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REVIEW ARTICLE

Title: A review of the literature on radiation recall phenomena in induced by COVID-19 infection or vaccination in cancer patients

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Abstract: Objective: Radiation recall (RR) is a known complication of coronavirus disease 2019 (COVID-19) and can cause severe disease. The aim of the present review was to provide additional insights into this phenomenon.Methods: The PubMed, Embase, Scopus, and Web of Science databases were searched until February 1, 2023, using the keywords radiation therapy, recall, and COVID-19, limiting the search to human studies and publications in English. The studies included case reports of patients who developed RR symptoms initiated by either COVID-19 infection or vaccination.Results: Twelve studies and 15 case reports were identified. RR reactions involved the skin, lungs, and laryngeal mucosa, of which radiation recall dermatitis (RRD) was the most frequent. Local symptoms were largely self-limiting, with only a few cases requiring anti-inflammatory drugs, and one patient needing a tissue transplant. Patients with radiation recall pneumonitis (RRP) resulting from infection experienced a drop in oxygen partial pressure to varying degrees. Symptoms after vaccination were mild. Radiation recall mucositis (RRM) in the laryngeal mucosa could pose a risk of death. Conclusions: In the era of COVID-19, RR is a complex toxicity that can occur after a wide range of radiotherapy doses. Most commonly, it presents in the skin. RRD symptoms were largely self-limiting, while RRP due to infection and RRM may be potentially life-threatening. Although there are relatively few reports of RR, it has been reported worldwide and various acute phase reactions to radiotherapy such as dermatitis, pneumonitis, and mucositis have been described. It has also been reported not only with viral infections but also with various vaccines.These reports are likely to be the tip of the iceberg, as RR is difficult to detect unless each patient and physician are aware of them. More attention and follow-up are required. These reports may also be a reference for infectious diseases in the future.

Keywords: COVID-19; Radiation Recall; radiation recall dermatitis; radiation recall pneumonitis;Radiation recall mucositis

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1. Introduction

The novel coronavirus disease 2019 (COVID-19) pandemic began in December 2019, and vaccines have been essential as cutting-edge measures to mitigate the adverse effects of the pandemic. Four distinct vaccines (mRNA-based, adenoviral vector-based, recombinant protein, and inactivated vaccines) have been approved. Cancer patients are permitted to use any of these vaccines and no precautions are specified for those receiving radiation treatment. However, it has recently been discovered that both COVID-19 infection and its vaccines can induce radiation recall (RR), an apparently novel phenomenon. RR is most commonly triggered by anti-tumor therapy but has also been reported to be caused by antibiotics, simvastatin, and hormone therapy [1-4]. Recently, several inflammatory reactions have been reported in irradiated tissues triggered by COVID-19 infection or its vaccines [5]. Currently, there appears to be an association between COVID-19 infection or vaccines and some form of RR. RR has been reported in various countries in response to different diseases and different vaccines. The clinical importance of RR lies in two aspects. Firstly, an appropriate diagnosis of RR should be made so that treatment can be tailored to its specific etiology, especially for those patients who were not followed up in the radiotherapy department. Secondly, the benefit of follow-up vaccination must be assessed with respect to the risk of exacerbating the reaction.

2. Materials and methods

We retrospectively searched for publications in the PubMed, Embase, Scopus, and Web of Science databases for review. Publications in English and on human subjects were searched until February 1, 2023, using the keywords radiotherapy, recall, COVID-19, Covid-19, and vaccine. Apart from one observational study, 12 other studies and 15 case reports on RR involving the skin, lungs, and laryngeal mucosa were identified. In the present review, we discuss the current understanding and evidence on RR and provide additional insights into this rare but sometimes severe disease.

Table 1. Case report of RRD caused by COVID-19.

