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CASE REPORT

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A case of anti-melanoma differentiation-associated gene 5 antibody-positive dermatomyositis-associated rapidly progressive interstitial lung diseases developed after administration of COVID-19 vaccine and subsequent pneumococcal vaccine

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Abstract

Five cases of anti-melanoma differentiation-associated gene 5 antibody-positive dermatomyositis-associated rapidly progressive interstitial lung diseases (anti-MDA5-positive DM-RPILD) following COVID-19 vaccination have been reported previously. We present the first case of the disease that developed following the sequence of COVID-19 infection, COVID-19 vaccination, and 23-valent pneumococcal polysaccharide vaccine (PPSV23) administration. A 75-year-old-Japanese man received the third dose of Pfizer COVID-19 vaccine 4 weeks after he had a mild COVID-19 infection. Eleven weeks after vaccination, he received PPSV23 for the first time. He developed fever, malaise, and anorexia the day after the PPSV23, rash a week later, and shortness of breath 2 weeks later. He was then admitted to a local hospital and treated with antibiotics, but his condition worsened. He was transferred to our hospital 4 weeks after the PPSV23 and was diagnosed with anti-MDA5-positive DM-RPILD. Despite intensive treatment, the patient died on the 10th hospital day.

KEYWORDS

23-valent pneumococcal polysaccharide vaccine, anti-melanoma differentiation-associated gene 5 antibody-positive dermatomyositis-associated rapidly progressive interstitial lung diseases, COVID-19

INTRODUCTION

Recent publications have shown a possible relationship between anti-melanoma differentiation-associated gene 5 (anti-MDA5) antibodies and COVID-19 infection and/or vaccines. Five cases of anti-MDA5-positive dermatomyositis-associated rapidly progressive interstitial lung diseases (DM-RPILD) following COVID-19 vaccination have been reported.[1] However, no case of anti-MDA5 antibody production has been reported after PPSV23 administration. We present the first case of the disease that developed following the sequence of COVID-19 infection, COVID-19 vaccination, and PPSV23 administration.

CASE REPORT

A 75-year-old-Japanese man with hypertension had mild COVID-19 infection with fever and sore throat and recovered without sequelae. He received the third dose of Pfizer (BNT162b2) COVID-19 vaccine 4 weeks after the COVID-19 infection and his first PPSV23 11 weeks after the COVID-19 vaccination. He developed a fever of 38.0°C the day after receiving the PPSV23, followed by malaise and anorexia, which persisted. One week after receiving the PPSV23, he developed rash on both shoulders, redness on the left elbow, and hyperkeratosis on both ears, the extensor side of the metacarpo-phalangeal joints (Gottron's sign),

