Peer review

1.In the three sentences: “This underscores the importance of broad differential diagnosis in endemic areas”, “This case emphasizes the necessity for rapid diagnostic tools and timely clinical suspicion in endemic regions to prevent complications”, “There must be a critical need for healthcare providers to maintain a high index of suspicion for malaria in patients presenting with fever in endemic areas, ensuring timely and accurate diagnosis, supported by comprehensive testing and vigilant monitoring to manage and prevent complications effectively.” I think you mean “non-endemic” rather than “endemic”, hence please replace the word “endemic” with the word “non endemic”.

2.On what basis was dengue initially suspected? Please discuss in the manuscript what clinical signs made the physician diagnose the patient with Dengue fever.

3.What was the significance of the hypogastric pain - if any? Please discuss in the manuscript.

4.you state “….Initial home management included acetaminophen, with transient improvement, but persistent fever led to an emergency room visit and subsequent discharge.”. What were her vital signs at discharge? Was she fever free for 24 hours? If not, why was she discharged? What was the initial diagnosis? Please present in the manuscript.

5.you state “…..Her medical history includes asthma, two prior hospitalizations, no surgeries, transfusions, or medications, and a complete vaccination schedule as per her mother.” Why had the patient been hospitalized two prior times? Please discuss. Did the vaccination schedule include Thyphoid? Was that the reason why Typhoid was ruled out as a dignosis? See: https://doi.org/10.31729/jnma.7624

6.The introduction section seems irrelevant to the case study. Please remove the description of drugs/vaccines and vector control strategies to treat and control Malaria. Instead, it should describe the symptoms of malaria and dengue and how they can overlap. It should also discuss why immunoglobulin tests for dengue may not necessarily indicate a dengue infection (about 95% of Santo Domingo patients are seropositive for the dengue virus, see: https://doi.org/10.3390/v14010162, also see: https://doi.org/10.1186/s12936-016-1666-y which is similar to your case presentation. All these references should be included in the manuscript with discussion. Lastly, concurrent Malaria and Dengue infection should be discussed.

7.Had the patient taken a trip or been near the border with Haiti? Did anyone ask her that? Should she have been asked that upon admittance? Should be included in the treatment algorithm (see point 9).

8.In the discussion and conclusion section, should a recommendation be included that all patients suspected of Dengue must be started on Malaria medication immediately prior to testing for Malaria? Would this be a reasonable suggestion from the viewpoint of a treatment algorithm (see point 9)? Please discuss in the manuscript.

9.Please make an attempt to construct a dengue and malaria treatment algorithm along the lines of this paper: https://jhss.scholasticahq.com/article/123179-investigating-treatment-approaches-for-immunothrombosis-through-an-examination-of-its-intricate-mechanisms, please present and discuss in the manuscript.

10.1. In the three sentences: “This underscores the importance of broad differential diagnosis in endemic areas”, “This case emphasizes the necessity for rapid diagnostic tools and timely clinical suspicion in endemic regions to prevent complications”, “There must be a critical need for healthcare providers to maintain a high index of suspicion for malaria in patients presenting with fever in endemic areas, ensuring timely and accurate diagnosis, supported by comprehensive testing and vigilant monitoring to manage and prevent complications effectively.” We changed the words endemic to non-endemic

11.2. We added the following paragraph in the clinical findings section in response to the diagnosis of dengue: In this case, dengue fever was initially suspected due to the patient’s clinical presentation and the regional prevalence of dengue in Santo Domingo. She had a high fever (39-39.5°C), which is a sign of dengue, persisting for five days despite home management with acetaminophen. Her pain localized to the hypogastric region, a symptom that can occur in dengue, particularly in cases involving complications of dengue with alarm signs. Lastly, despite her history of asthma, her respiratory rate was normal, and she was eupneic, ruling out any immediate respiratory involvement and strengthening suspicion of a febrile illness like dengue.

12.3. We added in the following paragraph in the patient information section to highlight the significance of the hypogastric pain: “The patient’s hypogastric pain was a key factor in the initial diagnosis of dengue, as abdominal pain is a common warning sign of severe dengue, often related to liver or gastrointestinal involvement. However, hypogastric pain can also occur in malaria due to splenic or liver enlargement. This overlap in symptoms contributed to the diagnostic challenge, as both dengue and malaria can present with similar abdominal discomfort. Ultimately, the pain added to the complexity of distinguishing between the two diseases in this case”. Furthermore, we added a source siting where the information of splenic or liver enlargement came from

13.4. We added “The patient was not fever-free, since her vital signs included a temperature of 38°C, a heart rate of 102 l/m, a respiratory rate of 24 r/m, and a blood pressure of 100/60 mmHg” after the sentence “….Initial home management included acetaminophen, with transient improvement, but persistent fever led to an emergency room visit and subsequent discharge.” The discharge was from the clinic to the emergency room, which is what the vital signs show.

