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CASE REPORT

Radiation Recall Pneumonitis COVID-19 Infection Induced After Adjuvant Breast Cancer Radiotherapy. A Known Phenomenon in an Unknown Pandemic Disease: A Case Report

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Abstract: The COVID-19 pandemic has opened several new disease scenarios, yielding novel syndromes that have never been seen before and resurrecting old inflammatory phenomena that are no longer recorded, such as radiation recall (RR) syndromes. Radiation recall syndrome is a limited field inflammatory reaction that occurs in a volume that was irradiated several months or years previously before being induced by a triggering factor. The most frequently reported phenomena are skin reactions; however, other organs could be involved, such as the lungs in radiation recall pneumonitis (RRP). It is a well-described inflammatory reaction that occurs within a pulmonary volume that was irradiated several months or years previously via radiotherapy (RT), triggered by factors such as drugs, including chemotherapy agents, immunotherapy, or vaccination. Indeed, during the COVID-19 pandemic, RRP following anti-COVID -19 vaccination or SARS-CoV2 infection was recently reported. ACE receptor-rich tissues such as lung or skin tissues were mainly involved. Herein, we present a case of RRP triggered by COVID-19 pulmonary infection in a woman who previously underwent adjuvant breast cancer radiotherapy. Although symptoms were typical, pulmonary CT findings depicted a unique distribution of ground-glass opacities (GGOs) throughout the previous radiation portals and mirror-like the radiation fields. Anamnesis and radiation plan evaluation were crucial in the diagnosis of RRP.

Keywords: recall syndromes, adjuvant radiotherapy, immune memory, ACE receptors

Introduction

The term "Radiation Recall (RR)" refers to an inflammatory reaction, caused by several triggering agents, that occurs in tissues that were irradiated several weeks or months after radiotherapy (RT). It is characterized by an inflammatory, quite symptomatic syndrome with clinical and radiological findings visible in the radiation port, miming the dose distribution pathway of the radiation beams. This phenomenon was first observed in 1959 by D'Angio et al who described a radiation recall skin reaction following the effect of actinomycin D after irradiation.[1] Since then, many reports on the triggering role of Adriamycin in activating a recall phenomenon in irradiated sites have been assessed.[2–6] According to published data, the skin seems to be the most important affected site; however, other organs such as the lungs, esophagus, small intestine, muscle, central nervous system, and the head and neck have been involved as well, leading to the occurrence of several organ RR syndromes.[7] There is much evidence on the triggering action of such cytotoxic drugs or immunotherapies in causing this phenomenon.[8,9] However, antibiotics,[10] simvastatin,[11] physics agents such as ultraviolet or sunlight exposure,[12,13] and new drugs such as immune checkpoint inhibitors[14–16] or tyrosine kinase inhibitors[17] have also been related to RR syndromes. Interestingly, during the COVID-19 pandemic, several RR phenomena have been recorded after anti-COVID-19 vaccination or SARS-CoV2 infection

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involving the skin or lungs.[18–20] The underlying mechanism has not been assessed yet. Many hypotheses have been put forward, including vascular or epithelial radiation-induced damage, which is linked to a remembered inflammation induced by a triggering event such as the viral infection.[21] The ACE receptor spread in these tissues could also be involved due to their high affinity to Spike protein.[22] However, the true mechanism remains unknown. Herein, we present a case of radiation recall pneumonitis (RRP) triggered by COVID-19 in a woman who had undergone adjuvant radiotherapy for breast cancer.

Case Presentation

Informed consent was obtained from the patient to publish this report. A 65-year-old woman was diagnosed with invasive stage III A (pT2 pN2 M0) ductal carcinoma of the right breast in 2016. She underwent breast-conserving surgery with quadrantectomy and then chemotherapy and adjuvant radiotherapy. Radiotherapy fields included the residual right breast and the supraclavicular area as per guidelines. A monoisocentric technique with 3D-conformal RT was provided. Two opposed multi-leaf collimators (MLC)-customized fields of 6–10 MV photon beams on the supraclavicular area and two tangential MLC-customized fields with 6 MV photon beams on the breast were applied (Figure 1A and B). The dose delivered was 50 Gy in 25 fractions (2 Gy per fraction) on each site. No acute or chronic side effects were reported during the delivery and follow-up.

