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Radiation Recall Phenomenon: A Literature Review

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Abstract

The radiation recall phenomenon is an inflammatory reaction on a previously irradiated area of the body that occurs due to exposure to triggering agents. In cancer setting, radiotherapy is often followed by chemotherapy or other systemic therapies, and this combination can trigger the radiation recall phenomenon. The triggering agents associated with this reaction are generally cytotoxic (e.g., chemotherapy); however, usage of non-cytotoxic agents has also been widely reported. This reaction manifested in various areas of the body, with the skin being the most common predilection site. There is no absolute range of radiation doses associated with this reaction. The interaction among radiotherapy components, triggering agents, and time of the agent's initiation influences the risk and onset of this phenomenon. Although known for a long time, the mechanism is still ambiguous. A series of hypothetical theories are described, including their relation to stem cell function and sensitivity, vascular damage, and drug hypersensitivity reactions. Management of this reaction may include modifying triggering agents, administration of steroids, and other symptomatic therapies. In severe cases, surgical intervention can be performed. Comprehensive observational or even experimental databases are needed for this phenomenon to be entirely understood.

Keywords: radiation recall phenomenon, recall reaction, radiotherapy, chemotherapy.

Introduction

Nowadays, primary modalities in cancer treatment consist of surgery, radiotherapy, chemotherapy, and other systemic therapies. Among the various therapeutic strategies used for managing malignant diseases, radiotherapy followed by chemotherapy and/or other systemic therapies has been widely practiced in clinical settings, and the outcome has been satisfactory in both curative and palliative intents. The combination of these modalities can sequentially trigger an event known as the Radiation Recall Phenomenon (RRP). RRP was first reported by D'Angio et al, in 1959, it is an event that is widely known to occur but often ignored and rarely reported.[1]

This phenomenon is an acute inflammatory reaction in an area of the patient's body that has previously received radiotherapy, its occurrence is triggered by certain pharmacological (for example, chemotherapy drugs) and non-pharmacological agents. Recall reactions can occur over a period of time, one week to years after radiation, with the onset of events varying from just minutes to weeks after exposure to agents.[2,3] The pathomechanism of the RRP is not yet clear. Depletion theory, dysfunction, stem cell hyper-sensitivity, vascular damage, and drug hypersensitivity were put forward. What is known is that the range of agents that induce this event and its predilection to occur in any organ that has been previously irradiated, although the skin is the most commonly reported site of RRP. Up to now, there is no specific standardized management of the RRP. Prolonging the time interval between post-radiation and initiation of the inducing agents, modification of the inducing agents, the use of steroids, non-steroidal anti-inflammatory drugs (NSAIDs), and other symptomatic therapies are

strategies expected to overcome this phenomenon.

Incidence

Kodym et al, in their observational study, reported the occurrence of radiation recall dermatitis in 8.8% of patients with different cancers (8 cases of 91 patients) who received chemotherapy after radiation.[4] In India, Harsh et al also performed a 7-year observational study and reported incidence of radiation recall dermatitis in 9.7% of patients with breast cancer (231 cases of 2374 patients). The majority of reactions occurred from the third week to 2 months after exposure to chemotherapy agents (81.7%), and doxorubicin was the most widely used chemotherapy agent.[5] Mizumoto et al reported 3 cases of RRP with Docetaxel usage in 171 patients (1.8%). These three cases used low-energy photons ≤6MV.[6] Radiation recall pneumonitis was reported to occur in 5.4% (14 cases of 257 patients) with Nivolumab use in patients with a history of radiation to the thoracic area. There were no significant potential risk factors for pneumonitis.[7]

Time concept in radiation recall phenomenon

Interval time between the completion of radiation and RRP incidence varies significantly from case to case. Reported time intervals range from 7 days to 25 years. The onset of RRP after exposure to the inducing agent also varies but is usually in the range of days to several weeks after first dose exposure, during administration, and even immediately after intravenous administration of the agent.[2,8] Camidge and Price obtained a time range of 7-840 days between radiotherapy and pharmacologic inducing agents in the occurrence of radiation recall dermatitis with a median interval of 39.5 days.[9] Benyounes et al reported the median time from completion of radiation to the inducing agent was 60 days (interquartile range [IQR] 45.5 – 63), and the median time induction to RRP was 43.7 days (IQR 30 – 55.1). Correlation between the time from radiation to the inducing agent and the time from the inducing agent to RRP was significant ($r = 0.21$, $p < 0.05$). The time from the inducing agent to RRP was shorter in skin involvement than in non-skin manifestation (15 days for skin, 45 days for non-skin [$p < 0.001$]).[10]