Author	age	sex	primary tumor	radiation site	RT Dose	Time interval	type of vaccine	Time onset	Drug	Reference No.
Soyfer	68	M	soft tissue sarcoma	1. CW and lung 2.lung, 3.lung	1. 50Gy/25F 2. 50Gy/5Fr 3. 45Gy/5Fr	1. 235d 2. 216d 3. 76d	mRNA	1.26d 2.5d	No	[7]
Soyfer	64	M	solitary fibrous tumor	1.lumbar spine 2. CW	1.36Gy/12Fr 2. 39Gy/13Fr	1.43d 2.38d	mRNA	1.27 d 2.6 d	-	[7]
Ross	64	F	breast cancer	1.CW andsupraclavicular 2.CW	1.50.4Gy 2.45-60Gy	1.9y 2.7y	viral vector	-	Yes	[10]
Aafcan	60	F	melanoma	right leg	30Gy/10Fr	2y3m	inactivated	5d	Yes	[8]
Marples	62	F	breast cancer	breast	-	3Y	viral vector	3d	No	[14]
	69	F			-	-		3d	-	
	56	F			-	3M		3d	-	
Ishikawa	51	F	breast cancer	CW and supraclavicular	50Gy/25Fr	46 d	mRNA	7 d	Yes	[11]
Stewart R	57	F	parotid gland carcinoma	periauricular and submandibular	66Gy/33Fr	6M	vector	3h	No	[12]

RRD radiation recall dermatitis M: Male F: femal CW: chest wall; Time interval(at end of radiotherapy to vaccination);Time to onset of reaction (final vaccination to RRD)

Table 2. Case report of RRP caused by COVID-19.

Author	age	sex	primary tumor	radiation site	RT Dose	Time interval	type of vaccine	Time onset	Drug	Reference No.
Kurosaki	78	F	lung cancer	1.lung and mediastinum 2.Brain metastasis 3.Whole-brain	1.45Gr/30Fr 2.30Gy/10Fr 3.18Gy/6Fr	3.5 years→2 years	-	after infection of 2d	-	[16]
Lazzari	65	F	breast cancer	supraclavicular area and breast	50Gy/25Fr	5 years	-	onset of infection	Yes	[17]
steber	66	M	lung cancer	right lung and mediastinum	45Gy/15Fr	8 month	mRNA Moderna	vaccine 3-5d	Yes	[19]
shinada	48	M	lung cancer	lung and mediastinum	60Gy/30Fr	1 year	mRNA Pfizer	2nd vaccine 19d	Yes	[20]
Hughes	67	M	lung cancer	1.whole brain 2.lung	1.- 2.60Gy/15Fr	1.8 year	mRNA	2nd vaccine 4d	Yes	[21]
Kurosaki	78	F	lung cancer	1.lung and mediastinum 2.Brain metastasis 3.Whole-brain	1.45Gr/30Fr 2.30Gy/10Fr 3.18Gy/6Fr	3.5 years→2 years	-	after infection of 2d	-	[16]

