

Dear Dr. Lian-Sheng Ma,

Thank you very much for your help for our manuscript entitled "*Acute mesenteric ischemia secondary to oral-contraceptive-induced portomesenteric and splenic vein thrombosis: A case report*" (Manuscript NO. 77075, Case Report). We have studied reviewers' comments carefully and made totally revision. We hope the changes could meet reviewers' approval.

The following is point-to-point response to the referees' comments and indicates where the modifications have been made, and it takes into account the views of all authors. Revised portions are underlined in red and deleted portions are covered in green in this letter. And the grammar have been reedited by MedE Medical Editing Group Inc., the editing number is Ref. MYCJLFME-MS2022061510R and we also uploaded its related EDITORIAL CERTIFICATE as a single document. We hope that the revision is acceptable.

Sincerely yours,

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Point to point response to editor's and reviewer's comments:

Questions from editor: Please note that the reviewers have deemed the quality of language in this manuscript unsuitable for publication. Please send the manuscript to a language editing company to improve the article for language and style. Please provide the certificate confirming that language editing has been performed at the same time as the response to the peer review comments.

Answer: Thank you very much for your question. According to your suggestion, we have sent the manuscript to the language editing company MedE Medical Editing Group Inc. to improve the article for language and style, the editing number is Ref. MYCJLFME-MS2022061510R, and we uploaded the related EDITORIAL CERTIFICATE as a supplementary material.

Questions from Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: This case report highlights the role of OCP as a risk factor for SVT. It is not particularly novel. I am somewhat uncomfortable with the management strategy. It appears that only a prophylactic dose of LMWH was given rather than a full dose. There was also no mention of any attempts to thrombolyse or attempt interventional radiological procedures in view of intestinal ischaemia (see Benmassaoud A. A stepwise thrombolysis regimen in the management of acute portal vein thrombosis in patients with evidence of intestinal ischaemia. *Aliment Pharmacol Ther.* 2019 Nov;50(9):1049-1058. doi: 10.1111/apt.15479. Epub 2019 Sep 5. PMID: 31489698). These measures could have avoided surgical intervention in a young patient. I also cannot see that a full screen for other provoking factors was done e.g. JAK2, PNH. It is well known that patients can have more than one provoking factor for thrombosis. I also question the 4 month course of DOAC. Most guidelines would recommend indefinite anticoagulation if there has been evidence of intestinal ischaemia. Baveno 7 should be referenced.

Major observations:

Question 1. It appears that only a prophylactic dose of LMWH was given rather than a full dose.

Answer: Thank you very much for your advise. We have reviewed the case records again, and the useage of LMWH sodium was each 5,000 U, subcutaneous injection twice a day. We have revised the corresponding part of the manuscript as you suggested. The weight of our patient is 50 Kg, and the recommended does for treating vein thrombosis is 100 U/kg, subcutaneous injection twice a day according to the instruction of LMWH sodium.

TREATMENT

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As planned, the nutrition team advised starting total parenteral nutrition after surgery, and simultaneously, she initiated subcutaneous LMWH 5000 U/d twice a day as advised by the anticoagulation specialist.

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Question 2. There was also no mention of any attempts to thrombolyse or attempt interventional radiological procedures in view of intestinal ischaemia (see Benmassaoud A. A stepwise thrombolysis regimen in the management of acute portal vein thrombosis in patients with evidence of intestinal ischaemia. *Aliment Pharmacol Ther.* 2019 Nov;50(9):1049-1058. doi: 10.1111/apt.15479. Epub 2019 Sep 5. PMID: 31489698). These measures could have avoided surgical intervention in a young patient.

Answer: Thank you very much for your question. Our patient was diagnosed as intestinal stenosis and incomplete intestinal obstruction caused by AMI secondary to PMSVT after admission, the treatment endpoint was to delay the removal of diseased bowel after the thrombus had completely

resolved or collateral circulation was established. Immediate anticoagulation could prevent thrombus extension and worsen intestine ischemia.

Thank you for providing us with excellent literature by Benmassaoud A. *et al.* We carefully reviewed the literature, and it is an effective and safe treatment protocol for patients with indirect evidence of intestinal ischemia from acute PVT, using initial low-dose systemic thrombolysis followed by local thrombolysis through a transjugular portal vein access, and resulted in good reconsultation rate.

To our patient, in the first multidisciplinary consultations, anticoagulation specialists and vascular surgeons recommended that immediate anticoagulation therapy with LMWH sodium, and thrombolytic therapy with urokinase is added if ineffective, when necessary, endovascular treatment by transcatheter thrombolysis was used for treatment.

We have revised our manuscript according to your suggestion as following:

TREATMENT

... and anticoagulation with low molecular weight heparin (LMWH) sodium 5000 U (100 U/kg), subcutaneous injection twice daily, which was commenced as the initial conventional therapy. Thrombolytic therapy with urokinase was added if this treatment was ineffective. If necessary, endovascular treatment with transcatheter thrombolysis was planned. The treatment endpoint was to delay the removal of diseased bowel after the thrombus had completely resolved or a collateral circulation was established.

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Question 3. I also cannot see that a full screen for other provoking factors was done e.g. JAK2, PNH. It is well known that patients can have more than one provoking factor for thrombosis.

