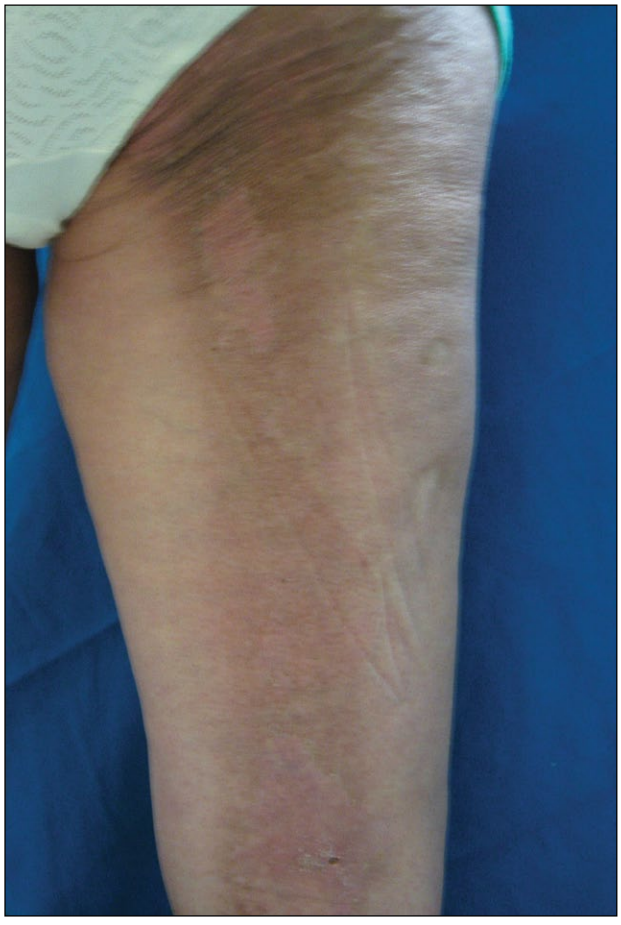
What Is Your Diagnosis?



A 62-year-old woman presented to the dermatology clinic with a burning, erythematous, hyperpigmented, and slightly scaly plaque extending from the right posterior buttock to the popliteal fossa of 3 days' duration. Prior to the development of the lesion, she underwent surgical placement of a titanium intramedullary nail to prevent a pending pathologic fracture of her right femur secondary to metastatic lung cancer. Following the hardware placement, she received 10 cycles of radiation therapy to her entire right thigh (30 Gy) over 2 weeks without development of acute radiation dermatitis. During radiation, she received 1 infusion of intravenous chemotherapy consisting of carboplatin, paclitaxel, and bevacizumab. A second treatment was administered 2 weeks later. To prevent excessive bleeding during an upcoming dental procedure, she received a third dose of solely intravenous carboplatin and paclitaxel 2 weeks after her second treatment and 3 days prior to the development of the lesion.

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Erin G. Adams, MD; Michael Brewer, MD; Kenneth J. Galeckas, MD

Dr. Adams is from and Dr. Galeckas was from the Department of Dermatology, Walter Reed National Military Medical Center, Bethesda, Maryland. Dr. Brewer is from DeWitt Army Medical Center, Fort Belvoir, Virginia. Dr. Galeckas currently is from InterMed, P.A., Portland, Maine.

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Correspondence: Erin G. Adams, MD, Department of Dermatology, 8901 Wisconsin Ave, Bethesda, MD 20889 (erin.adams@med.navy.mil).

The Diagnosis: Radiation Recall Dermatitis

Radiation recall dermatitis (RRD) is an inflammatory reaction limited to previously irradiated areas and occurs following the subsequent administration of a drug (Figure 1). This condition was first recognized more than 50 years ago when treatment with actinomycin D provoked a reaction in previously irradiated skin.[1] Radiation recall dermatitis most commonly is associated with chemotherapeutic agents such as doxorubicin, paclitaxel, docetaxel, etoposide, vinorelbine tartrate, vinblastine sulfate, gemcitabine hydrochloride, and capecitabine.[2] Few reports have associated RRD with other nonchemotherapeutic agents such as phentermine,[3] antitubercular drugs,[4] simvastatin,[5] hypericin (St John's wort),[6] tamoxifen citrate,[7] cefazolin,[8] cefotetan disodium,[9] gatifloxacin,[10] and levofloxacin.[11]

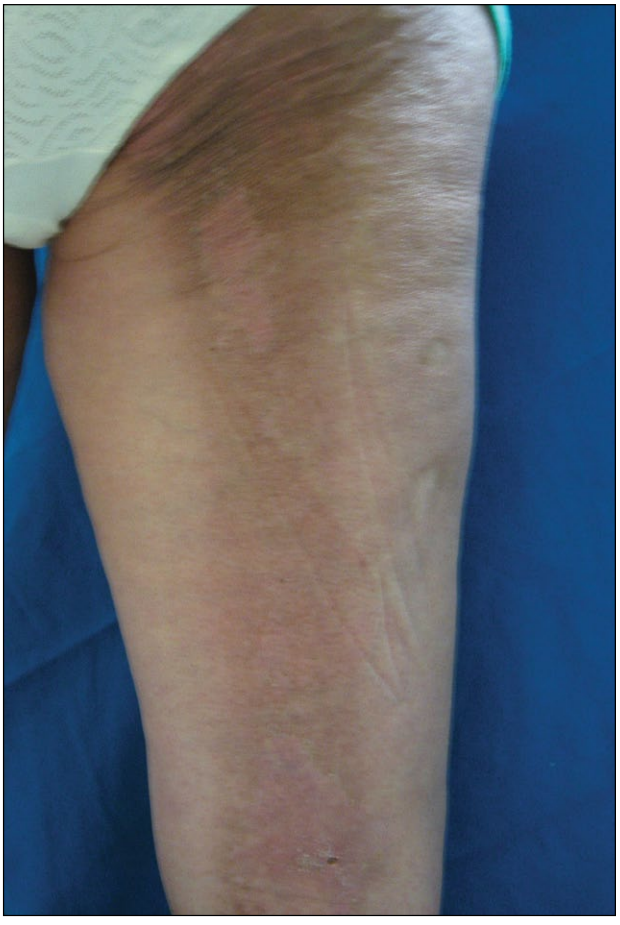

Figure 1. A hyperpigmented scaly plaque extending from the right posterior buttock to the popliteal fossa.