3. Experimental

Radiation Recall Dermatitis (RRD) RR can affect several tissues, although the skin is most frequently involved, and RRD typically displays the histological and clinical characteristics of acute inflammation [6]. In 6 case studies (Table 1) and one observational single-center research report, RRD was caused by COVID-19. These localized effects were treated successfully with anti-inflammatory drugs, and the symptoms were usually self-limiting. Soyfer et al. reported the first observation of RRD in two patients who had received the Pfizer mRNA COVID-19 vaccine [7]. These two patients presented at their clinic with a painful, erythematous rash distributed over the chest wall radiation field, leading to a diagnosis of RRD. Afacan et al. described a melanoma patient who experienced RRD after receiving an initial dose of the COVID-19 vaccine [8]. The 60-year-old woman had received radiation therapy (30 Gy/10fr) in four regions on her right leg 2 years and 3 months previously. RRD occurred at two sites of the previous irradiation area within 5 days of receiving the inactivated vaccine. Although multiple sites had been irradiated, the dermatitis only occurred on some sites rather than all. Stewart R et al. described a 57-year-old patient who had undergone prophylactic radiation therapy (66Gy/33fr) [9]. In this case, the time between vaccination and the occurrence of RRD was the shortest. After receiving her first dose of vaccine (the vector vaccine), she experienced pruritus, mild erythema, and itching in the radiation-exposed area within three hours. The symptoms worsened over the following three weeks, leading to a precisely articulated area of skin erythema conforming to the skin dose of around 55Gy. Simple analgesia was used to treat her symptoms, along with protective dressings. Three months later, she received the second dose of the vaccine without experiencing RRD symptoms. As can be observed from this case, patients may not be affected by the second dose of vaccination even if they have experienced RR after the first dose. Five case series of vaccine-induced dermatitis were reported in patients with breast cancer [10-12]. Most RRD symptoms in these studies were mild, which is consistent with the findings of the observational study [13]. Overall, 361 breast cancer patients were recruited. These patients had undergone postoperative breast external beam radiation therapy (EBRT) and received at least one dose of the COVID-19 vaccine. RRD was diagnosed in 20 of the patients (5.5%) with an average time between vaccination and the occurrence of RRD of four days (range, 1-14 days). The occurrence rate of RRD per dosage of the vaccination was 2.6%, with the risk significantly higher for the initial dose (4.4% vs 1%, p = 0.003) than for the second or third dose and occurred primarily when the vaccine was delivered during the first month after the completion of irradiation (12.5% vs 2.2%, p = 0.0004). In addition, RRD potentially caused by the COVID-19 vaccine appeared to be self-limiting, as demonstrated in the case report where only 4 of 20 patients were given anti-inflammatory drugs, while the initial symptoms of other patients gradually resolved. However, this study had several limitations. First, the analysis of RRD occurrence was based on data obtained by telephone survey and patient-reported symptoms. Second, RRD may develop years after EBRT but for the purpose of the study, the authors chose to restrict the sample group to patients who had received at least one dose of the COVID-19 vaccination within a year of completing EBRT. Third, the prevalence of RRD in the study may have been overestimated by the possible presence of prolonged skin radiotoxicity, which can manifest within 1 to 6 weeks following EBRT. Nevertheless, the study revealed that RRD usually occurs after receiving the first dose of the vaccine, with low to mild severity and typically self-limiting effects. Although RRD symptoms are usually mild, in some cases they can be severe. Ross et al. reported a patient who was initially diagnosed with breast cancer and underwent radiation therapy to the chest wall and axilla (50.4 Gy) for treatment in 2012 [11]. The patient suffered a skin relapse less than six months after becoming disease-free and underwent a second round of radiation therapy (dose: 45-60 Gy), which was completed in March 2014. Since then, she has remained disease-free, with late radiation therapy damage consisting of capillary dilatation and fibrosis in the chest wall. In April 2021, this woman contracted COVID-19, which caused burning, redness, and skin breakdown in her left chest wall. Her left breast wall was covered in severe erythema with clearly defined borders and a necrotic wound. Anatomically, these skin observations matched the radiation therapy dose gradient administered seven years earlier. The patient recovered from COVID-19 with conservative treatment; nevertheless, the necrotic region expanded after receiving her first viral-vector COVID-19 vaccine in July 2021. She intended to undergo vacuum-assisted wound closure and a potential autologous tissue transfer. In the six case reports above, a total of nine cases were involved. The median time from vaccination to the onset of RRD was 3 days (range, 3 h-7 days). RRD occurred over a wide range of time periods, from 38 days to 7 years following the completion of radiation therapy. Local symptoms were largely self-limiting, with only a few cases requiring anti-inflammatory drugs and one patient needing a tissue transplant. It is vital to note that a thorough medical history and physical examination are necessary to differentiate between this normally benign, self-limiting condition and recurring cancer. Radiation recall pneumonitis (RRP) McInerney et al. documented one of the early cases of radiation recall pneumonitis (RRP) in a young child who had been given adriamycin in 1976 [14]. RRP is diagnosed clinically based

