in the literature, diagnostic standards and therapeutic approaches have not yet been firmly established. PT INR should be routinely checked when warfarin is prescribed to prevent any problems. Intra-abdominal bleeding resulting from non-traumatic reasons or organ rupture within the abdomen is known as spontaneous hemoperitoneum. The presence of intra-abdominal bleeding from a non-traumatic origin is known as spontaneous hemoperitoneum. Hemoperitoneum from warfarin is a known side effect that can be fatal. It might be challenging to manage unexpected bleeding while keeping the INR under control and preventing thrombosis. If the INR is out of range, there is a higher risk of warfarin-induced bleeding. The spontaneous hemoperitoneum described in this case report was caused by warfarin over-toxicity in a patient with rheumatic heart disease. The indications and symptoms resemble a ruptured corpus luteal cyst or an ectopic pregnancy. Although the patients undergoing Anti-coagulant therapy, especially warfarin, may experience other symptoms like GI bleeding, Nausea, Hematuria and so on.

**Keywords:** warfarin, anti-coagulant, secondary hemoperitoneum, Bleeding, PT INR.

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## 1. INTRODUCTION

Warfarin is prescribed for conditions such as venous thromboembolism, atrial fibrillation, cerebral ischemia, and mechanical heart valves. However, the amount of anticoagulation needed varies according to the disease. Warfarin poisoning can result in spontaneous hemoperitoneum or bleeding in the retroperitoneal area[1-3]. The most significant risk factor for warfarin-induced severe bleeding, regardless of the justification for treatment, is an INR level over the therapeutic range, with the risk rising with INR > 3. Warfarin is frequently prescribed for deep vein thrombosis, prosthetic valve replacement, CVA, pulmonary embolism, atrial fibrillation, and valvular heart disease. The most frequent side effect of warfarin therapy is bleeding. Slight but definite blood loss has been documented in severe cases (annual rates range from 1% to 3 %)[4]. Substantial adverse effects may manifest if PT-INR is not closely managed when an anti-coagulant like warfarin is provided. These consequences can vary from minor tissue bruising to severe, life-threatening disorders, including cerebral or massive intraperitoneal bleeding. Adverse severe reactions are observed if the anti-coagulants are prescribed, leading to several complications if not monitored. These adverse events are mild to severe, like bruising the tissues and complicating intraperitoneal bleeding. The risk of intraperitoneal bleeding is difficult and even life-threatening. The anti-coagulant use is occasionally associated with several risk factors like hematuria, GI bleeding, etc. Intraperitoneal bleeding is a rare condition that has the symptoms of GI bleeding. Warfarin is prescribed for people at increased risk of developing harmful blood clots. This includes people with a mechanical heart valve, an irregular heart rhythm called atrial fibrillation, certain clotting disorders, or a higher risk of a clot after hip or knee surgery. Chances of bleeding are higher in patients with a more intense therapeutic range (INR between 2.5 to 3.5) than in patients with less severe therapeutic ranges (INR between 2 to 3)[3]. This is consistent with the findings in our case, where the INR levels were 8. Warfarin has a narrow therapeutic index; another management challenge is dose adjustment to achieve the target INR. Additionally, larger initial doses of warfarin suppress proteins C and S, resulting in over-anticoagulation and higher rates of bleeding[5,6]. The normal clotting mechanism is a complex process that involves multiple substances (clotting factors). The liver produces these factors and acts sequentially to form a blood clot. For the liver to have some clotting factors, adequate amounts of vitamin K must be available. Warfarin blocks one of the enzymes that use vitamin K to make some clotting factors, reducing their ability to work correctly in the blood. As a result, the clotting mechanism is disrupted, and it takes longer for the blood to clot. The goal of warfarin therapy is to decrease the clotting tendency of blood but not to prevent clotting completely. Therefore, the blood's ability to clot must be carefully monitored while a person takes warfarin. Warfarin dose is adjusted to maintain the clotting time within a target range.

## 2. CASE REPORT

Thirty-two years Mrs X, a Pallavaram resident and known case of rheumatic heart disease who underwent mitral valve replacement two years back, complained of abdominal pain, vomiting, and abdominal distension for five days. She also had a history of severe menstrual bleeding accompanied by the passage of clots during her last menstrual cycle, for which she didn't consult a doctor. After replacing the mitral valve, the patient initially underwent periodic INR testing, but they have not done so for the past six months.

