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CASE REPORT

ANA-Hep2 Positive with Anti-Rods and Rings Pattern in a Child without Hepatitis C under Treatment: Case Report

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Abstract

Background: The immunofluorescence pattern of antinuclear antibodies (ANA) called rings and rods (RR) has only recently been described. This pattern has been associated with patients with Hepatitis C at treatment. There are few studies that demonstrate their appearance in healthy individuals or with other health conditions. This study reports positivity of this autoantibody in a patient never exposed to the HCV virus, in order to understand its clinical significance.

Case summary: A 10-year-old male patient was admitted to a university hospital with suspected bronchopneumonia. A carrier of chronic lung disease, he underwent several tests including ANA, that was reagent for the nucleus (fine speckled pattern) and cytoplasm (RR pattern). The serological results for hepatitis and HIV were negative. The patient was discharged after 22 days in hospital and is being followed-up by the outpatient clinic. There was a subsequent suspicion of immunodeficiency and cystic fibrosis, but there remains no established diagnosis. The presence of the pattern without the coexistence of Hepatitis C or the use of drugs such as RBV/IFN is scarce in the literature. No correlation between the RR pattern and the patient's clinical presentation is clear, but some studies have reported the appearance of this pattern in individuals with polymedicinal therapies and autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus.

Conclusion: This report demonstrated that the anti-RR pattern cannot be exclusively related to HCV and more studies are required to understand it.

Keywords

Autoantibodies, Hepatitis C, Child, Case report

Abbreviations

ANA: Antinuclear Antibodies; RR: Rods and Rings; HCV: Hepatitis C; HIV: Human Immunodeficiency Virus; RBV: Ribavirin; IFN: Interferon; IFI: Indirect Immunofluorescence; IMPDH2: Inosine Monophosphate Dehydrogenase type 2; CTPS1: Cytidine Triphosphate Synthase type 1; IV: Intravenous; CRP: C-Reactive Protein; IgE: Immunoglobulin E; IgG: Immunoglobulin G; NHANHES: National Health and Nutrition Examination Survey

Introduction

Autoantibodies against self-antigens are trademarks of various autoimmune diseases. In the clinical laboratory, these autoantibodies against nuclear and cytoplasmic antigens are frequently screened by indirect immunofluorescence (IFI) in HEp-2 cells, also known as Antinuclear Antibodies (ANA-Hep2), which is the gold standard for the detection of these antibodies [1]. Several patterns have already been reported, some of which are quite specific for certain autoimmune diseases or the autoimmune condition itself, while others occur indiscriminately in individuals with or without autoimmune diseases [2,3].

The pattern of ANA-Hep2 called Rods and Rings (RR) has only recently been described. It consists of fibrillar structures with circular (2 to 5 µm diameter) or stick (3 to 10 µm) formats, located in the cytoplasm. These structures have at least two enzymes as targets: Inosine monophosphate dehydrogenase type 2 (IMPDH2) and

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CTPS1 - Cytidine Triphosphate Synthase type 1 [4]. The IV Brazilian Consensus for Autoantibodies on Hep2 Cells integrated the Rods and Rings pattern into the decision tree in 2013, classifying it as a cytoplasmic pattern not linked to other cytoplasmic patterns and dependent of substrate, since this pattern does not appear on all commercial substrates [5].

There are some hypotheses to try to explain the appearance of these antibodies, such as: Apoptotic bodies, epigenetic modifications or cross-reactivity between self and foreign proteins, playing a role in the generation of autoantibodies [6]. The generation of anti-RR antibodies has an additional hypothesis - the common use of ribavirin (RBV) and interferon-α (IFN) drugs in the treatment of Hepatitis C, which have been reported in several studies associated with the appearance of these autoantibodies [7-11]. Some of these studies, such as Keppeke, et al. [10], were used by the Brazilian Consensus that considered the RR pattern specific to people on Hepatitis C treatment in their last update [5].

The primary target and major component of RR structures is the enzyme IMPDH2. IFN/RBV were tested *in vitro* to determine their inhibitory effects on the enzyme in cell cultures and the consequent formation of anti-RR, showing that IFN had no effect, whereas Ribavirin induced RR formation by more than 95% of the cells [4,12]. Mycophenolic acid is also able to inhibit this enzyme, but the formation of RR antibodies was observed only *in vitro*, and no cases have been reported in patients [13]. The other enzyme identified as a component of RR, CTPS1, also demonstrated the formation of anti-RR antibodies when inhibited [14].

In contrast to the association of the RR pattern with HCV, additional studies [8,15-17] have demonstrated RR antibodies in healthy people or patients with other conditions, who had never been exposed to the HCV virus and/or were not using IFN/RBV. These data indicate that there must be other mechanisms involved in the generation of these antibodies which do not involve inhibition of the IMPDH2 enzyme.

The identification of a new autoantibody and its association with a specific pathology can improve the understanding of its pathophysiology and enrich the arsenal of diagnostic tests for this disease. It is important that new studies are constantly reported to understand the clinical significance of this cytoplasmic pattern [18]. As demonstrated, the pattern had been related to the hepatitis C virus and its treatment several times, but it has also been found in other clinical conditions and even in healthy individuals, in which case no hypothesis was suggested to explain the appearance of these autoantibodies. This demonstrates the importance of reporting new cases to improve understanding and formulate hypotheses about these autoantibodies and their associations with clinical conditions and clinical utility.

