Gynecologic Oncology Reports 35 (2021) 100682

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case report

Porphyria cutanea tarda exacerbation as a paraneoplastic syndrome in vaginal cancer resolved with chemoradiation

Sarah Z. Hazell [a], Amanda N. Fader [b], Akila N. Viswanathan [a,*]

[a] Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University School of Medicine, 401 N Broadway, Suite 1440, Baltimore, MD 21287, United States
[b] Department of Gynecology and Obstetrics, Kelly Gynecologic Oncology Service, Johns Hopkins School of Medicine, 600 N. Wolfe St., Phipps 287, Baltimore, MD 21287, United States

ARTICLE INFO

Keywords:
Radiation
Vaginal cancer
Porphyria cutanea tarda
Ionizing radiation

ABSTRACT

Porphyria Cutanea Tarda (PCT) is a rare paraneoplastic syndrome. The effects of therapeutic ionizing radiation in patients with PCT are not well understood. We report the case of a 55 year-old woman with a past medical history significant for kidney transplant with rejection and removal on hemodialysis, Stevens-Johnson syndrome, porphyria cutanea tarda, undifferentiated connective tissue disease probably systemic lupus, and hepatitis C, who underwent curative chemoradiation treatment for a recurrent vaginal squamous cell carcinoma. There was no increased acute toxicity and active porphyria cutanea tarda improved over the course of radiation treatment and fully resolved within 1 year. However, there was significant myofibrotic late toxicity within the treated region.

1. Introduction

Porphyrias are metabolic disorders due to altered activity of enzymes involved in the heme biosynthesis pathway. Porphyria cutanea tarda (PCT) is the most common of the porphyrias and is due to acquired inhibition of uroporphyrinogen decarboxylase (UROD) in the liver to less than approximately 20 percent of normal (Elder et al., 1981). Inhibition of UROD occurs in the presence of iron and a variable combination of acquired factors, such as alcohol, smoking, hepatitis C, estrogens, HIV infection, and UROD mutations (Egger et al., 2002). The reduction of UROD activity leads to hepatic accumulation of carboxylated porphyrinogens, which are then oxidized to the corresponding porphyrins (Anderson, 2001). Porphyrins accumulate in the skin and lead to cutaneous phototoxicity on exposure to light with a wavelength near 400 nm (Lim et al., 1984). PCT presents with blistering photosensitivity of the skin, especially on sun exposed areas. PCT is not known to be a paraneoplastic syndrome.

The effects of therapeutic ionizing radiation in patients with porphyrias are not well understood, and the only literature guiding risks of treatment is in the form of case reports. To date, the literature described eight separate cases of cancer patients with porphyria treated with radiation therapy. One case in which severe late toxicity was reported was a patient with PCT who received definitive radiation therapy for a lip cancer treated to 70 Gy (Gunn et al., 2010). He experienced acute toxicity as expected. However, 6 months after radiation was completed, he developed severe progressive soft tissue reactions within the previously treated field. He was treated for active porphyria and the ulcerations in the previously irradiated skin improved as his PCT went into remission, but the severe fibrotic changes and hypopigmentation persisted.

Rhomerbg and Offner reported 2 cases of patients with porphyria who underwent treatment with radiation therapy for glioblastoma multiforme [GBM] (Rhomberg and Offner, 2005). The first patient died 7 months after diagnosis and experienced extensive brain necrosis and progression of porphyria. The second patient died 1.5 months following diagnosis due to cardiopulmonary complications after receiving only 38 Gy.

Schaffer et al reported one female patient with a history of intermittent porphyria and breast cancer and one male patient with PCT and bladder cancer both treated with radiation therapy without any increase toxicity from what was expected (Schaffer et al., 2001). In another report, a patient with breast cancer and variegate porphyria was treated with radiation, with no reported exaggerated acute toxicity. Of note, the patient, similar to our patient, received an interstitial brachytherapy boost with Iridium-192 after external beam (Scarlett et al., 1995). However, acute and late toxicity were not specifically reported.

* Corresponding author at: 401 N Broadway, Suite 1440, Baltimore, MD 21231, United States.
E-mail address: anv@Jhu.edu (A.N. Viswanathan).

https://doi.org/10.1016/j.gore.2020.100682
Received 8 October 2020; Received in revised form 2 December 2020; Accepted 6 December 2020
Available online 15 December 2020

2. Material and methods

2.1. Case presentation

A 55 year-old woman with a past medical history significant for kidney transplant with rejection and removal on hemodialysis, Stevens-Johnson syndrome, porphyria cutanea tarda, undifferentiated connective tissue disease thought to be related to systemic lupus erythematosus, and hepatitis C, presented for radiation treatment for a recurrent vaginal squamous cell carcinoma.

