Case report

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Unilateral lower extremity lymphedema followed by COVID-19 vaccination in patients with cervical cancer history: two case reports

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The coronavirus disease 2019 (COVID-19) pandemic prompted the development of messenger RNA vaccines. Following extensive vaccination campaigns worldwide, several adverse reactions to these vaccines have been reported. This is a case series of unilateral lower extremity lymphedema after COVID-19 vaccination in two patients with a history of cervical cancer. An 82-year-old woman and a 68-year-old woman visited the outpatient clinic with unilateral leg edema after receiving a COVID-19 booster vaccine (BNT162b2; Pfizer-BioNTech) in the deltoid muscle. Both patients had a common history of cervical cancer treated with surgery, chemotherapy, and radiotherapy and were in complete remission. Gynecological evaluations, including laboratory and imaging studies, revealed no specific findings. Lymphoscintigraphy revealed delayed lymphatic drainage with diffuse dermal backflow in a unilateral lower extremity. This case series explores adverse reactions to COVID-19 vaccination in patients who are at high risk of developing lymphedema, providing novel data for similar clinical presentations.

Keywords: COVID-19 vaccines; mRNA vaccines; Lower extremity; Lymphedema; Uterine cervical neoplasms

Introduction

Since the outbreak of coronavirus disease 2019 (COVID-19), extensive research has been conducted, and significant efforts have been made in the manufacture and use of messenger RNA (mRNA) vaccines. Widely used vaccines include BNT162b2 (Pfizer-BioNTech), ChAdOx1 nCov-19 (AstraZeneca), and mRNA-1273 (Moderna). The commonly reported side effects of COVID-19 vaccines, including injection site pain, fever, fatigue, and myalgia, are similar to those of non-mRNA vaccines [1]. Other complications associated with mRNA vaccines have not yet been widely reported; however, rare cases of myocarditis and Bell's palsy have been documented [2]. Additionally, lymph node swelling near the injection site has been observed, which can be particularly concerning in patients with a history of cancer, because lymphadenopathy may also indicate cancer recurrence [3,4]. Notably, there have been reports of upper extremity lymphedema following COVID-19 vaccination in patients with a history of breast cancer [5,6].

Lymphedema is the accumulation of excessive lymphatic fluid in the lymphatic system and interstitial spaces, leading to soft tissue swelling, chronic inflammation, and reactive tissue fibrosis. Primary lymphedema is sporadic, rarely familial, and associated with complex malformations or genetic disorders. Secondary lymphedema arises from lymphatic stasis caused by tumor infiltration, lymph node dissection, radiotherapy, trauma, or infection [7]. Sec-

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ondary lymphedema of the lower extremities often occurs after gynecological cancer treatments, such as lymphadenectomy, chemotherapy, and radiotherapy. The incidence of lower extremity lymphedema in patients with gynecological cancer varies from 1.0% to 50% [8]. In most cases, lymphedema is diagnosed within the first year of gynecological cancer treatment [9]. Risk factors associated with lymphedema include age, body mass index, International Federation of Gynecology and Obstetrics stage, radiotherapy, lymph node dissection, and the number of lymph nodes removed [10]. Histopathologically, lymphedema progresses from dermal edema, which is often not easily visible in the initial stages, to chronic tissue changes, such as dilatation of lymphovascular channels in the subcutaneous tissue. These changes result in deformable edema in advanced stages. Thus, imaging modalities such as high-resolution ultrasound and lymphoscintigraphy may play an essential role in the accurate diagnosis of lymphedema [11].

We report two patients with a history of cervical cancer treated with pelvic lymph node dissection, chemotherapy, and radiotherapy, who achieved complete remission with no evidence of tumor recurrence. However, they developed unilateral lower extremity lymphedema after receiving a COVID-19 booster vaccination (BNT162b2).

Cases

Ethics statement: This case series was approved by the Institutional Review Board (IRB) of Daegu Catholic University Medical Center (IRB No: CR-24-086). The patients provided informed consent for the publication of this case report.