Answer: Thank you very much for your question. We have measured markers associated with prothrombotic conditions, including the prothrombotic testing included protein S: 67% (Normal range 55 - 145%); protein C: 81% (Normal range 60 - 140%); antithrombin-III: 90% (Normal range 75 - 125%); anticardiolipin antibodies IgG: 7.5 RU/ml (Normal range 0 - 12 RU/ml); anti- β 2-glycoprotein I antibodies: 14 RU/ml (Normal range 0 - 20 RU/ml); and lupus anticoagulant ratio: 1.0 (Normal range 0.8 - 1.2). None of the following were detected by PCR assay: factor V Leiden mutation, prothrombin G20210A mutation, JAK2V617F mutation. The results were reported 10 days after the specimens were sent to the laboratory.

We have revised our manuscript and added a full screen for markers associated with prothrombotic conditions as follows:

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Laboratory examinations

Anticardiolipin antibody was within the normal range. The prothrombotic testing included

protein S: 67% (Normal range 55 - 145%); protein C: 81% (Normal range 60 - 140%); antithrombin-III: 90% (Normal range 75 - 125%); anticardiolipin antibodies IgG: 7.5 RU/ml (Normal range 0 - 12 RU/ml); anti-β2-glycoprotein I antibodies: 14 RU/ml (Normal range 0 - 20 RU/ml); and lupus anticoagulant ratio: 1.0 (Normal range 0.8 - 1.2). None of the following were detected by PCR assay: factor V Leiden mutation, prothrombin G20210A mutation, JAK2V617F mutation. The results was reported 10 days after the specimens were sent to the laboratory.

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Question 4. I also question the 4 month course of DOAC. Most guidelines would recommend indefinite anticoagulation if there has been evidence of intestinal ischaemia. Baveno 7 should be referenced.

Answer: Thank you for your very important question. This question has puzzled our multidisciplinary team.

The American Association for the Study of Liver Diseases (AASLD) guidelines recommend at least three months of anticoagulation with traditional anticoagulants for all patients with acute PVT irrespective of presence of symptoms. Long-term anticoagulation therapy should be considered in patients with permanent thrombotic risk factors that are not correctable other wise (1). In addition, The American College of Chest Physicians recommends a minimum of three months of anticoagulation for symptomatic patients only and no anticoagulation for asymptomatic patients (2).

The physician instructed the patient (postoperation) to take one tablet of 20 mg rivaroxaban orally once daily for 4 months according to reference (1) and (2).

Your question are very important to our patient and provide a good literature. Baveno VII recommend anticoagulation should be given for at least 6 months in all patients with recent PVT in the absence of cirrhosis. After 6 months, long-term anticoagulation is recommended in patients with a permanent underlying prothrombotic state and should also be considered in patients without an underlying prothrombotic state (3). According to your suggestion, at a recent follow-up, our patient was advised to take one tablet of 20 mg rivaroxaban orally once daily for at least 6 months.

We have revised these in our manuscript as following:

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OUTCOME AND FOLLOW-UP

The patient was instructed to take one tablet of 20 mg rivaroxaban orally once daily for at least 6 mo

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Reference used in this question:

1. DeLeve LD, Valla DC, Garcia-Tsao G. American Association for the Study Liver Diseases. Vascular disorders of the liver. *Hepatology*. 2009; 49:1729-1764. doi: [10.1002/hep.22772](https://doi.org/10.1002/hep.22772).
2. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012; 141:e44S-e88S. doi: [10.1378/chest.11-2292](https://doi.org/10.1378/chest.11-2292).
3. Roberto de Franchis, Jaume Bosch, Guadalupe Garcia-Tsao, Thomas Reiberger, Cristina Ripoll. Baveno VII – Renewing consensus in portal hypertension. *Journal of Hepatology*. 2022; 76: 959–974. doi: [10.1016/j.jhep.2022.03.024](https://doi.org/10.1016/j.jhep.2022.03.024).

Reviewer #2:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Rejection

Specific Comments to Authors: In this paper, Zhao and colleagues report an interesting case of acute mesenteric ischemia secondary to portomesenteric and splenic vein thrombosis. Furthermore, they provide a short review of this topic based on their experience. The manuscript is well written. The authors are to be congratulated on the successful outcome in their patient. Nevertheless, I have the following comments: INTRODUCTION: - The authors state: “Although thrombosis of splanchnic venous system is uncommon, improved CECT has led to an increased incidence of this disease”. What has really increased? The incidence or the detection of splanchnic vein thrombosis? The real incidence may not have changed, although more patients could be diagnosed nowadays due to the increased accessibility of CT scans and improved sensitivity of diagnostic imaging techniques. Could the authors provide any information, reference or commentary on this point? CASE PRESENTATION: - Chief complaints: the authors explain that the patient had been hospitalized elsewhere before arriving to their hospital. How long was she hospitalized? How long it took from discharge to readmission? Had the patient ever received thromboprophylaxis during the previous admission? In affirmative case, which thromboprophylaxis? (eg, drug, dose...) Was any diagnostic abdominal imaging test (e.g. ultrasound, CT scan...) performed during the previous hospitalization? What about the determination of D-dimer or any other diagnostic test that could suggest the diagnosis of splanchnic vein thrombosis during the previous hospitalization? - History of present illness: did the symptoms start 11 days ago including the previous admission, or did the symptoms persist or worsen after the previous discharge? The timeline could be clearer. - History of past illness: who prescribed ethinidyl estradiol/drospirenone and which was its indication? (e.g. polycystic ovary syndrome, abnormal uterine bleeding, only contraception...). - Personal and family history: I think that in this case it is important to highlight if there is a personal or family history of venous thromboembolism, thrombophilia, cancer and/or pregnancy losses. How was her weight, height and body mass index? - Laboratory examinations: why was the determination of anticardiolipin antibodies performed in the acute phase? What subclasses of anticardiolipin antibodies were determined? (i.e. IgG or IgM). Why only anticardiolipin antibodies were determined? Why was the determination of anti-beta-2-glycoprotein I antibodies not included? Why were the prothrombin G20210A mutation and the factor V Leiden mutation +/- JAK2V617F mutation not included once you decided to test for anticardiolipin antibodies? - Imaging

