

中文題目：巨細胞感染性單核球增多症病人出現登革熱 NS1 抗原偽陽性

英文題目：False-positive Dengue NS1 antigen test in a patient with cytomegalovirus-related infectious mononucleosis: a case report.

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## Introduction

Dengue fever, a mosquito-borne disease caused by Dengue virus had several outbreaks in Taiwan, especially in southern Taiwan. The nonstructural protein 1 (NS1) antigen test is a useful tool with high sensitivity and specificity for early detection and diagnosis of dengue virus infections. However, like many rapid tests, NS1 antigen test can have false positive results. Here, we present a case of cytomegalovirus-related infectious mononucleosis with a false-positive NS1 antigen test.

## Case presentation

A 22-year-old female, with underlying history of hepatitis B virus carrier under tenofovir treatment, presented to our emergency department with high fever up to 40 degrees Celsius for one day. She also suffered from chest tightness, chest pain, general myalgia, abdominal pain, nausea, vomiting, and watery diarrhea for one day. Gum bleeding while brushing teeth was also noticed. The history of travel, occupation, contact, and cluster were unremarkable.

The laboratory data showed white blood cell 7300 / $\mu$ L (neutrophil 51%, lymphocyte 38%, and atypical lymphocyte 7%), platelet 123,000/ $\mu$ L, and alanine aminotransferase 38 U/L. The urinalysis revealed no pyuria. The chest X ray showed no patchy infiltration. Due to thrombocytopenia and elevated liver enzymes, the dengue NS1 antigen test was performed, which yielded positive result. The dengue IgM, IgG and dengue virus Polymerase Chain Reaction (PCR) were all negative. Under the impression of Dengue fever, she was admitted.

After admission, supportive care with intravenous fluid and symptoms-relieving medication were given. Fever subsided after one day and symptoms was also improving. However, the follow-up hemogram showed further elevation of atypical lymphocytes count to 13%. For the presence of atypical lymphocyte combined with hepatitis, , infectious mononucleosis was suspected, so antibodies of Epstein-Barr virus (EBV) and cytomegalovirus (CMV) were checked.

She was discharged after 6 days after symptoms improved. The follow-up data for dengue fever a week later showed negative for dengue virus NS1 antigen, dengue IgG, IgM, and dengue virus PCR. On the other hand, the CMV IgM and CMV IgG during admission showed positive, and the EBV IgM was negative with positive EBV IgG.

In summary, the patient was diagnosed with acute CMV-related infectious mononucleosis with false positive NS1 antigen test.

## **Discussion**

The diagnosis of dengue fever is based on the detection of dengue virus PCR, NS1 antigen, dengue IgM and dengue IgG. Among these diagnostic tools, the PCR is expensive and not always available, and the serology test can only detect antibodies after several days of infection. NS1 antigen, a highly conserved glycoprotein, can be detected after the onset of symptoms and will be undetectable after 7 days. The value and the role of NS1 antigen test is to detect and diagnose early Dengue infection rapidly. During the epidemic period, the sensitivity of the test is 89.7%, the specificity being 91.9%, according to a study in Taiwan.

Like other rapid antigen tests, the NS1 rapid antigen test may also yield false positive results. False-positive NS1 antigen results may occur in individuals with active infection due to other flaviviruses, including West Nile virus and yellow fever virus, which was reported in previous studies. False-positive NS1 antigen test was also found in a patient with cytomegalovirus infection in one study, and in a patient with COVID-19 infection in the other. As for the mechanism leading to false positive results, the Flaviviridae family shared similar NS1 antigen. However, there has been no clear mechanism so far to explain why cytomegalovirus or SARS-CoV-2 can yield false positive results. Besides, false positive NS1 antigen results were also detected in patients with hematological malignancies. Two case reports in 2015 and 2021 stated that NS1 antigen was detected in patients diagnosed with acute myeloid leukemia (AML), Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (ALL) and aggressive natural killer (NK) cell lymphoma.

The positive and negative predictive value of rapid antigen tests may vary with the prevalence of the disease. Take the influenza rapid antigen test for example. False-positive results are more likely to occur when the prevalence of influenza is low. The NS1 rapid antigen test may also share similar phenomena. Therefore, the NS1 rapid antigen test will be more reliable during the outbreak of Dengue virus.

The patient was admitted in May, 2021, which wasn't in the epidemic period of Dengue fever in Taiwan. Blood samples were taken for NS1 antigen, Dengue virus IgM, IgG, and Dengue PCR on day 2 and day 9 after the onset of symptoms. If our patient had Dengue virus infection, the result of Dengue PCR should be positive on day 2, and the Dengue IgM and IgG antibodies should be positive on day 9. Therefore, the Dengue fever was excluded, and the result of NS1 antigen test should be considered false-positive.

**Conclusion**

During the non-epidemic period of Dengue fever, if a patient is tested positive for NS1 antigen test, other pathogens or etiologies that can lead to false-positive results, such as cytomegalovirus, should also be taken into consideration.