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Case Report

Skin Metastasis of a p16-Positive Squamous Cell Carcinoma Mimicking Radiation Recall Dermatitis

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Abstract

Radiation recall dermatitis is an acute inflammatory reaction confined to previously irradiated skin that occurs after the administration of certain drugs. Herein, we report the case of a 48-year-old man irradiated for bilateral supraclavicular and right axillary lymph nodal metastases from p16-positive esophageal or occult head-and-neck squamous cell carcinoma (SCC). Several months after the completion of radiotherapy, systemic therapy with a combination of methotrexate and pembrolizumab was commenced. The patient developed increased skin pigmentation and inflammation generally consistent with the region that had previously been irradiated. The skin reaction progressed with a protruding mass after prednisolone treatment. A biopsy confirmed p16-positive SCC. Systemic therapy was given, but the patient died 2 months after the confirmation of skin metastasis. We believe that ionizing radiation can modulate the tissue microenvironment of skin and subsequently promote carcinogenesis. It may also alter the tissue response to anticancer therapy, including anti-programmed death-1/PD-ligand 1. Corticosteroids may worsen the skin lesions and conflict with immunotherapy.

Keywords: Esophageal cancer, hyperprogression, immunotherapy, p16-positive, radiation recall dermatitis, skin metastasis, squamous cell carcinoma

Introduction

Radiation recall dermatitis (RRD) describes the "recalling" of an effect similar in appearance to that of an acute radiation reaction in previously irradiated skin. The recall is triggered by the administration of certain drugs days to years after the radiotherapy has been completed.[1] Some drugs have been found to be more commonly involved with RRD, such as docetaxel, doxorubicin, gemcitabine, and paclitaxel.[2] Although the precise mechanism of RRD is not clear, several etiological hypotheses have been proposed. These mechanisms include changes in vascularization, DNA repair, radiation-impaired epithelial function of stem cells, and increased sensitivity to drugs.[1] Corticosteroids are commonly used in the treatment of external symptoms and to prevent recurrent reactions or reduce the severity of reactions during subsequent chemotherapy.[2,3] RRD is a rare phenomenon, and to the best of our knowledge,

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this is the first reported case of cutaneous metastasis of p16-positive squamous cell carcinoma (SCC) mimicking RRD. In this situation, applying corticosteroids may worsen the skin lesions.

Case Report

A 48-year-old man had the habits of drinking alcohol, smoking cigarettes, and chewing betel nut for more than 30 years. He presented with a right-side neck mass for several months. An excisional biopsy was obtained in April 2016, and the pathology reported SCC, p16 (70%), and Epstein–Barr encoding region *in situ* hybridization (–). A computed tomography (CT) scan of his head-and-neck demonstrated multiple enlarged neck lymph nodes at bilateral supraclavicular fossa. A gallium scan showed that the possibility of soft tissue lesion (s) (inflammation, infection, and tumor) in the right supraclavicular region could not be excluded. An upper gastrointestinal endoscopy in August 2016 showed an esophageal tumor, 22 cm from the incisors [Figure 1]. An endoscopic biopsy of the tumor was obtained, and the pathology reported SCC, moderately differentiated. Immunohistochemistry staining was positive for CK and p40. Thus, the final diagnosis was TxN2M1 (American Joint Committee on Cancer Staging Manual, seventh edition) esophageal SCC. The patient received several courses of chemotherapy with a combination of docetaxel, cisplatin, and fluorouracil, and he also received radiotherapy with 66 Gy in 33 fractions to bilateral neck lymph nodes from December 2016 to March 2017 [Figure 2]. An echo-guided biopsy of the right supraclavicular lymph nodes was obtained again in April 2017, and the pathology reported metastatic carcinoma, p63 (focal +), and CK5/6 (focal +). A right axillary bulky lymph node was identified soon thereafter, and he received four courses of chemotherapy with a combination of cetuximab, cisplatin, and etoposide. He also received radiotherapy with 60 Gy in 30 fractions to right axillary lymph nodes from June 2017 to July 2017 [Figure 3]. A Grade 2 radiation reaction was observed immediately after the radiation treatment which then regressed day by day [Figure 4]. However, a CT examination revealed disease progression as significantly enlarged lymph nodes in bilateral supraclavicular fossa, right axilla, mediastinum, and abdomen. Due to dysphagia, an upper gastrointestinal endoscopy was performed again, which revealed some gelatin-like depressed lesions over the esophagus, 25 cm below the incisors. The results of pathology showed SCC. A p16 immunostain with G175-405 clone was performed, and the results showed >75% p16-positive tumor cells with both nuclear and cytoplasmic p16 expression detected.

