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CASE REPORT

Drug-induced sarcoidosis-like reaction three months after BNT162b2 mRNA COVID-19 vaccination: A case report and review of literature

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Abstract

BACKGROUND

A 70-year-old man with hepatitis C virus-related recurrent hepatocellular carcinoma was admitted for further diagnosis of a 1 cm iso-hyperechoic nodule in segment (S) 5.

CASE SUMMARY

Gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced

magnetic resonance imaging (EOB-MRI) revealed the nodule in S5 with a defect at the hepatobiliary phase, hyperintensity on diffusion weighted imaging (DWI) and hypointensity on apparent diffusion coefficient (ADC) map. Contrast-enhanced computed tomography revealed hypervascularity at the early phase, and delayed contrast-enhancement was observed at the late phase. Contrast-enhanced ultrasound (US) revealed incomplete defect at the late vascular phase. Inflammatory liver tumor, lymphoproliferative disease, intrahepatic cholangiocarcinoma (small duct type) and bile duct adenoma were suspected through the imaging studies. US guided biopsy, however, showed a noncaseating hepatic sarcoid-like epithelioid granuloma (HSEG), and histopathological analysis disclosed spindle shaped epithelioid cells harboring Langhans-type multinucleated giant cells. One month after admission, EOB-MRI signaled the disappearance of the defect at the hepatobiliary phase, of hyperintensity on DWI, of hypointensity on ADC map, and no stain at the early phase.

CONCLUSION

That the patient had received BNT162b2 messenger RNA (mRNA) coronavirus disease 2019 vaccination 3 mo before the occurrence of HSEG, and that its disappearance was confirmed 4 mo after mRNA vaccination suggested that the drug-induced sarcoidosis-like reaction (DISR) might be induced by the mRNA vaccination. Fortunately, rechallenge of drug-induced DISR with the third mRNA vaccination was not confirmed.

Key Words: Drug-induced sarcoidosis-like reaction; BNT162b2 mRNA COVID-19 vaccine; Noncaseating granuloma; Ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging; Th1/Th2 profile; Case report

Core Tip: We describe a case of drug-induced sarcoidosis-like reaction (DISR) a noncaseating hepatic sarcoid-like epithelioid granuloma (HSEG). Histopathological analysis disclosed, characteristic spindle-shaped epithelioid cells harboring Langhans-type multinucleated giant cells. Two months and 5 mo after the third BNT162b2 messenger RNA (mRNA) coronavirus disease 2019 vaccination, the occurrence of HSEG was not confirmed before rechallenging the drug-induced DISR by the third mRNA vaccination.

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INTRODUCTION

A drug-induced sarcoidosis-like reaction (DISR) displaying a systemic granulomatous tissue reaction is indistinguishable from sarcoidosis and occurs in a temporal manner initiated by an antagonistic drug [1]. To date, there is no clinical distinction between DISR and sarcoidosis; both have been associated with bilateral hilar adenopathy, cutaneous lesions, uveitis, granulomatous infiltration of scars, hypercalcemia, elevated serum angiotensin-converting enzyme levels, and 18F-fluorodeoxyglucose uptake, all of which appear on positron emission tomography (PET) scans[1].

A 1 cm hepatic sarcoid-like epithelioid granuloma (HSEG) was diagnosed through histopathological examination in a 70-year-old man 3 mo after his receiving two BNT162b2 messenger RNA (mRNA) coronavirus disease 2019 (COVID-19) vaccinations. The disappearance of the HSEG was confirmed through imaging studies 4 mo after the mRNA vaccination.

CASE PRESENTATION

Chief complaints

A 70-year-old man with hypertension and diabetes mellitus was in October 2021 admitted to Kobe Asahi Hospital for evaluation of a 1 cm iso-hyperechoic nodule in segment (S) 5.

History of present illness

The patient had overcome hepatitis C virus (HCV) infection 16 years earlier with Pegylated interferon (PEG-IFN) α2b + Ribavirin for 24 wk, and a 1 cm hepatocellular carcinoma (HCC) in S2 was completely resected in 2017.

