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Teaching Case

Congenital ichthyosis patient with squamous cell carcinoma of the skin who received concurrent chemoradiation: A case report

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Introduction

Ichthyosis is a heterogeneous cluster of keratinization disorders.[1] Autosomal dominant ichthyosis vulgaris, the most common type, has an estimated incidence of 1 in 250 births, and X-linked recessive ichthyosis, the second most common form, has an incidence of 1 in 6000 male births.[2] In addition, there are approximately 6.7 in 100,000 cases of moderate-to-severe ichthyosis.[3] Congenital ichthyoses are caused by mutations in the genes responsible for keratinocyte differentiation and skin barrier function. To date, there are 36 known forms of inherited ichthyoses, with over 25 genes being implicated and multiple mutations for each gene.[4] In ichthyosis vulgaris, mutation of the filaggrin gene leads to a paucity or absence of the granular layer of the epidermis.[5] This results in abnormal epidermal hyperplasia with excessive formation of stratum corneum, accompanied by abnormal desquamation. The main clinical feature of this disease is dry and rough skin with marked scaling but without inflammation.[6] The skin of the abdomen and extensor surfaces is the most commonly affected, but the skin of the face and flexor surfaces is often spared.[4]

There is limited data on how patients with ichthyosis tolerate radiation therapy.[7] Here we describe a case of a patient with congenital ichthyosis who underwent a course of radiation therapy concurrently with chemotherapy for treatment of squamous cell cancer of the skin.

Case report

The patient is a 51-year-old white man with congenital ichthyosis. To our knowledge, the patient has not been formally genotyped. However, his family history, which includes his mother and sister (his only sibling) being affected by the same disorder, is consistent with an autosomal dominant ichthyosis vulgaris. The patient presented to his primary care physician with a small, painless, pink lesion located on the left knee. The lesion was initially treated with topical antifungal medications for approximately 12 months. Over the next 3 months, the patient noticed that the lesion began to grow rapidly and to become painful. A shave biopsy of the lesion was positive for moderately differentiated squamous cell carcinoma. The patient was subsequently referred to our institution for further management.

On physical examination, a 9-cm exophytic, malodorous, ulcerated, and necrotic lesion was observed in the anteromedial aspect of the left proximal tibia (Fig 1). The lesion also encompassed the anterior and medial aspect of

Conflicts of interest: None.

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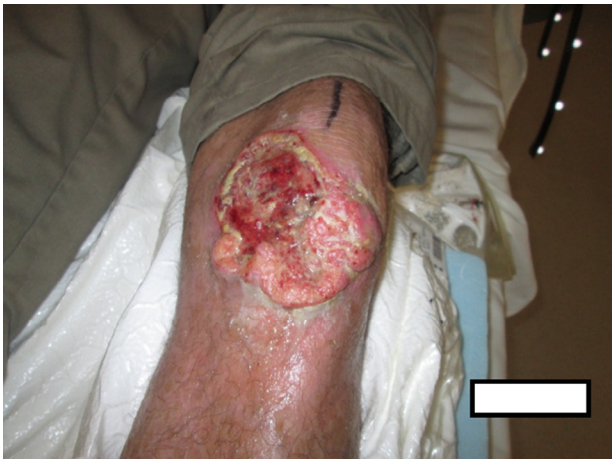

Figure 1 Left knee at presentation.

the proximal tibia and knee joint. There was no exposed bone or tendon. Neuromuscular and sensory functions in his left lower extremity were intact.

Magnetic resonance imaging (MRI) with intravenous contrast demonstrated an $8.3 \times 1.4 \times 4.9$ cm mass superficial to the patella and patellar tendon, without evidence of bone involvement. A fluorodeoxyglucose positron emission tomography–computed tomography scan demonstrated a hypermetabolic (maximum standardized uptake value of 12.3) mass within the skin overlying the left knee and a mildly enhancing (maximum standardized uptake value of 2.3) left inguinal lymph node. Biopsy of this lymph node was negative for malignancy. This case was discussed at our multidisciplinary tumor board, and it was determined that an adequate resection of this lesion was not possible short of an above-the-knee amputation. Consensus was reached for concurrent chemoradiation to the lesion.

The patient was simulated supine on a Phillips Ingenuity CT scanner (Phillips, Cleveland, OH) with a Vac-Loc (CIVCO Radiotherapy, Coralville, IA) for immobilization. Both legs were slightly frog-legged (ie, both thighs slightly abducted and externally rotated), and the left knee was raised slightly higher than the right, using a small styrofoam square under the Vac-Loc (Fig 1).

