



Newly diagnosed extranodal NK/T-cell lymphoma, nasal type, at the injected left arm after BNT162b2 mRNA COVID-19 vaccination

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Abstract

Anti-SARS-CoV-2 vaccines were developed in response to the coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although the BNT162b2 mRNA vaccine is effective, adverse effects have been reported. Here, we report a case of extranodal NK/T-cell lymphoma, nasal type (ENKL), of the left arm following BNT162b2 mRNA vaccination. A 73-year-old male presented with a lump in the left arm, which was the site where he received the BNT162b2 mRNA vaccine 3 months prior. He was treated with topical corticosteroids and debridement, but the tumor progressed. Additionally, fever, night sweats, and general fatigue were observed. Laboratory findings included thrombocytopenia, elevated lactate dehydrogenase, and soluble interleukin-2 receptor levels. Skin biopsy led to a diagnosis of ENKL. The patient was treated with a 50% dose of SMILE therapy and radiotherapy, resulting in regression of the tumor. It seems that latent Epstein–Barr virus (EBV)-infected NK/T cells were reactivated by vaccination and contributed to the onset of ENKL. This is the first report of ENKL after BNT162b2 mRNA vaccination. The present case highlights the possible risk of development of malignant lymphoma, including ENKL at the injection site, after BNT162b2 COVID-19 vaccination.

Keywords Extranodal NK/T-cell lymphoma · Nasal type · Epstein–Barr virus infection · BNT162b2 mRNA COVID-19 vaccination

Abbreviations

ENKL	Extranodal NK/T-cell lymphoma, nasal type
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
COVID-19	Coronavirus disease 2019
EBV	Epstein–Barr virus

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, continues to spread and remains an international public health emergency. The BNT162b2 mRNA vaccine (Pfizer/BioNtech) is effective in reducing SARS-CoV-2 infections [1]. However, local (such as redness, swelling, and tenderness) and systemic (such as fever, fatigue, and joint pain) reactions after BNT162b2 mRNA vaccination have been reported [2]. Transient lymphadenopathy has also been reported in 0.3% of BNT162b2 mRNA-vaccine recipients and is thought to cause robust vaccine-elicited immune responses [2]. However, malignant lymphoma, especially at a just injection site, rarely occurs after BNT162b2 mRNA vaccination.

Extranodal NK/T-cell lymphoma, nasal type (ENKL), is a natural killer (NK) cell malignancy mostly observed in Asian populations [3]. Approximately, 25% of patients with ENKL have disseminated disease, and the prognosis is extremely poor when treated with anthracycline-based

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chemotherapy [4]. The prognosis of ENKL is poor because normal NK cells express P-glycoprotein, which is associated with multidrug resistance (MDR) [5]. ENKL is associated with Epstein–Barr virus (EBV) reactivation [6]. Although EBV reactivation after COVID-19 vaccination has been reported [7], the relationship between ENKL and COVID-19 vaccination remains unclear.

Here, we report a case of ENKL at the site of the BNT162b2 mRNA COVID-19 vaccine injection. This is the first report of ENKL development following BNT162b2 vaccination.

Case presentation

A 73-year-old male received the first dose of BNT162b2 vaccination in June 2021 and second dose in July 2021. Systemic symptoms associated with vaccination were not observed. He never had COVID-19. In addition, the patient had no history of allergy including hypersensitivity to mosquito bites. His medical history included old myocardial infarction, cardiac aneurysm, hypertension, hyperuricemia, and dyslipidemia. His regular medications were warfarin, clopidogrel, nicorandil, amlodipine, enalapril, lansoprazole, carvedilol, rosuvastatin, and topiroxostat. In October 2021, the patient presented with a lump in the left arm at the site of vaccination 3 months after the second BNT162b2 vaccination. In November 2021, the patient visited nearby clinics. A 2 cm skin ulcer surrounded by subcutaneous induration and redness in his left arm was observed. Washing and topical azulene application were performed, but the subcutaneous induration remained and was accompanied by heat. In December 2021, he was treated with topical corticosteroids and debridement, but the tumor progressed. In January 2022, new ulcer appeared adjacent to the original lesion. The patient complained of fever, night sweats, general fatigue, and left arm pain. He was referred and admitted to our hospital in February 2022.