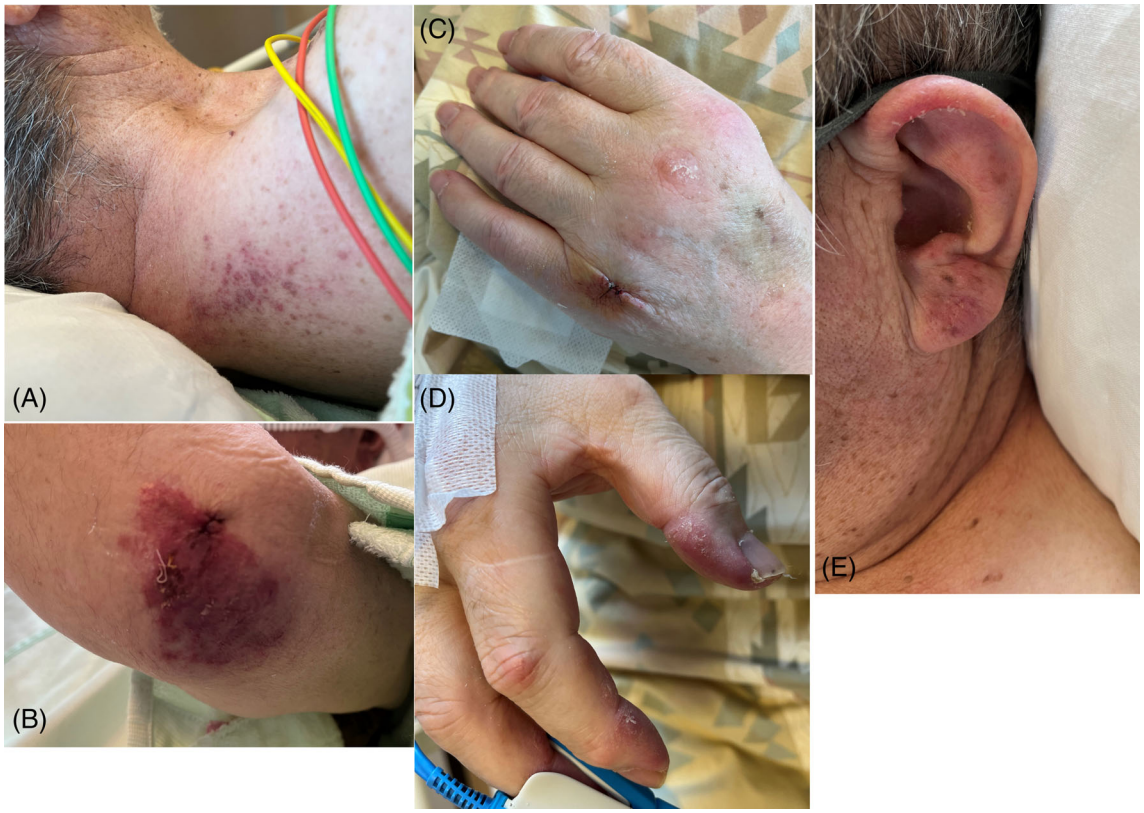

FIGURE 1 Photos taken on the day of hospitalization. The thread shows the stitches after the skin biopsy. (A) Rashes on both shoulders. (B) Erythematous macule over the left elbow (Gottron's sign). (C) Hyperkeratosis of the extensor side of the metacarpo phalangeal joints (Gottron's sign). (D) Hyperkeratosis of the fingers (mechanic's hands like). (E) Hyperkeratosis of the ears

and fingers (mechanic's hands like). Two weeks after receiving the PPSV23, the patient developed progressive shortness of breath and was admitted to a local hospital. His body weight decreased by 9 kg (104–95 kg) over 2 weeks after receiving the PPSV23. Antibiotic therapy for bacterial pneumonia was ineffective, and his respiratory condition worsened. He was transferred to our hospital 10 days after admission. His vital signs at the time of transfer were as follows: blood pressure, 117/89 mmHg; heart rate, 112 bpm; body temperature, 37.7 °C; respiratory rate, 23 times/min; and SpO_2, 86% while receiving 9 L/min oxygen through a reservoir mask. Chest computed tomography (CT) showed diffuse and subpleural ground-glass opacities and consolidations. Anti-MDA5-positive DM-RPILD was suspected based on the skin (Figure 1) and CT (Figure 2) findings. Manual muscle testing revealed no signs of weakness. His blood test results were as follows: normal complete blood count, normal creatine kinase, 54 U/L; increased aldolase, 11.9 U/L; increased lactate dehydrogenase, 317 U/L; increased C-reactive protein, 9.4 mg/dL; increased ferritin, 2405 ng/ml; and increased KL-6, 1108 U/ml. Antinuclear antibodies were negative. COVID-19 PCR and urinary antigen tests for S. pneumoniae and Legionella detection were also negative. Pulse therapy with methylprednisolone 1000 mg/day was initiated, and antibiotics were also administered (meropenem 1 g q8h and levofloxacin 500 mg q24h). The following day, his respiratory condition deteriorated further, and intravenous cyclophosphamide 1000 mg (500 mg/m^2) and tacrolimus (3 mg/day) were administered. On the 5th hospital day, a 4150-fold titre of anti-MDA5 antibody measured in the blood collected on admission was revealed. Tests for anti-SSA/Ro and anti-TIF1γ antibodies were negative. His oxygenation worsened and he was intubated and placed on a ventilator. Plasma exchange and intravenous immunoglobulin were administered. However, his condition did not improve and he died on hospital day 10. The pathological findings of the skin biopsy performed on admission showed liquefactive degeneration of the basal layer and hyperkeratosis and parakeratosis of the dermal tissue, which were consistent with dermatomyositis.

DISCUSSION

The patient developed anti-MDA5-positive DM-RPILD following the sequence of COVID-19 infection, COVID-19 vaccination, and PPSV23 administration.

MDA5 is an intracellular sensor of viral double-stranded RNA in the cytoplasm, and its expression is induced by RNA viruses (including coronaviruses). MDA5 triggers the innate immune response by driving the production of large amounts of type I IFN and downstream inflammatory