In March 2021, the patient came to our observation presenting with a fever, mild dyspnoea, and cough. She was still unvaccinated against COVID-19. The real-time polymerase chain reaction performed on a nasopharyngeal swab sample was positive for SARS-CoV2. Laboratory investigations revealed positive findings for SARS-CoV-2 nucleocapsid protein IgG, D-dimer, C-reactive protein, and the erythrocyte sedimentation rate. A complete blood count showed piatrinopenia (50.000/mm^3) while comprehensive metabolic panels were normal. Interleukin-6 levels were abnormal (50 pg/mL). Oxygen saturation was below 90%. The chest CT scan showed a straight and sharp opacity in the right lung miming the previous radiation treatment fields together with several GGOs in the contralateral lung. A crazy-paving pattern and thickened pulmonary interstitial tissue were observed, retracing the RT dose distribution of the treatment fields in the supraclavuclar area and the right lung behind the breast (Figure 2A and B). She was admitted to a COVID-19 Unit and treated, per protocol, with antibiotics, nebulized heparin, and dexamethasone, and was discharged after two weeks. The chest CT scan performed three months later revealed a complete resolution of GGOs with residual pulmonary fibrosis within the irradiated fields. (Figure 3A and B).

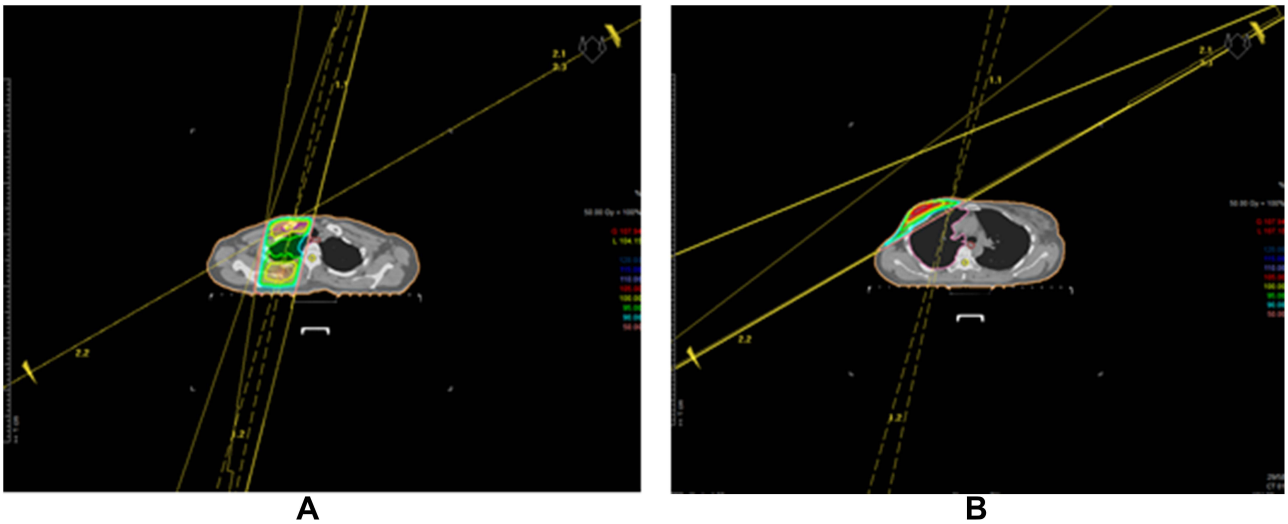

Figure 1 Images of adjuvant radiotherapy treatment plan. (**A**) The monoisocentric technique with two anteroposterior and posteroanterior fields for the right supraclavicular area. (**B**) Two opposed tangential hemifields for the breast.

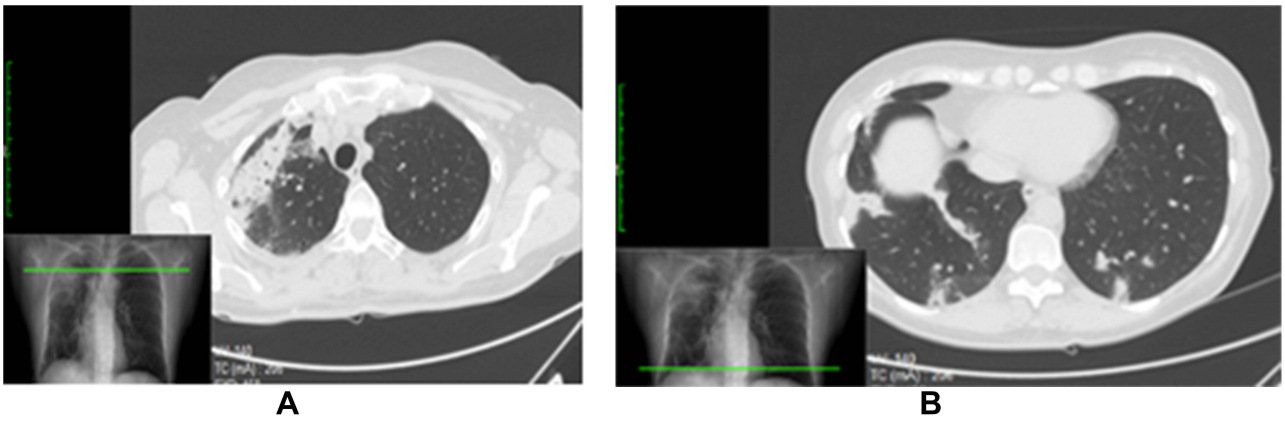

Figure 2 CT images showing findings of radiation recall pneumonitis. (**A**) A crazy-paving pattern and thickening pulmonary interstitium on the apex of right lung. (**B**) Thickening of the right lung included in breast tangential fields and ground glass opacities (GGO) spread in both lungs.