It should be noted that the concepts of recall reaction and acute radiation side effects are two different things and that this reaction is not a healing process from the acute side effects. The short time interval between completion of radiation and exposure to the inducing agent creates a potential for overlapping RRP with radiosensitization effects (increased radiation effect) and radiation side-effect relief. Camidge and Price suggest that reactions caused by the administration of the inducing agent under seven days after the last radiation should not be considered an RRP but a radiosensitizing effect. However, it does not rule out the two events co-occurring, considering that the RRP pathomechanism is not fully understood. The healing process of moderate to severe degree radiation side effects may take longer than seven days. If you are exposed to an inducing agent while healing is still ongoing, and the reaction seems to increase, it is not an RRP. RRP is established when radiation side effects has completely resolved prior to administration of the inducing agent.[8,9,11]

Clinical signs and symptoms

RRP mostly occurs on the skin and accounts for approximately two-thirds of all cases reported. Benyounes et al reported data on 179 patients with RRP and found the skin to be the site of predilection for most reactions (55.8%), followed by lung (16.2%), muscle (11.7%), and gastrointestinal system (3 and 2% for stomach and colon respectively). The intensity of severity is generally mild to moderate, although severe may occur (less than 10% of cases).[9,10]

Radiation recall dermatitis

The clinical presentation may include maculopapular eruption, erythema, vesicle formation, and wet desquamation. The degree of dermatitis varies from the mildest to the most severe, skin necrosis. These presentations may present with pruritus, a burning or painful sensation, and constitutional symptoms.[11,12] Until now, there has not been a specific classification for the severity of radiation recall dermatitis. Most of the literature uses the classification of acute toxicity morbidity criteria by the Radiation Therapy Oncology Group (RTOG) or the U.S. National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) for skin.

Other forms of radiation recall phenomenon

Many publications report this phenomenon occurs in various regions of the body according to previous radiation and may simultaneously occur with a skin recall reaction. In the upper gastrointestinal tract, mucous membranes are reported to manifest as low-grade mucositis to necrosis. In the lower digestive tract, gastritis, enteritis and intestinal obstruction, and colitis were noted. The respiratory tract area is reported to manifest as mucositis, epiglottitis, pneumonitis. In the

genitourinary area, cystitis, vulvitis, and vaginal necrosis were reported. Myositis also occurs in the muscles of the radiation area. Myelitis occurs in the palliative radiation of bones. There are two cases of radiation recall events reported in the central nervous system that manifests as neuritis and necrosis of the brainstem. Only one publication has reported on radiation recall cardiotoxicity.[11]

Pathomechanism

Many hypotheses are associated with the pathomechanisms of RRP, but there are no sufficiently strong evidence to support these hypotheses. Some of the most widely discussed theories are depletion, dysfunction and hypersensitivity of stem cells, vascular damage, and idiosyncratic drug sensitivity.

Depletion, dysfunction, and hypersensitivity of stem cell

In a normal state, stem cells will continuously have enough stable proliferation capacity. If there is any depletion (e.g., trauma) of its compartment, adult stem cell division will heighten to compensate. If trauma is repeated and massive, eventually, the proliferation capacity will decrease, and tissue failure will happen. The stem cells may enter the senescence phase where division may still occur but decreased and, when faced with trauma again, it becomes irreparable.[13]

