COVID-19 vaccine-induced recurrence of the radiation recall phenomenon in the laryngeal mucosa due to a VEGF inhibitor


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COVID-19 vaccine-induced recurrence of the radiation recall phenomenon in the laryngeal mucosa due to a VEGF inhibitor

Short Running Title: COVID-19 vaccine-induced RRP of the larynx

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Author responsible for statistical analysis:
Abstract

Background: The radiation recall phenomenon (RRP) is a rare and unexpected late complication of radiation therapy. Although it occurs predominantly in the skin, RRP of the upper respiratory tract has also been reported. In general, RRP is caused by anticancer agents,
and the coronavirus disease 2019 (COVID-19) vaccine has also been reported to cause it in recent years.

**Case presentation:** A 50-year-old woman who had received radiotherapy around the larynx 3 years previously and was receiving a docetaxel (DTX) + ramucirumab (RAM) regimen experienced recurrent sore throat. The administration of RAM was discontinued after gastroscopic examination revealed mucosal bleeding from around the larynx, which was thought to be RRP caused by RAM, a vascular endothelial growth factor inhibitor. After the remission of the RRP, the patient received a COVID-19 vaccine (Pfizer-BioNTech). Five days later, the appearance of cough and recurrence of sore throat worsened with time, and marked stridor was also observed. The patient was admitted, and steroid pulse therapy was administered for 3 days starting on day 18 after vaccination. On day 50 after vaccination, edema of the vocal cords improved.

**Conclusions:** When administering COVID-19 vaccines, it is important to consider that these vaccines may cause the RRP, which can be fatal in patients with a history of radiation therapy in the laryngeal region and treated with vascular endothelial growth factor inhibitors.
Introduction

The radiation recall phenomenon (RRP) can unexpectedly occur in patients who receive systemic therapy after a course of radiation therapy. The late effect is mainly reported as an acute skin reaction, which usually appears more than 1 week after the completion of radiation therapy. In addition to the skin, the onset of inflammation in the lungs and central nervous system has been reported. The RRP is induced by anticancer antibiotics, alkylating agents, antimetabolites, microtubule inhibitors, and molecular target drugs. The disease’s cause is unclear, but some immune system involvement has been suggested. In recent years, the RRP of the skin caused by coronavirus disease 2019 (COVID-19) vaccination was first reported by Soyfer et al. The RRP’s mechanism is not clear, but it is also thought to be related to the response to inflammation.

Although there are only a few reports of the RRP in the upper airway, RRP in the laryngeal region has been reported for a long time, and it has been reported in recent years that the RRP in the upper aerodigestive tract recurs due to stimulation by anticancer drugs, including vascular endothelial growth factor (VEGF) inhibitors. To the best of our knowledge, this is the first report of a COVID-19 vaccine-induced recurrence of the RRP in the laryngeal mucosa caused by a VEGF inhibitor.
Case presentation

A 50-year-old woman received radiation therapy at a dose of 67.2 Gy in 28 fractions to the larynx and upper peribronchial region for the postoperative recurrence (oligometastasis) of lung adenocarcinoma 3 years ago (Fig. 1). Complications of laryngeal mucositis grade 2 and radiation dermatitis grade 1 were observed but spontaneously resolved after irradiation. Detailed irradiation information is shown in Supplementary Fig. 1, and Fig. 2 shows the time course for this patient. Unfortunately, she relapsed with distant metastases about 1 year later and began treatment with the regimen of docetaxel (DTX) + ramucirumab (RAM) 1 year and 6 months after radiation therapy. Simultaneously, stereotactic radiosurgery at a dose of 25 Gy was performed for brain metastasis (Supplementary Fig. 2).

Although no late complications, such as laryngeal edema, occurred (Supplementary Fig 3a, 3b), 1 year and 4 months after the start of DTX + RAM, the patient had a recurrence of sore throat similar to the laryngeal mucositis experienced during radiotherapy, and a gastroscopic examination revealed mucosal bleeding from around the larynx, which was thought to be the RRP caused by RAM, the administration of which was subsequently aborted (Supplementary Fig. 3c). After switching to DTX alone, her sore throat did not flare up again and the RRP was
in remission. After two courses of DTX alone, the patient received a COVID-19 vaccine (Pfizer-BioNTech). Five days later, the appearance of cough and recurrence of sore throat worsened with time, and marked stridor was also observed; therefore, she was referred to the Department of Otolaryngology.