A 4 cm HCC between S7 and S8 was removed by microwave ablation in April 2020; however, due to local recurrence, the HCC was re-ablated in February 2021, and subsequent imaging studies including gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging (EOB-MRI) signaled disappearance of the HCC. Follow-up imaging studies with EOB-MRI in June 2021 also signaled disappearance of any recurrent tumor. Thereafter, the first, and after a three-week interval, the second mRNA vaccination were administered to the patient in June, without any particular side effects such as anaphylaxis, fever, fatigue, general malaise or muscle pain (Figure 1). From 2020 to 2021, except for the mRNA vaccine, no other particular drugs, injections, immune checkpoint inhibitors (ICIs), highly active antiretroviral therapy (HAART), IFNs, tumor necrosis factor (TNF)-α antagonists, BRAF inhibitors, methotrexate or Bacille de Calmette et Guérin (BCG) were administered.

History of past illness

He suffered a cerebral hemorrhage in 2008, myocardial infarction in 2010, and from prostatic cancer, bladder cancer and lower right ureter cancer in 2019. At surgery for bladder cancer, BCG was not administered.

Personal and family history

Nothing particular.

Physical examination

On admission, the patient weighed 59.0 kg, was 157.5 cm tall and had a BMI of 23.8; a physical examination showed no remarkable abnormalities.

Laboratory examinations

Laboratory values and tumor markers at admission are shown in Table 1.

Imaging examinations

MRI findings: Follow-up imaging studies with EOB-MRI in October, 2021 revealed a 1 cm defect in S5 at the hepatobiliary phase (Figure 2A).

EOB-MRI revealed hyperintensity on diffusion weighted image (DWI) (b value = 800 s/mm^3) (Figure 2B) and hypointensity on apparent diffusion coefficient (ADC) map, respectively (Figure 2C); however, imaging at the early phase was unattainable because of artifacts attributed to the patient's restlessness.

Computed tomography findings: Plain computed tomography (CT) revealed no nodule in S5 (Figure 2D). Contrast-enhanced CT (CECT) revealed a hypervascular nodule at the early phase (Figure 2E) and delayed contrast enhancement at the late phase in S5 (Figure 2F) in October, 2021.

Ultrasound findings: Plain ultrasound (US) revealed a 1cm iso-hyperechoic nodule in S5 (Figure 2G). Contrast-enhanced US (CEUS) revealed incomplete defect at the late vascular phase in S5 (Figure 2H) in October, 2021.

From all the above imaging findings inflammatory liver tumor, lymphoproliferative disease, intrahepatic cholangiocarcinoma (iCCA, small duct type) and bile duct adenoma (BDA) were suspected.

Histopathological examinations

US guided biopsy revealed a noncaseating HSEG with spindle shaped epithelioid cells harboring Langhans-type multinucleated giant cells, as determined by histopathological studies in October, 2021 (Figure 1, Figure 3A and B).

FINAL DIAGNOSIS

Based on the above findings, the present case was diagnosed as drug-induced hepatic sarcoidosis-like reaction (HSLR).

TREATMENT

Dermatological and ophthalmological examinations signified no suspicion of sarcoidosis. Also, lung CECT, US cardioechography and fluorine-18 fluorodeoxyglucose-PET (F-18 FDG-PET) pointed to no

