

# Does influenza subtype H1N1 have a place in the etiology of pityriasis rosea?

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## Abstract

**Introduction:** Pityriasis rosea (PR) is an acute, inflammatory skin disease of unknown cause. Various infectious agents including viruses have been proposed as causative agents and presence of influenza subtype H1N1 was shown in case reports with PR, but the relation was not conclusive. We hypothesized that there may be a relation between PR and H1N1, since both of them are prevalent in the same period as winter or season transitions.

**Aim:** To investigate the effect of the H1N1 virus in PR in this study.

**Material and methods:** Twenty-one female and 12 male PR patients who applied to Kirikkale University Faculty of Medicine Hospital Dermatology Outpatient Clinic were included in the study. Influenza subtype H1N1 IgM and IgG antibodies were detected by enzyme immunoassay (EIA) in sera of patients; tissue biopsy specimens were examined for influenza subtype H1N1 RNA by PCR.

**Results:** Seven (23%) of the 33 patients had positive IgM and IgG antibodies. Influenza subtype H1N1 RNA was not detected in the tissue samples of 33 PR patients.

**Conclusions:** According to the results of this study, we can say that influenza subtype H1N1 does not play a role in PR etiology.

**Key words:** pityriasis rosea, influenza, papulosquamous disease, viral etiology.

## Introduction

Pityriasis rosea (PR) is an acute, self-healing disease having an incidence of 0.3–3%, with oval, erythematous, squamous lesions in the trunk and extremities, usually following precursor plaque formation [1, 2]. Although the onset of a pioneering plaque, followed by widespread secondary lesions, and subsequent spontaneous healing support infectious etiology, the exact etiology of the disease has not yet been established [3].

We hypothesized that there may be a relation between PR and H1N1, since both of them are prevalent in the same period as winter or season transitions. In the past, PR cases that are thought to be linked to immunological mechanisms against influenza subtype H1N1 have been presented [4, 5].

## Aim

We aimed to investigate the effect of the H1N1 virus in PR in this study.

## Material and methods

Between January 2016 and January 2017, PR patients who applied to Kirikkale University Medical Faculty Hospital Dermatology Outpatient Clinic were included in the study. The patients were asked whether they had upper respiratory complaints (fever, cough, sore throat, joint and muscle pain) and influenza vaccination. Informed consent form was obtained from all patients. All patients were clinically evaluated every 2 weeks until recovery. Pityriasis rosea diagnosis by clinical examination was confirmed by skin biopsy and histopathological examination. Blood was drawn to biochemical tubes and a lesional skin tissue sample was taken with 5 mm punch biopsy instruments from PR patients. Blood collection and biopsy were done on the 7<sup>th</sup> day of the disease. Serum samples obtained from the blood and skin tissue samples were stored at –70°C in sterile conditions in Eppendorf conical tubes. IgM and IgG antibodies against influenza subtype H1N1 were investigated by an enzyme immunoassay (EIA) (Eastbiopharm, Hangzhou, China) test

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in serum of patients. H1N1 RNA was extracted from tissue samples of PR patients by a commercial kit (High Pure Nucleic Acid Isolation Kit, Roche Diagnostics, USA) according to the manufacturer's instructions. Before RNA extraction, tissue samples were exposed to tissue buffer (Roche, USA) at 60°C overnight and vortexed well. Extracted RNAs were amplified by the real-time RT-PCR method (LightMix Modular Influenza A H1(H1N1), Tibmobiol (Berlin, Germany) (LC Multiplex RNA Virus Master, Roche Diagnostics, USA).

## Results

Twenty-one female and 12 male PR patients who applied to Kırıkkale University Faculty of Medicine Hospital Dermatology Outpatient Clinic were included in the study. The ratio of female to male patients was found to be 1.75 : 1. The patients' ages ranged from 18 to 46; their average age was 28.66. Seven of the 33 (23%) patients had positive IgM and IgG antibodies. It was found that none of these patients had influenza vaccination and 2 of the 7 patients had upper respiratory tract infection within 4–6 weeks prior to admission. Influenza subtype H1N1 RNA was not detected in the tissue samples of 33 PR patients.

## Discussion

In the etiology of pityriasis rosea, HHV-6 and HHV-7 viruses were implicated and studies were carried out. In some studies it has been shown that these viruses play a role in PR etiology. However, not all of the patients had evidence of HHV-6 or HHV-7 as the etiologic factor [6]. Therefore, it can be surmised that PR may have an infectious etiology other than HHV-6 and HHV-7.

In our study, IgM and IgG antibody positivity was detected in seven patients for influenza subtype H1N1, but no findings of this virus were found in skin tissue samples. IgM and IgG antibodies are detected by ELISA within 2 weeks after influenza subtype H1N1 inoculation. The peak antibody level for the virus is detected within 4–7 weeks after infection and decreases slowly. Anti-viral IgM and IgG antibodies can be detected for many years after infection [7]. It is difficult to comment on whether antibody positivity detected by ELISA in this study is an acute infection or antibody positivity to a previous infection.

If serologic results that we found in our study are acute and/or past infection markers, we can say that influenza subtype H1N1 does not play a role in PR etiology because tissue samples cannot detect influenza subtype H1N1 RNA. If the serological results reflect an acute infection, we can make several possible conclusions. First, we can say that influenza subtype H1N1 does not play a role in PR etiology. Secondly, we may consider that influenza viruses do not infect epithelial cells or induce a large viral

load at such a level that the virus can be detected, as reported by Kwon *et al.* [4]. Thirdly, we can say that PR lesions are associated with increased cytokine release due to the inflammatory response during infection. Neurological symptoms of seasonal influenza virus infection are well known, but findings of this virus have not been detected in brain spinal fluid or tissue specimens. In this case, it was thought that neurological findings related to cytokine release increased with the inflammatory response [8]. Much like neurological findings, many studies have focused on the possible cause of immunity to viral immunity. The same situation may have been occurred in the pathology of PR, and thus PR may be a result of inflammation caused by cytokines that were released against to influenza subtype H1N1.

Finally, Cao *et al.* reported that the mean incubation period of the influenzae virus is 2 days (1–7 days) and the PCR results are positive on the 6<sup>th</sup> day of the disease (1–17 days) [9]. In our study, blood and skin tissue specimens from patients were taken on the 7<sup>th</sup> day after the onset of lesions. Another possibility is that this period is not compatible with the time of the virus. Due to the possible reasons mentioned above, we may not have been able to detect the virus RNA in the skin biopsy specimens. One of the shortcomings of our study is that the number of patients is low and there is no control group. It would be worthwhile to carry out this study with more patients and a control group.

According to the results of this study, we cannot determine a relationship between influenza subtype H1N1 and PR. To support this result, we believe that it would be appropriate to investigate influenza subtype H1N1 RNA from patients with acute influenza subtype H1N1 infection at appropriate times, in several consecutive skin biopsy specimens.

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## Conflict of interest

The authors declare no conflict of interest.

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