Diagnostic images were fused to the simulation CT dataset to facilitate target definition. As seen on Figure 2, the gross tumor volume consisted of the tumor as seen in the simulation and diagnostic images. To account for subclinical disease, a clinical target volume was defined as the gross tumor volume with a 1-cm expansion, excluding bone and air. A 5-mm margin was added to the clinical target volume to create the planning target volume.

Treatments were delivered with opposed lateral 6 MV photon beams on a Varian 21EX linear accelerator in accordance with the 3-dimensional plan (Varian Eclipse Treatment Planning System, Varian, Palo Alto, CA). Thirty-degree dynamic wedges were deployed for dose homogeneity. A 0.5-cm bolus (Superflab, CIVCO

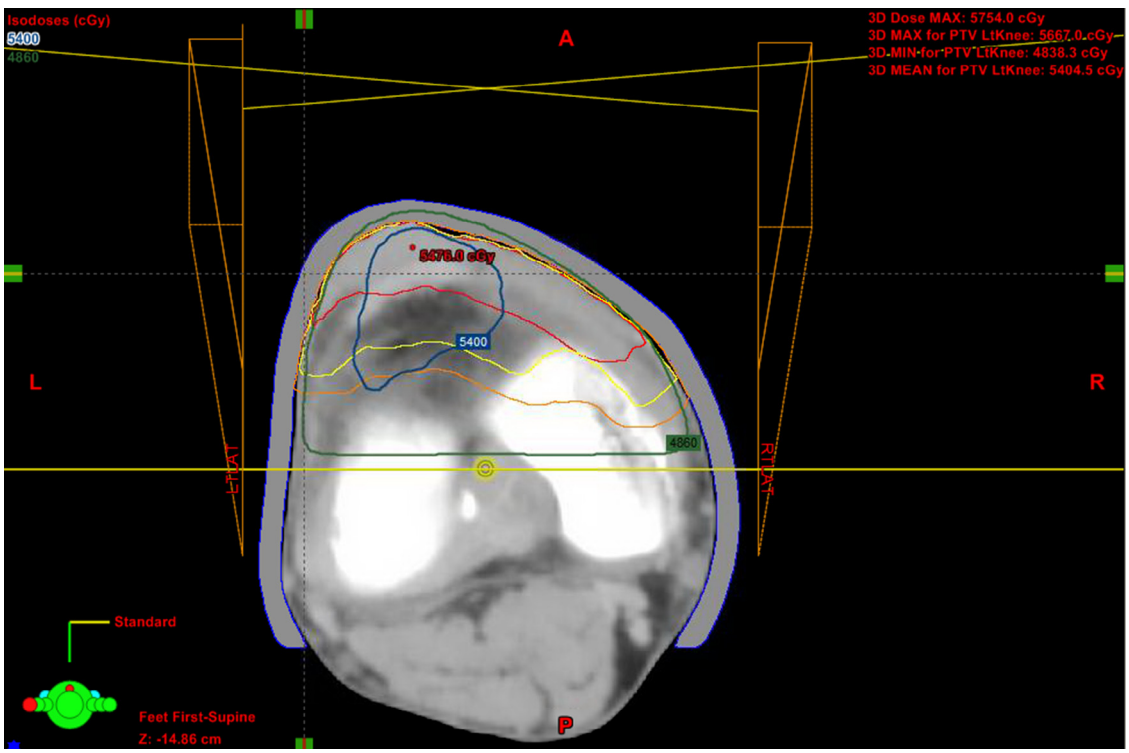

Figure 2 A representative axial image from the radiation treatment plan (gross tumor volume in red; clinical target volume in yellow; planning target volume in orange; 54.0 Gy in dark blue; 48.6 Gy in green; and Bolus in blue).

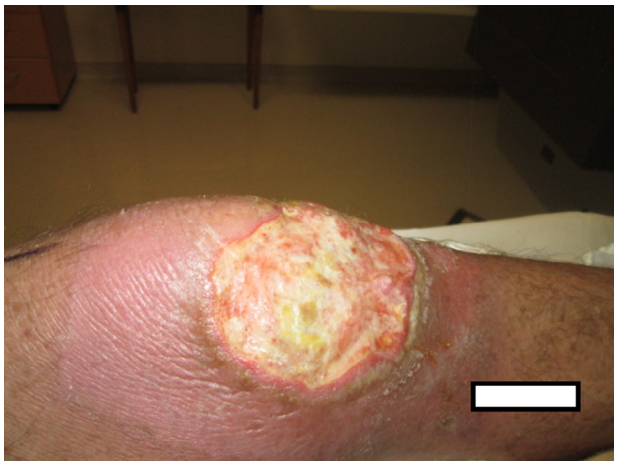

Figure 3 Left knee at the end of treatment.