Radiation exposure will decrease the proliferation capacity of stem cells, and when cytotoxic agents are given, it can be manifested as a radiation recall reaction.[8,13] This theory was supported by Seymour et al. Some components called surviving colonies arise as a result of the radiation, where it is said to have a capacity equivalent to normal, unirradiated cells. However, these colonies become a carrier of a lethal defect, genetically passed down from generation to generation, referred to as radiation-induced genomic instability.[14] Abadir and Liebmann proposed a theory of this stem cell, though depleted because of radiation, it attempts to adequately carry out its functional role by speeding up the cell cycle. As we know, rapid proliferating cells are very susceptible and sensitive damaged by treatment agents.[15]

This hypothesis, unfortunately, is not fully supported by the presence of some clinical and experimental facts. First, rechallenge or re-administration of inducing agents proved that not all rechallenged cases will show a more severe reaction than before and may even show no recurrence of radiation recall reactions.[9,11] Second, Kitani et al showed that despite the presence of lethal defects due to radiation, these defects can still be repaired during multi-fractionated radiation, and recall reaction may be caused by other cellular mechanisms.[16] Third, this theory is unable to explain the specific triggering agents and how non-cytotoxic and non-pharmacological agents can trigger this phenomenon. Last, a previously reported agent that triggered this phenomenon, when administered to another patient, did not show a recall reaction.[9,11]

Vascular damage

Blood vessels have three layers; tunica intima, media, and adventitia. Capillaries are very sensitive to radiation because they only have one endothelial layer, namely the intima, which is very radiosensitive.[17] When radiation exposure is prolonged and reoccurred, the endothelium's physiological protective effects are lost, and endothelial dysfunction results. Dysfunction is considered a maladaptive response to a pathological stimulus. As a result of not being able to carry out its normal function, there is a decrease in blood vessel tone, disturbances of blood homeostasis, inflammation, and edema, especially in areas of the endothelium exposed to radiation.[18]

When associated with RRP incidence, the inflammation that occurs due to endothelial damage results in a chaotic homeostatic environment. These local vascular changes may affect the inducing agent's pharmacokinetics and thus have the potential to alter the distribution, in this case leading to higher concentrations of these agents in previously irradiated areas.[9]

Idiosyncratic drug hypersensitivity

Camidge and Price stated that RRP's mechanism was not based on the cytotoxicity of a pharmacological agent; it is seen from the rarity, speed of onset, and extreme specificity of the inducing agent; however, it is based on the idiosyncratic hypersensitivity reaction of the drug.[9] In terms of frequency of incidence, RRP often occurs when first exposed to an inducing agent; this could be attributed to direct activation of the non-immunological inflammatory pathway in patients whose inflammatory threshold has decreased due to radiation. In fact, the unpredictable rechallenge effect, recall reactions that occur due to non-cytotoxic pharmacological agents, and the potential use of steroids in prophylactic prevention of RRP (for example, in radiation recall dermatitis) are consistent

with the hypothesis of drug hypersensitivity reactions.[9,11,19]

The radiotherapy aspect of radiation recall phenomenon

Azria et al reported a dose-related range of this phenomenon between 10-81 Gy.[11] The majority of case reports only reported the total radiation dose to the tumor and not the surrounding organs, making it difficult to determine the correct dose range. Scher et al found that 20 Gy was the threshold for radiation recall dermatitis in the neck area of patients with oropharyngeal cancer after topical pharmacological agents was applied following irradiation. Areas receiving doses below 20 Gy do not show this phenomenon.[20]

However, the case report presented by Stelzer et al showed something different. AIDS-associated sarcoma Kaposi received three different radiation therapy regimens (total doses 40, 20, and 8 Gy) in different areas of the skin. Only skin areas given a dose of 40 Gy experienced RRP after administration of chemotherapy Bleomycin.[21] Mallik et al reported a case of vertebral palliative radiation in two radiation areas at different doses (total doses of 20 Gy and 8 Gy). Both areas experienced radiation recall dermatitis, but the reaction was more severe in the areas receiving the 20 Gy dose.[22] The radiation dose (total dose or dose per fraction) independently does not fully explain how it affects this phenomenon. The combination of radiation dose and the interval of administration of the inducing agent may affect the incidence and reaction rate. More evidence is needed to demonstrate this possibility.

