Abstract: Radiation Recall Phenomenon (RRP) is an uncommon, late occurring, acute inflammatory skin reaction that emerges in localized areas coincident with previously irradiated radiotherapy (RT) treatment fields. RRP has been known to be triggered by a number of chemotherapy agents. To the best of our knowledge, this report is the first description of RRP following administration of the Pfizer-BioNTech vaccine for COVID-19, or any other currently available vaccine against COVID-19. Acute skin reactions were observed in two radiotherapy patients with differing timelines of RT and vaccinations. In both cases however, the RRP presented within days of the patient receiving the second dose of vaccine. For each RT course the treatment planning dosimetry of the radiation fields was compared to the area of the observable RRP. RRP developed within the borders of treatment fields where prescription dose constraints were prioritized over skin sparing. Our observation is currently limited to two patients. The actual incidence of RRP in conjunction with Pfizer-BioNTech vaccine or any other vaccine against Covid-19, is unknown. For cancer patients being treated with radiation with significant dose to skin, consideration should be given to the probability of RRP side-effects from vaccinations against COVID-19.
COVID-19 Vaccine Induced Radiation Recall Phenomenon

Short title: COVID-19, Vaccine, Radiation Recall Phenomenon

Viacheslav Soyfer¹, Orit Gutfeld¹, Sivan Shamai², Albert Schlocke¹, and Ofer Merimsky².

1- Department of Radiation Oncology, Division of Oncology, Tel-Aviv Medical Center, affiliated with Sackler School of Medicine, Tel-Aviv University

2-Unit of Soft Tissue and Bone Oncology, Division of Oncology, Tel-Aviv Medical Center, affiliated with Sackler School of Medicine, Tel-Aviv University

Corresponding author: Viacheslav Soyfer, MD

Email: slavas2506@gmail.com

Conflict of Interest: None.
Funding: None.
Research data are stored in an institutional repository and will be shared upon request to the corresponding author.
Acknowledgements” None
COVID-19 Vaccine Induced Radiation Recall Phenomenon

Abstract:

Radiation Recall Phenomenon (RRP) is an uncommon, late occurring, acute inflammatory skin reaction that emerges in localized areas coincident with previously irradiated radiotherapy (RT) treatment fields. RRP has been known to be triggered by a number of chemotherapy agents.

To the best of our knowledge, this report is the first description of RRP following administration of the Pfizer-BioNTech vaccine for COVID-19, or any other currently available vaccine against COVID-19. Acute skin reactions were observed in two radiotherapy patients with differing timelines of RT and vaccinations. In both cases however, the RRP presented within days of the patient receiving the second dose of vaccine.

For each RT course the treatment planning dosimetry of the radiation fields was compared to the area of the observable RRP. RRP developed within the borders of treatment fields where prescription dose constraints were prioritized over skin sparing.

Our observation is currently limited to two patients. The actual incidence of RRP in conjunction with Pfizer-BioNTech vaccine or any other vaccine against Covid-19, is unknown.

For cancer patients being treated with radiation with significant dose to skin, consideration should be given to the probability of RRP side-effects from vaccinations against COVID-19.

Introduction:

Radiation Recall Phenomenon (RRP) is a late effect, acute skin reaction associated with therapeutic irradiation, triggered by something other than radiation. It usually appears more than
one week after the completion of radiation therapy and is typically localized to the radiotherapy field entry points. The RRP is frequently wrongly misinterpreted for radio-sensitization if the skin reaction appears within 7 days following radiation treatment (1).

The radiation recall syndrome was first described by D’Angio et al in 1959 (2). Though oncologists are generally aware of RRP, little is known about its pathophysiology.

Burris H.A. et al, summarized the theories of RRP (3). The increased sensitivity of the stem cells in the field of radiation may result in an acute reaction to subsequent chemotherapy and idiosyncratic drug hypersensitivity reactions (1). The level of inflammation-mediating cytokines induced by radiation may be upregulated by chemotherapeutic agents (4).

Although the development of RRP is usually associated with cytotoxic drugs, there are several non-cancer treatment remedies which can evoke this syndrome (5,6,7,8,9).

Although RRP mostly presents in a mild form, in just under 10% of cases symptoms can be severe, and include moist desquamation in areas other than skin folds, and bleeding can be induced by minor trauma or abrasion (10).

The decision to utilize systemic cancer treatments in conjunction with radiotherapy is frequently limited by the risk for developing devastating skin reactions. In order to decrease the risk of severe RRP it is usually recommended to increase the time interval between radiation therapy and the start of chemotherapy (11).

The regulations imposed for the COVID-19 pandemic is challenging for a wide community of cancer patients, often requiring isolation and restricted visitation.
Clinical oncologists who deal with the administration of multiple systemic treatments and radiation therapy, must now factor Covid-19 vaccination into their treatment paradigms.

The official website of the American Society of Clinical Oncology states, "At this time, patients undergoing treatment may be offered vaccination against COVID-19 as long as any components of the vaccine are not contraindicated. Strategies such as providing the vaccine in between cycles of therapy and after appropriate waiting periods can be used to reduce the risks while maintaining the efficacy of vaccination" (12). The evolving dramatic changes in view of COVID-19 are beyond the discussion of this report. The RRP we observed associated with Pfizer-BioNTech vaccine was reported to the management of the Tel Aviv Medical Center following a process regulated by the Israel Ministry of Health.