1. Case 1

An 82-year-old woman visited the physical medicine and rehabilitation clinic with a 5-month history of right leg edema. She had received a COVID-19 booster vaccine (BNT162b2) in her right deltoid muscle 5 months previously. She reported that her right leg started swelling a week after vaccination, which worsened over time. The patient had a history of cervical cancer diagnosed 20 years previously and had undergone total hysterectomy, bilateral oophorectomy, bilateral pelvic lymph node dissection, adjuvant chemotherapy, and radiotherapy. The patient achieved complete remission after 5 years of treatment (Table 1). The patient had no history of diabetes mellitus, hypertension, or neurological diseases. On physical examination, the circumference of the right leg was greater than that of the left, with a maximal circumference difference of 9.5 cm, measured 10 cm above the upper margin of the patella (53.0 cm in the affected leg vs. 43.5 cm in the unaffected leg) (Table 2). Swelling in the right leg persisted despite elevation, and the skin had become dry, stiff, and thickened. Examination revealed pitting edema and a positive Stemmer's sign. Based on these findings, the patient was classified as having the International Society of Lymphology (ISL) stage 2 lymphedema. Despite significant swelling, the patient reported no functional impairments such as difficulty walking, climbing stairs, or bending over. Laboratory

Table 2. Circumference of lower extremity during complete decongestive therapy in the intensive phase in Case 1 patient

Region	Affected side (cm)				Unaffected side (cm)
	HD 1	HD 5	HD 9	HD 14	
AK-20 cm	62.0	60.1	59.0	55.5	53.0
AK-10 cm	53.0	53.0	53.2	46.5	43.5
Knee	44.0	42.0	45.1	41.9	36.3
BK-10 cm	44.6	41.5	41.4	40.9	35.2
BK-20 cm	38.5	34.0	33.0	33.0	31.6
Ankle	26.0	25.0	25.4	24.0	22.0

HD, hospital day; AK, above the knee, upper margin of the patella; BK, below the knee, lower margin of the patella; ankle, lower margin of the medial malleolus.

Table 1. Patient demographics

Variable	Case 1	Case 2
Vaccine type	Pfizer-BioNTech	Pfizer-BioNTech
Age (yr)	82	68
Body mass index (kg/m^2)	31.01	28.55
Lymphedema side	Right	Right
ISL stage	2	2
Onset after vaccination (wk)	1	2
Year of cancer diagnosis	2001	1996
Cancer treatment	Surgery (total hysterectomy and bilateral oophorectomy, bilateral pelvic lymph node dissection)	Surgery (radical hysterectomy, bilateral pelvic lymph node dissection)
	Adjuvant chemotherapy	Neoadjuvant chemotherapy
	Radiotherapy	Radiotherapy

ISL, International Society of Lymphology.

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findings, including complete blood cell count and C-reactive protein, D-dimer, and serum creatine kinase levels, were normal. Radiological evaluation revealed no specific findings in the lower extremities and ultrasonography showed no evidence of deep vein thrombosis. There were no signs of tumor recurrence in the follow-up gynecological evaluation (pap smear, pelvic computed tomography, and tumor markers). However, lymphoscintigraphy revealed a marked delay in lymphatic drainage with diffuse dermal backflow in the right leg (Fig. 1). These results indicated secondary lymphedema in the right lower extremity.

The patient received complete decongestive therapy (CDT) daily for 14 days, This comprehensive treatment approach included the following components: manual lymphatic drainage administered by a specialized therapist, multilayered compression bandaging using Mobiderm bandages (Thuasne Group, Saint-Étienne, France) for 21 to 23 hours daily, self-directed exercises to promote lymphatic drainage, and routine skin care. Following treatment, the right leg showed significant improvement, with a reduced circumference from 53 to 46.5 cm (measured 10 cm above the knee) and decreased hardness (Table 2). Before discharge, the patient was educated on the self-application of compression bandages and lifestyle modifications to manage lymphedema. At the 1-month follow-up appointment, the patient's swelling of the right lower leg had significantly improved and remained stable, with a minimal circumference difference of 0.2 cm compared with that of the left leg (43.7 vs. 43.5 cm, measured 10 cm above the knee).

