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Case Report

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A rare case: Rubella reinfection during pregnancy with persistent rubella IgM after abortion

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Abstract

A pregnant woman was diagnosed with Rubella re-infection in Northern Cyprus. The patient was unaware of her pregnancy when she sought medical attention for the pain, stiffness, and numbness in the fingers and hand joints without the presence of a rash. Following the confirmation of pregnancy as part of a routine check, Rubella IgM and Rubella IgG antibodies were assessed. Her Rubella IgM was in the grey zone reference units of the tests performed with the presence of Rubella IgG supporting and reinfection. Thus, further Rubella IgG avidity and Western blot were performed. Rubella IgG avidity was borderline. Hence, abortion was advised following the test results. Post-abortion, the Rubella IgM antibodies remained persistent for over 12 months.

Keywords: Rubella, re-infection, pregnancy, persistent Rubella IgM, Rubella IgG avidity

1. Introduction

Rubella is a mild childhood disease that presents a fever followed by a characteristic rash caused by the Rubella virus - also known as 3-day measles or German Measles. Humans are the only reservoir for this virus. It is a vaccine-preventable disease since the combined measles, mumps, and rubella (MMR) vaccine is available and is usually administered to children at the age of one. The route of transmission is airborne in postnatal cases and transplacental during pregnancy. It replicates in the nasopharynx and regional lymph nodes within the incubation period of 14 days. The first symptom for children is generally the rash, which initially starts on the face and then progresses to the rest of the body. On the other hand, for adults, arthralgia (joint pain) and arthritis may occur, especially in women. A rash may appear following joint pains frequently affecting the knees, fingers, and wrists. Manifestations of the disease are more severe if rubella is encountered during pregnancy (1,2). When a Rubella infection occurs during the first trimester of pregnancy, there is a high risk of stillbirth, and serious congenital malformations are possible. If the infection is contracted during the first 12 weeks of pregnancy, approximately 90% of pregnant women who develop rubella infection and rashes will have a fetus with congenital infection (3,4). Congenital rubella syndrome (CRS) has been associated with serious long-term sequelae, including microphthalmia, chorioretinitis, deafness, limb aplasia, and cognitive impairments such as microcephaly (5). More than 100.000 children with CRS are born in developing countries each year (6). Given the high probability of anatomical and functional anomalies as a consequence of the CRS, the decision to continue or terminate the pregnancy in such a situation is vital. In order to evaluate the presence or absence of the Rubella infection serological picture of the patient should be analaysed (7).

Rubella infection is rare in countries that have the MMR vaccine in their vaccination programs. Northern Cyprus is one such place where the MMR vaccine is included in the vaccine program and is administered to children at the age of one. Despite the low prevalence of the virus on the island, in 2020, a pregnant woman was diagnosed with Rubella re-infection, leading to the termination of her pregnancy due to the risk of abnormality in the fetus. After the abortion, persistent rubella, IgM continued for more than a year.

2. Case Report

A woman, aged 29, sought medical advice on October 15th, 2020, for arthralgia, unaware of her first pregnancy. A general routine checkup on biochemistry, complete blood count (CBC), and thyroid hormones were performed, and the results were normal. On October 21st, 2020, the patient received news of her pregnancy and started her gynecologist visits soon