The clinical presentation of RRD includes mild erythema similar to sunburn, ulceration, or even necrosis. However, RRD is not limited to the skin and also has been reported to occur viscerally.[12] The differential diagnosis for RRD includes radiosensitization, a reaction that develops within 7 days of radiation exposure[13]; herpes zoster infection; cellulitis; cutaneous hypersensitivity syndromes; photosensitivity; and contact dermatitis. In our patient, RRD and contact sensitivity to the intramedullary nail were the most likely diagnoses. However, titanium is a rare contactant. A 4-mm punch biopsy was performed and revealed interface dermatitis with numerous dyskeratotic keratinocytes (Figure 2). The pathologic differential included interface dermatitis, artificially damaged skin (drug, erythema multiforme, or other interface dermatoses), direct chemotherapy effect on the skin, or radiation. Biopsies rarely have been reported in the literature but usually show nonspecific changes.[13] Therefore, we considered the presence of the intramedullary nail to be coincidental and did not pursue a lymphocyte transformation test to evaluate for contact dermatitis from the implant. To our knowledge, no other cases of RRD involving medical hardware as either a causative or provocative factor have been reported.

Radiation recall dermatitis involves reactions that occur more than 7 days after radiation therapy. According to Camidge and Price,[13] the median

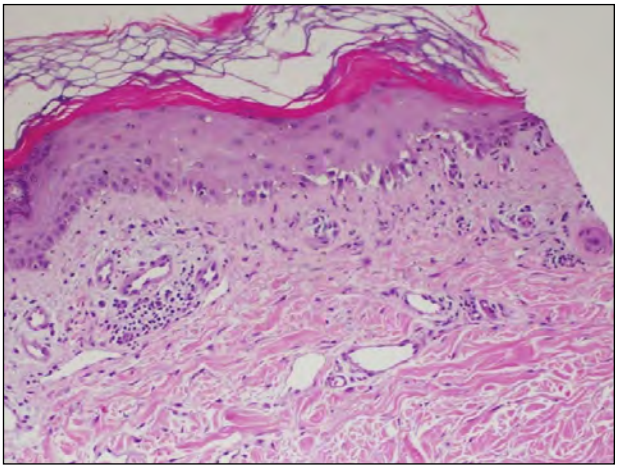

Figure 2. A 4-mm punch biopsy specimen taken from the right posterior leg demonstrated interface dermatitis with numerous dyskeratotic keratinocytes and focal keratinocyte atypia (H&E, original magnification ×10).

time between radiation therapy and RRD was 39.5 days (range, 7–840 days) with 7 years as the longest recorded interval. In our patient, the interval was approximately 32 days, and the lesion developed 3 days after her third chemotherapy treatment. Although RRD usually occurs after the first exposure to a recall-triggering drug, few case reports detail either a presensitization or time-lag phenomenon, with RRD skin reactions developing up to 2 months following drug exposure.[13] Additionally, RRD does not require an acute dermatitis during radiation[14] or a specific threshold of radiation. Doses have ranged from 10.0 to 61.2 Gy in reported cases.[13] The severity of the reaction may range from slight erythema to necrosis.

Radiation recall dermatitis remains a well-known occurrence, but its etiology is unclear. Camidge and Price[13] advocate an idiosyncratic drug hypersensitivity reaction involving direct nonimmune activation of inflammatory pathways. Vascular damage affecting pharmacokinetics of RRD-inducing drugs is another proposed mechanism.[14] Epithelial stem cell inadequacy due to radiation[13] as well as radiation-induced epithelial stem cell sensitivity to subsequent RRD-triggering drug challenges have been proposed as mechanisms of RRD.[5] Another potential etiology involves radiation inducing the expression of certain cytokines responsible for inflammatory response, which are upregulated when a precipitating agent is introduced.[15]

Treatment of RRD remains controversial because of dilemmas for physicians such as the possibility of discontinuing the potential offending chemotherapeutic agent, which may be the best treatment of the patient's disease, or the management of the acute symptoms of RRD. Both topical and oral steroids commonly are used in the treatment and prevention of RRD.[16] However, the time to resolution of symptoms in patients treated with steroids is similar to patients who have not been treated at all, ranging from 3 to 14 days in most cases.[13] In patients who are rechallenged with the potential offending agent, not all develop RRD again, and in many patients who do develop it again, the reaction is less severe.[13]

The incidence of RRD is difficult to ascertain because few authors report the total number of patients affected in relation to unaffected patients treated with similar therapy; therefore, this lack of information makes a denominator difficult to determine.[13] Additionally, authors lack standardization in case reports, and the literature is void of case-control studies or systemic reviews to better understand this entity.[6,13] More research is needed to classify and quantify the known cases. With well-designed studies, physicians may be able to mitigate the morbidity associated with RRD by selecting treatments with proven efficacy.

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