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Severe radiation therapy-related soft tissue toxicity in a patient with porphyria cutanea tarda: a case report and literature review

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Abstract

Background—Some porphyrias are associated with cutaneous phototoxicity due to photoactivation of porphyrins, but whether ionizing radiation can have an additive effect is not clear. We report a case of severe radiation therapy-related toxicity in a patient with porphyria cutanea tarda and review the literature.

Methods—A 50 year-old man with porphyria cutanea was treated for lower lip squamous cell carcinoma with definitive radiation therapy. During radiation therapy acute toxicity was of an expected onset and severity. Six months after treatment completion, he developed skin hypopigmentation, soft tissue fibrosis, and areas of painful denuded skin and crusting within the previous treatment field.

Results—Reports of 7 porphyria patients receiving radiation therapy to at least 9 separate sites were reviewed, with only one previous report suggestive of increased radiation therapy-related toxicity.

Conclusions—Based on this report and one other, caution is warranted when considering radiation therapy in patients with active porphyria.

Keywords

Porphyria; Radiation therapy; Cancer; Toxicity

Introduction

Porphyrias are rare metabolic disorders due to deficiencies of enzymes in the heme biosynthetic pathway leading to accumulation of pathway intermediates (1,2). The major clinical manifestations are either neurological or cutaneous. Excess porphyrins are transported to the skin and activated when exposed to long-wave ultraviolet light (UV-B) to produce free radicals, resulting in phototoxicity (3).

Porphyria cutanea tarda (PCT) presents with blistering skin lesions on sun exposed areas and is the most common and readily treated porphyria. Other symptoms include cutaneous

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fragility, facial hypertrichosis and hyperpigmentation, and liver damage (1,2). PCT results from an acquired deficiency of uroporphyrinogen decarboxylase, the fifth enzyme in the heme pathway. A multiplicity of susceptibility factors can be identified in individual patients, which may include alcohol use, smoking, estrogen, chronic hepatitis C, HIV infection, hemochromatosis, oxidative stress and an inherited partial enzyme deficiency (4,5).

The effects of therapeutic ionizing radiation in the porphyria patient are not clear. We describe a patient with PCT who developed unexpectedly severe soft tissue late toxicity after radiation treatment of a squamous cell cancer of the lower lip, and review previous reports of radiation treatment in patients with porphyria.

Materials and Methods

Case Report

A 38 year-old Caucasian man developed blistering skin lesions and was documented to have PCT in 1991. At that time he was treated by repeated phlebotomies over a 4 month period and experienced a complete remission of his skin lesions. A recurrence in 1997 at age 44 was again treated successfully by phlebotomy. Crusted lesions recurred on the backs of his hands in 2003. He presented in 2004 at age 50 with a 3 cm exophytic lesion involving the cutaneous aspect of the lower left lip. Biopsy showed squamous cell carcinoma. Clinical and CT examination of the neck and chest X-ray did not show regional lymph node or pulmonary involvement. Review of the literature at that time did not show PCT to be a clear contraindication to radiation therapy, and the patient elected definitive radiation therapy rather than potentially extensive surgery for this T2N0M0 (AJCC 2002) cutaneous lower lip cancer. He was treated to a total dose of 70 Gy to the lower lip lesion and 50 Gy to the bilateral upper neck (levels I and II), via opposed lateral beam arrangement (figure 1) and 3D conformal radiation therapy technique, with sequential field reductions, using 6 megavolt photons for all fields except for 9 megaelectron volt electrons used over the posterior cervical strips.

During radiation therapy, he developed confluent mucositis of the oral cavity and patchy moist desquamation of skin within the treatment field, both of expected onset and severity considering the total dose and tumor location, but the time course was protracted with slow resolution over 15 weeks. By six months after treatment completion, he began to develop progressively severe, sharply demarcated skin hypopigmentation with skin sclerosis and subcutaneous fibrosis and retraction, with areas of denuded skin and crusting. These soft tissue changes were within and limited to the previous radiation field (figures 1 and 2). He also developed severe lower face and upper neck soft tissue pain within the same time period.

In 2005 blistering skin lesions were present on the backs of his hands, arms, face, ears and neck, and PCT was again documented by increases in urine total porphyrins (2,528 nmol/L, reference range 0–300) with a predominance of uroporphyrin and heptacarboxylporphyrin (49% and 42% of the total, respectively), and total plasma porphyrins of 14.8 mcg/dL (range <0.9) with a fluorescence emission peak at 620 nm. Susceptibility factors for PCT in this case included alcohol use, smoking and chronic hepatitis C, whereas HIV infection, estrogen use and hemochromatosis gene mutations were excluded. His erythrocyte uroporphyrinogen decarboxylase activity was normal, which is consistent with sporadic rather than familial PCT.