Case Description

A 10-year-old male, weighing 25 kilograms, was admitted to the emergency room with a cough, general decline and vomiting. Previously diagnosed with chronic lung disease, he was hospitalized with suspected bronchopneumonia. Before hospitalization, he was using Nitrazepam 5 mg for a neurological condition. At admission, he received Ceftriaxone 1.25 g IV twice a day and Oxacillin 1.25 g IV four times a day. Chest radiograph showed bilateral alveolar consolidations and left pleural effusion, with laboratory tests showing CRP 22.8 mg/dL and a hemogram with the number of leukocytes in the normal range, but with a left shift of neutrophils (15% of bands). After worsening of the condition, he was admitted to the pediatric ICU, where he received Methylprednisolone 2 mg/kg four times a day, Terbutaline 1 µg/kg/min., Midazolan 4 µg/kg/min. and Ketamine 20 µg/kg/min. The presence of hypochromic cutaneous lesions was diagnosed as prurigo strophulus with a biopsy and increased levels of IgE. After two days, with radiation worsening and suspecting of sepsis, the antibiotics were changed to Vancomycin 60 mg/kg once a day, Cefepime 120 mg/kg once a day and Azithromycin IV 500 mg once a day, with a good response. After one week of hospitalization, Fentanyl 2 µg/kg/min and Adrenaline 0.2 µg/kg/min were also added. A tomography of the chest was performed, which showed bronchiectasis and a ground-glass opacity, leading to the suspicion of cystic fibrosis, which caused the patient to start using Pulmozyme® 1 amp once a day. During hospitalization, he received nebulization of Beclomethasone twice a day and a beta-blocker eight times a day. A pediculosis crisis was treated with Ivermectin plus Deltamethrin.

During the hospitalization, other laboratory tests were performed, among them the test – ANA-Hep2 for autoantibody, with a reagent result for the nucleus (fine speckled) and cytoplasm (rods and rings) with a titer of 1/160. Serological results for viral hepatitis and HIV were negative, with IgG positive to Herpes Simplex type 1. No clinical correlation with the result of ANA-Hep2 was found in the patient's medical record, so he was discharged after 22 days and instructed to return to the pediatric outpatient clinic to evaluate the suspicion of an immunodeficiency syndrome and cystic fibrosis, which was discarded with a negative sweat test.

Discussion

Anti-RR antibodies are still poorly understood. The correlation of their detection with some clinical conditions has changed in recent years; it was initially considered specific to patients infected with Hepatitis C under treatment with ribavirin/interferon when first discovered, but several articles have shown that this pattern can be detected in other clinical conditions or even in healthy individuals [11,17].

The appearance of anti-RR in healthy individuals has

already been demonstrated [17]; based on data from the National Health and Nutrition Examination Survey (NHANHES), the results of anti-RR antibodies in the non-clinical population of the United States were evaluated. This research examined a sample of 4738 people, with anti-RR positive results in 39 patients and a single hepatitis C virus infection between them. Another 79 people infected with the virus had negative results for Anti-RR. One individual under RBV/IFN treatment had RR positivity. The only characteristic found in common in individuals who were positive for anti-RR antibodies, without previous HCV infection, was medication use, which was reported in 21 of the 39 patients. Eleven out of the 21 individuals used various medications and one third used anti-hypertensives.

Other studies described non-HCV patients with anti-RR antibodies, despite being a minority. Carcamo, et al. [15] demonstrated that 15 of 23 people with anti-RR results also had a previous HCV infection, indicating that the remaining eight were from an unexposed population. Another study [15], using IMPDH2 as a substrate in a radioimmunoprecipitation assay, showed specific autoantibodies in patients without HCV (13 of 42). Climent, et al. [8] analyzed 22,915 patient samples, finding RR positivity in 87 of them. Of these, 84% had positive serology for HCV and the rest (16%) had other conditions such as rheumatoid arthritis, Wilson's disease, systemic lupus erythematosus, and polyarthralgia, among others.

Although most cases with the appearance of the RR pattern are related to HCV-positive patients under treatment, the appearance of anti-RR results in other conditions shows that it is not linked to a specific situation. Studies showing anti-rods and rings in non-HCV and interferon/ribavirin patients have detected certain similarities between these patients, such as autoimmune diseases, chronic diseases and polymedication [8,17].

Some autoantibodies have been showed as activators of some biological processes in humans, as classically showed at Graves' disease, or more recently in Systemic Sclerosis (SSc) [14]. Fibrotic aspects in SSc are related to anti-PDGFR (antibodies against platelet-derived growth factor receptor) or AECA (anti-endothelial cells), what could imagined as a pathological role of anti-RR, once patients with HCV and anti-RR demonstrated more fibrosis in liver than patients with HCV and without anti-RR [8].

The case reported here shows the detection of autoantibodies, using the ANA-Hep2 test, with a pattern called anti-rods and rings (RR), in a non-HCV-infected child. This case has originality, because of the patient's age and the absence of the main factor generating this type of autoantibody. However, other hypotheses for the appearance of anti-RR found in the literature are present in this patient, such as a chronic disease (pulmonary disease) and polymedication, even though this condition only occurred during his hospitalization for a short period of time. Although the patient has not obtained a conclusive diagnosis, the appearance of ANA-Hep2 positivity for anti-RR may be related to a hyper-reactivity of the child's immune system, causing a temporary autoimmune condition, also leading to the skin hypersensitivity reactions and increased levels of IgE antibodies.

Conclusion

This case is atypical considering the appearance of autoantibodies to the anti-rods and rings pattern and helps to show that this pattern is not linked to a specific clinical condition. Therefore, more studies are necessary to determine which stimuli lead to the modification of self-antigens, thus resulting in the generation of this type of autoantibody.

Authors' Contribution

M.M., R.A.M.: Conception and design, drafting of the manuscript. R.F.G., R.A.M.: Conception and design, critical revision of the manuscript.

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