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PEER-REVIEW REPORT

Name of journal: *World Journal of Hepatology*

Manuscript NO: 87734

Title: Acute Liver Failure: A Rare But Reversible Complication of Pylephlebitis

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 00051081
Position: Peer Reviewer
Academic degree: MD
Professional title: Associate Professor
Reviewer's Country/Territory: Turkey
Author's Country/Territory: United States

Manuscript submission date: 2023-08-25

Reviewer chosen by: AI Technique

Reviewer accepted review: 2023-09-01 06:10

Reviewer performed review: 2023-09-02 15:46

Review time: 1 Day and 9 Hours

Scientific quality	[Y] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[Y] Grade A: Excellent [ ] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[Y] Grade A: Excellent [ ] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

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Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

1- The authors can revise the reference style to make it more consistent and professional-looking according to WJH criteria. 2- The abstract and discussion sections should be revised to acknowledge that this is not the first case of hepatic failure secondary to amebic abscesses. The authors should also include the other reports, like Saltzman et al. (1978), as references. a. Saltzman DA, Smithline N, Davis JR. Fulminant hepatic failure secondary to amebic abscesses. Am J Dig Dis 1978; 23:561 – 7. b. https://www.researchgate.net/publication/368663272_Acute_Liver_Failure_An_Unusual_and_Reversible_Complication_of_Pylephlebitis 3- The authors should discuss the possibility of hepatic arterial vascular abnormalities in the case presentation and discussion sections. 4- The discussion should also include Lemièrre's syndrome, which is caused by Fusobacterium necrophorum and can lead to thrombosis of the jugular vein after an opportunistic head and neck infection. Because the infections distal to the head due to fusobacterium spp. are mostly related to malignancy elsewhere (like strep bovis and colorectal carcinoma relation).

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Reviewer's code: 05814543
Position: Peer Reviewer
Academic degree: MD
Professional title: Doctor
Reviewer's Country/Territory: Germany
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Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

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Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This is a case report of an otherwise healthy patient presenting wiht acute abdominal pain who received a diagnosis of pylephlebitis (with complete thrombosis of main and left portal veins) and acute liver failure, which was reversed. The article is well-written in clear English. The case presentation includes all relevant medical information. The Authors highlight clearly the teaching points of this case and its clinical interest already in the Abstract. Their argument is valid: indeed, on the one hand this case is a good example of a rare etiology that should be considered in the differential diagnosis of acute abdominal pain; on the other hand, the report is also potentially useful for the research line on septic thrombophlebitis, because it shows a potentially very important clinical association (with acute liver failure) as well as a pointer for future research that may accelerate diagnosis (risk factors for hypercoagulation). An additional point of value is the successful report of the use of anticoagulation, which fits perfectly the ongoing debate on the inthe indication of anticoagulation in septic thrombophlebitis. While, of course, no firm conclusions can be drawn from a single case report, observational research (including case reports) should keep the attention high on the topic until

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higher-quality evidence is available. Their discussion of what is known on the pathogenesis of pylephlebitis and what can be theorized on the pathogenesis of acute liver failure seen in their case is to-the-point and well substantiated. I do have a number of questions and suggestions for mostly minor amendments. MAJOR COMMENTS 1. Throughout the article. Gram-negative bacteria are known to be more strongly associated with septic thrombophlebitis than gram-positive bacteria. The Authors write „polymicrobial bacteria“, but it is striking, informative and probably not due to chance that both bacteria found in blood cultures are Gram-negative anaerobes that have already been reported to be associated with septic thrombophlebitis. Therefore, it would be more informative to write throughout the article „Polymicrobial Gram-negative anaerobic bacteremia“ than just „polymicrobial bacteremia“. It is not just any microbes that were found – it is microbes with quite specific features known to or at least theorized to cause this rare condition. In addition, there is quite a strong debate on whether infections likely to be due to Fusobacterium should be treated with aminopenicillins + beta-lactamase inhibitors or directly with anti-anaerobic antibiotics, with each physician's opinion mainly based on how likely Fusobacterium is likely to be resistant to aminopenicillins. This case reports of a Fusobacterium and Bacteroides both resistant to aminopenicillin + beta-lactamase inhibitor, thus supporting (so much as a single case report can be used as a source of evidence) the case of those in favour of using broader-spectrum antibiotics. 2. Case presentation: While „high intensity heparin drip“ should in any case be spelled „high-intensity heparin drip“ (because „high intensity“ is a qualifier of „drip“ here, thus used as an adjective) this is still not medically correct. There is no specific definition of „low-intensity“ or „high-intensity“ heparin drip. What instead has a formal, standardized definition and would be informative and valuable is to known whether the heparin dosis was prophylactic or therapeutic (for non-standard dosages that are in-between, the term „sub-therapeutic“ or

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„intermediate-dose“ could be accepted). This would be very useful for the current debate and research line in the use of anticoagulation in septic thrombophlebitis and may even facilitate retrieval of this case report and inclusion in future systematic reviews or meta-analyses. Therefore, please replace „high-intensity“ with „therapeutic“, „prophylactic“ or „sub-therapeutic“ or even with the exact dose (but the patient's weight should then also be specified if the dosage was weight-adjusted). 3. Please add the duration of hospitalization (how many days from presentation to discharge?). 4. Was it checked whether the portal vein thrombus displayed partial or total resolution? If yes, what was seen? 5. Discussion: The Authors write „Thrombophlebitis is characterized as an inflammatory disorder of veins due to the presence of a venous thrombosis [Liebermann 1961]“. This definition is not entirely correct, because the term „thrombophlebitis“ is used by clinical practitioners in thrombosis and hemostasis to refer to any association of venous wall inflammation with a thrombus, with no statement on the causal direction (whether the thrombus caused the inflammation or, conversely, the inflammation caused the thrombus), as both are possible. The National Library of Medicine's „thombophlebitis“ entry is defined as „inflammation of a vein associated with a blood clot“, which does not firmly entail the causality clot > inflammation (in fact, „Lemierre syndrome“ is a sub-entry of thrombohplebitis, but in that condition the clot is known to follow the inflammation!). The opposite interpretation as the one stated by the Authors (that the inflammation causes the thrombus) is also commonly found: for instance, the current definition of „Thrombophlebitis“ in the Merriam-Webster medical dictionary is „inflammation of a vein with formation of a thrombus“, and the Mayo clinic's website also defines thrombophlebitis as „an inflammatory process that causes a blood clot to form and block one or more veins, usually in the legs“ (https://www.mayoclinic.org/diseases-conditions/thrombophlebitis/symptoms-causes/syc-20354607). Based on these considerations, it would be more appropriate and