examinations: the authors explain that abdominal ultrasound was performed before contrast-enhanced CT (CECT). Doppler ultrasonography has a sensitivity of 89-93% and a specificity of 92-99% for the diagnosis of PVT, and has become the first line diagnostic test for PVT. Nevertheless, PVT was not diagnosed in this case by abdominal ultrasound, although thrombosis of the right branch of portal vein (PV) and main vessels of PV was subsequently diagnosed by CECT. Could the authors include any rationale about this missed PVT diagnosis by abdominal ultrasound in the discussion? - Imaging examinations: the patient underwent 4 contrast-enhanced CT scans in a period of 31 days despite her good clinical evolution. What about radiation exposure in this young woman? Are 4 contrast-enhanced CT scans justified in such a reduced time lapse? Could she be managed with fewer CT scans or by using alternative imaging tests, such as an abdominal MRI? Could the authors include any comments on this topic in the discussion section? TREATMENT: - The patient received anticoagulation with low molecular weight heparin (LMWH) 5000 U, subcutaneous injection twice daily. Which LMWH was used? How was the patient's weight at that time? - Rivaroxaban 20 mg was then given orally for anticoagulation instead of LMWH injection. It is important to include in the discussion the rationale for this decision. DOACs are not recommended for the treatment of splanchnic vein thrombosis in current clinical guidelines (AASLD 2009, AISF 2011, ACCP 2012, Baveno VI 2015 and EASL 2016). Any reference to these guidelines and to any study that might support the use of rivaroxaban in this case is missing. There is little evidence to support this decision, which needs to be discussed. Some of the few studies that could support this decision are: • Hanafy AS, Abd-Elsalam S, Dawoud MM. Randomized controlled trial of rivaroxaban versus warfarin in the management of acute non-neoplastic portal vein thrombosis. *Vascul Pharmacol.* 2019;113:86–91. doi:10.1016/j.vph.2018.05.002 • Janczak DT, Mimier MK, McBane RD, et al. Rivaroxaban and apixaban for initial treatment of acute venous thromboembolism of atypical location. *Mayo Clin Proc.* 2018;93(1):40–47. doi:10.1016/j.mayocp.2017.10.007 - When did the patient receive the last dose of LMWH before the scheduled laparotomy? What class of LMWH and dose did she receive? When was LMWH reintroduced after scheduled surgery? (i.e. the same day of the surgery, the first day after the surgery...). OUTCOME, FOLLOW-UP AND DISCUSSION: - The authors conclude that this is an oral-contraceptive-induced PMSVT, but further investigations for other potential aetiological factors for splanchnic vein thrombosis were not performed during the follow-up, as recommended by de 2016 EASL guidelines (European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu. EASL Clinical Practice Guidelines: Vascular diseases of the liver. *J Hepatol.* 2016;64(1):179-202). Thus, this young woman should be tested for thrombophilia, including Factor V Leiden, Prothrombin G20210A mutation, antiphospholipid syndrome, protein C and S deficiency, and antithrombin deficiency. In addition, the most prevalent mutations related to myeloproliferative neoplasm and splanchnic vein thrombosis (JAK2V617F +/- CALR) should be considered. Furthermore, the use of rivaroxaban should be avoided when any of these conditions are present (e.g. antiphospholipid syndrome). All these important considerations and many bibliographic references regarding splanchnic vein thrombosis management are lacking in the discussion. - What attitude was adopted regarding contraception at splanchnic vein thrombosis diagnosis and during follow-up? Once the diagnosis is clear and the patient starts anticoagulation, do you think that hormonal contraception should be discontinued? What about contraception planning during anticoagulation and after its discontinuation? - What criteria were used to maintain anticoagulation for 4 months? If the authors considered that it was a thrombotic

event provoked by transient risk factor (i.e. hormonal contraception), the 2016 EASL guidelines recommend at least 6 months of anticoagulation. Any consideration to this point is absent from the discussion. - The authors state that “Wolters et al demonstrated that D-dimer, as an early serum marker of AMVT, could assist with decision-making and timely treatment of AMVT (12)”. First of all, reference 12 is not from Wolters et al (it is from Yang *et al*). Second, there are some limitations in the use of D-dimer that are not assessed in the discussion. Although some studies showed that mean D-dimer values are increased in patients with SVT, D-dimer can also be elevated in other conditions, such as liver cirrhosis or hepatocellular carcinoma, which reduces its diagnostic predictive value in splanchnic vein thrombosis.

Question 1. INTRODUCTION: - The authors state: “Although thrombosis of splanchnic venous system is uncommon, improved CECT has led to an increased incidence of this disease”. What has really increased? The incidence or the detection of splanchnic vein thrombosis? The real incidence may not have changed, although more patients could be diagnosed nowadays due to the increased accessibility of CT scans and improved sensitivity of diagnostic imaging techniques. Could the authors provide any information, reference or commentary on this point?