Table 1 Laboratory values and tumor markers

AST	34 U/L (7-38 IU/L)	HbA1c	6.3% (4.6%-6.2%)
ALT	15 U/L (4-44 IU/L)	HCV Ab	(+)
ALP	118 U/L (36-126 IU/mL)	HCV RNA	(-)
LDH	206 U/L (120-240 U/L)	HBs Ag	(-)
γ-GTP	104 U/L (< 40 IU/L)	HBs Ab	(-)
T-Bil	1.0 mg/dL (0.2-1.2 mg/dL)	HBc Ab	(-)
TP	9.0 g/dL (6.5-8.2 g/dL)	sIL-2R	937 U/mL (122-496 U/mL)
Alb	4.6 g/dL (3.9-4.9 g/dL)	Lysozyme	16.7 μg/mL (5.0-10.0 μg/mL)
AMY	126 U/L (38-136 U/L)	ACE	12.5 U/L (7.7-29.4 IU/L)
CRP	0.52 mg/dL (< 0.30 mg/dL)	IgG	2464 mg/dL (800-1750 mg/dL)
BUN	21.2 mg/dL (< 40 IU/L)	IgA	547 mg/dL (100-450 mg/dL)
Cre	1.28 mg/dL (0.61-1.04 mg/dL)	IgM	50 mg/dL (45-300 mg/dL)
WBC	5200/μL (3600-9000/μL)	ANA	(-)
RBC	325 × 10^4/μL [(410-530) × 10^4/μL]	AMA	(-)
Hb	10.6 g/dL (13-18 g/dL)	AFP	3.3 ng/mL (< 10.0 ng/mL)
Plt	17.2 × 10^4/μL [(12-30) × 10^4/μL]	PIVKA-II	26 mAU/mL (< 40 mAU/mL)
FBG	110 mg/dL (60-110 mg/dL)	CA19-9	26.8 U/mL (< 37.0 U/mL)
		CEA	1.4 ng/mL (< 5.0 ng/mL)

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; LDH: Lactate dehydrogenase; γ-GTP: γ-glutamyl transpeptidase; T-Bil: Total bilirubin; TP: Total protein; Alb: Albumin; AMY: Amylase; CRP: C-reactive protein; BUN: Blood urea nitrogen; Cre: Creatinine; WBC: White blood cellt; RBC: Red blood cell; Hb: Hemoglobin; Plt: Platelet; FBG: Fasting blood glucose; HbA1c: Hemoglobin A1c; HCV Ab: Hepatitis C virus antibody; HCV RNA: Hepatitis C virus ribonucleic acid; HBs Ag: Hepatitis B virus S antigen; HBs Ab: Hepatitis B virus S antibody; HBc Ab: Hepatitis B virus C antibody; sIL-2R: Soluble interleukin-2 receptor; ACE: Angiotensin-converting enzyme; IgG: Immunoglobulin G; IgA: Immunoglobulin A; IgM: Immunoglobulin M; ANA: Antinuclear antibodies; AMA: Anti-mitochondrial antibody; AFP: Alpha-fetoprotein; PIVKA-II: Protein induced by vitamin K absence or antagonist II; CA19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen.

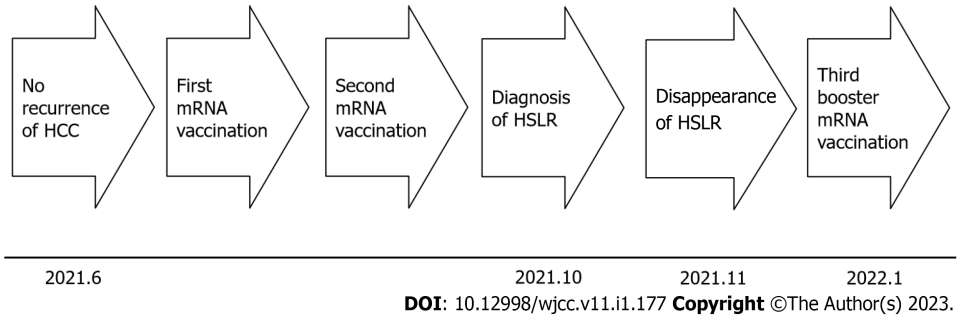

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Figure 1 Clinical course of the patient. HCC: Hepatocellular carcinoma; HSLR: Hepatic sarcoidosis-like reaction.

suspicion of sarcoidosis. The patient's clinical course was monitored without any treatment. EOB-MRI, one month after the diagnosis of HSEG and four months after the mRNA vaccination, signified the disappearance of the defect at the hepatobiliary phase (Figure 2I), the hyperintensity on DWI, the hypointensity on ADC map and no stain at the early phase, in November 2021 (Figure 1).

