

May 26th, 2020

## Response to reviewer

We would like to appreciate the reviewers for careful and thorough reading of this manuscript and for the thoughtful comments and constructive suggestions, which help to improve the quality of this manuscript. We reflected most of the suggestions made by the reviewers. Our response follows (the reviewer's comments are in italics).

*1. How robust was their literature sure? Was it a systematic literature review? If so, what was the methodology?*

Thanks for the good point. We judged that there was a correlation between influenza infection and superior mesenteric venous (SMV) thrombosis because the patient had symptoms of high fever, myalgia, and abdominal pain at the same time. It is unlikely that influenza will cause SMV thrombosis. We investigated other causes of SMV thrombosis (abdominal mass, acquired thrombophilia, inherited thrombophilia, personal history of other thromboembolism, etc.) in patients, but there were no specificities other than influenza infection. Therefore, though not having a high incidence, we concluded that Influenza infection caused SMV thrombosis.

This manuscript is a case report; the cause of SMV thrombosis could be the influenza infection. Previously, there was a retrospective cohort study<sup>[1]</sup> that influenza infection promoted coagulation and blockage of several blood vessels. However, there were only two case report of SMV thrombosis. We hope that many people will perceive that influenza infection can provoke SMV thrombosis through this report.

[1] Bunce PE, High SM, Nadjafi M, Stanley K, Liles WC, Christian MD. Pandemic H1N1 influenza infection and vascular thrombosis. *Clin Infect Dis* 2011; **52**: e14-17 [PMID: 21288835 DOI: 10.1093/cid/ciq125]

*2. The angle is clearly the rare cause - viral in origin as the provoking cause of this thrombotic phenomenon, could the author's provide more information of other viral causes, or microbiological causes as a review as well.*

As suggested by the reviewer, we looked for studies that showed other viral and bacterial infections can cause thrombosis. We inserted that into the manuscript **(sixth sentence on page ten)**.

**"Also, thrombosis is observed in 6.4 % of patients with acute cytomegalovirus (CMV) infection [2] and 2.6/10000 patient-years with chronic human immunodeficiency virus (HIV) infection [3]. Deep vein thrombosis is highly occurred after community-acquired upper respiratory infection and urinary tract infection [4], and hypercoagulation and disseminated intravascular coagulation (DIC) are caused by several bacterial infections like sepsis [5]."**

- 2 Justo D, Finn T, Atzmony L, Guy N, Steinvil A. Thrombosis associated with acute cytomegalovirus infection: a meta-analysis. *Eur J Intern Med* 2011; **22**: 195-199 [PMID: 21402253 DOI: 10.1016/j.ejim.2010.11.006]
- 3 Sullivan PS, Dworkin MS, Jones JL, Hooper WC. Epidemiology of thrombosis in HIV-infected individuals. The Adult/Adolescent Spectrum of HIV Disease Project. *AIDS* 2000; **14**: 321-324 [PMID: 10716509 DOI: 10.1097/00002030-200002180-00015]
- 4 Smeeth L, Cook C, Thomas S, Hall AJ, Hubbard R, Vallance P. Risk of deep vein thrombosis and pulmonary embolism after acute infection in a community setting. *Lancet* 2006; **367**: 1075-1079 [PMID: 16581406 DOI: 10.1016/S0140-6736(06)68474-2]
- 5 Davis RP, Miller-Dorey S, Jenne CN. Platelets and coagulation in infection. *Clin Transl Immunology* 2016; **5**: e89 [PMID: 27525062 DOI: 10.1038/cti.2016.39]

*3. Finally and most importantly in the current climate? Did they make an attempt to rule out COVID-19 in this patient or not?*

We performed the COVID-19 test at the time of influenza test together and the result was negative. As suggested by the reviewer, we added the text **(fourth sentence on page eight)**.

**"Since the patient's symptoms were considered atypical for SMV thrombosis, a nasopharyngeal swab for a seasonal influenza test was performed. In addition, nasopharyngeal swab for COVID-19 was performed by taking account of recent pandemic situation.**

**The test showed a positive result for influenza B. The test for COVID-19 was negative."**

Again, Thank you for your thoughtful review. Our manuscript is developing further with your help.