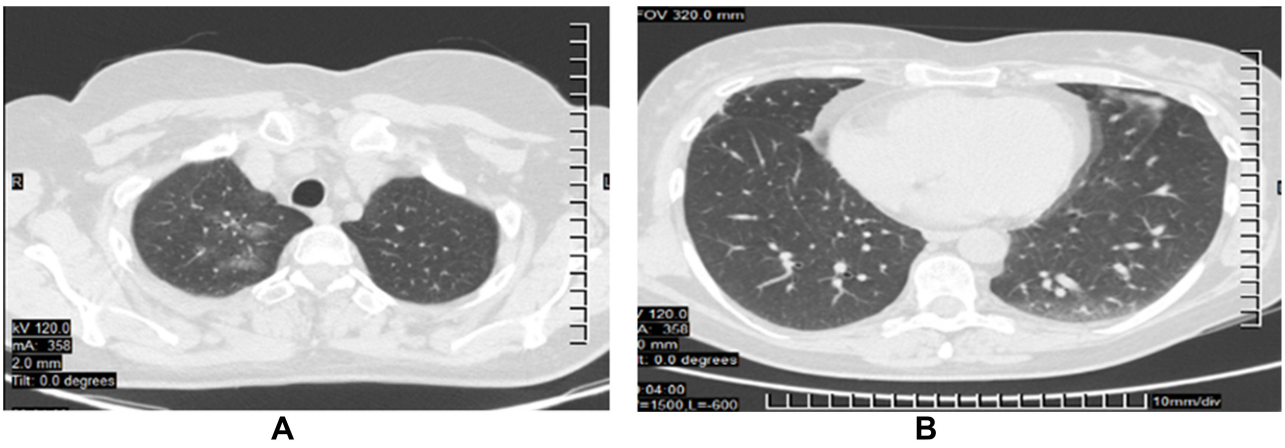

Figure 3 Chest CT images after three months showing complete resolution with mild fibrosis. (**A**) Complete resolution in the supraclavicular area. (**B**) Same result in the right lung included in the tangential radiation fields; no opacities in both lungs.

Discussion

As mentioned above, RR syndromes refer to an inflammatory process occurring within a previously irradiated volume, following triggering factors that could be chemical (drugs), environmental (ultraviolet light), or biological (virus).[21] Among drugs, chemotherapy, antibiotics, antimetabolites, and vaccines have been involved in this process.[23] Interestingly, during the COVID-19 pandemic, this phenomenon has been reported after anti-COVID-19 vaccine administration, and few cases have been reported to be COVID-19-related.[18–20] Even if the skin has been identified as the most involved site, RR has been detected in other organs such as the lungs, esophagus, small intestine muscle, central nervous system, and the head and neck, depending on variations in tissue tolerance and the local repair mechanism. The time-lapse between the end of radiation therapy and the occurrence of the recall phenomenon ranges from 7 days to 15 years according to published reports. Moreover, no absolute radiation dose thresholds have been reported. To this concern, Yeo et al reported a skin reaction occurring only in the irradiated skin involved in the highest radiation doses (from 18.7 Gy to 21.5 Gy) but no reasonable relationships with the time and dose were established.[24] Neither fractionation schedule seems to influence this phenomenon. However, due to its wide spectrum of severity grades, RR syndromes have also been graded according to Common Terminology Criteria for Adverse Events version 3.0.[25]

Concerning the lung's involvement in RRP, the first case was reported in 1976 by McInerney, that of a pediatric patient who was given Adriamycin.[26] Long after that, cases involving several newer anticancer drugs, such as taxanes or gemcitabine, have been reported too. Ding et al recorded RRP in eight out of twenty patients who received several cycles

of consolidation chemotherapy with taxanes after lung irradiation.[27] Moreover, Schwarte et al described severe RRP in a patient who had received salvage chemotherapy with gemcitabine after RT on the mediastinum for esophageal cancer.[28] In addition, nivolumab has been related to this reaction in irradiated lungs.[29] More recently, Min Wang described RRP after lung radiotherapy triggered by sintilimab, another novel anti-PD-L1 immune checkpoint inhibitor.[30]

During this pandemic, several cases of RR syndrome have been reported, with skin reactions as the main findings. Soyer et al described acute skin reactions in two irradiated patients with underlying anti-COVID-19 vaccination with differing timelines of RT and vaccine administration.[19] Regarding breast cancer radiotherapy reports,[31] a severe radiation recall chest wall skin reaction in a 64-year-old woman who underwent chest wall radiotherapy several years before COVID-19 has recently been published.[32] Interestingly, in this case, the severe skin findings correlated anatomically with the radiotherapy dose gradient delivered previously, miming a picture of breast cancer relapse.