2. Case 2

A 68-year-old woman presented to the physical medicine and rehabilitation clinic with a 3-month history of right leg edema. She had received a COVID-19 booster vaccine (BNT162b2) in her right deltoid, followed by sudden swelling of her entire right leg at 2 weeks post-vaccination. The patient had a history of cervical cancer diagnosed 15 years previously and had been treated with radical hysterectomy with bilateral pelvic lymph node dissection, neoadjuvant chemotherapy, and radiotherapy. The patient achieved complete remission with no post-treatment complications (Table 1). The patient had no history of diabetes mellitus, hypertension, or neurological diseases. On physical examination, the circumference of the right leg was greater than that of the left, with a maximal circumference difference of 12.3 cm, measured 20 cm below the lower margin of the patella (41.3 cm in the affected leg vs. 29.0 cm in the unaffected leg) (Table 3). Swelling in the right leg failed

Table 3. Circumference of lower extremity during complete decongestive therapy in the intensive phase in Case 2 patient

Region	Affected side (cm)				Unaffected side (cm)
	HD 1	HD 5	HD 7	HD 10	
AK-20 cm	61.0	59.0	59.0	57.4	53.0
AK-10 cm	56.5	53.2	53.2	51.2	45.0
Knee	46.0	42.0	42.0	42.2	39.5
BK-10 cm	49.3	44.0	42.7	43.0	37.7
BK-20 cm	41.3	37.7	36.0	36.4	29.0
Ankle	31.0	29.8	28.7	28.7	24.0

HD, hospital day; AK, above the knee, upper margin of the patella; BK, below the knee, lower margin of the patella; ankle, lower margin of the medial malleolus.

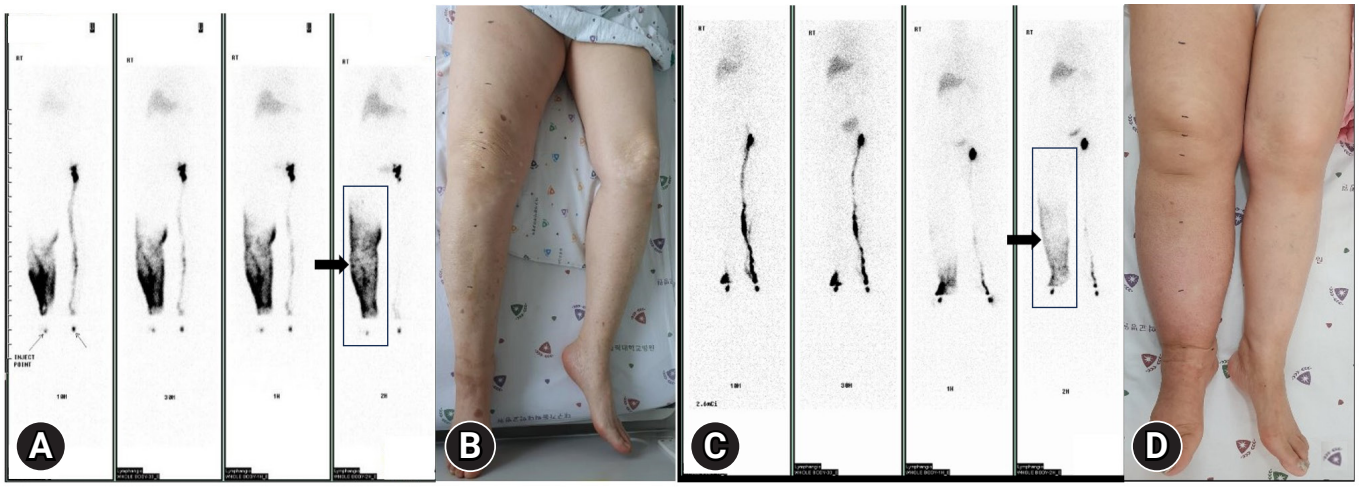

Fig. 1. (A, B) An 82-year-old woman and (C, D) a 68-year-old woman diagnosed with lymphedema in the right lower extremity after coronavirus disease 2019 booster vaccination. (A, C) Lymphoscintigraphy images acquired for 2 hours show decreased lymphatic transport and diffuse dermal backflow (arrows) in the right lower extremity. (B, D) The photograph shows diffuse swelling of the right lower extremity and decreased skin creases on the dorsum of the foot and knee on the right side compared with the left side.