Regarding energy, most of the existing case reports use low energy, 6 MV. One case report by Sakaguchi et al reported the use of 10 MV energy also causes this phenomenon. Patients with vertebral metastatic prostate cancer were irradiated with an APPA field, 10 MV photons of energy, and 1: 2 beam weighting. Interestingly, RRP does not occur in the posterior skin areas, which receive a higher dose than the anterior, despite using the same energy.[23] It is different from Sroa et al, who reported irradiated the APPA pelvis with 6MV energy for the AP field and 18 MV for PA. RRP occurs in areas that receive higher energy.[24] This difference in findings only raises doubts about the correlation between dose, radiation energy, and RRP incidence.

The pharmacological aspect of radiation recall phenomenon

First reported related to the use of Actinomycin D was by D'Angio et al. They found several facts arising from the results of these observations, one of which was found that Actinomycin D can reactivate the 'latent' effect of radiation on normal tissues that previously received radiation which was then with normal appearance. The reaction was limited to previously irradiated areas, and the shorter the chemotherapy interval after radiation will show a more pronounced reaction.[1]

Over time, many other pharmacological agents have been reported to cause RRP. Extensive chemotherapy agents, usually cytotoxic and cytostatic, are known to precipitate RRP. It is not clear whether this phenomenon due to the use of chemotherapy agents from a particular class or related to the dosage and regimen scheme given because until now, no typical

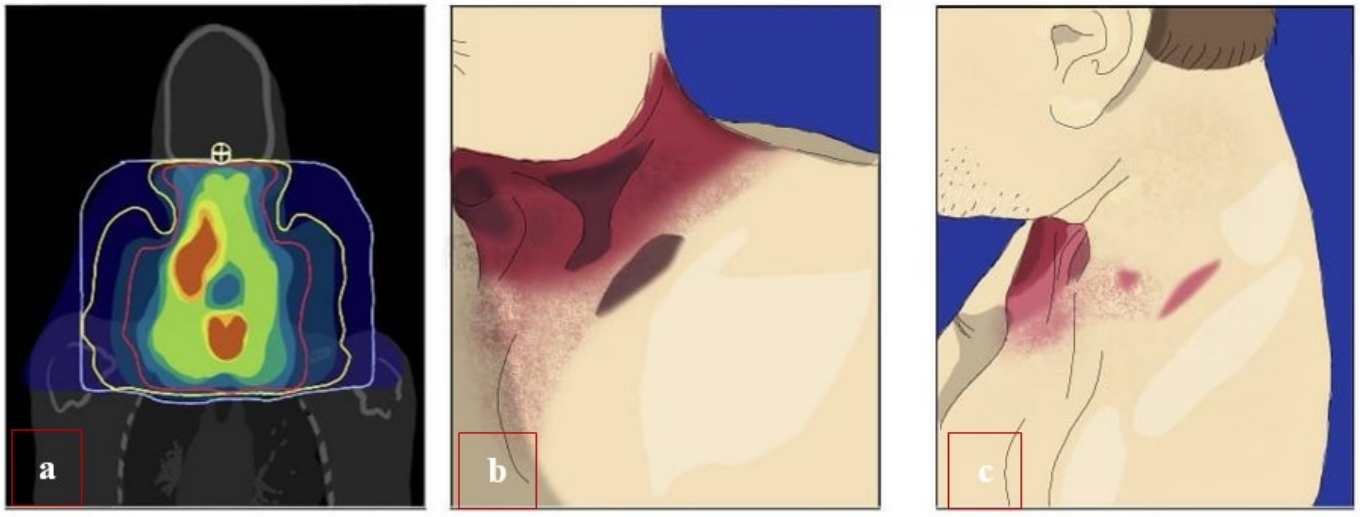

Figure 1. Case illustration of radiation recall dermatitis; (a) Dosimetric area of radiation showed isodose of 20 Gy (red), 10Gy (yellow), 5 Gy (blue); (b) Development of same characteristic dermatitis on the exact previous area of radiation after topical inducing agent and (c) Day 15 on reaction.
Adapted with modification from: reference no. 20

characteristics of these agents have been identified. Most of the RRP-inducing chemotherapy agents are derived from the alkylators, taxanes, anthracyclines, other antibiotics, antimetabolites, and alkaloids. Taxanes and anthracyclines account for nearly 20% and 30% of RRP-related cases, respectively.[2,11]