2.2. Oncologic history

She initially presented with discomfort during intercourse in 2013. Exam prompted a right vaginal biopsy which demonstrated vulval intraepithelial neoplasm (VIN) 3 with focal ulceration. She then underwent an exam under anesthesia, radical excision of right vulvar/vaginal lesion and right inguinal sentinel lymph node dissection. Pathology demonstrated a Stage IA vaginal carcinoma with focal invasion in the setting of diffuse VIN 2-3. Deep margins were negative and peripheral margins were positive. She was counseled regarding re-excision versus close observation, and due to her multiple comorbidities, she elected for close observation.

A Pap smear in 2015 demonstrated atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (ASC-H). Patient was asked to return for colposcopy and biopsies. She underwent exam under anesthesia, Pap smear, colposcopy with vaginal biopsies and endocervical curettage. Exam found a firm, fixed right lateral vaginal mass approaching the introitus as well as an enlarged, somewhat fixed right inguinal lymph node. Biopsies were performed of the vaginal mass with pathology demonstrating squamous cell carcinoma.

Positron-emission tomography (PET) scan showed an intensely avid mass in right side of the vagina, a 4.6 × 3.6 cm right inguinal mass, a 0.9 cm right external iliac lymph node, and multiple moderately FDG avid mediastinal, bilateral axillary, porta hepatis/porta caval and retroperitoneal lymph nodes of normal size (lower FDG avidity than vaginal mass and thought to be related to connective tissue disease).

2.3. Porphyria cutanea tarda history

In 2015, patient presented to dermatology clinic with ill-defined, erythematous, scaly macules/patches scattered on bilateral upper arms and mild dyshidrotic vesicles noted on lateral finger on bilateral hands. Suspected to be eczema, she was given clobetasol and triamcinolone cream. She presented in follow up a few months later without improvement and laboratory work-up revealed elevated porphyrins (2154.6 mcg/L), with low UROD (0.54 Relative Units), supporting diagnosis of porphyria cutanea tarda. The low UROD level supported PCT Type II (genetic), potentially triggered by dialysis, hepatitis C, and/or iron infusions.

Dermatology recommendation was to discontinue iron infusions, initiate phlebotomy during dialysis, and avoid sun exposure. She was also started on plaquenil 400 mg daily for underlying connective tissue disorder. Following initial interventions, there was little improvement in PCT lesions.

3. Results

Patient was seen in consult by radiation oncology in August 2016 and initiated treatment with daily external beam radiation and concurrent cisplatin. Intensity modulated radiation therapy treated the primary vaginal lesion, inguinal lymph nodes, and pelvic lymph nodes to 4500 cGy in 25 fractions. Weekly cisplatin was given at 50% of standard dose due to renal issues.

She required a treatment break after 25 fractions due to grade 3 acute dermatitis in the inguinal/perineal regions, which was managed with sitz bath and Domeboro skin care as well as oxycodone 15 mg po prn for pain. PCT lesions dramatically improved during her treatment course and in follow-up (Fig. 1).

After treatment break, external beam radiation was resumed with a cone down to the involved right inguinal lymph node for an additional 20 Gy in 10 fractions to a total dose of 65 Gy.

MR-guided interstitial high dose rate (HDR) brachytherapy was used to boost the primary vaginal lesion with an additional 20 Gy in 5 fractions, completed January 2017. At 2 week follow up appointment, PCT appeared to be resolving, but she did have some nodularity on the skin in the area where the interstitial template was sutured, thought to represent scar tissue versus skin infection. She was given a 7 day course of Ciprofloxacin. She did develop intermittent rectal bleeding and underwent colonoscopy 7 months after completing radiation, which was consistent with radiation proctitis. An area of active oozing was treated with argon plasma coagulation with improvement in the rectal bleeding. She was also treated for hepatitis C with Zepatier and had an undetectable viral load in 2018.

15 months following completion of radiation, she had no evidence of any skin lesions. Fig. 1 shows the resolution of her skin lesions over time. On exam, she did have a fixed firm mass in the right groin. However, fine needle aspiration pathology revealed only necrotic debris with calcification consistent with treatment effect with extensive tumor necrosis. Fig. 2 shows the right inguinal lymph node at the time of diagnosis and subsequent scans following treatment.

She continued to have a fibrotic reaction in right inguinal region causing right lower extremity lymphedema and was subsequently treated with 60 hyperbaric oxygen treatments with some response. She then received a one-month steroid taper along with lymphedema therapy with a dramatic reduction in the lymphedema. At her 24-month follow up, she reported improved pain and mobility in her right leg and groin following these interventions. PET/CT from September 2018, as seen in Fig. 3, shows mildly FDG avid soft tissue thickening with effacement of the intermuscular fat planes, likely related to radiation related myonecrosis, without any evidence of recurrent malignancy. She continued to have no evidence of skin lesions related to PCT, but did have clinical and radiographic findings of myositis. A myositis panel was positive for Anti-U1RNP antibody, which is found in 10–15% of myositis cases, usually as an overlap syndrome involving other connective tissue diseases (Love et al., 1991; Targoff, 2002). An MRI of the pelvis in February 2019 demonstrated extensive patchy muscular edema on T2-weighted images, concentrated in the abductor groups. Follow-up within 1 year and up to 4 years after treatment shows complete resolution of the porphyria cutanea tarda and no evidence of vaginal cancer. She has significant residual fibrosis in the irradiated groin and vaginal stenosis at the level of her vaginal dilator insertion.