Answer: Thank you very much for your question. We must say sorry, this is our wrong expression. In fact, what we are trying to say is that the disease is increasingly reported from better investigation facilities now. We have advised our manuscript according to your suggestion as follows:

INTRODUCTION

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Although thrombosis of splanchnic venous system is uncommon, the disease is increasingly reported from better investigation facilities such as CECT ⁽²⁾.

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Question 2. CASE PRESENTATION: - Chief complaints: the authors explain that the patient had been hospitalized elsewhere before arriving to their hospital. How long was she hospitalized? How long it took from discharge to readmission? Had the patient ever received thromboprophylaxis during the previous admission? In affirmative case, which thromboprophylaxis? (eg, drug, dose...) Was any diagnostic abdominal imaging test (e.g. ultrasound, CT scan...) performed during the previous hospitalization? What about the determination of D-dimer or any other diagnostic test that could suggest the diagnosis of splanchnic vein thrombosis during the previous hospitalization? - History of present illness: did the symptoms start 11 days ago including the previous admission, or did the symptoms persist or worsen after the previous discharge? The timeline could be clearer.

Answer: Thank you very much for your question. The patient has been hospitalized elsewhere before arriving to our hospital. She had been hospitalized in local hospital for 11 days since she presented with continuous abdominal pain accompanied by abdominal distention, nausea and

vomiting. It took less than 24 hours from discharge to readmission, she was readmitted to our hospital for further diagnosis and treatment the same day she was discharged from the local hospital. The patient had not ever received thromboprophylaxis during the previous admission, because she was diagnosed with ileus only, without considered as AMI or splanchnic vein thrombosis. Investigations were carried out with increased WBC count and Abdominal/pelvic X-rays showed dilated segmental bowel loops , and normal biochemical test and abdominal ultrasonography finding. D-dimer or any other diagnostic test that could suggest the diagnosis of splanchnic vein thrombosis did not carried out. The symptoms start 11 days ago included the previous admission. The abdominal pain and distention were persisting but did reduce nausea and vomiting after the previous discharge. We have advised our manuscript according to your suggestion as following:

...

Chief complaints

A 28-year-old woman was admitted to the emergency department because of continuous abdominal pain around the umbilicus and epigastrium accompanied by abdominal distention, nausea and vomiting for 11 d. She denied fever, diarrhea, constipation, hematochezia and melena. She had been hospitalized elsewhere before coming to our hospital. She had been hospitalized in a local hospital due to continuous abdominal pain around the umbilicus and epigastrium accompanied by abdominal distention, nausea and vomiting, where she underwent laboratory tests, abdominal ultrasonography and abdominal/pelvic X-rays, and was diagnosed with ileus, and treatment included fasting and water, gastrointestinal decompression, and intravenous antibiotics and fluid replacement. None of these alleviated the abdominal pain and distention but did reduce nausea and vomiting. However, the etiology of ileus could not be clearly defined and the patient's symptoms did not improve significantly during hospitalization. She was then transferred to our hospital for further diagnosis and treatment.

History of present illness

The patient had been hospitalized for 11 days in a local hospital due to continuous abdominal pain accompanied by abdominal distension, nausea and vomiting prior to admission to our hospital.

The symptoms started 11 d ago and the patient complained of persistent abdominal pain and distention.

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Question 3. History of past illness: who prescribed ethinidyl estradiol/drospirenone and which was its indication? (e.g. polycystic ovary syndrome, abnormal uterine bleeding, only contraception...). - Personal and family history: I think that in this case it is important to highlight if there is a personal or family history of venous thromboembolism, thrombophilia, cancer and/or pregnancy losses. How was her weight, height and body mass index?

Answer: Thank you for your very important question. We have revised our manuscript according to your suggestion as following:

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History of past illness

The patient had been taking oral contraceptives (ethinyl estradiol 0.03 mg and drospirenone 3 mg/d) to treat abnormal uterine bleeding, prescribed at gynecology department of local hospital for 13 mo prior to presentation.

Personal and family history

The patient denied smoking or drinking alcohol, and her family history was unremarkable. She had no personal or familial history of thrombosis, thrombophilia, cancer and pregnancy losses.

Physical examination

Her body mass index was 20.5 kg/m², weight was 50 kg, and height was 156 cm.

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Question 4. - Laboratory examinations: why was the determination of anticardiolipin antibodies performed in the acute phase? What subclasses of anticardiolipin antibodies were determined? (i.e. IgG or IgM). Why only anticardiolipin antibodies were determined? Why was the determination of anti-beta-2-glycoprotein I antibodies not included? Why were the prothrombin G20210A mutation and the factor V Leiden mutation +/- JAK2V617F mutation not included once you decided to test for anticardiolipin antibodies?

Answer: Thank you for your very important question. We have measured markers associated with prothrombotic conditions, including Prothrombotic testing included protein S, 67% (normal range 55-145%), protein C, 81% (normal range 60-140%), antithrombin-III, 90% (normal range 75-125%), in addition, anticardiolipin antibody IgG, 7.5 RU/mL (normal range 0-12 RU/mL), anti-β2-glycoprotein I antibodies, 14 RU/mL (normal range 0-20 RU/mL) and lupus anticoagulant ratio, 1.0 (normal range 0.8 - 1.2). None of the following were detected by PCR assay: factor V Leiden mutation, prothrombin G20210A mutation, and JAK2V617F mutation. These results were obtained 10 days after the specimens were sent to the laboratory.