on the development of acute inflammation in previously irradiated lung parenchyma, with symptoms including dry cough, low-grade fever, and shortness of breath. Pharmacological treatments, particularly chemotherapy, are typical causes, but recently there have been increasing reports of RRP following targeted and immune checkpoint inhibitor (ICI) therapy [5,15]. Concerns about overlapping inflammatory reactions in patients undergoing ICI therapies and COVID-19 infection have emerged during the COVID-19 period, which could exacerbate the onset of lung inflammation. Based on the CT results, RRP was mainly restricted to areas of the lung that had been previously irradiated. The limited reports available suggest that either the vaccine or the virus may have caused the RRP. Table 2 shows a total of five cases, two of which were caused by infection and three by vaccination. Patients with RRP caused by infection experienced varying degrees of reduced oxygen partial pressure, while patients with RRP due to vaccination had mild symptoms. One case described a 78-year-old woman who developed RRP triggered by COVID-19 infection 3.5 years after receiving radiation therapy for lung cancer [15]. On day 7, her respiratory condition rapidly deteriorated following a positive COVID-19 test. The chest radiograph revealed substantial shadows at the site of previous radiation exposure, and the SpO2 rapidly decreased to 74%. Rapid respiratory status deterioration required 4 L of oxygen. Another case of RRP due to infection was a 65-year-old woman diagnosed with breast cancer (pT2N2M0) in 2016 [16]. She underwent postoperative adjuvant radiation therapy (50Gy/25fr) to the supraclavicular region and breast. After contracting COVID-19, she experienced fever, mild dyspnea, and cough, and her oxygen saturation fell below 90%. A chest CT revealed many ground-glass opacities (GGOs) in both lungs. Three months later, a chest CT showed persistent lung fibers in the radiation-damaged region, although the GGO was completely resolved. Shadows consistent with the irradiated field appeared to have been caused by COVID-19 in these patients, leading to decreased oxygen saturation. Following their COVID-19 infections, the patients were clinically diagnosed with RRP, which improved with further therapy. The authors reported that two patients met the diagnostic criteria for RTOG level 3. In a case presented by Steber et al., a 66-year-old man received local consolidation radiation therapy to the right lung and continued with maintenance immunotherapy. He remained asymptomatic for eight months after completing radiation therapy [17]. Three to five days after receiving his first COVID-19 vaccination, eight months after his initial radiation treatment, he experienced symptoms resembling pneumonitis. Three days after receiving his second dose, he noticed that his cough had become more frequent. That the RRP was caused by the COVID-19 vaccination was strongly supported by the association between the first appearance of symptoms just a few days after the first dosage and the development of severe symptoms a few days after the second dose. Furthermore, the CT findings, which were mostly limited to certain regions, indicated the possibility of RRP. Shinada et al. stated that their patient had undergone chemoradiation therapy for a tumor in the right lung and mediastinum (60 Gy/30 fr) [18]. After completing the chemoradiation therapy, Durvalumab was given every two weeks for a year, and there were no disease recurrences or serious adverse effects. The patient received the COVID-19 vaccination and developed a fever and dry cough 19 days following the second vaccine; CT imaging indicated an infiltrate shadow in the right middle and lower lobes, encompassing the earlier radiation field. In both cases, the patients experienced prompt healing after taking prednisolone [17, 18]. Hughes described a 67-year-old man who had undergone radiation therapy (60 Gy/15fr) for metastatic lung cancer [19]. The patient received two doses of an mRNA COVID-19 vaccination 18 months after radiation therapy. Four days after the second dosage, a PET/CT scan revealed RRP. This resolved spontaneously without any treatment. Vaccines developed to protect against potential future infections must trigger an immune response similar to the infection itself [21]. The case report on the development of RRP after an infection mentioned that the vaccine's inflammatory state might increase the risk of RR. Unlike RRD, a second dose of the vaccine may aggravate clinical symptoms in patients with RRP In the five case reports above, a total of five patients developed RRP a median of 18 months (range, 8 months-5 years) after the completion of radiation therapy. While symptoms of RRP due to infection were mild, they could become life-threatening due to the infection. The authors did not discourage any participant who had received thoracic irradiation in the past or was currently on an ICI from getting vaccinated against COVID-19 [17]. However, if a patient who had received chest irradiation becomes infected with COVID-19, it was suggested to monitor the chest findings closely. Radiation recall mucositis (RRM) The only reported case of COVID-19 vaccine-induced RRM in the laryngeal mucosa was caused by treatment using a vascular endothelial growth factor (VEGF) inhibitor [21]. Three years before, the 50-year-old patient underwent RT (67.2 Gy/28fr) to the upper peribronchial area and larynx. The patient experienced bleeding of the laryngeal mucosa around the larynx, which was thought to be RRD caused by RRM. Treatment for RRM was subsequently aborted, followed by remission of the RRD. However, this patient developed RRD after the first COVID-19 vaccination. Five days later, the patient developed a cough and sore throat, which worsened over time, and marked stridor was observed, and a tracheotomy was considered. After four weeks of steroid pulse therapy, the edema of the vocal cords improved. It is worth noting that while RR occurs primarily on the skin, it can also affect the mucosa of the upper respiratory tract, especially when VEGF inhibitors are used. In addition, it can be induced by COVID-19 vaccines. RRM can be fatal in patients with a history of RT in the laryngeal region and treatment with VEGF inhibitors.