## 3. PAST HISTORY

The patient underwent mitral valve replacement two years back in March 2020 for severe pulmonary hypertension and mitral stenosis. The patient has taken the tablet clopidogrel 75mg OD and tablet warfarin 1mg and 2mg OD on alternate days. No history of diabetes, bronchial asthma, thyroid disease, or epilepsy. No record of drug allergies.

## 4. MARITAL HISTORY

She was married for 12 years, and it was a non-consanguineous marriage.

## 5. OBSTETRIC HISTORY

The last childbirth was six years ago, she had two alive children, and both were normal vaginal deliveries. During both pregnancies, she did not experience any cardiac decompensation during the antenatal, intrapartum, or postnatal periods.

## 6. MANAGEMENT

The patient was conscious, alert, clinically pale, and had a PR of 110/min and a BP of 90/60 mmHg at arrival time. Her abdomen was distended, and a vague lump was felt in the suprapubic area. On per vaginal examination, an 8x7 cm nonspecific mass was felt through the anterior fornix and fullness was detected in both lateral fornices and cervical motion tenderness. The cervix was firm; the uterus was retroverted and bulky. On investigation, Urine Gravindex was negative, serum Beta HCG was not detectable, and ultrasound finding ruled out ruptured ectopic pregnancy. Following her admittance, her investigations were Total WBC count: 19300; Hemoglobin: 5 g/dl; Platelet count: 3.09 lakhs; INR: 8, APTT: 40.02 seconds; Prothrombin Time: 18. 08 seconds; Serum Bilirubin: 2. 1mg; Serum Albumin: 2g; IgM Negative results for Covid RT-PCR and Dengue. CT abdomen showed Ascites, a hyperdense collection of 8.2*6. 7 cm in the pouch of Douglas, suggesting an organized haemorrhage and bilateral basal pleural thickening with calcification. After obtaining the cardiologist's opinion, she was put on Inj. Heparin 5000 IU IVQ6H and advised stopping using warfarin. She was advised to follow conservative management; if surgery was necessary, it should be done under heparin coverage. She had four units of packed cell transfusion, IV antibiotics, and conservative management that included close monitoring of her vital signs, abdomen circumference, and coagulation profile was followed. Patient recovered following conservative management. After five days, a repeat abdominal CT and ultrasonography revealed that the haematoma had shrunk to 5x4 cm in the POD and that the bilateral ovaries were healthy.