According to recommendation of Baveno VII, “DOACs can be considered the primary option in selected cases in the absence of so-called “triple positive” anti-phospholipid syndrome.”, in addition, These results were obtained 10 days after the specimens were sent to the laboratory. So, markers associated with prothrombotic conditions were carried out immediately after admission.

Sorry, we only listed DOACs- related marker, and we had added other markers to the manuscript as following:

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Laboratory examinations

Anticardiolipin antibody was within the normal range. Prothrombotic testing included protein S, 67% (normal range 55-145%), protein C, 81% (normal range 60-140%), antithrombin-III, 90% (normal range 75-125%), in addition, anticardiolipin antibody IgG, 7.5 RU/mL (normal range 0-12 RU/mL), anti-β2-glycoprotein I antibodies, 14 RU/mL (normal range 0-20 RU/mL) and lupus anticoagulant ratio, 1.0 (normal range 0.8 - 1.2). None of the following were detected by PCR assay: factor V Leiden mutation, prothrombin G20210A mutation, and JAK2V617F mutation. These results were obtained 10 days after the specimens were sent to the laboratory.

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Question 5. - Imaging examinations: the authors explain that abdominal ultrasound was performed before contrast-enhanced CT (CECT). Doppler ultrasonography has a sensitivity of 89-93% and a specificity of 92-99% for the diagnosis of PVT, and has become the first line diagnostic test for PVT. Nevertheless, PVT was not diagnosed in this case by abdominal ultrasound, although thrombosis of the right branch of portal vein (PV) and main vessels of PV was subsequently diagnosed by CECT. Could the authors include any rationale about this missed PVT diagnosis by abdominal ultrasound in the discussion? - Imaging examinations: the patient underwent 4 contrast-enhanced CT scans in a period of 31 days despite her good clinical evolution. What about radiation exposure in this young woman? Are 4 contrast-enhanced CT scans justified in such a reduced time lapse? Could she be managed with fewer CT scans or by using alternative imaging tests, such as an abdominal MRI? Could the authors include any comments on this topic in the discussion section?

Answer: Thank you for your suggestion. For our patient, the use of CDUS was limited by overlying bowel gas, and in addition, MRA was unsuitable for the patient, who has limited breath holding due to abdominal pain. To avoid excessive X- ray radiation, only the upper abdomen was exposed during CT scan during her hospitalization. For her less radiation exposure, we recommended MRA since the second follow-up. We have revised our manuscript according to your suggestion as follows:

DISCUSSION

... Although splanchnic thrombosis is rare, the widespread use of CECT in patients with abdominal pain can advance diagnosis from 1 wk to 1 d^[8]. A filling defect in the MV is the most common finding on CT imaging in patients with MVT. Characteristic CT findings of intestinal wall ischemia include bowel wall thickening and persistent enhancement, pneumatosis intestinalis and PV gas^[9,10]. However, these findings have poor diagnostic sensitivity for bowel infarction and transmural necrosis^[10,11]. The EASL Clinical Practice Guidelines^[11] and AASLD Practice Guidelines^[12] propose color Doppler sonography (CDUS) and CECT as the primary imaging techniques for diagnosing acute splanchnic vein thrombosis. Lukas *et al* demonstrated that CDUS and CECT are both equally reliable in assessing the grade and extent of acute splanchnic vein thrombosis^[13]. The diagnostic sensitivity and specificity of CDUS in detecting portal vein thrombosis (PVT) varies from 66% to 100%^[14]. Angiography has historically been the reference standard for the diagnosis of AMI. However, this is an invasive procedure and infrequently performed in the acute setting^[15]. In AMI secondary to venous occlusion, ultrasound may reveal focal SMV or portal thrombus, and help in reducing the differential causes of abdominal pain; however, actual image quality and reproducibility of the results is operator dependent and limited by overlying bowel gas^[16]. Magnetic resonance angiography (MRA) has high sensitivity and specificity for evaluation of SMA occlusions. However, MRA is time consuming and not as freely available as CT, which limits its usefulness in the acute setting^[17]. In our patient, the use of CDUS was limited by overlying bowel gas, and MRA was unsuitable due to the patient having limited breath holding due to abdominal pain. To avoid excessive X-ray radiation, only the upper abdomen was exposed during CT scanning.

Reference used in this question:

11. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Vascular diseases of the liver. *J Hepatol*. 2016;**64**:179-202. [PMID: 26516032 DOI: 10.1016/j.jhep.2015.07.040] [Cited by in Crossref: 291] [Cited by in F6Publishing: 202] [Impact Index Per Article: 41.6] [Reference Citation Analysis] [Track Full Text]