July 29th, 2020

Response to reviewer

We would like to appreciate you for careful and thorough reading of this manuscript and for the thoughtful comments and constructive suggestions, which help to improve the quality of this manuscript. We reflected most of the suggestions made by the reviewers. Our response follows (the reviewer's comments are in italics).

*1. I didn't understand from your manuscript how you diagnosed "Influenza Virus Infection"? What diagnostic test did you use: "RT-PCR", "ELISA", "Influenza A/B Antigen Test, Flocked swabs" or other?*

Thanks for the good point. We collected samples through nasopharyngeal swab and diagnosed by Influenza A/B rapid antigen test. Following reviewer's clear point, we modified the manuscript as follows (**second sentence on page eight**):

**"Since the patient's symptoms were considered atypical for SMV thrombosis, a sample was collected through a nasopharyngeal swab and an Influenza A/B rapid antigen test was performed."**

*2. Please indicate the "Sensitivity and Specificity" of the Influenza diagnostic test.*

*3. Please write the brand and manufacturer of the Influenza diagnostic test.*

When conducting diagnostic tests, it is very important to know the sensitivity and specificity. We tested using the "The BD Veritor™ Plus System for Rapid Detection of Flu A+B" kit, sensitivity 81.3% (71.1%, 88.5%, 95% confidence interval), specificity 98.2% (95.7%, 99.3%, 95% confidence interval). As suggested by the reviewer, we inserted the sentences below into the manuscript (**fourth sentence on page eight**).

**"The influenza test was performed using "The BD Veritor™ Plus System for Rapid Detection of Flu A+B" kit, sensitivity 81.3% (71.1%, 88.5%, 95% confidence interval),**

specificity 98.2% (95.7%, 99.3%, 95% confidence interval). In addition, after collecting samples through nasopharyngeal swab, COVID-19 test by RT-PCR was performed by taking account of recent pandemic situation."

**4. Which influenza subtype did you find: Influenza B Virus (Yamagata), Influenza B Virus (Victoria) or other?**

Unfortunately, after the rapid antigen test, we did not perform virus culture tests to distinguish subtypes. If we had figured out which subtype caused thrombosis, this manuscript would have had more scientific significance. Thanks for the keen pointing out for reporting the lack of this study.

**5. Please add the following scientific publications to the section "Introduction" (and to the section "References")**

We reviewed the papers recommended by the reviewer and judged it to reinforce the points of this manuscript. Thank you for recommending good literature. We decided to add this to the introduction and references of manuscript (15th sentence on page six).

**"However, in rare cases, SMV thrombosis may occur due to viral infection such as influenza. It is worth noting influenza's extraordinary complications, since influenza A and B infections is occurring in large quantities worldwide regardless of age <sup>[1-3]</sup>."**

- 1 Korsun N, Angelova S, Trifonova I, Georgieva I, Voleva S, Tzotcheva I, Mileva S, Ivanov I, Tcherveniakova T, Perenovska P. Viral pathogens associated with acute lower respiratory tract infections in children younger than 5 years of age in Bulgaria. *Braz J Microbiol* 2019; **50**: 117-125 [PMID: 30637646 DOI: 10.1007/s42770-018-0033-2]
- 2 Korsun NS, Angelova SG, Trifonova IT, Georgieva IL, Tzotcheva IS, Mileva SD, Voleva SE, Kurchatova AM, Perenovska PI. Predominance of influenza B/Yamagata lineage viruses in Bulgaria during the 2017/2018 season. *Epidemiol Infect* 2019; **147**: e76 [PMID: 30869003 DOI: 10.1017/S0950268818003588]
- 3 Popov G, Baymakova M, Andonova R. Clinical and epidemiological characteristics of hospitalized patients with Influenza type B in the 2017-2018 season. *General Medicine* 2018; 20(4): 3-8.

Again, Thank you for your thoughtful review. Our manuscript is developing further with your help.