Case Report

Anticoagulation status post radiofrequency ablation in a patient with hepatocellular carcinoma and delayed bleeding event

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ABSTRACT

Restarting anticoagulation is a tricky component of patient care. This is a case of a 65-year-old female presenting with hepatocellular carcinoma. A nonocclusive thrombus in the main portal vein was also identified. Six days postradiofrequency ablation (RFA), the patient's hemoglobin dropped to critical values and noncontrast computed tomography of the abdomen/pelvis revealed high density free fluid consistent with a bleed. The patient was medically managed and accepted for transfer to another hospital for IR-guided TIPS procedure. Patient recovered without any other complications. In conclusion, VTE prophylaxis be routinely initiated immediately following hepatectomy in hemodynamically stable patients without signs of active bleeding and should bleeding occur halt source then restart anticoagulation immediately.

Case report

A 65-year-old female with a past medical history of hypertension controlled via diet presented with the chief complaint of nonproductive cough for 3 days, complicated by progressive dyspnea on exertion for week and chronic leg swelling. In the primary care clinic, she was found to have deranged liver function tests without history of alcohol, and she tested negative for hepatitis serology. She also denied family history of liver disease. ANA was positive at 1:80 titters. She demonstrated no pruritus or jaundice. In the Emergency Department, the patient received azithromycin and ceftriaxone.

The patient was admitted to the medical floor for further management. A chest X-ray revealed a pleural effusion. Non-contrast chest computed tomography (CT) revealed a large

Fig. 1 – Arterial phase contrast enhanced CT demonstrating arterially enhancing hepatic lesion suspicious for hepatoma (black arrow).

Fig. 2 – Noncontrast CT demonstrating placement of RITARFA probe at previously noted hepatoma.

right pleural effusion causing compressive atelectasis of the right lung, focal infiltrate of the left lower lobe suggesting pneumonia, and possible cirrhosis with abdominal ascites. D-dimer level was found to be elevated, so therapeutic lovenox was started for possible pulmonary embolism, evaluation for which was limited due to the right-sided pleural effusion. Thoracentesis was performed for the effusion and CT chest was repeated for a pulmonary embolisim (PE), which was negative. The effusion fluid was determined to be transudate, and medical cytology was negative for malignant cells. Gastroenterology (GI) was then consulted and provided their recommendations.

CT abdomen without contrast revealed liver cirrhosis with moderate amount of abdominal and pelvic ascites, a large right pleural effusion with compressive atelectasis in the right lung base, and a 3 × 4 cm enhancing mass in the right lobe of the liver.

CT abdomen with contrast revealed hepatocellular carcinoma with nonocclusive thrombus in the main portal vein. Cirrhosis, perihepatic, and perisplenic ascites were also present, depicted in Figure 1. Subsequent magnetic resonance imaging of the abdomen revealed hepatocellular carcinoma involving the right lobe of the liver (segment VIII), findings suspicious for nonocclusive thrombosis in the main portal vein, perihepatic and perisplenic ascites, and cirrhosis.

Antibody studies revealed antismooth muscle antibodies 1:40 titer, negative antimitochondrial antibody, and normal alpha-1 antitrypsin level. Carcinoembryonic antigen (CEA) was 3.2 and Ca-19 was negative. Despite the imaging findings, Alpha-fetoprotein (AFP) was low (3.7) so Surgical Oncology was consulted to evaluate the need for biopsy, and/or surgery. Although it was not initially thought that anticoag-

ulation was required for the portal vein thrombus, lovenox was restarted based on the recommendations of Oncology and Surgical Oncology after Esophagogastroduodenoscopy (EGD) showed no varices (May 2, 2017). Surgical Oncology with Interventional Radiology performed radiofrequency ablation of the hepatoma. General anesthesia was provided, as well as local with 1% lidocaine. The patient's liver was scanned without contrast and an appropriate site on the skin was chosen, prepped, and draped in sterile fashion. After local lidocaine was administered, dermatotomy was performed. The guide needle from a RITA RFA probe kit was advanced into the lesion. The location was verified with CT.

The probe tines were deployed and 1 radiofrequency ablation was performed as seen in Figure 2 in the tumor bed with a 5-cm burn zone. As the RFA probe was removed, radiofrequency ablations were performed in the needle track with partial deployment of the tines for hemostasis. A sterile dressing was applied to the skin, and a completion CT scan was performed. The patient tolerated the procedure without complications and left the suite in stable condition. Postprocedure findings included a stable large left pleural effusion. No significant postprocedure hemorrhage was noted. On Postoperation day (POD) 2 lovenox 1mg/kg SC Q12h was initiated.