Systemic therapy with a combination of methotrexate and pembrolizumab was commenced in September 2017, and a third course was completed in late October. During the treatment course, we detected increased skin pigmentation and inflammation limited to the region that had previously been irradiated [Figure 5]. A diagnosis of RRD was highly suspected, and thus, oral prednisolone 20 mg BID was given. A subsequent CT examination showed new lymphadenopathies at the right neck and subcarinal region. Approximately 1 week after the commencement of the prednisolone, the skin lesions progressed with partial protrusion [Figure 6]. A skin biopsy of both the flat macule and protruding part was performed, and the results of pathology showed carcinoma, compatible with metastasis [Figure 7]. A p16 immunostain with G175-405 clone was performed, and the results showed >75% p16-positive tumor cells with both nuclear and cytoplasmic p16 expression detected. Cutaneous metastasis over previously irradiated areas with hyperprogression after immunotherapy was highly suspected. He received systemic therapy with a combination of bevacizumab, mitomycin, pembrolizumab, and low-dose cyclophosphamide. However, the disease progressed, and he died 2 months after the confirmation of skin metastasis.

Discussion

Skin metastasis accounts for 0.7%–9% of all metastases and may be the first evidence of an internal malignancy or a sign

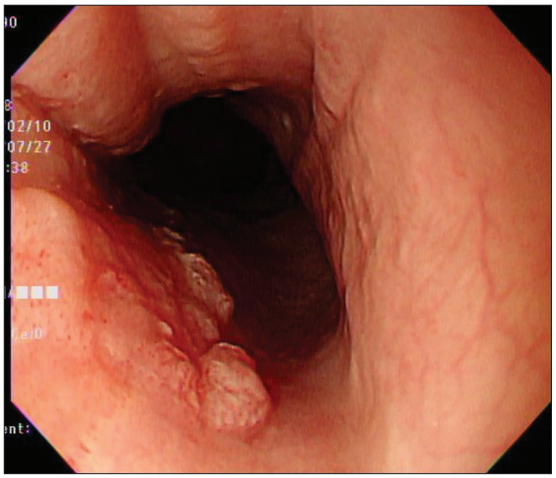

Figure 1: Upper gastrointestinal endoscopy showed a tumor at the esophagus, thoracic upper third

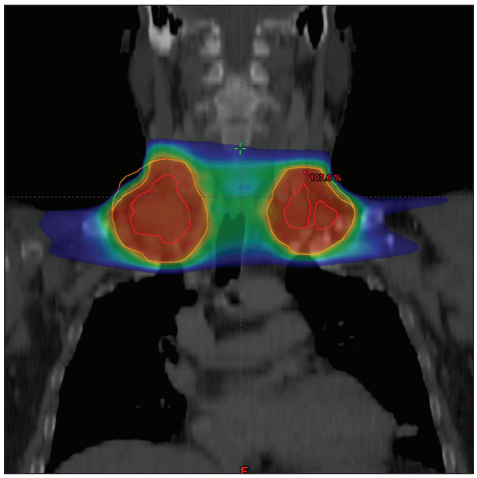

Figure 2: The patient received radiotherapy with 66 Gy in 33 fractions to bilateral neck lymph nodes from December 2016 to March 2017

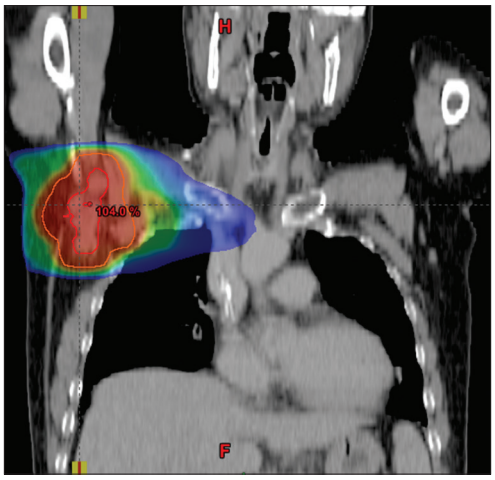

Figure 3: The patient also received radiotherapy with 60 Gy in 30 fractions to right axillary lymph nodes from June 2017 to July 2017