Radiotherapy) was placed on the skin. The plan resulted in 95% of the planning target volume receiving at least 96% of the prescribed dose.

The patient received a daily dose of 1.8 Gy, 5 days per week, to a total dose of 54 Gy. The patient received 7 doses of weekly intravenous cisplatin at 40 mg/m^2, 6 doses concurrently with the radiation therapy, and the seventh dose administered 3 days after completion of radiation therapy. The patient tolerated this course of treatment well and did not require any treatment breaks or dose reduction. At the end of treatment, the patient reported decreased pain and increased movement of this left knee joint. Not surprisingly, the patient developed very limited areas of dry desquamation (Fig 3), consistent with acute grade 1 skin toxicity, based on the Radiation Therapy Oncology Group acute toxicity criteria.[8]

The patient returned to our clinic 1 month after completion of treatment and demonstrated near-complete resolution of the skin erythema and desquamation (Fig 4) and near-complete resolution of the superficial knee pain.

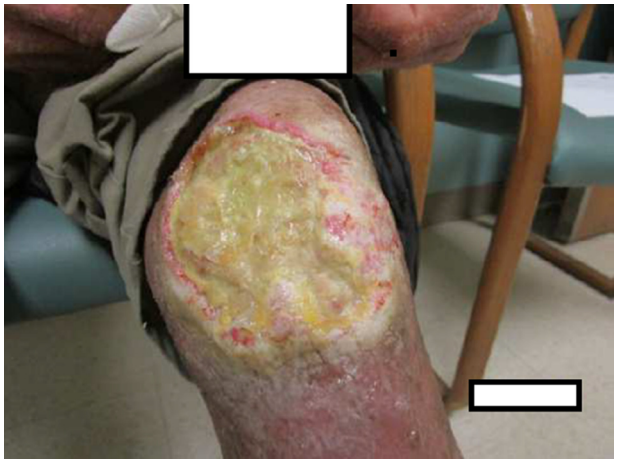

Figure 4 Left knee at 1-month follow-up.

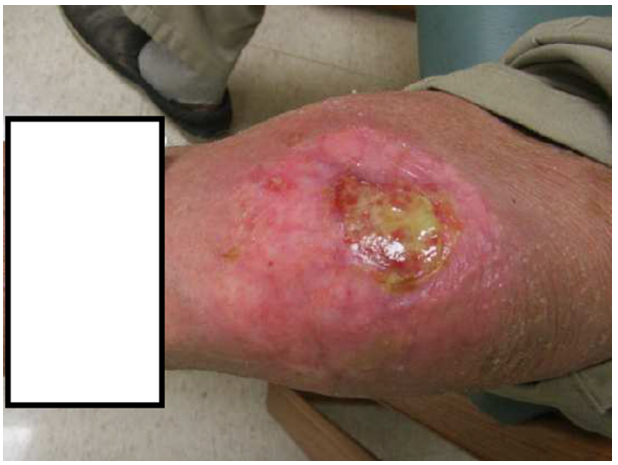

Figure 5 Left knee at 6-month follow-up.

The patient returned to our clinic again 3 months after completion of therapy with a repeat MRI showing no evidence of tumor recurrence. Incidentally, this scan demonstrated an asymptomatic, nondepressed, subchondral fracture at the inferior-lateral femoral trochlea and an anterior, weight-bearing, lateral femoral condyle fracture. On physical examination, the patient was asymptomatic with a full range of motion of the left knee.

At the 6-month follow-up, the patient continued to have very mild pain in the skin overlying the left knee that did not require analgesic medications. There was no visible or palpable tumor at the site of the treatment (Fig 5). An MRI at that time did not show evidence of disease progression and showed resolution of the imaging findings previously interpreted as subchondral femoral fractures.

Unfortunately, 1 year after completion of therapy, the patient presented with a rapidly enlarging, nontender, left inguinal lymph node and ulceration at the site of the original tumor (Fig 6). An MRI demonstrated a necrotic left groin mass with peripheral enhancement that measured $40 \times 32 \times 46$ mm. A fine-needle aspiration of the left inguinal lymph node was consistent with metastatic squamous cell carcinoma. The patient is currently receiving salvage therapy consisting of intravenous pembrolizumab 200 mg every 21 days.