Likewise, non-cytotoxic agents can vary significantly in causing this phenomenon. Several anti-cancer drugs have been reported, including targeted molecular agents, hormonal therapy, immunotherapy, and some non-cancer drugs such as anti-tuberculosis, anti-inflammatory, antibiotics, and topical herbal agents, Simvastatin, and others.[2,8,11]

Then how exactly do pharmacological agents induce RRP? When associated with pathomechanism, most cytotoxic agents are DNA intercalation agents such as the antibiotic class, which disrupts DNA molecules and triggers free radicals. Genomic instability due to radiation makes cells vulnerable to free radical attack. The most likely mechanism is that these agents inhibit cellular recovery after radiation exposure by inhibiting DNA repair.[25] For non-anti-cancer agents, the mechanism of RRP is always related to the pharmacodynamics of each agent. For example, statin drugs inhibit mevalonate metabolism and isoprenoid production. This may give a pleiotropic effect on cellular processes ranging from cholesterol synthesis to growth control and tumor growth inhibition, which can then cause recall reactions on exposure.[26] Antibiotics are more widely described in terms of the idiosyncratic hypersensitivity reaction mechanism. The potentiation of non-anti-cancer agents in inducing RRP should be investigated further.

The non-pharmacological aspect of radiation recall phenomenon

Non-pharmacological agents that have been reported are cold weather and UV rays. Idiopathic RRP cases have also been reported. Uniquely all events induced by non-pharmacological agents are radiation-reltaed, being a radiosensitizer or chemoradiation.

UVB induces a cytokine cascade and vasoactive and neuroactive mediators in the skin resulting in an inflammatory response. If it passes the threshold for damage, keratinocytes activate the apoptotic pathway, and cell death occurs. This may play a role in the incidence of RRP related to the pathomechanism of non-immunological pathway activation. Melanin may be a determinant of the incidence of UV-induced RRP, particularly eumelanin.[27]

Skin conditions such as urticaria and pruritus can occur when the skin is exposed to cold temperatures below 4^{o}C, especially when conditions are humid and windy. Urticaria is caused due to the release of histamine, leukotriene, and other mast cell mediators after exposure to allergens or environmental factors. Ex-vivo and in-vivo studies have demonstrated that human mast cells (HMC-1) increase the expression of histamine, tryptase, and inflammatory cytokines after exposure to ionizing radiation and local skin side-effects reactions occur. RRP may occur because cold weather precipitates sequelae due to radiation.[28,29]

Radiation recall phenomenon and coronavirus disease 2019 (COVID-19)

Coronavirus disease 2019 or better known as COVID-19 is an outbreak that started in December 2019. It was first discovered in Wuhan City, Huber Province of China. There were several cases of RRP linked to COVID-19. One case report of suspected RRP after COVID-19 infection[30], three cases of radiation recall dermatitis, and one case of radiation recall pneumonitis associated with the administration of the COVID-19 vaccine (Pfizer-BioNTech, Sinovac, Moderna).[31-33]

Up to date, there are no case reports of infection-causing RRP. It is known that COVID-19 infection can cause an immune system reaction such as a cytokine storm. A decrease in blood oxygen saturation without symptoms called happy hypoxia, due to one of the factors including the presence of angiotensin-converting enzyme-2, slowly causes lung damage, which may precipitate radiation recall pneumonitis in previously irradiated lung areas. Another theory is that the presence of a small amount of SARS-CoV-2 virus deposited in the lung alveoli releases pro-inflammatory cytokines and causes RRP.[30] As with infections, vaccines used to prevent future infection must first induce an immune response. The presence of a local hypersensitivity reaction triggered by the vaccine causes an increase in pro-inflammatory cytokines which is already elevated in the area that has been irradiated.[9,33]

The COVID-19 infection and vaccination will continue indefinitely, doctors can be wary of the potential for RRP in patients with a history of radiation.

Histopathology characteristics

The histopathological characteristics of RRP are not widely described in the literature, although there have been several published case reports discussing the biopsy findings.

