LETTER OF EDITOR

False-Positive Dengue NS1 Antigen in Influenza and Other Febrile Illnesses

KFM AYAZ[a], MIZANUR RAHMAN[b], RUMMANA RAHIM[c], ABU HASAN[d]

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Dear Editor,

Dengue virus (DENV) infections have unpredictable clinical outcomes, ranging from asymptomatic or minor febrile illness to severe and fatal disease[1]. May to September is the typical dengue season in Bangladesh and this year (2023) dengue outbreak has taken a worrisome turn with a record number of case fatality (five times higher than last year)[2]. The mentioned time is also the spreading season of influenza virus (April to September with peak in July & August)[3]. Besides dengue, many influenza and other respiratory pathogens can cause almost similar clinical presentations -fever, bodyache, cough, cold, generalized weakness, headache, urticaria, nausea, vomiting, diarrhea etc[4]. As the focus of febrile patients shifted towards dengue in the recent outbreak, a subset of influenza and other febrile illnesses are masked by misdiagnosis.

Laboratory methods of dengue virus detection include viral antigen (NS1), antibodies (IgM & IgG) and viral nucleic acid (RT-PCR). Commercial kits for rapid detection of NS1 antigen have been developed and adopted as corroborative evidence for the early laboratory confirmation of dengue in endemic regions[5-6]. The reported sensitivity of the nonstructural protein 1 (NS1) antigen tests ranges between 48.5% and 58.6%, and the specificity ranges between 92.5% and 99.4%. The combined sensitivity of the dengue NS1 antigen and immunoglobulin M (IgM) antibody test increases to 89.9– 92.9%, with a specificity of 75.0–88.8%[7]. Sensitivity of commercially available diagnostic kit for IgM and IgG is also comparatively low. In that case the only reliable test is viral nucleic acid detection by real time PCR which is costly and accessible in limited health care facilities[8].Utilizing such tests on patients with a low pre-test probability may lead to a heightened occurrence of false-positive results, potentially causing complexities in clinical assessment and delaying the commencement of the most suitable treatment for the individual patient.

We present findings from 10 cases of NS1 antigen false positives, despite negative results in dengue RT-PCR tests. These individuals were concurrently screened for respiratory tract infections by respiratory panel PCR test (can identify 22 different pathogens). Among the 10 cases, 7 patients tested positive for Influenza A, and 1 tested positive for parainfluenza 4. Two patients were exempted from respiratory pathogen evaluation due to their mild clinical symptoms. In these patients, the platelet count is not decreased; instead, two cases exhibited thrombocytosis. Other supportive laboratory parameters including the sign of plasma leakage, elevated liver enzymes were also not found in these cases.

As of today, no documented evidence suggests cross-reactivity between the influenza and dengue NS1 antigen tests. However, a limited number of case reports have indicated potential cross-reactivity between NS1 and COVID-19 antigens[9]. Additionally, there is evidence

a. Dr. Khan Fariduddin Mohammad Ayaz, Department of Internal Medicine, Evercare Hospital Dhaka, Bangladesh
b. Mizanur Rahman, Molecular Diagnostics lab, Department of Laboratory Medicine, Evercare Hospital Dhaka, Bangladesh.
c. Rummana Rahim, Molecular Diagnostics lab, Department of Laboratory Medicine, Evercare Hospital Dhaka, Bangladesh.
d. Abu Hasan, Molecular Diagnostics lab, Department of Laboratory Medicine, Evercare Hospital Dhaka, Bangladesh.

Address of Correspondence: Dr. Khan Fariduddin Mohammad Ayaz, Department of Internal Medicine, Evercare Hospital Dhaka, Bangladesh.

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to suggest that patients with hematological malignancies may exhibit false-positive results for dengue NS1[10]. Furthermore, it is worth noting that the NS1 antigen titers in the false-positive cases were lower compared to typical NS1-positive cases. Therefore, when faced with cases showing a borderline positive NS1 result but a negative dengue PCR, caution should be exercised before initiating dengue-specific treatment, as it's essential to rule out other potential respiratory pathogens. Concurrently conducting influenza testing alongside dengue NS1 testing and promptly administering specific influenza treatment can reduce the mortality rate among patients with febrile illnesses.

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