Treatment of PCT with low-dose hydroxychloroquine (100 mg by mouth twice weekly) was started in 2006. Because the response was poor after 5 months, treatment was changed to

repeated phlebotomy, and his porphyrin levels decreased gradually over the next year with clearing of the blistering lesions on his hands and arms with improvement of his face lesions. During this time he also underwent hyperbaric oxygen treatment in preparation for a tooth extraction with some temporary improvement of his face lesions. However, the skin hypopigmentation, fibrosis, retraction, and pain persisted within the previous treatment field, requiring chronic narcotic analgesic use. He had a complete and durable clinical response of the lip lesion and neck control at 4 years.

Results

Literature Review

We identified 4 previous reports describing 7 patients diagnosed as having porphyria who received radiation therapy to at least 9 separate sites. Details of the present and previously reported cases are provided in Table 1. These include 4 patients with a diagnosis of PCT (Cases 1–4, including the present case) (6,7), 1 patient with acute intermittent porphyria (Case 5) (6) and 1 patient with variegate porphyria (Case 6) (8). The diagnosis of porphyria was poorly documented and reported porphyrin levels were minimally increased in 2 additional cases (Case 7 and 8, Table 1) (9).

Cases 3 and 4 (7) were described before high pressure liquid chromatography methods were widely used to confirm a diagnosis of PCT (by demonstrating substantial increases in both uroporphyrin and heptacarboxylporphyrin). Nonetheless, these patients did have substantial porphyrin levels due to a cutaneous porphyria that was most likely PCT. They received radiation therapy for lymphoma for brain (Case 3) or multiple lymph node involvement (Case 4), and no details regarding any reactions to radiation therapy were reported (7). Acute intermittent porphyria is usually not associated with substantial increases in circulating porphyrins. However, Case 5 with acute intermittent porphyria and breast cancer reported by Schaffer *et al* (6) also had end stage renal disease, which in acute intermittent porphyria can be associated with substantial elevations in plasma porphyrins and even photosensitivity (10). Case 6, with variegate porphyria and breast cancer was treated with relatively high radiation doses, including an interstitial implant; the acute reactions were not thought to be out of the ordinary, and no late reactions were described (8). Thus, cases 1–6 all had porphyrias causing substantial porphyrin elevations at the time of radiation therapy, but the severe late soft tissue manifestations in our case (Case 1) contrasted with little or no exaggerated effect of radiation in the other 5 cases (Table 1).

Rhomberg and Offner reported two patients with glioblastoma multiforme, who carried diagnoses of porphyria and were treated with radiation therapy and concurrent chemotherapy. One patient suffered substantial brain necrosis after 60 Gy and the other showed tumor necrosis after 38 Gy (9). However, the biochemical basis for the diagnosis of porphyria in these cases is not convincing, and porphyrin levels were only slightly elevated, which would most likely preclude an adverse interaction between radiation and excess porphyrins.

Discussion

Here we report a case of severe radiation therapy-related toxicity in a patient with PCT treated with definitive radiation therapy for lip cancer. Acute reactions in our patient were not greater than expected for definitive radiation therapy for a lip cancer treated to 70 Gy, but were somewhat slow to resolve. However, within six months after completing radiation therapy he developed exaggerated and progressive soft tissue reactions. These were treated initially with conservative topical measures and narcotic analgesics. Because his PCT was active, he was later started on low-dose hydroxychloroquine therapy, which was not

effective, followed by repeated phlebotomy, with gradual clearance of blistering skin lesions on the backs of his hands, arms and face. Ulcerations of the previously irradiated skin also improved as his PCT went into remission, but the severe fibrotic changes and hypopigmentation persisted.

The few case reports of patients with porphyria who underwent radiation therapy, some of which did not comment on radiation toxicity, are summarized in Table 1. Based on experience with two cases with elevated porphyrin levels, Schaffer *et al* concluded that porphyria patients should have no increased side effects from radiation (6). Scarlett *et al* did not find any exaggerated acute reactions in a patient with variegate porphyria, and late toxicity was not mentioned and therefore presumably did not occur (8). Our patient had 70 Gy delivered to a superficial target, whereas the aforementioned reports treated deeper targets and used lower total doses, except in one patient where an interstitial breast implant was used, but the skin dose in that case was still probably less than our case. Therefore, it is possible that the exaggerated skin and subcutaneous skin reactions seen in our case were related to the total dose and targeting of the superficial skin.

In Cases 1–6 summarized in Table 1, including our patient (Case 1), either (i) plasma porphyrin concentrations were elevated, (ii) urine porphyrins were increased in types of porphyria in which both plasma and urine porphyrin elevations are expected to be correlated, or (iii) in Case 5, plasma porphyrins were elevated in a patient with acute intermittent porphyria due to concurrent renal disease. Although Rhomberg and Offner suggested caution when treating brain tissue in porphyria patients based on experience with two patients with glioblastoma multiforme (Cases 7 and 8, Table 1) treated with radiation therapy and concurrent chemotherapy who then developed brain necrosis after 60 Gy (Case 7) and tumor necrosis after only 38 Gy (Case 8) (9), the biochemical findings they reported do not convincingly support a diagnosis of porphyria or the presence of elevated circulating porphyrin levels.