12. **DeLeve LD**, Valla DC, Garcia-Tsao G; American Association for the Study Liver Diseases. Vascular disorders of the liver. *Hepatology*. 2009;**49**:1729-1764. [PMID: 19399912 DOI: 10.1002/hep.22772] [Cited by in Crossref: 599] [Cited by in F6Publishing: 436] [Impact Index Per Article: 46.1] [Reference Citation Analysis] [Track Full Text]
13. **Sturm L**, Bettinger D, Klinger C, Krauss T, Engel H, Huber JP, Schmidt A, Caca K, Thimme R, Schultheiss M. Validation of color Doppler ultrasound and computed tomography in the radiologic assessment of non-malignant acute splanchnic vein thrombosis. *PLoS One* 2021;**16**:e0261499. [PMID: 34929009 DOI: 10.1371/journal.pone.0261499] [Cited by in Crossref: 0] [Impact Index Per Article: 0] [Reference Citation Analysis] [Track Full Text] Open
14. **Tessler FN**, Gehring BJ, Gomes AS, Perrella RR, Ragavendra N, Busuttil RW, Grant EG. Diagnosis of portal vein thrombosis: value of color Doppler imaging. *AJR Am J Roentgenol*. 1991;**157**:293-296. [PMID: 1853809 DOI: 10.2214/ajr.157.2.1853809] [Cited by in Crossref: 121] [Cited by in F6Publishing: 93] [Impact Index Per Article: 3.9] [Reference Citation Analysis] [Track Full Text]
15. **Oliva IB**, Davarpanah AH, Rybicki FJ, Desjardins B, Flamm SD, Francois CJ, Gerhard-Herman MD, Kalva SP, Ashraf Mansour M, Mohler ER 3rd, Schenker MP, Weiss C, Dill KE. ACR Appropriateness Criteria ® imaging of mesenteric ischemia. *ACTA ACUST UNITED AC* 2013;**38**:714-9. [PMID: 23296712 DOI: 10.1007/s00261-012-9975-2] [Cited by in Crossref: 102] [Cited by in F6Publishing: 66] [Impact Index Per Article: 11.3] [Reference Citation Analysis] [Track Full Text]
16. **Reginelli A**, Genovese E, Cappabianca S, Iacobellis F, Berritto D, Fonio P, Coppolino F, Grassi R. Intestinal Ischemia: US-CT findings correlations. *Crit Ultrasound J*. 2013;**5 Suppl 1**:S7. [PMID: 23902826 DOI: 10.1186/2036-7902-5-s1-s7] [Cited by in Crossref: 44] [Cited by in F6Publishing: 15] [Impact Index Per Article: 4.9] [Reference Citation Analysis] [Track Full Text] Open
17. **Meaney JF**. Non-invasive evaluation of the visceral arteries with magnetic resonance angiography. Eur

[Radiol. 1999;9:1267-1276. \[PMID: 10460359 DOI: 10.1007/s003300050833\] \[Cited by in Crossref: 27\] \[Cited by in F6Publishing: 18\] \[Impact Index Per Article: 1.2\] \[Reference Citation Analysis\] \[Track Full Text\]](#)

Question 5. TREATMET: - The patient received anticoagulation with low molecular weight heparin (LMWH) 5000 U, subcutaneous injection twice daily. Which LMWH was used? How was the patient's weight at that time? - Rivaroxaban 20 mg was then given orally for anticoagulation instead of LMWH injection. It is important to include in the discussion the rationale for this decision. DOACs are not recommended for the treatment of splanchnic vein thrombosis in current clinical guidelines (AASLD 2009, AISF 2011, ACCP 2012, Baveno VI 2015 and EASL 2016). Any reference to these guidelines and to any study that might support the use of rivaroxaban in this case is missing. There is little evidence to support this decision, which needs to be discussed. Some of the few studies that could support this decision are: • Hanafy AS, Abd-Elsalam S, Dawoud MM. Randomized controlled trial of rivaroxaban versus warfarin in the management of acute non-neoplastic portal vein thrombosis. *Vascul Pharmacol.* 2019;113:86–91. doi:10.1016/j.vph.2018.05.002 • Janczak DT, Mimier MK, McBane RD, et al. Rivaroxaban and apixaban for initial treatment of acute venous thromboembolism of atypical location. *Mayo Clin Proc.* 2018;93(1):40–47. doi:10.1016/j.mayocp.2017.10.007 - When did the patient receive the last dose of LMWH before the scheduled laparotomy? What class of LMWH and dose did she receive? When was LMWH reintroduced after scheduled surgery? (i.e. the same day of the surgery, the first day after the surgery...).

Answer: Thank you for your question. In this study, low molecular weight heparin sodium was used. The patient's weight was 50 kg at that time. The patient receive the last dose of LMWH somdium(5,000 U) at 6 h prior to the scheduled laparotomy, LMWH sodium (5,000 U/12 h, twice a day) reintroduced at the first day after the surgery.

We have revised our manuscript as follows:

DISCUSSION

... It is increasingly possible to treat MVT conservatively with early anticoagulation in an effort to avoid or delay bowel resection. In our patient, following the second multidisciplinary consultation, the anticoagulation specialist recommended 20 mg rivaroxaban orally for anticoagulation instead of LMWH injection according to the Baveno^[22] recommendation, although direct oral anticoagulants (DOACs) are not recommended for the treatment of splanchnic vein thrombosis in the EASL Clinical Practice Guidelines^[11] and AASLD Practice Guidelines^[12]. In addition, Janczak DT *et al* indicated that DOACs (rivaroxaban and apixaban) have comparable efficacy and safety in patients with venous thrombosis as in patients with typical venous thrombosis, similar to enoxaparin^[23]. Hanafy AS *et al* indicated that rivaroxaban can improve the short-term survival rate

in patients with acute HCV-related non-neoplastic PVT, and its efficacy and safety have been confirmed^[24]. Our patient received LMWH sodium and rivaroxaban sequentially for 31 d, and the thrombus in the PV and SV completely resolved, remnant thrombus in the SMV was obliterated, and collateral circulation was well developed as shown by CECT. An increasing number of cases of MVT are resolved by nonsurgical treatment or delayed surgical treatment^[15-17,25-27].