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cautious to re-write this sentence into „Thrombophlebitis is characterized by a venous inflammation accompanied by venous thrombosis“. In addition, the old reference by Liebermann et al. 1961 is not entirely suitable to support the reader who needs more information, because it focused on any venous thrombosis and quite specifically on the relation of venous thrombosis with cancer. The term „thrombophlebitis“, back then, was used loosely to refer to any vein thrombosis, not necessarily in association with inflammation. 6. Discussion: In the sentence „Pylephlebitis typically occurs in response to an abdominal inflammatory process that results in uncontrolled infection in the regions adjacent or draining into the portal venous system“, The review on septic thrombophlebitis by Chirinos and al. (reference 13) is now relatively outdated. In addition, while the Discussion is quite comprehensive, no mention is made of the important point (as it guides treatment!) of the bacteria associated with pylephlebitis in this case and other studies. Therefore, the sentence should be extended as follows: „Pylephlebitis typically occurs in response to an abdominal inflammatory process that results in uncontrolled infection in the regions adjacent or draining into the portal venous system, most often caused by Gram-negative anaerobic bacteria“, and the reference by Chirinos et al. should be replaced by a more recent comprehensive review on the topic such as PMID: 32726825 (DOI: 10.1055/a-1177-5127), which also includes more updated information on the bacterial etiology and antibiotic use in pylephlebitis and other forms of septic thrombophlebitis. . 7. Discussion. The Authors speculate that „this thromboembolic event may rapidly occur in the same manner as pulmonary embolism, preventing adequate hemodynamic compensatory responses“. However, there is a key difference in the pathogenesis of these two conditions. Pulmonary embolism is an embolization of a fragment of a deep vein thrombus to lower-caliber veins, while the mechanism the Authors postulate is embolization from several small thrombi into the "larger portal veins“; that is, the emboli are supposed to stop in vessels

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of higher caliber. Please comment on this problem and consideror mention the possibility that liver failure may originate from the alternative mechanism of diffuse microemboli in the smaller hepatic vessels. 8. Discussion. After the sentence „The role of anticoagulation is a is an area of current controversy“, it would be appropriate to cite, in addition to reference 29 (1996 article by Baril et al.), the above-mentioned, more recent review PMID: 32726825 (DOI: 10.1055/a-1177-5127), which points the reader to the broader problem of anticoagulation in all forms of septic thrombophlebitis. 9. Discussion. The acronym „PVT“ is not defined anywhere. If the Authors mean „portal vein thrombosis“, simply write it out („(…significantly improved the rate of resolution of the portal vein thrombosis“). MINOR COMMENTS a) Throughout the article: Please write the names of common active ingredients in lower case instead of capitalizing them („acetaminophen“ instead of „Acetaminophen“, „heparin“ rather than „Heparin“, „ampicillin/sulbactam“instead of „Ampicillin/Sulbactam“, „rivaroxaban“ instead of "Rivaroxaban“, „metronidazole“ instead of „Metronidazole“). This is the normal scientific writing convention for active ingredients / generic drug names that are not proprietary names. b) Abstract: „labs“ is common in daily medical jargon, but it is unsuitable in formal academic medical English. I suggest replacing it with „laboratory investigations“ or „laboratory tests“. In the Abstract: „(…) and laboratory investigations demonstrating new-onset acute livere failure“. Please search and amend throughout the article. c) Abstract: In „new onset acute liver failure“, „new onset“ should have a hyphen, because it is used as a qualifier: please correct into „new-onset acute liver failure“. d) Introducton: I suggest amending into „ALF typically manifest within a few days of an acute insult“ or „ALF typically manifest within a few days of a triggering insult“ because it is the first time in the paragrah that the necessity of an insult for ALF is mentioned. e) Case presentation: Please report the body temperature also in Celsius grades, as the World Journal of Hepatology has an

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international readership. f) Case presentation. Instead of „Additional infectious workup“ I suggest that the Authors use the more clear and formal „Additional investigations for a source of infection“. g) Case presentation: In „failed to reveal an infectious source“, while „infectious“ is commonly used and accepted, the word „infective“ would be slightly more correct. „infectious“ is more often used to mean „contagious“, whereas „infective“ means „caused by a microbiological organism“ (Merriam-Webster's medical dictionary: „infectious disease = a disease caused by the entrance into the body of organisms which grow and multiply there"; "infective" = producing or capable of producing infection."). This is why the technical name of endocarditis is "infective endocarditis" and not "infectious endocarditis". I therefore suggest to use "infective source" or "source" (if you already use "infective source" at the beginning of the sentence as suggested above) or "infection focus" or "focus of infection". h) Case presentation: I suggest that the Authors write, rather than „hypercoagulable risk factors“, „risk factors for hypercoagulability“ (because it is not the risk factors themselves that are „hypercoagulable“; it is the patient's blood).