Microscopic skin abnormalities were found in the form of follicular hyperkeratosis with mild to moderate epidermal acanthosis and pustulosa, irregular

proliferation, and increased mitosis above the basal stratum, some of which were atypical. Vacuolization in the dermo-epidermal junction can also be seen, and there is degeneration of the balloon of varying degrees with necrosis. There is an infiltration of perivascular inflammatory cells in the dermis, vascular ectasia with atypical endothelial cells, accompanied by dermal fibrosis. Necrosis and sclerosis can occur in subcutaneous fat.[34]

In the digestive system organs such as the rectosigmoid, there are microabscesses, severe inflammation of the mucosa and lamina propria, and telangiectasis, which is highly suggestive of radiation colitis.[35] The lungs are found with chronic inflammation with mucosal congestion, leukocytic infiltration, exudative alveolitis, giant cells, and hyperplasia of pneumocyte type 2 and fibrosis.[36]

Management of radiation recall phenomenon

There is no standardized management of RRP until today. It depends only on the organ systems that show the reaction and the degree of reaction. It is advisable to modify the inducing agent such as lowering the dose, temporary or permanent suspension, rechallenge, and changing the agents; use some treatment to relieve signs and symptoms such as topical and systemic corticosteroids, NSAIDs, and antihistamines. Several local therapies have also been reported, using local irrigation, wound dressings with silver sulfadiazine and hydrogel, sodium hyaluronate, and moisturizer cream. Some cases require topical or systemic antibiotic therapy because of infection. Hyperbaric oxygen therapy has also been shown to be of benefit in some cases.[8,11] The algorithm of management can be seen in **Figure 2**.

When the degree of reaction is not severe, reactions may resolve spontaneously without drug intervention, and close observation approaches are adequate. Supportive medical care may be needed when reactions occur in internal organs, and sometimes surgical intervention is required for severe cases.[8,11]

The decision to continue or discontinue the inducing agent is confusing in the management of RRP. This should always be considered knowing that the inducing agents are mostly cytotoxic chemotherapy agents and/or cytostatics, which are crucial in the treatment of cancer patients. If we choose to continue with the inducing agent, it is recommended that we delay until the affected area has completely healed and/or modified the dosage to reduce the chance of a reaction re-appeared. The use of pre-rechallenge steroids can also be considered to prevent excessive inflammatory responses, although this has not been fully proven. If we decide to stop the inducing agent, we have to be sure that there is an alternative agent that is as effective as before. All risks and benefits must be taken into consideration in the decision-making, and of course, must be based on the doctor's objective clinical judgment and the patient's individual preferences.[2,11,25]

Conclusion

RRP incidence has been known to exist for more than 50 years and has been reported to manifest in almost all areas of human organs that have received radiation followed by a wide variety of inducing agents, both pharmacological and non-pharmacological forms. Although the pathomechanism of the incidence of RRP is not clear and there are still many contradictions in the theoretical hypothesis, the current facts suggest that the idiosyncratic local reaction of drug hyper-sensitivity, with or without increased cellular sensitivity due to radiation induction, is best suited to demonstrate its correlation with this phenomenon. This phenomenon results from a complex interaction among the components involved in the radiation, the dose and type of the inducing agent, and the time interval between radiation and the inducing agent's initiation. By minimizing the radiation dose and lengthening the time interval between the completion of radiotherapy and the inducing agent's initiation, the risk of RRP can be reduced. There is no guideline on the management of RRP. The decision to continue or discontinue the inducing agent should always be considered carefully because most of the inducing agents are used to treat cancer patients. Hopefully, the decision-making can provide benefits and improve the quality of life for patients.

Suggestion

It is hoped that all RRP incidents found in clinical practice in the future can be appropriately recorded. It includes the radiation components (total dose, isodose distribution, radiation type, and energy), the inducing agent components (type and dose regimen), time components (radiation interval to inducing agent, the onset of reaction), the form of radiation recall (involved organs and degree of reaction), histopathology if possible, and management (given intervention and time to resolution) as well as rechallenge and after-effects. With complete data, we hope to get a deeper scientific understanding of how this phenomenon occurs.