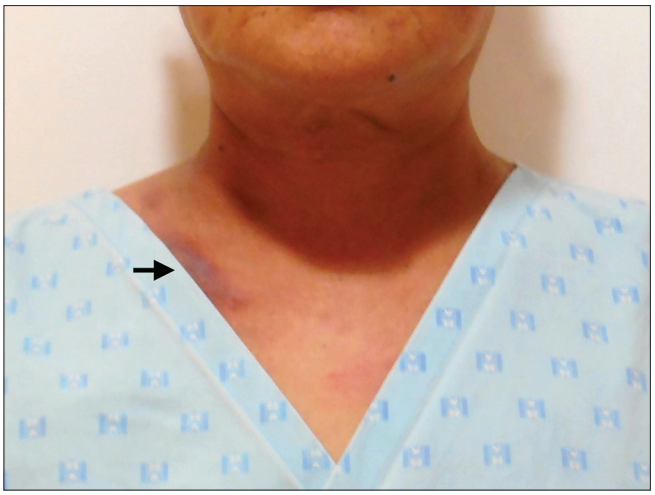

Figure 4: A Grade 2 radiation reaction was observed immediately after the radiation treatment and then regressed day by day

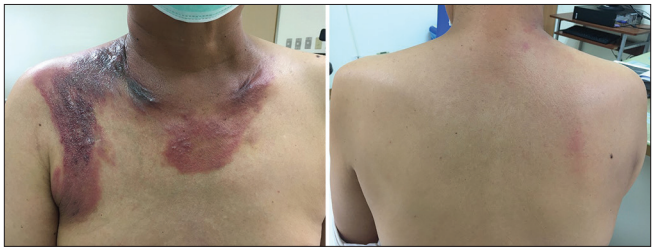

Figure 5: Increased skin pigmentation and inflammation limited to the region that had previously been irradiated

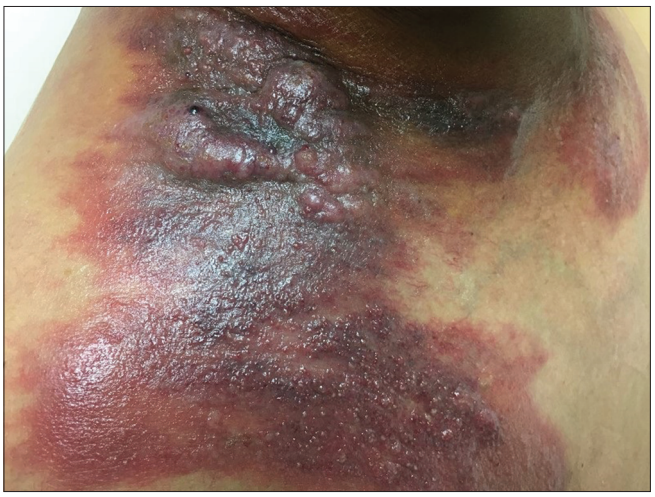

Figure 6: The skin lesions progressed with partial protrusion

of recurrence. The most common skin metastasis encountered in clinical practice is breast carcinoma, probably reflecting the occurrence of the primary tumor.[4,5] In men, the oral cavity is also a common source.[5,6] Skin metastasis from esophageal SCC is extremely rare. Wu *et al*.[7] investigated 3218 patients with Stage IV esophageal SCC or adenocarcinoma, and the most common site of distant metastasis was the liver, followed by distant lymph nodes, lung, bone, and brain. Skin metastasis was not mentioned. Shaheen *et al*.[8] reviewed esophageal cancer metastasis to unexpected sites using the PubMed database between 1982 and 2017 and included 147 articles and 164 patients. Unexpected metastasis spreads to uncommon sites such as the skin was found in 21 patients. Due to its rarity, we cannot definitely conclude that our patient's skin and neck nodal metastasis was from the esophagus, although all of our imaging and endoscopy studies highly indicated the primary esophageal cancer. Skin metastatic SCC with an unknown primary source usually begins somewhere in the mouth, throat, or larynx.[9] We cannot exclude the possibility that this is a case of occult head-and-neck cancer with synchronous esophageal and supraclavicular nodal metastasis. We checked the p16 expression of esophageal cancer and skin metastasis, and both were p16-positive; however, this could not help us to distinguish the primary cancer origin. Nowadays p16 immunostaining is used as a surrogate marker for transcriptionally active human papillomavirus (HPV) in HPV-related oropharyngeal SCC, with the discriminative criteria described by Lewis *et al*.[10] Evidence dating back over three decades has indicated an association between HPV infection and esophageal SCC.[11] Nevertheless, Ludmir *et al*.[12] reviewed multiple meta-analyses and concluded that the p16 overexpression is an unreliable marker of HPV status in esophageal SCC.