Computed tomography (CT) and nasopharyngoscopy revealed swollen vocal cords and edema of the surrounding mucosa over the subglottis (Fig. 3a, 3c left). Since there was a risk of needing a tracheotomy if the edema worsened, the patient was managed in the hospital, and steroid pulse therapy (methylprednisolone 500 mg by intravenous injection) was administered for 3 days starting on day 18 after vaccination. Two weeks after the steroid pulse therapy, the CT and nasopharyngoscopy findings (Fig. 3b, 3c right) did not show considerable improvement in the edema of the vocal cords (rather, it had slightly worsened), but after another 2 weeks (day 50 after vaccination), edema of the vocal cords improved (Fig. 4). A time course of blood examination is shown in the lower part of Fig. 2. There was no increase in the inflammatory response before and after radiotherapy and chemotherapy including DTX+RAM, but after the first vaccination, there was an increase in the inflammatory response (C-reactive protein 0.04 → 2.85 mg/dL) and white blood cell/neutrophil (6400/4740 → 12500/10880 /μL) count. After steroid pulse therapy, both parameters showed a decreasing trend with improvement in the
inflammatory findings in the larynx. Up until the last follow-up, the area around the larynx where radiotherapy was administered has been recurrence-free. The patient involved in this case report provided informed consent.

Discussion

The COVID-19 vaccines have been developed to overcome the SARS-CoV-2 viral pandemic and have had some effect on infection control. However, side effects of the vaccine, such as myocarditis, have been reported, and at the same time, cases of vaccine-induced RRP have been reported one after another (Table 1). As in the case of anticancer drug-induced RRP, skin reactions are the most frequently reported, but there are also reports of pneumonia. There are some reports of patients being treated with molecularly targeted agents or immune checkpoint inhibitors, which may have modified a vaccination-induced inflammatory or immune response. The present case differs from the previous RRP cases in three unique aspects: the risk of fatality was caused by edema of the laryngeal mucosa, the vaccine was used in combination with a VEGF inhibitor, and the RRP, which was induced because of RAM and subsided after RAM discontinuation, flared up following vaccination.
The side effects associated with the combined use of VEGF inhibitors and radiotherapy have been previously discussed\textsuperscript{11, 12}. Although the combination of radiotherapy with bevacizumab for pancreatic cancer was reported as feasible\textsuperscript{13}, clinical trials regarding side effects on the airway mucosa have been discontinued due to tracheoesophageal fistulas in lung cancer patients treated with bevacizumab and chemoradiation\textsuperscript{14}, and similar events have been reported with RAM\textsuperscript{15}. There may be a difference in the sensitivity of the gastrointestinal tract and airway mucosa to the combination of VEGF inhibitors and radiation. With the recent advent of molecular target-based agents, there have been reports of RRP caused by bevacizumab, as in the present case\textsuperscript{16}. Gastrointestinal bleeding has also been reported in patients treated with bevacizumab after radiotherapy\textsuperscript{17}, which may be related to the RRP.

The RRP’s exact pathogenesis remains unclear. Some investigators have suggested that it may be the result of vascular damage, epithelial stem cell sensitivity, or drug hypersensitivity of the irradiation field, in addition to upregulated inflammation-mediated cytokines induced by chemotherapeutic agents\textsuperscript{1, 3}. The pathological evaluation of the RRP on the skin caused by the COVID-19 vaccine showed epidermal intercellular edema, lymphocyte exocytosis, rare necrotic keratinocytes, and increased dermal collagenization and fibrosis, suggesting the intervention of immunocompetent cells to inflammation\textsuperscript{7}. Inflammatory cytokines and vascular endothelial
damage-related cytokines, including VEGF, are elevated in SARS-CoV-2 infection and have been reported to be associated with severe disease. It is unclear whether the COVID-19 vaccination caused an increase in cytokines such as VEGF, but at least its side effect, myocarditis, is thought to be partly due to the involvement of elevated inflammatory cytokines.

In the present case, the RRP due to a VEGF inhibitor was caused to relapse by the vaccine with an increased inflammatory response, suggesting the involvement of cytokines elicited by the vaccine-induced immune response.