Materials and Methods:

In our radiotherapy department, we observed two patients who developed acute skin reactions in previously irradiated areas after receiving two doses of Pfizer-BioNTech vaccine. The reactions were diagnosed as RRP.

Case Presentation -- Patient No. 1:

A 68-year-old otherwise healthy male was diagnosed with a metastatic soft tissue sarcoma (unclassified spindle cell sarcoma) involving the soft tissues of the posterior chest wall, and one lesion in the right lung. Preoperative radiation therapy of 50 Gy in 25 fractions with electrons (mixed 9 and 12 MeV) prescribed to 90% isodose level, with 0.5 cm bolus over the entire field was delivered to his back (Fig 1a).
Over the last two weeks of the electron course, the patient received SBRT, 50 Gy in 5 fractions to a lesion in the right lower lobe. Two months after the RT, the patient underwent a complete resection of the residual disease in the posterior chest wall. This was followed by an additional course of SBRT to two other lesions, 45 Gy in 5 fractions (Fig 2). The patient did not receive any systemic chemotherapy during the observed period, nor any therapeutic drugs known to cause RRP.

Six months following the initial RT to the posterior chest wall, the patient received his first Covid-19 vaccination, followed by a second shot 21 days later. This sequence of RT and vaccinations is detailed in the timeline (Fig. 3).

Five days after the second shot of the vaccine, an acute skin reaction developed, associated with pain, burning sensation, redness and mild skin exfoliation in the area of the posterior chest wall electron field (Fig 1b). It can be seen that the electron port shape closely resembles the erythematic area.

The RRP was treated symptomatically with topical steroids and pain killers. The reaction resolved within a few days. No pulmonary symptoms were reported, and no RRP developed in areas other than described.

Case Presentation -- Patient No. 2:

A 64-year-old male, otherwise healthy, suffering from metastatic soft tissue sarcoma (solitary fibrous tumor) received radiation to two treatment sites: lumbar vertebrae after surgery for spinal cord compression, and subsequent palliative radiotherapy to a painful metastatic lesion in the right chest wall.
The lumbar spine was treated by two posterior oblique 6 MV photon fields (Fig. 4) which provided partial skin sparing.

The chest wall tumor was treated with two tangential 6 MV photon fields with 0.5 cm bolus covering the treatment area resulting in coverage of the target with high but tolerable skin dose (Fig 5a).

The first shot of vaccine was administered five days prior to the conclusion of the RT. The second dose of vaccine followed 21 days later, approximately two weeks after cessation of RT. This sequence is detailed in the timeline (Fig 6).

Six days following the second vaccination, an acute skin reaction was noted, manifested by skin redness and itching sensation. No local therapy nor pain killers were needed. The reaction faded slowly within the following week (Fig 5b).

RRP was not observed on the skin covering the lumbar spine.

Discussion:

One of the promising ways to overcome the COVID-19 pandemic is through recently developed vaccines. For some radiotherapy patients, receiving the highly effective vaccination will supersede any low risk RRP side-effects that potentially may occur from concurrent or prior radiotherapy. To the best of our knowledge, our clinical observations are the first RRP reported following administration of the Pfizer-BioNTech vaccine for COVID-19. The real incidence of this phenomenon is unknown. We cannot conclude nor predict the elapsed time following radiation therapy that will not induce RRP. Notable, in one of our patients the RRP erythema
appeared 6 months after the radiation exposure, the other occurrence only shortly after the cessation of radiotherapy. Similarly, the determination of a radiation dose threshold responsible for RRP cannot be estimated from this small observation.

Conclusion:

For cancer patients, recommendations regarding vaccination are evolving. We observed in our clinic the development of Radiation Recall Phenomenon in two patients with varying courses of radiotherapy, seemingly triggered by a COVID-19 vaccine. Reasonable considerations should be applied to decisions regarding vaccination of on-treatment radiotherapy patients. Patients and physicians should be aware of the potential for the RRP side-effect following Covid-19 vaccination.

References:


Figure captions:

- Figure 1a: Posterior chest wall treatment plan (Pt #1).
- Figure 1b: Acute skin reaction following COVID-19 vaccination (Pt #1).
Figure 2: SBRT dose distributions for lung treatments (Pt #1).

Figure 3: Timeline for Patient #1

Figure 4: Lumbar spine treatment plan-oblique fields (Pt #2)

Figure 5a: Anterior chest wall treatment plan (Pt #2)

Figure 5b: Acute skin reaction following COVID-19 vaccination (Pt #2).

Figure 6: Timeline for Patient #2
Figures 1a and 1b.
Figures 2a and 2b
Figure 3.

- Preop RT to primary tumor in back, 50 Gy in 25# Day 0-Day 34
- SBRT to RLL, 50 Gy in 5# Day 19-Day 34
- Surgery Day 99
- SBRT to RML and LLL, 45 Gy in 5# for each, Day 159-Day 169
- RRP DAY 235

Timeline:
- 1st dose of vaccine DAY 209
- 2nd dose of vaccine DAY 230
Figure 4.
Figure 5.
Figure 6.