Clinical and Experimental Rheumatology 2021; 39: 1410-1412.

Palindromic rheumatism following COVID-19 infection evolved to rheumatoid arthritis after COVID-19 reinfection

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Received on October 28, 2021; accepted in revised form on November 4, 2021.

Key words: rheumatoid arthritis, palindromic rheumatism, COVID-19 infection

Competing interests: none declared.

ABSTRACT

A 33-year-old woman developed palindromic rheumatism (PLR) several weeks following an infection with severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2). Three months later, she developed full blown seropositive rheumatoid arthritis (RA) following COVID-19 reinfection. Although the occurrence of the joint diseases and the COVID-19 infections maybe fortuitous, knowing the enormous effects of COVID-19 infection on the human immune system, it is difficult to ignore the temporal relationship between the appearance of PLR after the first COVID-19 infection and the transition to full blown RA following her COVID-19 re-infection.

Case report

A 33-year-old woman who works as a computer scientist in Israel, was infected with severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) in September 2020. She presented with malaise, dysgeusia and dysosmia. A reverse transcriptase polymerase chain reaction (RT-PCR) test confirmed the diagnosis. Her symptoms subsided after 12 days. Repeat RT-PCR test for COVID-19 10 days later was negative.

Two months later the patient developed palindromic rheumatism (PLR) affecting her MCP and PIP joints. The frequency of the attacks was about once a month and each episode lasted a week.

In January 2021, the patient travelled to Slovakia to visit her parents. Before the flight, she was tested for COVID-19 and was found negative. A month later, when she returned to Israel, she was checked for COVID-19 and resulted positive in two successive RT-PCR tests. This time she denied any symptoms or signs of COVID-19 infection. However, her parents in Slovakia developed severe COVID-19 infection.

Four weeks later, the patient developed short bouts of low-grade fever, mild abdominal and chest pains. Her joint disease became persistent rather than episodic with daily morning stiffness lasting an hour. Two months later (April 2021), the fever, abdominal and chest pains resolved but the arthritis worsened. Work-up revealed elevated CRP and ESR, negative RF and borderline ANA (in immunoassay). Serum anti CCP antibodies (ACPA) was positive [6 U/Ml, (0-3)]. Hydroxychloroquine was initiated with no improvement.

In October, the joint disease affected her knees and wrists too. Physical examination revealed tender, swollen and warm PIP and MCP joints (Fig. 1). Testing for ANA was negative by immunofluorescence, RF was negative, but the anti CCP remained positive (6.3 U/Ml). Based upon symmetric arthritis, morning stiffness and positive anti-CCP, a diagnosis of rheumatoid arthritis (RA) was made. Prednisone and weekly methotrexate were initiated followed by significant improvement.

Discussion

The above case raises several questions: did the patient have a single prolonged course of COVID-19 infection or two separate infections? Secondly, is there any association between COVID-19 infection and the onset of palindromic rheumatism or to its progression to RA after re-infection?

Regarding the first question, it seems to be two different infections. The first was caused by the alpha-variant of SARS-CoV2, dominant then in Israel, whereas the second infection was induced by the delta-variant, which by then, had emerged in Slovakia. The multiple negative RT-PCR tests between both infections support this notion. With regard to the second question, theoretically, arthralgia or arthritis may be associated with infections in four ways.

1. Arthralgia or arthritis may be one of the features of the acute viral infection as happens in Hepatitis B, Hepatitis C, Parvovirus, and Epstein-Barr virus as well as in SARS-CoV-2 (1).
2. A joint disease may appear 2–3 weeks following an acute viral infection, *i.e.* post-infectious arthritis, usually involving a single large joint and occasionally presenting as polyarthritis (2).
3. Viral infection may trigger a chronic joints disease such as RA. For example, CMV was considered for years as the main culprit in this disease (3). Similarly, one may suggest that SARS-CoV-2 can also induce RA.

4. Finally, the common occurrence of COVID-19 infection and arthritis may be absolutely co-incidental without any causal relationship.

Since the joint symptoms in our patient appeared after full recovery from the first COVID-19 infection, the arthritis could not be attributed to the acute infection. The symmetric small joints involvement with positive ACPA exclude the diagnosis of post-infectious arthritis. Therefore, the likely explanations are either a viral infection triggering RA or coincidence of two separate clinical conditions.

Viral agents, especially those capable of causing a latent infection (*e.g.* CMV), have often been hypothesised to be co-factors of the pathophysiology of RA (4). However, countries with higher rates of CMV latent infection do not have higher prevalence of RA (5). This observation weakens the hypothesis that CMV infection is the causative agent of RA. In addition, Derksen *et al*. studied 61 patients, 5 weeks after COVID-19 infection and found no increase in the incidence of ACPA (6). On the other hand, many studies described the numerous effects of SARS-CoV-2 on the immune system including the cytokine storm and the proinflammatory complications (7, 8). Moreover, another study revealed ANA, anti-neutrophil cytoplasmic antibodies and anti-phospholipid antibodies in sera of COVID-19 infected patients (9). Roongta *et al*. reported of a patient with post-COVID-19 RA who had severe lung involvement. They suggested that lung involvement may be a risk factor for RA onset via generation of ACPA (10).