OUTCOME AND FOLLOW-UP

According to his will, the third booster mRNA vaccination was administered to the patient in January 2022 seven months after the second mRNA (Figure 1). Follow up-imaging studies with EOB revealed no stain at the early phase, no defect at the hepatobiliary phase, no hyperintensity on DMI and no hypoin-

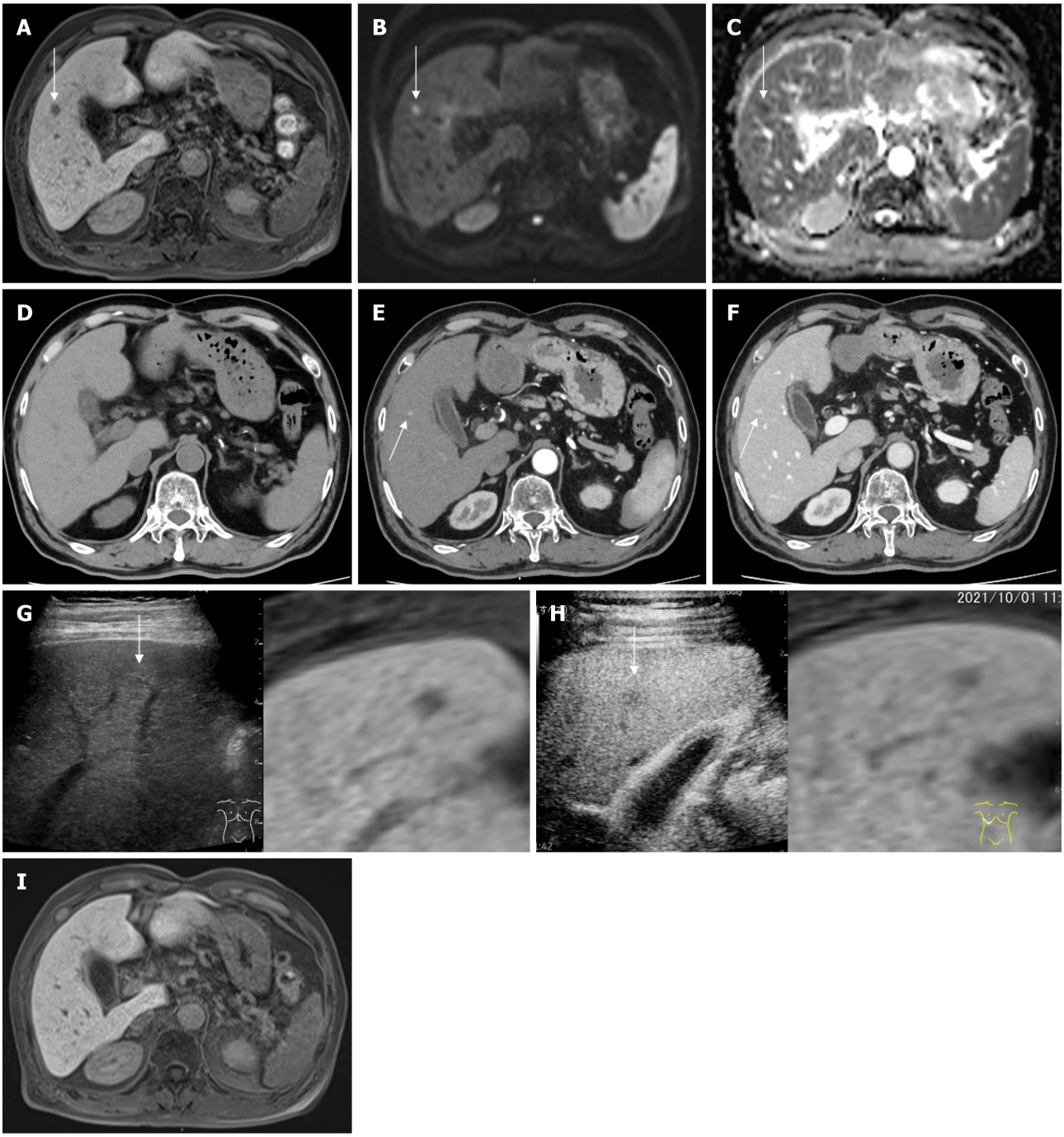

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Figure 2 Image findings. A: Gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging (EOB-MRI) finding, 1 cm defect in S5 at the hepatobiliary phase (white arrow); B: EOB-MRI finding, 1 cm hyperintensity in S5 on diffusion weighted imaging (white arrow); C: EOB-MRI finding, 1 cm hypointensity in S5 on apparent diffusion coefficient map (white arrow); D: Computed tomography (CT) finding, no nodule in S5; E: Contrast-enhanced CT (CECT) finding, 1 cm hypervascular nodule in S5 at the early phase; F: CECT finding, 1 cm delayed contrast enhancement at the late phase; G: Plain ultrasound (US) finding, 1 cm iso-hyperechoic nodule in S5 (reference with EOB-MRI), hepatobiliary phase (white arrow); H: Contrast-enhanced US finding, Incomplete defect in S5 at the late vascular phase (reference with EOB-MRI), hepatobiliary phase (white arrow); I: MRI finding, disappearance of the defect in S5 at the hepatobiliary phase.