Repeat chest X-ray revealed a repeat pleural effusion on the right side, prompting Pulmonary to be consulted. Lovenox and Coumadin were held in preparation for thoracentesis; however, activated partial thromboplastin time (aPTT) and international normalized ratio (INR) continued to be elevated and thoracocentesis had to be deferred. Overnight from POD 6 to POD 7, the patient's hemoglobin dropped from 10.3 to 6.5 without any clinical signs of bleeding. Repeat chest X-ray was unchanged. Patient was approached POD 7 regarding inclusion in case study. Bedside stool guaiac was negative. Noncontrast CT of the abdomen/pelvis was ordered to rule out retroperitoneal
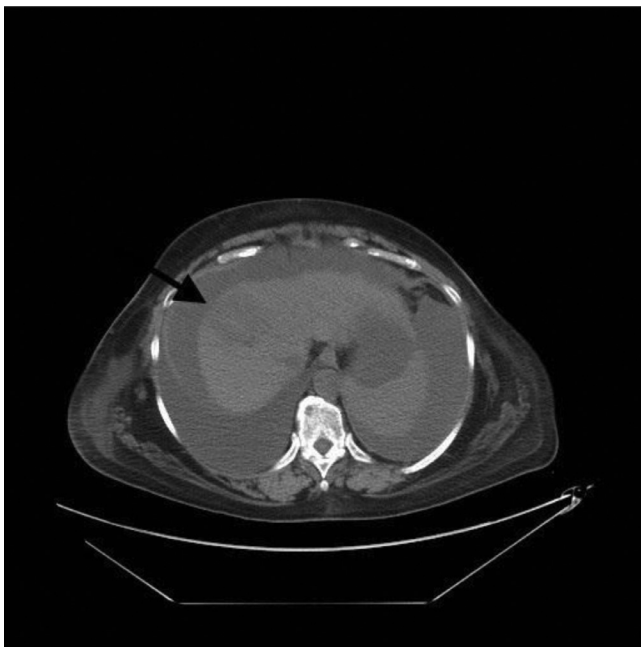
Fig. 3 – Noncontrast CT with black arrow demonstrating hypotenuse region corresponding to the prior lesion.(black arrow). There are significant ascites and large pleural effusions.

Fig. 4 – Noncontrast CT with high density fluid compatible with hemoperitonium (black arrow).

bleed; it revealed a moderate amount of high density free fluid within the abdomen and pelvis concerning blood products as seen in Figures 3 and 4. No Sentinel bleed was identified.

On repeat CBC (Complete Blood Count), hemoglobin improved from 6.5 to 7.7. The patient started on 75cc/hr normal saline and albumin. Type and screen were repeated and 2 units PRBCs were put on hold. Transfusion consent was obtained. The patient was tachypneic and hypotensive at 88/57 mm Hg. BUN (Blood urea Nitrogen)/creatinine levels increasedand ammonia level remained normal. A Foley catheter was placed and the patient had a urine output of approximately 5cc before becoming anuric. Oncology recommended a hematology workup, which was sent. Step Down was called and the patient was accepted for transfer.

The patient was admitted to the Step Down Unit with the impression of acute drop in hemoglobin secondary to intraperitoneal bleed in a patient with coagulopathy, with a recent history of RFA and acute renal failure. The coagulopathy and anemia were corrected with three units of fresh frozen plasma and three units total of Packed Red Blood cells (PRBC) respectively. The patient became increasingly hypotensive overnight, prompting administration of a 2-liter IV bolus including albumin 12.5 every 6 hours, as well as a dopamine drip. Her vital signs and hemodynamics improved, as well as her renal function and blood pressure. INR corrected and aPTT returned to normal. Bedside ultrasound revealed no echogenic pleural fluid, but it did show echogenic ascites in the dependent part of the peritoneal cavity. The patient's vital signs and labs were monitored regularly, and she was treated accordingly. Her abdominal pressure was elevated at 35. Once hemo-

dynamically stable and medically optimized, she was transferred to the medical floor for further management.

On the medicine floor, the patient went for IR-guided abdominal paracentesis. Three liters of serosanguinous fluid was drained without complications. The ascetic fluid was sent for medical cytology. Acute kidney injury showed signs of resolving. The patient continued to be hemodynamically stable. Foley catheterization was continued for strict monitoring of ins and outs. The patient continued to improve clinically and was discharged from the hospital. A 6-month follow-up demonstrated successful RFA with no CT evidence of residual tumor as seen on Figure 5.