to resolve with elevation, and the skin had become dry, stiff, and thickened. Examination revealed pitting edema and a positive Stemmer's sign, indicating ISL stage 2 lymphedema. The skin changes and persistent swelling suggested chronic lymphatic dysfunction. The patient did not report any functional impairments such as difficulty walking, climbing stairs, or bending over. Laboratory investigations and plain radiography revealed no significant findings. Ultrasonography revealed no evidence of deep vein thrombosis. There were no abnormal findings in the follow-up gynecological evaluation (pap smear, pelvic computed tomography, and tumor markers). Lymphoscintigraphy revealed delayed lymphatic drainage with diffuse dermal backflow in the right lower extremity, consistent with lymphedema (Fig. 1). These findings confirmed the diagnosis of secondary lymphedema in the right lower extremity.

Despite 1 year of outpatient treatment with manual lymphatic drainage and pneumatic compression therapy, the lymphedema showed limited improvement. The patient was admitted to our department for CDT. She received intensive CDT daily, which included manual lymphatic drainage administered by a specialized therapist, multilayered compression bandaging using Mobiderm bandages, self-directed exercises to promote lymphatic drainage, and routine skin care. She was advised to use multilayered compression bandages for 21 to 23 hours each day and was discharged after 10 days of daily intensive CDT (Table 3). Following this treatment regimen, the patient's right leg showed significant improvements, with a reduction in circumference from 41.3 to 36.4 cm (measured 20 cm below the knee) and decreased tissue hardness, indicating effective lymphedema management. At the 2-month follow-up appointment, the swelling of the right lower extremity was well controlled (circumference: 52.8 cm in the affected leg vs. 45.0 cm in the unaffected leg, measured 10 cm above the right knee).

Discussion

This case series presents two patients who developed extensive unilateral swelling of the lower extremity following administration of the Pfizer COVID-19 booster vaccine (BNT162b2), suggesting a potential association between the vaccine and the development of lymphedema. Lymphoscintigraphy confirmed unilateral lower extremity lymphedema with dermal backflow in both patients. Although intensive CDT led to some symptom improvement, complete remission was not achieved, indicating progression to chronic lymphedema.

Since the introduction of COVID-19 vaccines, there have been concerns regarding vaccinations, particularly concerning the potential side effects and adverse events associated with vaccinations. In particular, the Pfizer vaccine, an mRNA vaccine, induces a strong immune response, leading to inflammation and swelling of the lymph nodes [3,4]. Following vaccination, immune cells in the lymph nodes recognize the antigen and mount a response to produce antibodies to combat the virus. This immune activation can cause inflammation and swelling in the lymph nodes nearest the injection site, which is a natural response to the vaccine [3,4]. A previous cohort study showed that Pfizer vaccine-associated hypermetabolic lymphadenopathy was more frequently observed after the booster dose (53.9%) than after the first dose (36.4%) [3]. Additionally, previous cohorts have demonstrated a relatively higher rate of lymphadenopathy after COVID-19 vaccination in patients with cancer (38.8%) than in the general population (6.65%) [4]. Notably, there have been some reports of ipsilateral upper extremity lymphedema developing in patients with breast cancer after COVID-19 vaccination in the deltoid muscle of the affected side [5,6]. Thus, the Centers for Disease Control and Prevention recommends that the COVID-19 vaccine be administered to the opposite arm or leg in patients at risk of lymphedema.

Recently, rare case reports have described bilateral lower extremity swelling following COVID-19 vaccination in the deltoid muscle. For instance, a 79-year-old woman without underlying diseases developed transient bilateral lower extremity lymphedema 1 week after receiving the second dose of the Pfizer COVID-19 vaccine [12]. Similarly, a 68-year-old man with a history of COVID-19 experienced bilateral lower extremity lymphedema combined with cellulitis 3 days after receiving the second dose of the Sinopharm COVID-19 vaccine (BBIBP-CorV) [13]. Unlike these cases of temporary lymphedema, our patients had a history of cervical cancer diagnosed > 20 years ago and were in complete remission, with no prior signs or symptoms of lymphedema. Both patients underwent surgery including pelvic lymph node dissection and radiotherapy. They developed unilateral leg edema 1 and 2 weeks after receiving the Pfizer COVID-19 booster vaccination.