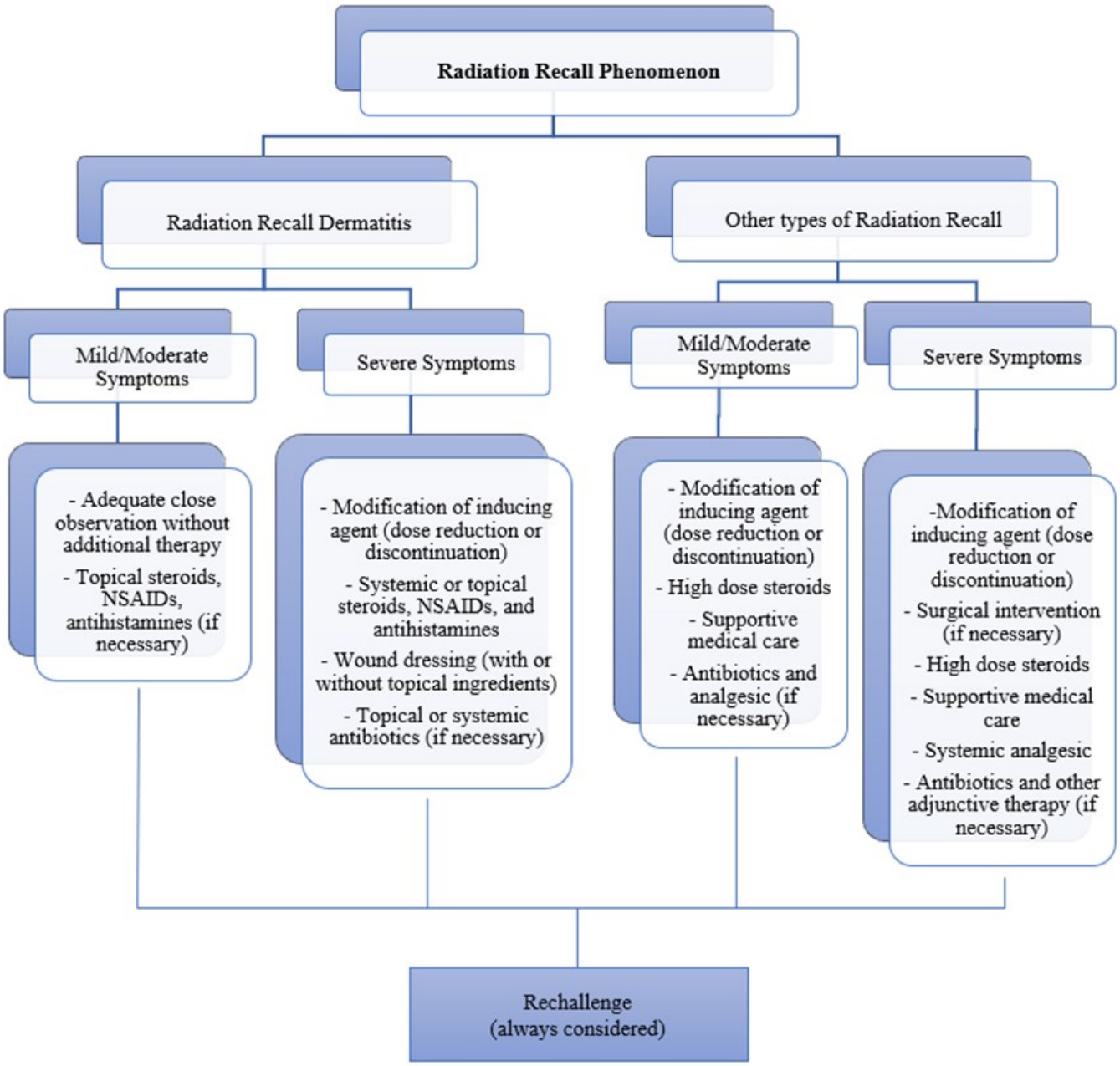

Figure 2. RRP management algorithm (based on Caloglu et al with modification).
Adapted with modification from: reference no. 8

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