Discussion

Radiofrequency (RF) thermal ablation has gained acceptance as a safe, effective method for treating malignancies in various organs, including the liver, lungs, kidneys, and bones [1].With a success rate of approximately 80%, RFA excels in reducing transmission of pain noninvasively, with minimal risk of complications. Major complications have been reported to occur in 2%-5.7% of cases, with procedure-related mortality in less than 1% [2,3]. In hepatocellular carcinoma (HCC), major complications such as peritoneal hemorrhage, tumor cell seeding, intrahepatic abscess formation, and bowel perforations occur in about 2.2% of cases [4]. Observed minor symptoms include pain, skin burns, fever, biloma, hematoma, and pneumothorax [4]. RF ablation-associated vascular complications include bleeding (arterial and venous), pseudoaneurysm or arteriovenous fistula from direct traumatic injury, and hepatic vein and portal vein thrombosis (PVT) from thermal injury [1,2]. The

Fig. 5 – Month post-RFA demonstrating postablation zone with no residual arterial enhancement. Resolution of pleural effusion and ascites (black arrow).

most common complication of RF ablation is intra-abdominal bleeding (0.5%-0.7% of cases), caused by either mechanical injuries occurring when the RF electrode transverses a vessel, or thermal injuries sustained during the ablative procedure [1,5]; although it is more frequently attributed to the direct trauma of needle positioning on small vessels not visualized on ultrasound (US) [2,3]. The most common presentation of this particular complication is increasing abdominal pain following the procedure, and its presence is easily confirmed with US or CT [3]. The risk of bleeding with electrode placement is less than 2%, and depends on a number of factors, including tumor location and the extent of liver disease. This risk is higher in cirrhotic patients (who often present with associated disorders of coagulation), and patients possessing HCC tumors with increased vascularity compared to metastases [1,2].

Tumor size, low platelet count, and tumors located in segment VII of the liver have been identified as risk factors for intraperitoneal bleeding, although this complication is often benign in its course with spontaneous resolution [3]. The approach to venous bleeding (intra-abdominal and intrahepatic) is usually conservative (ie, blood transfusion), whereas arterial bleeding and intraperitoneal hemorrhage are more severe, potentially requiring surgery or endovascular intervention, along with blood transfusion [2,3,6]. Ablation of subcapsular tumors is associated with increased risk of subcapsular hematoma formation, and abdominal wall hematomas have also been reported to occur [3].

To lessen the risk of bleeding, procedures are performed when a patient has achieved a predefined level of hemostasis. According to the Society of Interventional Radiology standards of practice, procedural laboratory testing/management to ensure hemostasis prior to RF ablation should include correcting INR to less than 1.5, ensuring platelet count is above 50,000/mm³ (transfuse if less), and withholding one dose of low molecular weight heparin before the procedure

[5]. Clopidogrel should also be withheld 5 days before the procedure, but aspirin may continue [5]. When to restart anticoagulation post-RF ablation, however, has not yet been addressed.

This patient's bleeding occurred from POD 7-8 and was accompanied by a significant drop in hemoglobin, signifying that the bleed began acutely. This patient's presentation is inconsistent with a bleed occurring as a complication of the RF ablation, since RF ablation bleeding tends to occur within hours of the procedure. Although a definitive cause could not be identified, especially in the absence of radiological evidence identifying a sentinel bleed, the fact that the bleeding began in closer temporal proximity to commencement of anticoagulation raises the question of whether anticoagulation was administered with appropriate timing postoperatively.