Physical examination revealed fever (body temperature, 39.1 °C) and 6 cm and 3 cm ulcerated tumors in his left arm (Fig. 1). A complete blood count revealed thrombocytopenia (platelet count, 87,000 platelets/ μ L). Serum biochemistry revealed elevated NT-proBNP (328 pg/mL), ferritin (2,740 ng/mL), lactate dehydrogenase (LDH; 1,371 U/L), and soluble interleukin-2 receptor (sIL-2R; 5,456 U/mL) levels. The IgG antibody titers to the viral capsid antigen (EBVCA-IgG) and nuclear antigen (EBNA) of EBV were 1:320 and 1:160, respectively. The early antigen of EBV (EBEA-IgG) was not elevated. EBV DNA was detected (7.0×10^4 copies/mL) (Table 1). Computed tomography (CT) and magnetic resonance imaging (MRI) revealed an intramuscular tumor in the left arm. Positron emission tomography (PET)–CT showed accumulation of fluorodeoxyglucose



Fig. 1 A clinical image of the ENKL lesion of the left arm

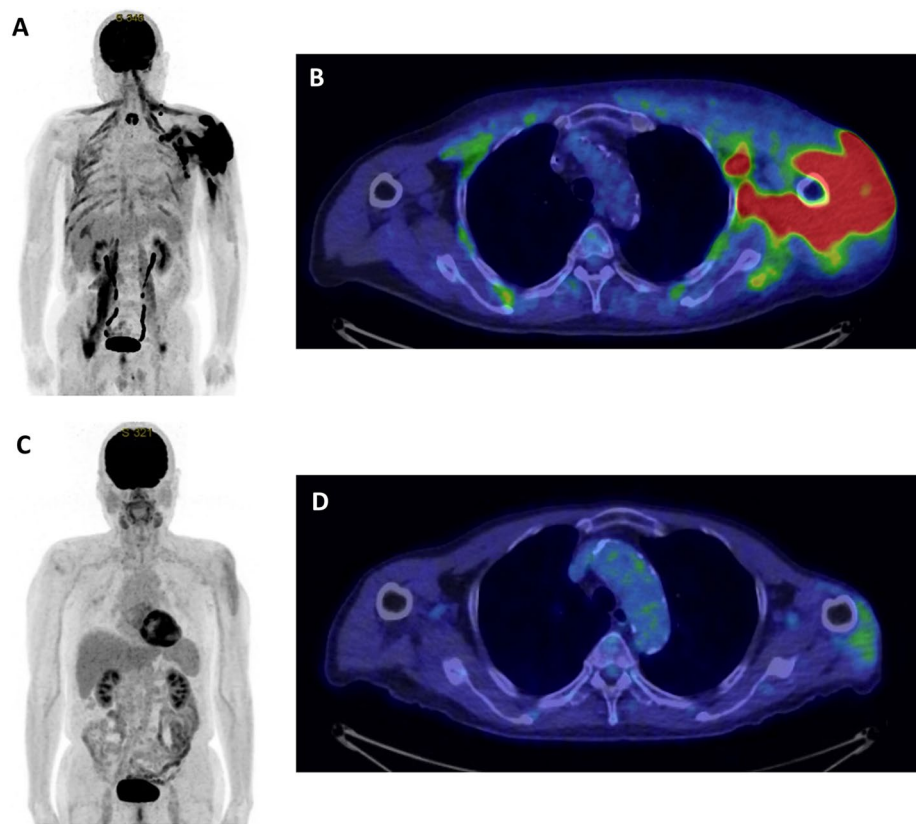
(FDG) in the left arm and muscles surrounding the humerus and left axillary lymph nodes (Fig. 2A, B). The skin biopsy was performed from the skin and subcutaneous fatty tissue of the left arm, including the ulcerated tumor and normal skin. Pathological examination showed infiltration of abnormal lymphocytes positive for cluster of differentiation (CD) 3, CD56, CD30, granzyme-B, perforin, and Epstein–Barr encoded RNA (EBER) from dermis to subcutaneous fatty tissue. Immunohistochemistry revealed that these cells were negative for CD4, CD5, CD8, CD10, CD20, CD79a, and TIA-1. The Ki-67 index was 80%. On the basis of these findings, the patient was diagnosed with ENKL. A bone marrow biopsy revealed no evidence of lymphoma involvement. We diagnosed the disease stage as Ann Arbor stage IV-B.