There are various morphological variants of skin metastasis, such as multiple erythematous infiltrating papules and nodules, ulcerations, vesicles, keloids, and many other rarer ones.[6] Anil *et al*. reported an unusual case of metastatic breast carcinoma presenting as erythematous skin plaques mimicking radiation dermatitis.[13] Lymphatic and hematogenous routes are the most common pathways for skin metastasis. Many steps have to be met for metastasis to occur. First, the primary tumor has to be large enough to release a sufficient number of neoplastic cells into the circulation or lymphatic system. These cells need to avoid being destroyed by the immune system. To establish metastases, the neoplastic cells need to attach and penetrate vessel walls. Thrombi form around neoplastic cells through

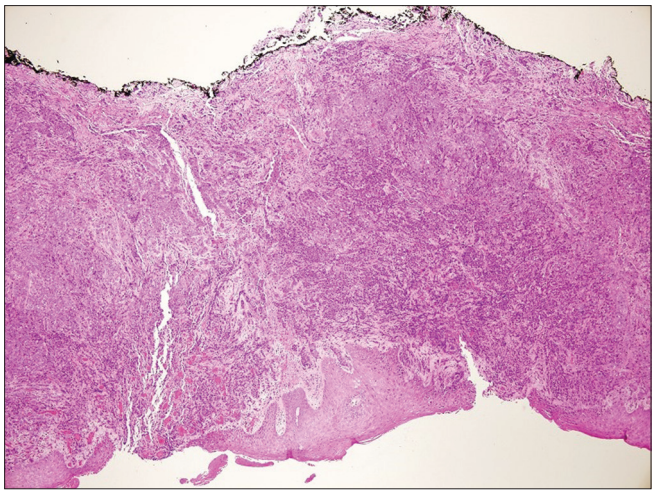

Figure 7: Microscopically, both sections show neoplastic nests or cell infiltration beneath mostly intact surface epithelium

endothelial cell injury and serve to protect the neoplastic cells, and subsequently, new metastasis becomes established and obtains nutrition through diffusion, and finally forms its own vessels.[5] Skin metastasis within a radiation field is a rare occurrence.[14] It is widely accepted that localized insults to the skin can make the region more susceptible to disease or infection, which is termed as "isotopic response"[15] or an "isoradiotopic response."[16] An isoradiotopic response refers to secondary dermatoses arising in radiation fields. Ruocco *et al*. postulated a mechanism of pathogenesis for isotopic and isoradiotopic responses. They suggested that cutaneous disease or injury (including ionizing radiation) can spoil lymph drainage and alter neuromediator signaling. These changes lead to an "immunocompromised district" that is particularly susceptible to subsequent infections, tumors, or immune disorders.[17] In addition, dysregulation of cytokines in the radiation field has been implicated.[18] Radiation-induced damage to endothelial cells has also been postulated to result in trapping of tumor cells, thereby enhancing the development of metastasis.[19] In our case, methotrexate, as a very strong sensitizer, may have enhanced the radiation effect by inhibiting DNA repair.[20] It also has been reported to be associated with RRD.[21] Thus, we initially considered our case to be a presentation of RRD rather than skin metastasis.

It is noteworthy that the skin metastasis progressed after the administration of pembrolizumab and prednisolone. Pembrolizumab is an immune checkpoint inhibitor, especially monoclonal antibodies targeting programmed death-1 (PD-1), which can reinvigorate exhausted T cells and has shown therapeutic benefits. Corticosteroids exert immunosuppressive effects mediated by suppressing delayed hypersensitivity reactions by direct action on T-lymphocytes.[22] The long-term (>2 weeks) use of high-dose steroids (prednisone equivalent >10 mg) during anti-PD1 therapy has been reported to potentially be associated with poorer survival outcomes.[23] The efficacy of pembrolizumab in our case may have been weakened by prednisolone. The skin tumor progression in our patient could also be regarded as hyperprogression. Hyperprogression has yet to be clearly defined, but it is sometimes described as an acceleration of the tumor growth rate following treatment with immune checkpoint inhibitors compared to previous treatments. The pathophysiological mechanisms of hyperprogression remain largely unknown. Saâda-Bouzid *et al*.[24] observed hyperprogression in 29% of their patients with R/M head-and-neck SCC who were treated with anti-PD1/PD-ligand 1 (PDL1), and they concluded that previous irradiation may have played a role for almost all cases of hyperprogression occurred in patients who had at least locoregional recurrence in an irradiated field. Radiotherapy causes the production of tumor antigens that alter the immune environment,[25] which may facilitate rapid progression within the irradiation field.

Conclusion

We postulate that ionizing radiation can modulate the tissue microenvironment of skin and subsequently promote carcinogenesis. It may also alter the tissue response to anticancer therapy, including anti-PD1/PDL1.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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