In liver tumor patients undergoing hepatectomy, coagulation status, prevalence of venous thromboembolism (VTE), and safety of anticoagulation thromboprophylaxis continue to be topics of significant debate [7]. The risk of symptomatic postoperative VTE in these patients is approximately 2.9%, and it increases with the extent of the hepatectomy, exceeding the risk of VTE in most other major abdominal surgeries several-fold [7]; 2 studies analyzing more than 11,000 hepatectomies between them demonstrated that VTE risk exceeded major bleeding events and was strongly associated with mortality [8,9]. Traditionally, PT/INR was used to determine timing of anticoagulation VTE prophylaxis, vitamin K administration, delivery of fresh frozen plasma (FFP) and cryoprecipitate, and safety of invasive device removal after hepatectomy; but recent studies have shown PT/INR to be inadequate, suggesting in should not be used on its own to guide management [7]. To this point, a recent review addressing VTE prophylaxis in liver surgery was unable to find any studies (1) supporting the practice of withholding VTE prophylaxis in patients with no signs of bleeding for any specific duration postoperatively, or for any predetermined PT/INR; or (2) demonstrating an increased risk of bleeding when VTE prophylaxis was commenced immediately following liver surgery in patients with no signs of postoperative bleeding. As such, the authors recommended that postoperative VTE prophylaxis be routinely initiated immediately following hepatectomy in hemodynamically stable patients without signs of active bleeding (ie, stable hemoglobin values, platelets >100,000/mm³, INR <1.8), and continued until the patient is either discharged or returns to full mobility [7]. Generally, North American guidelines suggest the use of formal assessment tools (ie, Caprini VTE scores) to assess patients' risk of postoperative bleeding. Commencement of anticoagulation with achievement of hemostasis, typically either on the evening of or the morning after surgery, is the reported standard of care at MDACC and Duke University in North America; and although no specific guidelines regarding thromboprophylaxis posthepatectomy are clearly defined in the UK, there seems to be a similar general suggestion to commence anticoagulation with achievement of hemostasis, tailored to individual patient VTE risk [7]. Regarding actual clinical practice of individual surgeons, a 2014 study inviting surgeons to complete a web-based survey on VTE prophylaxis practices identified numerous factors that increased the likelihood of surgeons choosing to administer VTE chemoprophylaxis posthepatectomy, including a history of DVT/PE

(89%), hypercoagulable diagnosis (88%), obesity (84%), multiple medical comorbidities (67%), combined operations (65%), and early postoperative complications other than hemorrhage (38%) [10]. Consistent with other studies, no consensus on method or timing of postoperative anticoagulation was identified: 47% of respondents stated that they routinely wait until POD 1 to commence pharmacological VTE prophylaxis, and 35% until there are no signs of coagulopathy [10].Based on these studies, there is nothing to suggest that the timing of recommencing anticoagulation in this patient was premature. The simultaneous presence of PVT in this patient, however, added an additional level of ambiguity to her case.

As a common complication of liver cirrhosis, associated with declining liver function and decreased blood flow in the portal vein, PVT was not necessarily a surprising finding in this patient; prevalence in patients with cirrhosis has been reported to be as high as 25% [11], with an annual incidence ranging from 4.6% to 17.9% [12]. Although cirrhosis was traditionally considered a hypocoagulable state with an increased bleeding risk, recent evidence suggests patients with cirrhosis have reductions in both procoagulant and anticoagulant factors produced by the liver, resulting in a new hemostasis. It has even been suggested, although not confirmed, that increased generation of endothelial factor VII, von Willebrand factor, and thrombin in cirrhotic patients may contribute to a state of hypercoagulability, facilitating the development of PVT. Other factors noted to be associated with PVT development include the presence of large portocollateral vessels, previous variceal bleeding, and low platelet count [12]. Ultimately, because PVT suggests the presence of coagulopathy, and coagulopathy in cirrhotic patients is particularly difficult to assess using standard laboratory tests (PT/INR), treating PVT in cirrhotic patients with anticoagulants can be especially difficult [13].

Currently, the goal of PVT treatment is to prevent extension of the thrombus to the superior mesenteric vein, or more ideally to achieve recanalization [12]. PVT has been observed to progress in 60-71% of cases without anticoagulation; but spontaneous recanalization has also been observed in up to 70% of patients without anticoagulation, calling into question its necessity. Overall, however, studies appear to suggest that anticoagulation is safe for PVT treatment in cirrhotic patients; although it should be noted that no randomized controlled study exists comparing anticoagulation to placebo to assess bleeding risk. Recent research also fails to address differences in the severity of bleeding episodes between cirrhotic patients receiving anticoagulants and those who are not, with no clear concord on the type of anticoagulant to be used [12]. A recent meta-analysis did demonstrate, however, that anticoagulation in cirrhotic patients with PVT was safe (not associated with an increase in major or minor bleeding) and beneficial (associated with partial or complete PVT recanalization after approximately 6 months of treatment), with low molecular weight heparin administration significantly asso-

ciated with complete resolution of thrombi [13].The unusual timing of the bleed in this patient requires consideration of alternative causes, which can only be surmised based on clinical course and the available evidence.

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