The patient had a history of myocardial infarction and a cardiac aneurysm. Transthoracic echocardiography showed a diffuse hypokinetic ventricle with an ejection fraction (EF) of 40%. We thought it necessary to reduce the intensity of chemotherapy because the patient was older and had low cardiac function. The patient was treated with SMILE therapy reduced to 50% dose (day 1: methotrexate 1 g/m²; day 2–4: ifosfamide 750 mg/m², etoposide 50 mg/m², and dexamethasone 40 mg/body; and days 8, 10, 12, 14, 16, 18, and 20: L-asparaginase 3000U/m²) [8]. On day 20 of the first course of 50% SMILE therapy, the patient developed melena. The patient underwent upper gastrointestinal endoscopy, which revealed a multifocal hemorrhagic gastric ulcer. Endoscopic hemostasis was performed, and the melena disappeared. The tumor in the left arm regressed gradually. After three courses of 50% SMILE therapy, the quantity of EBV DNA in the plasma decreased ($< 2.0 \times 10^2$ copies/mL). Additionally, the levels of LDH (185 U/L) and sIL-2R (631 U/mL) reduced significantly; however, anorexia, delayed clearance of methotrexate, and renal failure were also observed (decline in eGFR: 28.6 mL/min/1.73 m²). The patient discontinued the 50% SMILE therapy due to the toxicity. PET–CT was performed, and regression of the lesion in the left arm was

Table 1 Laboratory findings at diagnosis in a patient with ENKL after BNT162b2 vaccination

Complete blood count		Biochemistry		Serology	
WBC	6600/ μ L	TP	6.8 g/dL	CRP	5.16 mg/dL
Neu	83%	Alb	3.2 g/dL	IgG	1178 mg/dL
Mono	2%	AST	124 U/L	IgA	408 mg/dL
Lym	14%	ALT	94 U/L	IgM	60 mg/dL
RBC	$578 \times 10^4/\mu$ L	LDH	1371 U/L	Ferritin	2740 ng/mL
Hb	17.1 g/dL	γ -GTP	283 U/L	sIL-2R	5456 U/mL
Ht	50.40%	ALP	73 U/L	NT-proBNP	328 pg/mL
MCV	87.2 fL	Cr	1.15 mg/dL	HTLV-1 Ab	(-)
Ret	1.0%	UA	4.7 mg/dL	EBV DNA	7.0×10^4 copies/mL
Plt	$8.7 \times 10^4/\mu$ L	BUN	21 mg/dL	EBVCA-IgG	320
Coagulation tests		Glc	160 mg/dL	EBEA-IgG	< 10
PT-INR	1.23	Na	133 mmol/L	EBNA	160
APTT	37.5 s	K	4.5 mmol/L		
Fib	268 mg/dL	Cl	99 mmol/L		
FDP	6.2 μ g/mL	Ca	8.1 mg/dL		
		T.Bil	1.0 mg/dL		
		CPK	518 U/L		

Fig. 2 PET-CT findings. **A–B** PET-CT image at diagnosis. Accumulation of FDG was detected in the left arm, muscles surrounding the humerus, and the left axillary lymph nodes. **C–D** PET-CT images after the three courses of 50% SMILE therapy. The accumulation of FDG markedly decreased



confirmed (Fig. 2C–D). We considered the response to be a partial response (PR). The residual lesion was localized; therefore, radiotherapy was applied to the left arm (50 Gy with 25 fractions).

Discussion

The COVID-19 pandemic, March 2020, led to the development and rapid approval of anti-SARS-CoV-2 vaccines. Although vaccination has prevented the incidence of COVID-19 and COVID-19-associated deaths, its safety profile has not been fully elucidated. Myocarditis has been reported as a severe adverse event of the BNT162b2 mRNA vaccine (Pfizer–BioNTech) [9]. Although vaccination-induced lymphadenopathy has also been reported [10], there are a few reports about the occurrence of lymphoma after BNT162b2 mRNA vaccination. Recurrence of T-cell lymphoma [11, 12] and newly diagnosed diffuse large B-cell lymphoma (DLBCL) shortly after BNT162b2 mRNA vaccination [13] has been previously reported (Table 2). Lymphoma onset in these cases occurred shortly after the injection of the vaccine (maximum of 2 weeks post-administration). Our patient took 3 months from vaccination to the onset of ENKL. This is not the typical clinical course presented in previous reports. Although the lymphoma lesions of previous reports were not observed at the vaccine injection sites, our case had a lymphoma lesion in the skin and muscle at the BNT162b2 mRNA-vaccine injection site. It is possible that our case is of different pathogenesis from previous reports, in that the disease occurred relatively late after vaccination and at the site of vaccine injection.