It is important to note that the RRP occurs primarily on the skin but can also occur in the mucosa of the upper respiratory tract, especially with the use of VEGF inhibitors, and can also be induced by the COVID-19 vaccine. Clinical trials using VEGF inhibitors for recurrent head and neck cancers including patients with prior radiation therapy have also been recently conducted. Furthermore, although the COVID-19 vaccination booster is expected to be promoted worldwide, it is important to consider that the RRP can be fatal in patients with a history of radiation therapy in the laryngeal region and treated with VEGF inhibitors.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or conflicts of interest to disclose.
personal relationships that could have appeared to influence the work reported in this paper.

References


**Figure legends**

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**Fig. 1.** Radiation treatment plan for oligometastasis of postoperative lung adenocarcinoma

**Fig. 2.** Timeline for this case

RT: radiation therapy, CDDP: cisplatin, PEM: pemetrexed, DTX: docetaxel, RAM: ramucirumab, SRS: stereotactic radiosurgery, mPSL: methylprednisolone, WBC: white blood cells; Neu: neutrophils; CRP: C-reactive protein
Fig. 3. Computed tomography (CT) imaging and nasopharyngoscopy findings after COVID-19 vaccination
CT images at 5 days after COVID-19 vaccination (a) and at 2 weeks after steroid pulse therapy (b). (c) shows nasopharyngoscopy images before and after the steroid pulse therapy.

Fig. 4. Nasopharyngoscopy image showing relief of edema
<table>
<thead>
<tr>
<th>Auther, Year</th>
<th>Region of RRP</th>
<th>Age/Sex</th>
<th>RT plan</th>
<th>Type of Vaccine</th>
<th>Period between RT and Vaccination</th>
<th>Period between Vaccination and RRP</th>
<th>Treatment prior vaccination</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soyfer et al., 2021</td>
<td>Skin (2 cases)</td>
<td>68/ M, 64/ M</td>
<td>50</td>
<td>8 month, 5 Fr, Gy/2</td>
<td>Pfizer-BioNTech (both)</td>
<td>2nd, 2nd</td>
<td>None</td>
<td>(2)</td>
</tr>
<tr>
<td>Stewart et al., 2021</td>
<td>Skin</td>
<td>57/ F</td>
<td>56</td>
<td>6 month, 3 Fr, Gy/3</td>
<td>AstraZeneca</td>
<td>1st, 6 months</td>
<td>None</td>
<td>(6)</td>
</tr>
<tr>
<td>Afacan et al., 2021</td>
<td>Skin</td>
<td>60/ F</td>
<td>30</td>
<td>2 years, 3 Fr, Gy/1</td>
<td>Sinovac</td>
<td>1st, 5 days</td>
<td>Dabrafenib + Trametinib</td>
<td>(7)</td>
</tr>
<tr>
<td>Hughes et al., 2021</td>
<td>Lung</td>
<td>67/ M</td>
<td>60</td>
<td>1.5 years, 5 Fr, Gy/1</td>
<td>NA (mRNA vaccine)</td>
<td>2nd, 4 days</td>
<td>None</td>
<td>(8)</td>
</tr>
<tr>
<td>Shin ada et al., 2021</td>
<td>Lung 48/ M</td>
<td>60 Gy/3 Fr</td>
<td>Pfizer-BioNTech</td>
<td>1 year</td>
<td>2nd</td>
<td>19 days</td>
<td>Durvalumab</td>
<td>(9)</td>
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<tr>
<td>Steber et al., 2021</td>
<td>Lung 66/ M</td>
<td>45 Gy/1 Fr</td>
<td>Moderna</td>
<td>8 month</td>
<td>2nd</td>
<td>5 days</td>
<td>Pemetrexed + Pembrolizumab</td>
<td>(10)</td>
</tr>
<tr>
<td>Present case</td>
<td>Larynx 50/ F</td>
<td>67.2 Gy/2 Fr</td>
<td>Pfizer-BioNTech</td>
<td>3 years 1st</td>
<td>(worsening)</td>
<td>Docetaxel + Ramucirumab</td>
<td>Present case</td>
<td></td>
</tr>
</tbody>
</table>

**Table 1. Review of reported cases with RRP by COVID-19 vaccine.**

RRP: radiation recall phenomenon, RT: radiation therapy, Fr: fraction, mRNA: messenger ribonucleic acid