4. Results

RR induced by COVID-19 vaccination or infection is an uncommon clinical phenomenon [1-4]. As COVID-19 vaccines continue to be administrated on a large scale, clinicians should be aware of the possibility of RR in patients with a previous history of radiotherapy. Our review provides an updated description of RR, with the hope of mitigating some of the confusion regarding specific situations. RR reactions can involve the skin, lungs, and laryngeal mucosa. RRD occurs most frequently. The majority of local cutaneous symptoms are self-limiting. Since most cancer patients have a long post-radiation course, doctors should carefully determine whether symptoms seen during follow-up are malignant or treatment-related. Patients with RRP due to infection tend to experience a drop in oxygen partial pressure, while vaccination-induced symptoms are mild [10,15-19]. Therefore, even for RRD and RRP, the authors recommend COVID-19 vaccination for patients undergoing treatment, as long as there are no contraindications to any of the vaccine components. Furthermore, RRM can be fatal in patients with a history of RT in the laryngeal region and who have been treated with VEGF inhibitors [21]. COVID-19 vaccination in these patients should be approached with caution. However, most patients would likely not be affected by the second dose of vaccine even if they experienced RRD following the first dose [8]. However, in the case of RRP, the second dose may worsen the symptoms [9]. There are several limitations to this study. First, the review was limited by the quality of the published evidence on RR. Moreover, the toxicity was retrospectively graded based on the description and images provided in the case reports. However, our objective in this review was to attempt to provide a comprehensive analysis of RR given the lack of uniformity in the reported literature. To the best of our knowledge, this is the first review of this phenomenon.

5. Conclusion

Although there are not many reports of RR, it has been reported worldwide and various acute phase reactions to radiotherapy such as dermatitis, pneumonitis, and mucositis have been described. It has also been reported not only with coronavirus infections but also with various vaccines. These reports are likely to be the tip of the iceberg, as RR associated with COVID-19 is difficult to detect unless each patient and physician is aware of it. We clinicians need to pay more attention, together with follow-up. At the same time, these reports may provide a reference for infectious disease-associated complications in the future.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This is a review and does not involve ethics-related information

CONFLICT OF INTEREST

No conflict of interest between authors

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All individuals listed as authors must have contributed substantially to the design, performance, analysis, or reporting of the work and are required to indicate their specific contribution. Anyone (individual/company/ institution) who has substantially contributed to the study for important intellectual content, or who was involved in the article's drafting the manuscript or revising must also be acknowledged.

References

References must use Endnote.

References should be provided exactly in the journal's specific format.

[1] Burris HA 3rd, Hurtig J. Radiation recall with anticancer agents. Oncologist. 2010. 15(11): 1227-37.

[2] Wernicke AG, Swistel AJ, Parashar B, Myskowski PL. Levofloxacin-induced radiation recall dermatitis: a case report and a review of the literature. Clin Breast Cancer. 2010. 10(5): 404-6.

[3] Abadir R, Liebmann J. Radiation reaction recall following simvastatin therapy: a new observation. Clin Oncol (R Coll Radiol). 1995. 7(5): 325-6.