Lower extremity lymphedema is one of the most disabling side effects of surgery and radiotherapy for gynecological cancers. A previous study indicated that cervical cancer survivors had 3.5-fold higher odds of developing lower extremity lymphedema if they received radiotherapy and 3.3-fold higher odds if they underwent lymph node removal than patients who did not undergo lymph node dissection [14]. In another retrospective study, 84% of the patients with gynecological cancer developed lymphedema within the first year after cancer diagnosis [9]. Lymphoscintigraphy is the standard diagnostic method for lymphedema and provides valuable insights into lymphatic drainage and flow. Although not used in our cases, high-frequency ultrasound imaging has recently

emerged as a supplementary diagnostic tool to assess soft tissue changes, such as dermal edema and fibrosis, which are often challenging to detect during physical examinations [15]. It is noteworthy that our patients had never manifested lymphedema clinically for decades before receiving the COVID-19 booster vaccination. If sudden lymphedema manifests in patients with a history of cancer, it may indicate potential cancer recurrence. Therefore, a thorough cancer workup should be prioritized before exploring other potential causes. Both patients in our study underwent gynecological evaluations, and no specific findings were noted during their cancer workup.

Lymphedema often worsens gradually, sometimes worsening years or even decades after lymphatic injury. This observation suggests that lymphatic injury and the resulting blockage of lymph flow may not be the sole factors involved in the development of lymphedema. Other pathological events are likely necessary for lymphedema progression. Experimental and clinical studies spanning several decades have implicated the critical role of inflammation in the pathophysiology of lymphedema [16,17]. Avraham et al. [16] observed that lymphatic stasis resulted in CD4+ T cell inflammation and T-helper 2 differentiation in a mouse model of lymphedema, showing that CD4+ inflammation is a critical regulator of tissue fibrosis and lymphatic dysfunction in lymphedema. Fu et al. [17] reported that inflammatory genes were correlated with a higher number of symptoms attributed to lymphedema in patients with breast cancer. The authors speculated that the cause of lymphedema in the described cases, which did not occur for a long time, might be related to the induction of an inflammatory response due to the vaccine. COVID-19 vaccination may cause lymph node inflammation in patients with lymphatic vessel damage. A notable feature of COVID-19 mRNA vaccines is their ability to easily enter the lymphatic system because they are enclosed in lipid nanoparticles approximately 100 nm in diameter. Lipids are known to be transported to the lymphatic system more efficiently [18], and particles of 10 to 100 nm can easily access the lymphatic system [19]. COVID-19 mRNA vaccines have been shown to stimulate dendritic cells in the lymph nodes, leading to the upregulation of interferon-inducible genes. This could lead to the production of numerous proinflammatory cytokines required for antigen-specific stimulation of naïve T and B lymphocytes [20]. Thus, this inflammation of the lymph nodes may have altered the lymphatic shape, influenced the lymphatic drainage function, and aggravated lymphedema in our two patients with cervical cancer.

This study details unilateral lower extremity lymphedema following COVID-19 mRNA booster vaccination in patients with a history of cervical cancer. To our knowledge, these are the first reported cases of post-vaccination unilateral lymphedema in patients with prior gynecological cancer treatment. Although the exact mechanism remains unclear, we hypothesized that the immune response triggered by the vaccine may have caused inflammation in the lymph nodes, potentially contributing to the onset of lymphedema. This case underscores the importance of vigilance among healthcare providers when administering COVID-19 mRNA vaccines to patients with preexisting lymphatic issues, as vaccination may exacerbate or trigger lymphedema. Clinicians should consider a thorough lymphatic assessment before and after vaccination in such patients. However, further studies are required to validate and expand upon these findings.

Article information

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Author contributions

Conceptualization, Data curation, Formal analysis, Project dministration, Supervision: HKC; Methodology: JIJ, HKC; Visualization: JIJ; Writing-original draft: JIJ, HKC; Writing-review & editing: HKC.

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