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thereafter. The pregnancy initially seemed in normal progression. In the second month of pregnancy, on 10th November 2020, Rubella IgM analysis showed grey-zone levels of 1.37 Index (range: 0.00-1.19), and IgM and IgG for Cytomegalovirus (CMV), *Toxoplasma gondii* were all reported to be negative. The patient's IgG was only positive for Rubella with 82.3 IU/mL (range: 0.0-4.9). Both Rubella IgG (ARCHITECT, Abbott Ireland Diagnostics, Sligo, Ireland) and IgM (ARCHITECT, Abbott Ireland Diagnostics, Sligo, Ireland) tests were performed with the ARCHITECT i1000SR (Abbott Diagnostics) device using the chemiluminescence immunoassay (CLIA) method. Rubella IgM test was repeated three times for control and yielded the same results. The patient's Rubella IgG avidity was performe; resulting in the 60% borderline threshold (ranges: below 40% for low avidity, 40%-60% for borderline, and above 60% for high avidity). Furthermore, a Western blot was performed to investigate Rubella virus glycoproteins E1 and E2. This test yielded a positive value for E1 and a borderline value for E2 (E1 band positivity appears after 4-5 days of encountering the Rubella virus, whereas the E2 protein band appears after the third month of encountering the Rubella virus), suggesting that the patient had an acute infection. Rubella IgG avidity and Western blot tests were performed at Ankara Duzen Laboratory, Turkey. Guided by these results, the patient's gynecologist and the infectious disease experts jointly suggested an abortion (performed on November 27th, 2020). In the two months following the abortion, the patient's Rubella IgM levels were routinely checked to monitor any changes. Nine months later, in August 2021, the patient's Rubella IgG test result was 84.7 IU/mL, and the Rubella IgM test result showed a change from grey zone to positive with a 2.69 Index (range: 0.00-1.19) using the same kits and device.

The Rubella IgM analysis was repeated on September 20th, 2021, with different kits and devices (Beckman Coulter Access 2), which resulted positive in 15.8 AU/mL (reference 0.0-0.8). Rubella IgG avidity tests with Western blot were both repeated on September 13th, 2021, showing an increase in Rubella IgG avidity. Similarly, E1 and E2 proteins appeared positive upon Western blot, revealing an infection in the last three months. Although the infection had cleared, the patient's Rubella IgM was persistent. In consultation with other papers in the field and available tests at the Near East University Hospital, cross-reactivity to other diseases, including syphilis, Epstein Barr virus (EBV), Rheumatoid factor (RF), and a large panel of Rheumatological diseases, were all negative.

The patient's partner's Rubella IgG and Rubella IgM levels were also analysed on 13th September and 8th November 2021 to check if any viral transmission occurred. The partner's Rubella IgG and Rubella IgM both yielded negative results, suggesting the viral transmission of Rubella most likely did not occur between the partners.

3. Discussion

This case report was prepared to draw attention to persistent rubella IgM in pregnant women. Studies have reported that rubella seroprevalence is 87% in the United States, 85.8% in Italy, and 85-96% in Turkey (8). In Northern Cyprus, this rate was reported as 90.2% (9). Rubella infection is rare in many developed countries due to the success of vaccination programs but continues to occur in areas with low vaccine uptake, such as developing countries with no vaccination programs (4,10).

Due to the CRS consequences, it is recommended that women who are planning to become pregnant should assess their immunization against Rubella. If they are not immunized, the MMR vaccine should be received, and since the MMR vaccine is an attenuated vaccine, pregnancy should be delayed for at least four weeks after its receivement (11). On the other hand, if the pregnancy was not planned, and there is a suspected Rubella infection during pregnancy, detection of Rubella IgM antibodies is recommended by WHO (World Health Organization) and the CDC (Centers for Disease Control and Prevention) as the frontline diagnostic test for surveillance and diagnosis of Rubella inection (5). Accurate diagnosis of acute primary Rubella infection in pregnancy is critical, and serological testing is required since many cases are subclinical. Currently, the ELISA method is accepted as a convenient and sensitive method for measuring rubella-specific IgG and IgM antibodies (12). Rubella IgM reaches a detectable level by the ELISA test after 4-5 days of clinical symptoms, whereas IgG appears slightly later (5-8 days after the onset of rash) and, once developed, will persist throughout life. The presence of positive Rubella IgM antibodies with low avidity IgG antibodies is indicative of primary rubella infection in the last six weeks. Whereas, positive IgM with high IgG avidity (≥%60) indicates rubella infection older than 13 weeks (3,13).