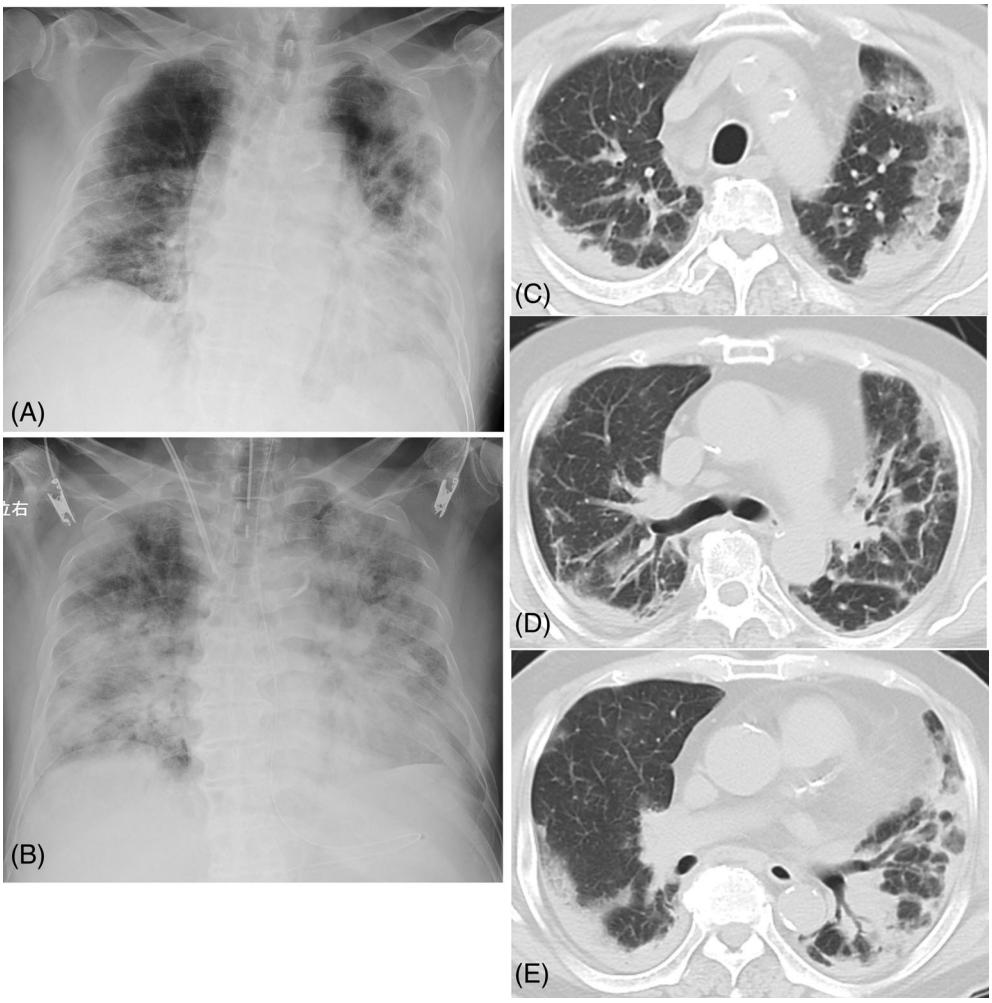

FIGURE 2 (A) Chest X-ray on admission. (B) Chest X-ray on the 5th hospital day. (C–E) Computed tomography findings at the time of transfer to our hospital showing diffuse and sub-pleural ground-glass opacities and consolidations

mediators.[2] Recent publications have demonstrated a possible relationship between anti-MDA5 antibodies and COVID-19 infection and/or vaccines. Wang et al. reported that anti-MDA5 antibodies were present in 48.2% of patients with COVID-19. The titre of anti-MDA5 antibody was 6.60 ± 5.50 fold and correlated with severe disease and poor outcomes.[3] Additionally, MDA5 is triggered by the mRNA COVID-19 vaccine with resultant activated dendritic cells.[4] Five cases of anti-MDA5-positive DM-RPILD that developed after COVID-19 vaccination have been reported, with onset occurring 2–7 days after the administration of the COVID-19 vaccine.[1] Since our patient did not experience any particular changes in his health after the administration of the third dose of COVID vaccine until he received the PPSV23, the onset of his anti-MDA5-positive DM-RPILD was considered to be 78 days after the COVID-19 vaccination, which was much later than previous reports. Given the number of days to onset, our case could be PPSV23-induced anti-MDA5-positive DM-RPILD.PPSV23 has been reported to stimulate the immune system through recognization by dectin-2 (a pattern recognition receptor different from MDA5) on the plasma membrane. To the best of our knowledge, no case of anti-MDA5 antibody production, including the development of anti-MDA5-positive DM-RPILD, has been reported after PPSV23 administration. However, one case of antisynthetase syndrome associated with interstitial lung disease that developed 2 days after receiving PPSV23 and recombinant zoster vaccine has been reported.[5]

The pathogenic mechanism in our case is unknown, though we suspect that anti-MDA5 antibodies were produced in the body after COVID-19 infection and/or vaccination, and the onset of anti-MDA5-positive DM-RPILD was triggered by PPSV23 administration.

COVID-19 vaccine and PPSV23 have established the merits of vaccination. During the COVID-19 pandemic, more elderly people may be willing to take not only the COVID-19 vaccine but also the PPSV23 in the future. Herein, we report a rare but life-threatening case of which clinicians should be aware. We also hope that this case will trigger further research that will clarify whether PPSV23 alone or PPSV23 administration after COVID-19 vaccination affects the development of anti-MDA5-positive DM-RPILD and reveal the potential mechanism of this complication.

AUTHOR CONTRIBUTIONS

Saeko Takahashi: the patient's physician and primary author. Ai Kato, Kanako Hashimoto, Tomohiro Takehara, Kota Ishioka, and Satoshi Takanashi were involved in intensive care management and review of the work and final improvement of the article.

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CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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