The patient herein, did not have any pulmonary involvement. She had a typical course of PLR which progressed to sero-positive RA. Observational series have shown that 10–66% of the patients with PLR evolve to RA (11). Female sex, hand involvement and positive ACPA or RF were found to be prognostic factors for RA progression. Our patient was a female, her disease involved her hands and she was positive for ACPA. Therefore, evolution of PLR to RA was expected. Since, only 6 cases of post-COVID19 RA have been reported to date, a causal relationship between the two entities seems unlikely (1). However, over the last months, more and more data about the wide interplay between COVID-19 infection and the human immune system is accumulated. Among which are its potential to cause long term complications such as "long COVID syndrome" and multisystem inflammatory syndrome in children (MIS-C), etc, Therefore, it is difficult to totally ignore the temporal relationship between the appearance of PLR after the first COVID-19 infection in our patient and the transition to full blown RA following her COVID -19 re-infection. This course of events merits further investigation and clarification.

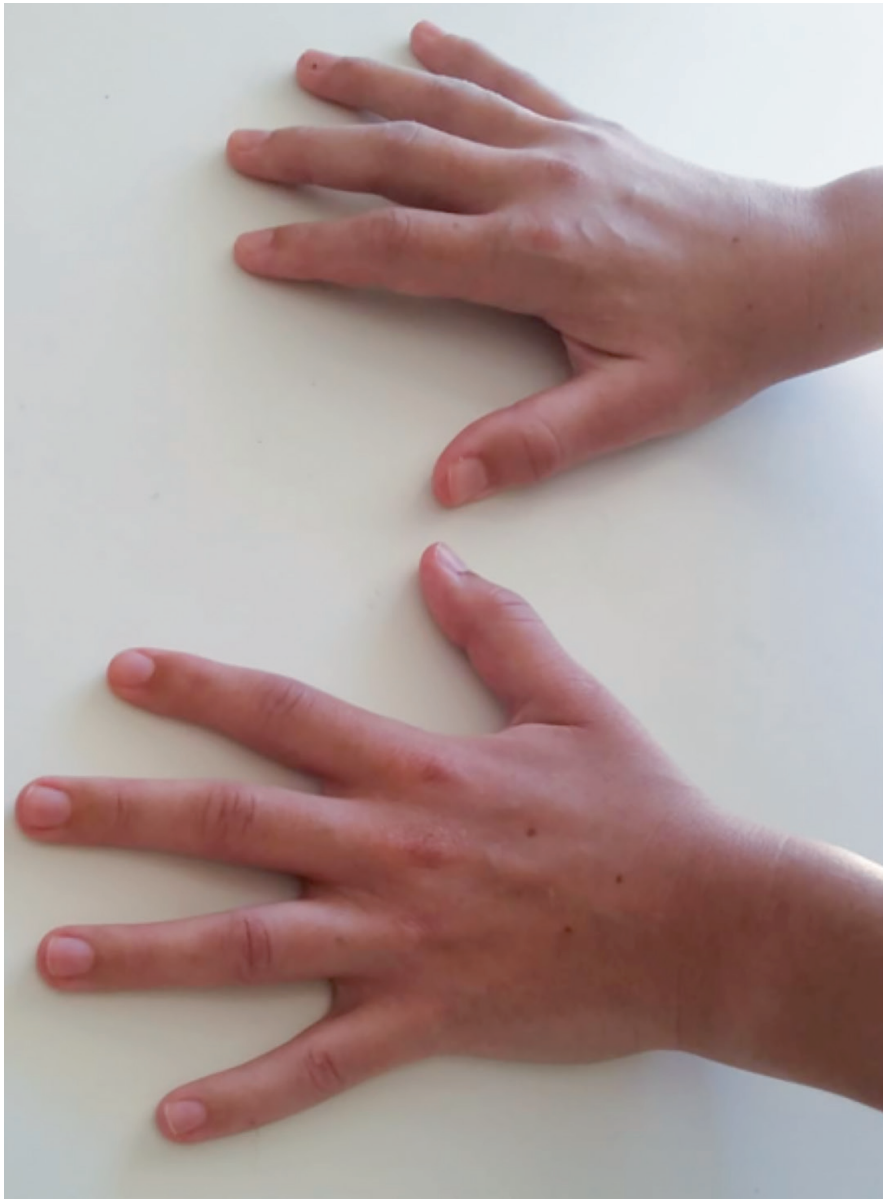

Fig. 1. Some swollen PIPs and MCPs of the patient on both hands.

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