There was no evidence of causal relationship between BNT162b2 mRNA vaccination and ENKL in this case, but we speculated that vaccination might lead to the development of ENKL in a manner similar to severe mosquito bite allergy (SMBA). SMBA is a rare EBV-positive NK-cell lymphoproliferative disorder mainly reported in children. Patients with SMBA exhibit skin lesions at

bite sites (bulla, necrosis, ulcer, and necrosis), high temperature, lymphadenopathy, and hepatosplenomegaly [6, 14]. Moreover, cases of SMBA developing into ENKL, systemic chronic-active EBV infection (CAEBV), and hemophagocytic lymphohistiocytosis (HLH) have been reported [15–18]. On the other hand, the reactivation of EBV induced by BNT162b2 mRNA vaccination has been reported [7, 19, 20]. In our case, we speculated that hypersensitivity to vaccination might have triggered the reactivation of EBV and the development of ENKL. Although our case was not typical for SMBA in terms of the onset in elderly patients and long latency period from vaccination to disease onset, the skin biopsy revealed reactivation of EBV and suggested a pathology similar to SMBA. In addition, the elevated EBV-IgG was absent in our case. In a previous study, it was reported that EBV-IgG can be negative in the patient with hypersensitivity to mosquito bites [21]. It was also reported that the patients with NK-cell CAEBV do not always have elevated EBV-specific antibody titers in contrast to the T-cell CAEBV that have high titers of EBV-specific antibody [15]. Therefore, the low level of EBV-IgG in our patient could suggest the reactivation of EBV in NK cells.

This case has two limitations about the relationship between BNT162b2 mRNA vaccination and ENKL. First, strictly speaking, we could not identify the exact site of vaccine administration, because we do not have the record of the site of vaccination. However, according to the patient, the site of ulcerated tumors coincided with the vaccine injection site. Second, topical steroid application and debridement might have contributed to the development of ENKL. The duration of these treatments was almost 1 month. This might be responsible for the development of ENKL. However, no steroid application and no surgical procedure were performed from the onset of a lump in the left arm in

Table 2 Summary of cases with malignant lymphoma after BNT162b2 vaccination

Case	Age(years)/sex	Disease	Disease status	Latency period	BNT162b2 vaccination	Site	Lesion at injection site	Treatment	References
1	79/M	Primary cutaneous CD30-positive LPD	Recurrence	2 days	First	Left axilla	No	NA	[11]
2	60/M	MF	Recurrence	4 weeks	First	Skin	No	NA	[12]
3	73/M	MF	Recurrence	10 days	First	Skin	No	NA	[12]
4	67/M	DLBCL	Newly diagnosed	14 days	Second	Left axilla	No	R-CHOP	[13]
5	80/M	DLBCL	Newly diagnosed	1 day	Second	Left axilla	No	R-miniCHOP+RT	[13]
6	73/M	ENKL	Newly diagnosed	3 months	Second	Left arm	Yes	50% SMILE+RT	*

M male, F female, NA not available, LPD lymphoproliferative disorder, MF mycosis fungoides, DLBCL diffuse large B-cell lymphoma, RT radiotherapy, * present case

October 2021 to December 2021. In this period, the ulcer and subcutaneous induration developed without treatment. Thus, we thought that the BNT162b2 mRNA vaccination possibly contributed to the onset of ENKL. Further studies to investigate the mechanism regulating the onset of ENKL after the mRNA vaccination are needed.

This is the first report of ENKL after BNT162b2 mRNA vaccination. Although the relationship between ENKL and vaccination remains unclear, our case provides new insights into lymphomagenesis after vaccination and the pathogenesis of ENKL.

Declarations

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval The patient gave his informed consent for this case report to be published.

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