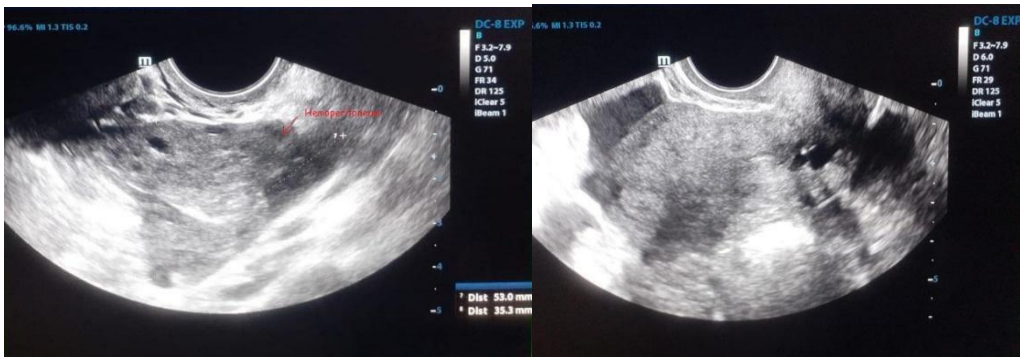

Fig 1: Ultrasonography of abdomen and pelvis showing organized haematoma

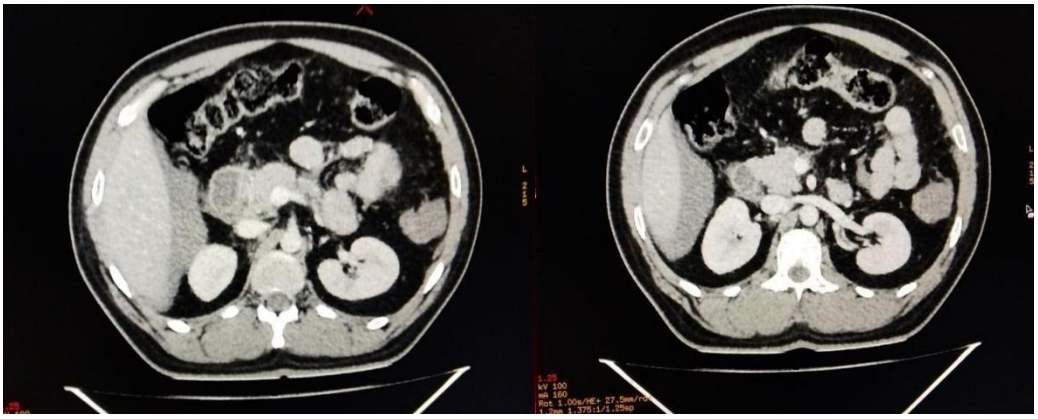

Fig 2: CECT abdomen and pelvis showing organized haematoma

***Figure 1 shows the USG abdomen and pelvis showing the Hematoma as a localized blood collection. Figure 2 shows the CECT abdomen and pelvis where the organized hematoma is formed. After five days, warfarin was restarted. Her haemoglobin increased to 10.2 g/dl.The repeat valueof other investigations were INR 1.32, APTT 32.3 seconds, Serum Albumin 3.4g, and serum Bilirubin 1. 3mg. The cytology of ascitic fluid revealed reactive effusion. Her clinical and symptomatic status improved, and the abdominal distention subsided. The patient was discharged with instructions to return for a follow-up ultrasound in 15 days. She was further managed with routine INR monitoring, and warfarin dose adjustments after her ultrasound showed normal findings.***

## 7. DISCUSSION

Cardiac prosthetic valve replacement has the risk of thrombosis. The risk of valve thrombosis and thromboembolic events depends on the kind and placement of the prosthetic valve as well as other factors such as a history of previous thromboembolic events, atrial fibrillation, and the prosthesis in the mitral position. Both heparin and warfarin carry this risk. In our situation, spontaneous intraperitoneal bleeding led to intestinal irritability, resulting in nausea and discomfort. Both a USG and a CT scan can be used to diagnose the hemoperitoneum. The CT scan is crucial since it is a sensitive approach for determining the location and degree of haemorrhage. We used nasogastric decompression, bowel rest, electrolyte imbalance correction, and blood transfusion for anaemia correction, and There are case reports of spontaneous hemoperitoneum with warfarin intake. It can be intraperitoneal or retroperitoneal haemorrhage[3,4]. Such patients may present with shock, three or intestinal obstruction. Sometimes bleeding can occur in intramuscular planes, such as in the anterior abdominal wall or retroperitoneally into the iliopsoas muscle and present as iliopsoas hematoma with compression of the femoral nerve[6]. FFP to correct coagulopathy in our instance of anticoagulant-induced bleeding. As a result of the patient's cardiac condition (with mechanical valve replacement), heparin was administered as a temporary fix[6]. To be safe, oral anticoagulation was continued after the hematoma had resolved with routine INR monitoring. Regular systemic examination and INR monitoring are necessary for optimal results and reduced morbidity, and they should be maintained in the range of 2.0 - 3.5 to prevent such catastrophic outcomes. Taking warfarin safely and effectively is challenging due to a complex dose-response relationship[7].

In our case, where clinical findings raised the suspicion of ruptured ectopic pregnancy/ruptured corpus luteal cyst, ultrasonography and βhCG helped to reach a diagnosis. However, studies suggest that a computerized tomography scan is the best imaging modality to diagnose such cases[12]. In most cases, the intraperitoneal bleeding, mainly secondary hemoperitoneum in anticoagulation therapy, leads to several side effects such as cramping, abdominal pain, Nausea, vomiting and even constipation. Even the Bowel sounds are depressed or absent[8]. The initial values of INR may be deceiving as bleeding may occur despite normal INR[4]. Nevertheless, it can show the areas of hematoma or bleeding and prevent undue surgical intervention. The only way to avoid such a catastrophe is to carefully monitor the INR, prevent overdosage and keep in mind drug interactions while prescribing other drugs to patients on warfarin[16].