However, during the COVID-19 pandemic, new scenarios have been observed, with some difficulties in the differential diagnosis when the lungs are involved.[33] A case of RRP has been reported after COVID-19 vaccination by Shinada et al. In this case, acute pneumonitis developed in a previously irradiated field post-vaccination, one year after the last dose of irradiation.[34]

Another case of RRP triggered by COVID-19 vaccination was reported by Steber et al in a patient with oligometastatic non-small cell lung cancer who had previously undergone local consolidation radiotherapy to the right lung and mediastinum. In this case, the patient complained of pneumonitis with symptoms similar to those of COVID-19 pneumonia, including dry cough, low-grade fever, and shortness of breath. Radiological features of pneumonitis were found inside the previously-irradiated lung volume through the beams' pathway. This patient developed symptoms of pneumonitis within three to five days of receiving the first COVID-19 vaccine injection.[18] Moreover, Huges et al reported a case of vaccination-induced RRP diagnosed via an FDG-PET CT scan four days after receiving the second dose of the mRNA COVID-19 vaccine in a patient with lung adenocarcinoma who had undergone radiotherapy followed by chemotherapy and pembrolizumab eighteen months earlier.[35] A suspected case of RRP has also been reported by Kuroaski et al.[20] Certain authors have described a suspected case of a 78-year-old woman who received definitive radiation therapy for small cell lung cancer three and a half years before the COVID-19 pandemic and developed a rapid decline in her respiratory status. She died but an autopsy was not performed. Chest radiography revealed a strong shadow at the prior irradiation site, evoking the phenomenon of radiation recall. Also, our case could be considered emblematic of RRP triggered by well-documented COVID-19 in a patient (survivor), which was later treated. Due to the absence of histologically proven samples, its mechanism has not been elucidated yet. To this concern, several hypotheses have been advanced. A biological hypothesis highlights the effect of a triggered inflammatory reaction among the cells remaining in the irradiation field after radiation therapy as a "remembered reaction."[21] Another theory is based on the radiation-induced depletion of normal tissue stem cells, leading to a limited capacity to proliferate and maintain the functionality and morphologic integrity of the tissues involved.[36] Thus, triggering insulting agents may induce sufficient cell damage that cannot be reversed in that irradiated area. Moreover, a reasonable hypothesis to be considered is the hypersensitivity mechanism based on the role of radiation therapy in lowering the normal tissue inflammatory response threshold so that it can be more sensitive to the relevant triggering factors.[37] In the case of lung irradiation, it is well known that irradiation induces lung injury, including alveolar-capillary barrier damage, and the activation of resident platelets and macrophages responsible for an initial inflammatory cascade. Then follows neutrophil recruitment and degranulation, leading to an orchestrated cytokine storm. Among them, interleukin-1, interleukin-6, platelet-derived growth factor-b, tumor necrosis factor-α, and transforming growth factor-β are involved, all of which are responsible for the occurrence of fibrosis in the chronic phase.[38] It has been postulated that these cells continue to secrete low levels of cytokines after irradiation. Then, the intervention of a triggering agent might lead to an upregulation of these cytokines, causing a recall reaction. As for the pulmonary damage induced by COVID-19, its affinity is well established for lung tissues and its effects could include acute lung injury (ALI) and adult respiratory distress symptoms (ARDS).[39,40] Thus, a combination of lung injuries caused by COVID-19 in a previously- irradiated lung volume could explain the RT effect findings on CT scans of the chest, indicating RRP. This possible mechanism could fit the theory of a "remembered reaction", which involves immunological memory. Another explanation could be the triggering effect of the SARS-CoV2 virus in tissues with

elevated concentrations of ACE2 receptors, such as the lungs, and keratinocytes as described above, in light of the high affinity of Spike protein for host ACE receptors.[22]

This is one of the first papers to show a clear relationship between documented COVID-19 pulmonary infection and RRP, with a specific reactivation of an inflammatory process in previously-irradiated lung fields. Despite the novelty of this pandemic, RRP, as a well-known phenomenon triggered by SARS-CoV2, should be considered by radiation oncologists as a differential diagnosis when evaluating patients with localized symptoms and a history of radiotherapy.

Ethics Statement

The study was approved by institutional ethics committee board of San Giuseppe Moscati Hospital ASL Taranto in Brindisi (Italy). Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Consent for Publication

Patient's informed consent has been obtained.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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