Phototoxic effects of porphyrins in human porphyrias are maximal with exposure to light at wavelengths near 400 nm, corresponding to the Soret peak of the porphyrin absorption spectrum, which is far beyond the wavelength of therapeutic ionizing radiation (6,8). Radiation sensitization by gadolinium texaphrin, an expanded metalloporphyrin (11,12), has been shown to be specific for gadolinium rather than the expanded porphyrin (13). Nonetheless, tissue responses to radiation might be additive to those that occur following porphyrin photoactivation, which results in activation the complement cascade (14,15) and dermal mast cells (16), leading to thickening of blood vessel basement membranes (17). Furthermore, porphyrins and especially uroporphyrin have been shown *in vitro* to stimulate collagen production by fibroblasts independent of light exposure (18). These effects are similar and potentially additive to those of the late fibrotic response to radiation therapy (19). Of note, porphyrias are not associated with a known increased risk of cutaneous malignancy (20).

Our case is to our knowledge the first in which an enhanced soft tissue late reaction to radiation treatment was observed in a patient with porphyria and documented substantial elevations in circulating porphyrins. Although it is not established that porphyria contributed to this reaction, it seems reasonable to recommend treating PCT before radiation therapy in the future, if a delay of several months is clinically acceptable. In almost all cases of PCT, normal or near-normal porphyrin levels can be achieved in this period of time with a regimen of repeated phlebotomies or low-dose hydroxychloroquine or chloroquine (21,22). Furthermore, in patients with cutaneous porphyrias being considered for radiation therapy, caution is warranted, especially when the skin dose is expected to be high, and treatment approaches that do not include radiation therapy should be considered.

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Figure 1.
Initial left lateral radiation therapy portal.

Figure 2.
(a) Photograph taken two years after completing radiation therapy showing hypopigmentation, fibrosis with retraction, and crusted ulcerations. (b) Additional view demonstrating hypopigmentation, sclerotic skin, and crusted lesion on lower lip.

Table 1

Case reports of radiation therapy in patients with porphyria.

	Porphyrin Diagnosis	Porphyrins elevated during treatment	Cancer Type	Radiation Therapy Summary	Toxicity/Comments	Reference
1	PCT	Yes	Cutaneous lip cancer	Definitive radiation therapy, 70 Gy to lower lip and 50 Gy to bilateral upper neck.	<i>Acute Toxicity:</i> mucositis and dermatitis of expected onset and severity, but slow to resolve. <i>Late Toxicity:</i> severe skin hypopigmentation and sclerosis with subcutaneous fibrosis and retraction, with areas of denuded skin and crusting.	This report
2	PCT	Yes	Bladder	Pelvic radiation, 45 Gy, with a 9 Gy boost.	<i>Acute Toxicity:</i> slight perianal skin erythema and diarrhea. <i>Late Toxicity:</i> none.	Schaffer et al, 2001 (6)
3	PCT		Non-Hodgkin Lymphoma	Brain radiation, 32.5 Gy.	<i>Toxicity:</i> Not specifically reported.	Maughan et al, 1979 (7)
4	PCT		Hodgkin Lymphoma	Radiation to multiple lymph node bearing areas above and below the diaphragm, 32 treatments.	<i>Toxicity:</i> Not specifically reported.	Maughan et al, 1979 (7)
5	Acute Intermittent Porphyria	Yes*	Breast	Initially treated to left chest wall and regional nodes, 50 Gy with 10 Gy boost. Later treated for brain and mediastinal metastases, 46 and 50 Gy respectively.	<i>Acute Toxicity:</i> slight erythema of chest wall skin. <i>Late Toxicity:</i> none. <i>Acute Toxicity:</i> none severe. <i>Late Toxicity:</i> short follow up.	Schaffer et al, 2001 (6)
6	Variegate porphyria	Yes	Breast	Left breast and supraclavicular and internal mammary regions, 50 Gy; followed by a 10 Gy photon boost; followed by 20 Gy Iridium-192 interstitial implant.	<i>Acute Toxicity:</i> marked skin erythema with small area of moist desquamation. <i>Late Toxicity:</i> Not specifically reported.	Scarlett et al 1995 (8)
7	Acute Hepatic Porphyria		Glioblastoma Multiforme	Concurrent chemoradiation, 60 Gy	Extensive brain necrosis and deterioration of porphyria.	Rhomberg and Offner (9)
8	Porphyria type unclear		Glioblastoma Multiforme	Concurrent chemoradiation, completed 38 of a planned 60 Gy.	Patient died during radiation therapy of cardiopulmonary insufficiency. Tumor showed necrosis after 38 Gy.	Rhomberg and Offner (9)

* Plasma porphyrins are not substantially elevated in AIP except, as in this patient, in the presence of advanced renal disease (10).

PCT = Porphyria cutanea tarda