tensity on ADC map in March and in July 2022, 2 mo and 5 mo after the third mRNA vaccination.

DISCUSSION

Four common categories of drugs that have been associated with the development of DISR are ICIs[2-4], HAART[5-7], IFNs[8-10], and TNF-α antagonists[11-13]. Also, several drugs such as BRAF[14-16] inhibitors, methotrexate and BCG have been associated with the development of syndromes indistinguishable from sarcoidosis, and are described as DISR. Like sarcoidosis, DISR does not necessarily

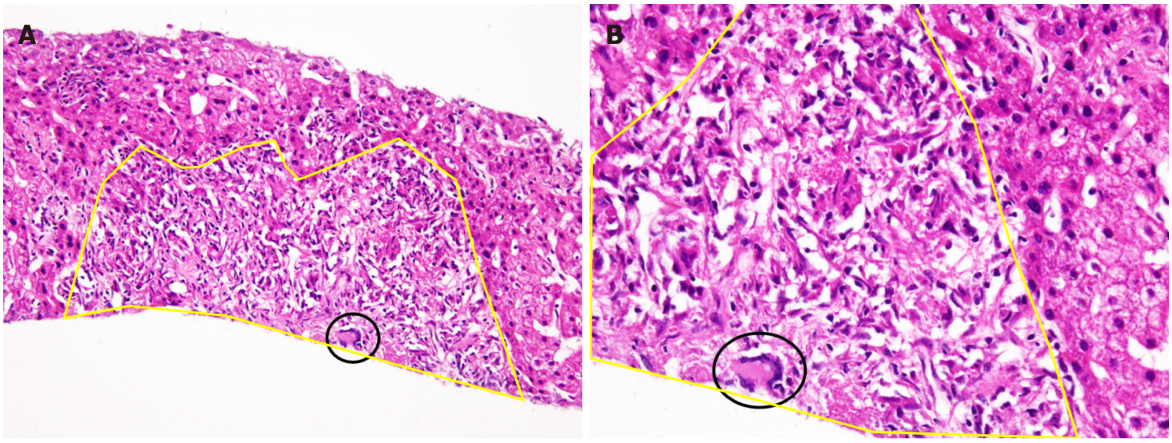

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Figure 3 Histopathological findings. A: Hematoxylin and eosin (HE) staining, low magnification Noncaseating hepatic sarcoid-like epithelioid granuloma with spindle shaped epithelioid cells (encompassed by yellow line) harboring Langhans-type multinucleated giant cells (circled black) (HE × 40); B: HE staining, high magnification of A (HE × 100).

require treatment because it causes no significant symptoms, quality of life impairment, or organ dysfunction. Standard anti-sarcoidosis regimens seem to be effective in treating DISR; alternatively, discontinuing any antagonistic drug tends to ameliorate or resolve DISR, thus constituting another effective treatment. Unlike sarcoidosis, DISR often resolves after discontinuation of the antagonistic agent, but may recur with rechallenge[1].