...

Question 5. All these important considerations and many bibliographic references regarding splanchnic vein thrombosis management are lacking in the discussion. - What attitude was adopted regarding contraception at splanchnic vein thrombosis diagnosis and during follow-up? Once the diagnosis is clear and the patient starts anticoagulation, do you think that hormonal contraception should be discontinued? What about contraception planning during anticoagulation and after its discontinuation? - What criteria were used to maintain anticoagulation for 4 months? If the authors considered that it was a thrombotic event provoked by transient risk factor (i.e. hormonal contraception), the 2016 EASL guidelines recommend at least 6 months of anticoagulation. Any consideration to this point is absent from the discussion.

Answer: Thank you for your suggestion. In the first multidisciplinary consultations among emergency surgeons, vascular surgeons, anesthetists, anticoagulation specialists, nutrition specialists and gynecologists, gynecologists recommended that oral contraceptive be discontinued immediately, and use a contraceptive ring to control birth after the patient recovered. At the second follow-up visit, the patient was given a contraceptive ring in the gynaecology department.

Thank you very much again. Your question are very important to our patient and provide a good literature. This question has puzzled our multidisciplinary team.

The American Association for the Study of Liver Diseases (AASLD) guidelines recommend at least three months of anticoagulation with traditional anticoagulants for all patients with acute PVT irrespective of presence of symptoms. Long-term anticoagulation therapy should be considered in patients with permanent thrombotic risk factors that are not correctable other wise ⁽¹⁾. In addition, The American College of Chest Physicians recommends a minimum of three months of anticoagulation for symptomatic patients only and no anticoagulation for asymptomatic patients ⁽²⁾.

The physician instructed the patient (postoperation) to take one tablet of 20 mg rivaroxaban orally once daily for 4 months according to reference ⁽¹⁾ and ⁽²⁾. According to your suggestion, we carefully reviewed the 2016 EASL guidelines. In addition, According to your suggestion, at a recent follow-up, our patient was advised to take one tablet of 20 mg rivaroxaban orally once daily for at least 6 months. We have revised our manuscript as following:

...

TREATMENT

Hence, multidisciplinary consultations were conducted with emergency surgeons, vascular

surgeons, anesthetists, anticoagulation specialists, nutrition specialists and gynecologists, and treatment plans were : gastrointestinal decompression; total parenteral nutrition; intravenous antibiotic cefminox 1.0 g, twice daily; and anticoagulation with low molecular weight heparin (LMWH) sodium 5000 U (100 U/kg), subcutaneous injection twice daily, which was commenced as the initial conventional therapy. Thrombolytic therapy with urokinase was added if this treatment was ineffective. If necessary, endovascular treatment with transcatheter thrombolysis was planned. The treatment endpoint was to delay the removal of diseased bowel after the thrombus had completely resolved or a collateral circulation was established. Further urgent surgical intervention should be performed when intestinal necrosis with impending perforation or peritonitis is suspected. The gynecologists recommended that oral contraceptive be discontinued immediately, and a contraceptive ring for birth control should be used when the patient recovered.

To improve her treatment, multidisciplinary consultation was conducted again. Total enteral nutrition was performed with nasointestinal tubes according to the nutrition specialist's advice, and the anticoagulation specialists recommended that 20 mg rivaroxaban should be given orally for anticoagulation instead of LMWH injection, and the PT level was monitored according to her prothrombotic test results.

OUTCOME AND FOLLOW-UP

The physician instructed the patient to take one tablet of 20 mg rivaroxaban orally once daily for 4 mo. at least 6 mo.

Reference used in this question:

1. DeLeve LD, Valla DC, Garcia-Tsao G; American Association for the Study Liver Diseases. Vascular disorders of the liver. Hepatology. 2009 May;49(5):1729-64. doi: 10.1002/hep.22772.
2. Ageno W., Gallus A. S., Wittkowsky A., Crowther M., Hylek E. M., Palareti G. Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. CHEST. 2012; 141(2, supplement):e44S–e88S. doi: 10.1378/chest.11-2292.

...

Question 7: The authors state that “Wolters et al demonstrated that D-dimer, as an early serum marker of AMVT, could assist with decision-making and timely treatment of AMVT (12)”. First of all, reference 12 is not from Wolters et al (it is from Yang et al). Second, there are some limitations in the use of D-dimer that are not assessed in the discussion. Although some studies

showed that mean D-dimer values are increased in patients with SVT, D-dimer can also be elevated in other conditions, such as liver cirrhosis or hepatocellular carcinoma, which reduces its diagnostic predictive value in splanchnic vein thrombosis.

Answer: Thank you for your suggestion. We have corrected these mistakes in our manuscript according to your reminding as follows:

DISCUSSION

... but **Wolters**Yang *et al* demonstrated that D-dimer, as an early serum marker of AMVT, could assist with decision-making and timely treatment of AMVT ⁽¹²⁾. Additionally, it has been reported that serum D-dimer level at admission has high diagnostic sensitivity for AMI ⁽¹²⁾, however, D-dimer can also be elevated in other conditions, such as liver disease, cardiovascular disease or cancer, which reduces its diagnostic predictive value in splanchnic vein thrombosis^[19]

Reference used in this question:

19. Eric D Johnson, John C Schell, George M Rodgers. The D-dimer assay. *Am J Hematol*. 2019, 94(7):833-839. doi: 10.1002/ajh.25482.