## 8. MECHANISM OF ACTION

A coumarin oral anti-coagulant called warfarin is used to prevent and treat thromboembolism. Warfarin treatment relies on physiologic, environmental, and hereditary variables[8]. Warfarin metabolism involves the liver enzyme Cyp2C9. CYP2C9*2 and CYP2C9*3 are two frequent allelic variations linked to decreased enzyme activity. Compared to

others, those who inherit one or two copies of CYP2C9*2 or CYP2C9*3 are more sensitive to warfarin, need lower doses of the drug, and have a higher risk of haemorrhage when starting the drug[9]. Warfarin acts on VKORC-1, a vitamin K epoxide reductase complex subunit. It is the predominant allele in Asian populations and may help explain why Indian patients frequently require less warfarin than others. Inherited variations in VKORC 1 impact warfarin effectiveness. Additionally, warfarin prevents the production of the natural anti-coagulant proteins C and S, leading to high bleeding rates. Because warfarin has a limited therapeutic index, doctors who prescribe it must adjust the dosage to achieve the desired thrombus prevention for the prescribed indication and prevent fatal dose-related toxicity[10]. Blood protein C and protein S synthesis and the blood coagulation factors II, VIII, X, and VII are inhibited by drugs like warfarin. Two of the best indicators of warfarin-induced bleeding are the degree of warfarin therapy and the length of treatment within the therapeutic range.[11] Compared to patients with less intense therapeutic ranges, those with more intense therapeutic ranges (INR levels of 2.5 to 3.5) have a higher risk of bleeding (INR values of 2 to 3). This result supports our research, which showed that INR values were 8. Warfarin's limited therapeutic index, which makes it challenging to attain a specific INR, presents another management problem. According to studies, patients' reactions to medication administration might differ significantly between and among individuals depending on their age, gender, nutrition, coexisting illnesses, interactions with other medications, and genetic differences (CYP2C9 and VKORC 1)[13]. Studies have found that patients with homozygous CYP2C9*3 mutations and heterozygous VKORC1 mutations are more susceptible to warfarin therapy, and the course of treatment must be modified accordingly. Additionally, warfarin suppresses proteins C and S at greater starting doses, which can lead to over-anticoagulation and bleeding [14,15]. Clinical signs raised the possibility of an ectopic pregnancy that had ruptured or a ruptured corpus luteal cyst, and ultrasonography supported this assumption.

## 9. CONCLUSION

In conclusion, warfarin-treated patients with acute abdominal pain with intraperitoneal bleeding and spontaneous intraperitoneal bleeding should be considered a differential diagnosis. Withholding the medication, giving FFP and PCV transfusions, and adjusting the dose can all be used to manage warfarin-related toxicity. Only thorough INR monitoring to avoid overdosage and drug interactions, as well as routine patient follow-up with INR reports, can stop such an incident from happening. Before starting warfarin, performing genetic mutation studies on the two genes mentioned above is advisable to prevent toxicity. It's a difficult task, and a lesson learnt to balance the patient's symptoms while keeping the INR within the desired range, continuing anticoagulation for the indication by switching to heparin, and resuming warfarin once everything looks good. It can be managed conservatively by monitoring the toxicity and altering or reducing the dose of Warfarin.

## 10. ABBREVIATIONS

PT - Prothrombin test
INR - International normalized ratio
FFP - Fresh Frozen Plasma
PCV - Packed Cell Volume
APTT - Activated Partial Thromboplastin clotting time
CT - Computed Tomography
RT PCR - Reverse Transcriptase polymerase chain reaction
POD - postoperative delirium
BP - Blood Pressure
HCG - Human Chorionic gonadotropin
CVA - CerebroVascular Accident
PR - Pulse rate
CECT - Contrast Enhanced Computerised Tomography

## 11. AUTHORS CONTRIBUTION STATEMENT

Dr.T.G. Revathy Conceptualized and gathered the data concerning this work. Dr C. Minu Priya contributed to providing the necessary data towards designing the manuscript.

## 12. ETHICAL APPROVAL STATEMENT

The Ethical Committee statement approval was obtained from the IHEC, Department of obstetrics and gynaecology, Sree Balaji Medical College and Hospital Chrompet. Informed consent and authorisation for publishing the case report were obtained from the patient. The patient was assured of the confidentiality of the study, and a detailed explanation was given regarding the research and its importance.

## 13. CONFLICT OF INTEREST

Conflict of interest declared none.

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