14.5. We added the following sentences in the patient information section: “The patient was hospitalized two prior times due to episodes of stomach pain and consistent fever. The patient was worried that the symptoms indicated recurring or unresolved underlying conditions, possibly linked to infections or inflammatory processes, that warranted medical intervention. In both instances, the recurrent fever and abdominal pain raised concerns about the potential for serious conditions such as viral or bacterial infections, gastrointestinal issues, or other systemic inflammatory responses, necessitating hospitalization for closer monitoring and treatment. Typhoid fever was ruled out in this case based on the patient’s clinical presentation and laboratory findings. While typhoid shares some overlapping symptoms with conditions like malaria and dengue—such as fever and abdominal pain—the patient did not exhibit signs of typhoid, such as a step-wise fever pattern, rose-spot rash, or significant gastrointestinal symptoms like diarrhea or constipation. Laboratory testing, particularly blood cultures, further supported the exclusion of typhoid. The blood culture was negative after 48 hours, and the thick blood smear confirmed the presence of hematozoa, leading to a diagnosis of malaria.”

15.6. The deleted parts of the introduction were about vectors and treatments and we added the following where we talk about malaria and dengue symptoms and its overlap: Malaria and dengue are

two common illnesses in tropical and subtropical regions that often present with overlapping symptoms, complicating diagnosis. Both diseases share symptoms such as fever, chills, headache, and muscle pain, making it easy to misdiagnose one for the other, especially in regions where both are non-endemic. Malaria, caused by Plasmodium species, may present with additional symptoms like anemia, jaundice, and cerebral malaria in severe cases. Dengue, a viral infection transmitted by Aedes mosquitoes, can be accompanied by retro-orbital pain, rash, and joint pain, sometimes progressing to severe forms like dengue hemorrhagic fever or shock syndrome. The host immune response plays a crucial role in combating Malaria, with immunoglobulins (Ig) being key players in the body's defense. Various types of immunoglobulins, including IgG, IgM, and IgA, contribute to this response, each with unique functions. IgG antibodies are essential for neutralizing parasites, providing long-lasting immunity. On the contrary, IgM antibodies typically indicate recent infections and can enhance inflammation, potentially leading to severe disease manifestations. Diagnosing malaria becomes further complicated by other mosquito-borne diseases, such as dengue. Serological tests for dengue rely on detecting specific immunoglobulins, particularly IgM and IgG, to determine the presence of an infection. However, these tests may not necessarily indicate a current dengue infection due to the potential for cross-reactivity with other flaviviruses, leading to false-positive results. This overlap can create diagnostic confusion, especially in regions where malaria and dengue co-circulate. Concurrent infections of dengue and malaria, while rare due to the different habitats of their vectors and the activities of different carrier mosquitoes, have been documented a lot in African countries. Numerous instances of concurrent infections between the dengue virus (DENV) and the malaria protozoans Plasmodium falciparum and Plasmodium vivax have since been reported. The symptoms of each infection may mask those of a simultaneous second infection, resulting in delays in treatment and severe complications. Notably, Plasmodium knowlesi has emerged as a common cause of malaria in Malaysia, associated with one of the highest rates of mortality. Some areas with high rates of both malaria and dengue are those in Southeast Asia. The rate of infection for febrile patients is about 0.99%. The manifestations of concurrent malaria and dengue are high fever and myalgia. Overall, concurrent malaria and dengue infection isn't common. The malaria mosquito vector mainly lies in the forest while the dengue mosquito vector mainly lies in the city. Thus, it's hard for both to overlap. Additionally, the concurrent infection can be forgotten as it's easy for one diagnosis to be made without taking into account of possible second diagnoses.

16.7. We added the following few sentences to patient information: "There was no indication that the patient had traveled near the border with Haiti, and no one specifically asked about recent travel history at the time of admittance. This is an important point, as recent travel to areas where malaria is more prevalent could have influenced the diagnostic process and treatment decisions. The patient's history did not suggest recent exposure to high-risk malaria zones, which delayed the consideration of malaria in the differential diagnosis." https://wwwnc.cdc.gov/travel/yellowbook/2024/itineraries/haiti

17.8. We said no to the suggestion of starting all patients suspected of Dengue on malaria medication. We wrote "While the diagnostic workup was thorough, empiric treatment with antimalarial medication prior to confirmation could have led to unnecessary side effects, such as nausea, dizziness, or even more severe reactions associated with medications like Chloroquine and Primaquine. Such side effects, especially in pediatric patients, highlight the need for judicious use of antimalarial drugs and emphasize the importance of confirming the diagnosis before initiating treatment. Additionally, an algorithmic approach recommending simultaneous testing for both dengue and malaria in endemic or non-endemic areas where both diseases are plausible would be more appropriate. It avoids unnecessary medication while ensuring that prompt treatment is available once the diagnosis is confirmed." for the Discussion and "...it is equally important to avoid initiating antimalarial treatment without confirmation, given the risks of side effects and contributing to drug resistance. A balanced approach involving rapid diagnostic

tools, clinical suspicion, and simultaneous testing for diseases like dengue and malaria would lead to more effective and targeted treatment strategies" for the Conclusion. Source: https://iris.who.int/bitstream/handle/10665/95116/9789241506489_eng.pdf

18.9. We added a treatment algorithm to the manuscript before our follow ups and outcomes. It addresses treatment for the patient's malaria as well as the case of dengue. [IMAGE IS ON RESEARCH PAPER] Additional Edits: - Changes to the references (added and removed) - added dengue to key words, removed sub saharan africa, added non-endemic

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Thank you for addressing my comments. Accepted.