Reviewer #3:

Scientific Quality: Grade C (Good)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Major revision

Specific Comments to Authors: The manuscript was read with interest. There are few pitfalls in the case presentation, some of which are pointed out below: Language and style: - There are several syntax errors throughout the paper that necessitates appropriate corrections with the help of a scientific writer. Introduction: - the statement "Although thrombosis of splanchnic venous system is uncommon, improved CECT has led to an increased incidence of this disease" is wrong. In fact, the disease is increasingly reported from better investigation facilities now. Case presentation: - The reference ranges for normal lab values are not provided (WBC count, CRP, PCT, D-dimer etc.) - international normalized ration (INR) should be international normalized ratio (INR) - It is unusual to have normal lactate level in this patient with acute mesenteric ischemia - Treatment is not clear - What is Cefminox and which LMWH was used (should have mentioned the dose in Units/Kg also). Discussion: - Why there is discrepancy between the reported prevalence of MVT in the introduction and discussion with same reference cited?!

Answer: Thank you for your suggestion. We will proofread our manuscript, and we have revised the mistakes according to your remaining.

Question 1: Introduction: - the statement "Although thrombosis of splanchnic venous system is uncommon, improved CECT has led to an increased incidence of this disease" is wrong. In fact, the disease is increasingly reported from better investigation facilities now.

Answer: Thank you very much for your suggestion. We have revised our manuscript according to your suggestions.

INTRODUCTION

... Although thrombosis of the splanchnic venous system is uncommon, the disease is increasingly reported from better investigation facilities such as CECT ⁽²⁾.

...

Question 2: Case presentation: - The reference ranges for normal lab values are not provided (WBC count, CRP, PCT, D-dimer etc.) - international normalized ration (INR) should be international normalized ratio (INR) - It is unusual to have normal lactate level in this patient with acute mesenteric ischemia.

Answer: Thank you very much for your suggestion. We have revised our manuscript according to your suggestions as follows:

...

Laboratory examinations

Laboratory tests performed on the day of admission showed an elevated white blood cell count of $25.5 \times 10^9/L$ (normal range, $3.5-9.5 \times 10^9/L$), C-reactive protein (CRP) 206 mg/mL (normal range, 0.0-6.0 mg/mL), procalcitonin (PCT) 0.6236 ng/mL (normal range, 0.0000-0.5000 ng/mL) and D-dimer 15.88 $\mu g/mL$ (normal range, 0.00-1.00 $\mu g/mL$). Hematocrit, platelet count, and kidney and liver function tests were normal. Prothrombin time was 13.6 s (normal range, 9.4-12.5 s), activated partial thromboplastin time (aPTT) was 30.2 s (normal range, 25.4-32.4 s) and international normalized ratio (INR) was 1.16 (normal range, 0.80-1.20). Arterial blood gas analysis showed the following: pH 7.40, partial pressure of oxygen 89 mmHg, partial pressure of carbon dioxide 35 mmHg, bicarbonate concentration 23.1 mmol/L, and lactate concentration 1.1 mg/dL. Prothrombotic testing included protein S, 67% (normal range 55-145%), protein C, 81% (normal range 60-140%), antithrombin-III, 90% (normal range 75-125%), in addition, anticardiolipin antibody IgG, 7.5 RU/mL (normal range 0-12 RU/mL), anti- $\beta 2$ -glycoprotein I antibodies, 14 RU/mL (normal range 0-20 RU/mL) and lupus anticoagulant ratio, 1.0 (normal range 0.8 - 1.2). None of the following were detected by PCR assay: factor V Leiden mutation, prothrombin G20210A mutation, and JAK2V617F mutation. These results were obtained 10 days after the specimens were sent to the laboratory.

...

Question 3: It is unusual to have normal lactate level in this patient with acute mesenteric ischemia.

Answer: Thank you very much for your question. We were also somewhat skeptical when we received blood lactate result from arterial blood gas analysis. On the 2nd day of admission, arterial blood gas analysis were performed again, and blood lactic acid level was still within the normal range. We thought it might have something to do with her treatment at a local hospital.

Question 4: Treatment is not clear - What is Cefminox and which LMWH was used (should have mentioned the dose in Units/Kg also).

Answer: Thank you very much for your question. Cefminox is a derivative of cephamycin and its antibacterial spectrum is similar to that of the third generation cephalosporin, and it is a wide-spectrum antibiotics. In this study, LMWH sodium was used.

We have revised our manuscript according to your suggestions as following:

TREATMENT

.... intravenous antibiotic cefminox 1.0 g, twice daily; and anticoagulation with low molecular weight heparin (LMWH) sodium 5000 U (100 U/kg), subcutaneous injection twice daily, which was commenced as the initial conventional therapy.

...

Question 5: Discussion: - Why there is discrepancy between the reported prevalence of MVT in the introduction and discussion with same reference cited?!

Answer: Thank you very much for your question. We have revised our manuscript according to your suggestions as follows:

INTRODUCTION

... The etiology of MVT in 75% of patients can be identified, with MVT induced by oral contraceptives accounting for 4%–5% of all MVTs and for 9%–18% in young women^[7].

...