Discussion

We report the case of a patient with congenital ichthyosis who was treated with external beam radiation therapy concurrently with cisplatin for a large cutaneous squamous cell cancer in the left knee.

The true incidence of skin cancers among patients with ichthyosis is unknown. However, we have found a few case reports that suggest an increased risk of skin malignancies in patients with various forms of ichthyoses.[9-12]

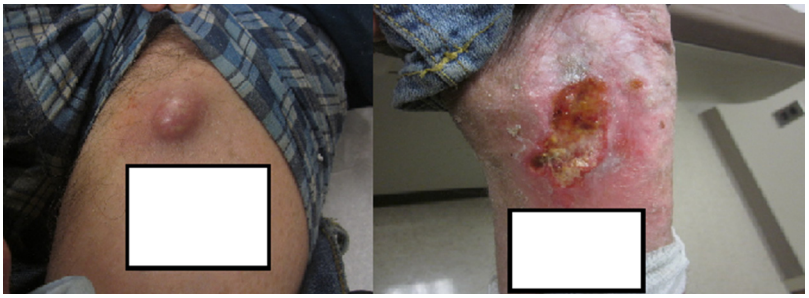

Figure 6 Left groin and left knee at 1-year follow-up.

According to the National Comprehensive Cancer Network Guidelines for Squamous Cell Skin Cancer (Version 1.2017, October 3, 2016), radiation therapy is contraindicated in patients with genetic conditions predisposing to skin cancer (including basal cell nevus syndrome and xeroderma pigmentosum) and connective tissue diseases, including scleroderma. However, this list does not include ichthyosis. Furthermore, we were unable to find any published reports on patients with ichthyosis who received radiation therapy concurrently with chemotherapy.

As far as we know, there is a lack of prospective randomized trials to evaluate the advantage of adding chemotherapy to radiation therapy for treatment of advanced skin cancers. However, we are aware of retrospective reports of small cohorts of patients with advanced cutaneous squamous cell carcinomas of the head and neck region that show the feasibility of concurrent chemoradiation.[13,14] Another retrospective report suggests the additive benefit of platinum-based agents but not of taxanes or cetuximab to radiation therapy in the treatment of advanced squamous cell carcinomas of the skin.[15] Recently, a small, prospective, phase 2 study of a cohort of 21 patients with advanced cutaneous squamous cell carcinomas of the head and neck (14 of them stage 4) who received 66 to 74 Gy concurrently with weekly cisplatin or carboplatin showed a 1-year disease-free survival rate of approximately 50%.[16]

There is a profound lack of literature regarding how patients with ichthyosis tolerate radiation therapy with or without chemotherapy, except for a case report describing the development of subcutaneous calcifications in a patient with ichthyosis who received 41 Gy in 10 fractions to the mediastinum.[7] In fact, there is a lack of objective data to predict the acute and long-term side effects of a typical definitive dose (up to 70 Gy) in a patient with ichthyosis, especially concurrently with cisplatin. Frankly, we were concerned that this patient would not be able to tolerate a conventional course of concurrent chemoradiation; therefore, we chose a slightly lower dose of 54 Gy, a dose that is typically used to treat smaller skin cancers, to ensure patient safety. In retrospect, the dose selected may have been too low to achieve durable local control of an advanced lesion such as this.

Conclusion

To our knowledge, this is the first case report of a patient with congenital ichthyosis who received radiation therapy concurrently with chemotherapy. The patient initially had an excellent treatment response to concurrent chemoradiation, with minimal toxicity. The patient had an uneventful recovery from the side effects. Our case indicates that this regimen can safely be utilized in the treatment of squamous cell carcinoma of the skin arising in patients with congenital ichthyosis. However, additional follow-up may be warranted for our appreciation of long-term side effects of this regimen.

Unfortunately, the patient experienced a recurrence both locally and regionally after 1 year. In light of this recurrence, and because the patient tolerated this regimen well, a higher dose of radiation to the primary as well as elective nodal irradiations to the regions at risk could be considered, with caution, in this patient population.

In summary, we report here that a patient with congenital ichthyosis and advanced squamous cell carcinoma of the skin can tolerate a course of radiation therapy up to 54 Gy concurrently with cisplatin. The treatment resulted in disease control at the site of the primary for approximately 1 year.

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