In the present case, one month after the diagnosis of HSLR, and four months after the mRNA vaccinations, EOB-MRI signified the disappearance of the defect at the hepatobiliary phase, the hyperintensity on DWI, the hypointensity on ADC map and the stain at the early phase, in November 2021, without the administration of any treatment, all of which is compatible with the clinical course of DISR.

Because DISR can be confused with other clinical conditions, including infections, other drug reactions, and malignancies, it is important to recognize this disease entity because misdiagnosing it may lead to unnecessary or inappropriate testing and treatment[1].

During follow-up of the present case, frequent imaging studies for HCV-related recurrent HCC were conducted to survey any multicentric occurrence and intrahepatic metastasis.

Imaging studies disclosed a 1cm defect in S5 at the hepatobiliary phase, diffusion restriction with hyperintensity on DWI and hypointensity on ADC-map through EOB-MRI, hypervascularity in the early phase and delayed contrast enhancement at the late phase through CECT, and incomplete defect in the late vascular phase through CEUS.

From above imaging studies, inflammatory liver tumor[17], lymphoproliferative disease[18], iCCA (small duct type)[19] and BDA[20] were suspected.

Nonetheless, histopathological examination with the use of US guided biopsy revealed a noncaseating HSEG with spindle shaped epithelioid cells harboring Langhans-type multinucleated giant cells.

IFN-α has been widely used for the treatment of chronic hepatitis B virus, hepatitis C infection, and various cancers such as chronic leukemia, malignant melanoma, and renal cell carcinoma. In many cases, IFN-α-induced DISR has been detected between 6 and 104 wk after the start of therapy[1].

In the present study, however, the relation between IFN-α and DISR was ruled out, especially that 16 years earlier the patient had undergone PEG-INF-α2b + Ribavirin treatment that resulted in SVR.

The exact immunopathogenesis of DISR is unknown; however, several hypotheses have been proposed according to the kinds of drugs and injections administered[21-23].

Ipilimumab, an ICI, enhances patient capability to mount an antitumor immune response; the resulting T-cell proliferation and increased expression of T-helper (Th) 1-associated markers can potentially induce DISR because these abundant cells in active sarcoidosis are thought to be integral to the development of sarcoid granuloma[21].

Increased production of IFN-α has been linked to Th1 polarization and Th2 inactivation with an enhanced level of granuloma-promoting cytokines such as interleukin (IL)-2, IL-8, IL-12, IL-18, and IFN-γ[22].

It is likely that the TNF-α soluble receptor is an unopposed type I IFN product that promotes a shift toward a Th1/Th2 profile, and the neutralization of soluble TNF-α can promote the activation of specific autoreactive T cells[23].

Irrespective of slight differences among the three above injections, they share some common significant characteristics such as favorable Th1 and inactivated Th2 profiles in terms of immune characteristics.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the ensuing COVID-19 have afflicted 608.6 million people in a worldwide pandemic, and as of 12 September 2022, deaths approaching 6.51 million have been reported. Obviously, safe and effective vaccines are needed urgently.

The mRNA vaccine is a lipid nanoparticle-formulated, nucleoside-modified RNA vaccine that encodes a prefusion-stabilized, membrane-anchored SARS-CoV-2 full-length spike protein[24-27].

Regarding T cell immune reaction to the mRNA vaccine, concurrent production of neutralizing antibodies, activation of virus-specific $CD4^+$ and $CD8^+$ T cells, and robust release of immune-modulatory cytokines such as IFN-γ represent a coordinated immune response to counter viral intrusion[28].

The T cell-related immune characteristics such as a favorable Th1 and inactivated Th2 profiles by the mRNA vaccine[28] have shown common immune characteristics similar to that of ICIs[21], IFN[22], TNF-α[23] which induce DISR.

In the context of common immune characteristics, mRNA can induce DISR under some presently-unknown conditions[24].