[4] Foster LM, Mahoney ME, Harmon MW, Allen JW, Luh JY. Radiation recall reaction with letrozole therapy in breast cancer. Clin Breast Cancer. 2014. 14(3): e95-7.

[5] Jan PR, Chang JW, Wu CE. Radiation Recall Pneumonitis: A Rare Syndrome That Should Be Recognized. Cancers (Basel). 2022. 14(19): 4642.

[6] Bhangoo RS, Cheng TW, Petersen MM, et al. Radiation recall dermatitis: A review of the literature. Semin Oncol. 2022. 49(2): 152-159.

[7] Soyfer V, Gutfeld O, Shamai S, Schlocker A, Merimsky O. COVID-19 Vaccine-Induced Radiation Recall Phenomenon. Int J Radiat Oncol Biol Phys. 2021. 110(4): 957-961.

[8] Afacan E, Öğüt B, Üstün P, Şentürk E, Yazıcı O, Ad ışen E. Radiation recall dermatitis triggered by inactivated COVID-19 vaccine. Clin Exp Dermatol. 2021. 46(8): 1582-1584.

[9] Stewart R, McDowell L. Radiation Recall Phenomenon Following COVID-19 Vaccination. Int J Radiat Oncol Biol Phys. 2021. 111(3): 835-836.

[10] Marples R, Douglas C, Xavier J, Collins AJ. Breast Radiation Recall Phenomenon After Astra-Zeneca COVID-19 Vaccine: A Case Series. Cureus. 2022. 14(1): e21499.

[11] Ross RB, Rabinovitch RA. Radiation recall after COVID-19 infection. Lancet Oncol. 2022. 23(4): e197.

[12] Ishikawa Y, Umezawa R, Yamamoto T, et al. Radiation recall phenomenon after administration of the mRNA-1273 SARS-CoV-2 vaccine. Int Cancer Conf J. 2022. 11(1): 91-95.

[13] Vinante L, Caroli A, Revelant A, et al. Radiation recall dermatitis induced by COVID-19 vaccination in breast cancer patients treated with postoperative radiation therapy. Breast. 2022. 65: 49-54.

[14] Mclnerney DP, Bullimore J. Reactivation of radiation pneumonitis by adriamycin. Br J Radiol. 1977. 50(591): 224-7.

[15] Kurosaki H, Utsumi N, Miura K. A Case of Suspected Radiation Recall Pneumonitis After a COVID-19 Infection. Cureus. 2021. 13(3): e13688.

[16] Lazzari G, Giua R, Verdolino E, et al. Radiation Recall Pneumonitis COVID-19 Infection Induced After Adjuvant Breast Cancer Radiotherapy. A Known Phenomenon in an Unknown Pandemic Disease: A Case Report. Cancer Manag Res. 2022. 14: 2299-2304.

[17] Steber CR, Ponnatapura J, Hughes RT, Farris MK. Rapid Development of Clinically Symptomatic Radiation Recall Pneumonitis Immediately Following COVID-19 Vaccination. Cureus. 2021. 13(4): e14303.

[18] Shinada K, Murakami S, Yoshida D, Saito H. Radiation recall pneumonitis after COVID-19 vaccination. Thorac Cancer. 2022. 13(1): 144-145.

[19] Hughes NM, Hammer MM, Awad MM, Jacene HA. Radiation Recall Pneumonitis on FDG PET/CT Triggered by COVID-19 Vaccination. Clin Nucl Med. 2022. 47(3): e281-e283.

[20] Sreepadmanabh M, Sahu AK, Chande A. COVID-19: Advances in diagnostic tools, treatment strategies, and vaccine development. J Biosci. 2020. 45(1): 148 [pii].

[21] Tatekawa S, Hoshino S, Takemoto N, et al. COVID-19 vaccine-induced Recurrence of the Radiation Recall Phenomenon in the Laryngeal Mucosa Due to a VEGF Inhibitor. Adv Radiat Oncol. 2022. 7(6): 101048.