Once a pregnant woman comes into contact with a suspected case of rubella, a serum sample should be tested for Rubella IgG within 12 days to determine whether she is immunized or not. Positive detection of anti-rubella antibodies in the advancing weeks of pregnancy that were detected as negative before can evidence the presence of an acute infection. In addition, IgM antibodies can be detected in maternal circulation approximately 4-5 weeks after infection and may be associated with acute infection. In the case of positive rubella IgM, it is crucial to distinguish acute infection from recurrence. Rubella IgM can persist from one to six years after natural infection, vaccination, or asymptomatic infection. In such cases, the Rubella IgG avidity test is recommended to evaluate acute rubella infection (3,8,13).

Another possibility is the re-infection with Rubella. Such cases are defined when there is an increase in Rubella IgG antibody and IgM antibody is either not produced or found in low titres. Whereas in primary infection, a significant rise in Rubella IgG and IgM occurs. Fetal Rubella infection as a result of maternal re-infection is rare and the risk of transmitting

infection is lower when compared to a primary infection. The studies suggested that the establishment of lifelong immunity neither occurs in a primary attack nor in successful immunisation. Hence, reinfection is possible and can be confidently diagnosed from the initial sample after the contact results in a positive Rubella IgG antibody followed by a rise in the titre of initially diagnosed negative or in low-titres of IgM. In this case report, it is not sure if the samples were obtained in initial contact or taken weeks after infection. This is the limitation of this study; however, the case is very close to meeting the criteria of a re-infection, considering the patient was vaccinated to MRR at the age of one and had a record of past infection (14).

Existing literature indicates that a case of persistent Rubella IgM positivity throughout pregnancy and after abortion has not been encountered previously. Furthermore, when borderline avidity results are obtained, the acute infection should be investigated with techniques such as Western blot or real-time polymerase chain reaction (RT-PCR), and termination of the pregnancy should be once evaluating all results. Since there was no Rubella PCR test available in Northern Cyprus at the time, no tests were performed to investigate if the patient was shedding the virus when the patient was initially diagnosed with re-infection. It should also be noted that this was the patient's first pregnancy, without any history of encounters with children with the presentation of Rubella infection. This suggests that adults can carry and shed the virus without the presence of other symptoms (e.g. rash) within the population. Public awareness around asymptomatic Rubella infection should be raised to inform parent candidates and prevent such cases from happening.

Isaac et al. tested Rubella IgM by two different methods (indirect enzyme-linked immunosorbent assay [ELISA] and capture enzyme immunoassay [EIA]) and emphasized that false positive results were common in both Rubella IgM tests. The low positive predictive value (PPV) for Rubella IgM tests is not unexpected, as PPV decreases among populations with low disease prevalence. Rubella IgG avidity testing may provide additional information to help classify rubella reports in non-endemic countries where the PPV for Rubella IgM tests may be low (15). In our case, Rubella IgM results were supported by Rubella IgG avidity and Western blot methods.

In conclusion, Rubella IgM positivity may result from several other factors, including IgM persistence followed by vaccination, false positivity to other viral infections such as CMV, EBV, measles virus, and human parvovirus B19, the presence of rheumatoid factor, and through natural or re-infection (15,16). Hence, in rare cases, Rubella IgM positivity may be a true infection. The findings of this case report were to emphasise the fact that IgM positivity may not always be false positivity and could be the result of primary or re-infection. Thus, the results should be completely investigated, especially in pregnant women, to prevent the consequences of CRS (16). In this case, it was a true infection as the Western blot test was positive for specific proteins, and abortion was suggested for the possibility of CRS. The patient got pregnant approximately after a year of the abortion in December 2021, and her Rubella IgM and IgG were positive during her second pregnancy. She gave birth to a healthy baby in August 2022.

Conflict of interest

The authors declared no conflict of interest.

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Authors' contributions

Concept: N.S., E.G., Design: N.S., E.G., K.S., T.Ş., Data Collection or Processing: N.S., G.E., U.H, Analysis or Interpretation: K.S., T.Ş., E.G., U.H., Literature Search: N.S., Writing: N.S.

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