Recently a 44-year-old male patient has demonstrated mRNA vaccine-associated sarcoidosis the so-called DISR as confirmed by histopathological examination, and lymphadenopathy as disclosed by FDG-PET/CT. The patient had received the first dose of the mRNA vaccine a few days before CTCA/CMR and the second dose the day before FDG-PET/CT. Further examination of FDG PET/CT images revealed a triangular uptake of intramuscular FDG at the injection site in the left arm. Since the second dose of the vaccine was given in the interval between the CTCA/CMR and the PET/CT in the ipsilateral arm, and the enlargement of the left axillary lymph node was more prominent in the PET/CT scan than in the CTCA, the intramuscular FDG was interpreted as indicative of an inflammatory reaction. Nonetheless, to further determine the underlying nature of ilo-mediastinal lymphadenopathies, endobronchial ultrasound-guided transbronchial needle aspiration was carried out on stations 4R and 11R, and histopathological analysis revealed a sarcoidal-type granulomatous inflammation[29]. This report, however, showed discrepancy between the location of the enlargement (the left axillary lymph node) and the location of histopathological examination (ilo-mediastinal lymph node) after the second dose of the vaccine. Finally, the authors diagnosed this case as the so-called DISR[29].

In addition, very recently two histologically confirmed sarcoidosis cases due to BNT162b2 vaccination have been reported.

One is 61-year-old man after first mRNA vaccination. He developed sarcoidosis as manifested as uveitis, bilateral hilar lymphadenopathy, angiotensinconverting enzyme elevation, and epithelioid and giant cell granuloma formation in the lung soon after the first BNT162b2 injection[30].

Another is 43-year-old man who presented intermittent cough after the third dose of COVID-19 vaccination. 18 F-FDG PET/CT showed high uptake of one solitary nodule in the right middle lobe, mediastinal lymph nodes, bilateral hila, and multiple nodules under the right pleura, mimicking the malignancy.

Nevertheless, the biopsy confirmed distinct noncaseating granulomas[31].

In the present case, during the clinical course, no other particular drugs, injections, checkpoint inhibitors, HAART, IFN and TNF-α antagonists, BRAF inhibitors methotrexate and BCG, except for the mRNA vaccine, were administered.

The elevated level of sIL-2R observed in the present case was compatible with the previous papers [32-35].

Taken together with above reports[29-31], the present case suggests that the sarcoidosis-like reaction might be induced by the mRNA vaccination.

Above mRNA induced DISR cases were multiple nodules of DISR. Even though the present case was a single nodule of DISR, the present case was also considered as mRNA induced DISR compatible with Chopra's criteria that does not exclude a single nodule of DISR from DISR.

To the best of our knowledge, the present case may be the first on mRNA-induced HSLR, especially that to date no other such case has been reported in the literature.

The novel Omicron (B.1.1.529) variant, first identified in South Africa on November 24, 2021, has put the whole world on red alert[36]. Based on the unprecedented number of mutations (> 32 mutations in the Spike protein), and enhanced transmissibility (three times more infectious and severe than the original Wuhan strain). The World Health Organization announced on 26 November 2021 that the novel Omicron variant was of concern. As of February 2022, it has grown into the dominant variant all over the world.

CONCLUSION

Fortunately, rechallenge of drug-induced sarcoidosis like reaction was not confirmed two months after the third booster mRNA vaccination. That, however, does not necessarily deny the possibility of DISR with mRNA vaccination in the present case.

Further accumulation of relative cases is needed to clarify the clinical characteristics of mRNA-induced sarcoidosis-like reaction, its prevalence, predisposition, and past history.

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FOOTNOTES

Author contributions: Kim SK conceived the case and wrote the manuscript; Kim SR observed the clinical course of the patient and made the figures; Fujii T, Okuda T, Fujii Y, Hayakumo T, Nakai A, Suzuki R, Sasase N, and Otani A observed the clinical course of the patient; Kobayashi H and Kumabe T conducted the radiological examinations and interpreted the imaging findings; Koma YI, Sasaki M, and Nakashima O conducted histological examinations.

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