4. Discussion

We herein report a case of patient with vaginal cancer and porphyria cutanea tarda, and complete resolution of both after curative chemoradiation. Porphyria cutanea tarda has rarely been reported to present as a paraneoplastic syndrome. There remains a theoretical concern for increased toxicity and side effects caused by ionizing radiation in patients with a history of porphyria cutanea tarda. However, there is limited literature to help guide treatment in these patients. Of the eight documented cases in the literature, there were only two cases of reported increased toxicity at a dose of 60–70 Gy (Gunn et al., 2010; Rhomberg and Offner, 2005). There was either no mention of toxicity or no reported increase in toxicity in the remaining cases. However, one of the documented cases of toxicity resulted in severe progressive soft tissue reactions with fibrotic changes 6 months after completing definitive head and neck radiation (Gunn et al., 2010). In the case we have presented, there was no increased acute toxicity and active PCT seemed to improve over the course of radiation treatment with complete resolution of the PCT at 6 months following treatment. However, there was

Fig. 1. (A) Ill-defined, erythematous, scaly macules/patches over bilateral hands consistent with porphyria cutanea tarda at the start of treatment. (B) Improvement of lesions by the end of radiation treatment. (C) Resolution of lesions 3 months following treatment. (D) No evidence of skin lesions 6 months following treatment.

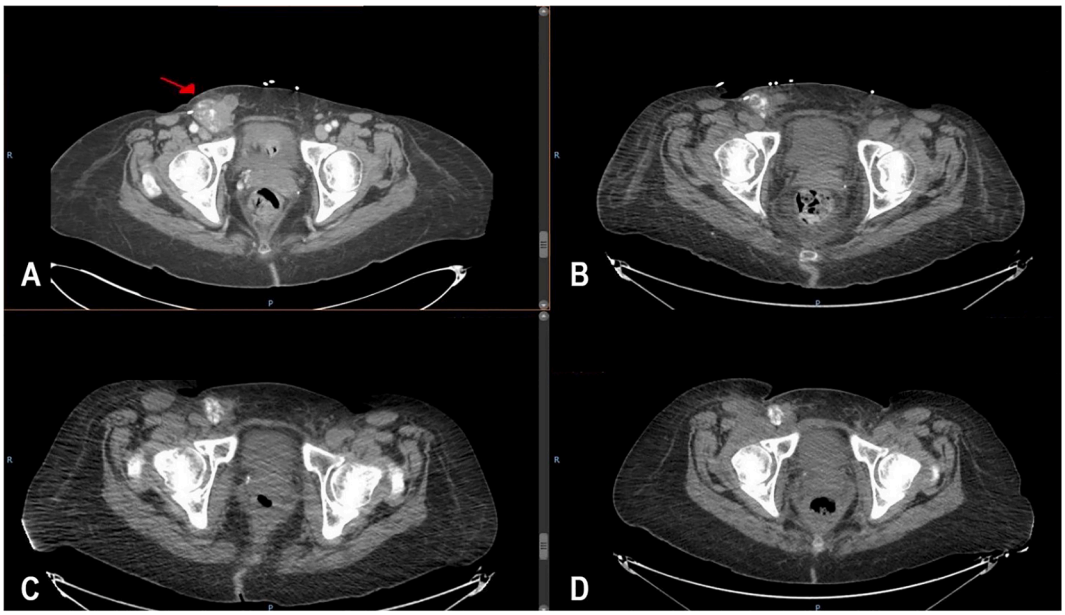

Fig. 2. Computed tomography (CT) images of right inguinal mass (A) Axial CT image at the time of diagnosis. Arrow points to the right inguinal mass. (B) Axial CT image 1 month following radiation treatment. (C) Axial CT image 7 months following radiation treatment. (D) Axial CT image 15 months following radiation treatment. Biopsy of residual right inguinal mass showed necrotic debris.

significant late toxicity within the treated region with a myofibrotic reaction that is currently being closely managed by a rheumatologist.

When porphyrins accumulate in the skin and are exposed to wavelengths within the ultraviolet A and visible light ranges, near 400 nm, the porphyrins enter an excited state and release photons, which ultimately leads to tissue damage. The photons generated in therapeutic ionizing radiation have wavelengths in the range of 10^{-11} to 10^{-13} m, which is well below the range thought to activate porphyrins.

Whether her history of connective tissue disease/systemic lupus erythematosus was related to late toxicity including myositis and proctitis is unknown. Limited case reports should be cautiously generalized to a patient population. In this case, the patient's curative approach to cancer has resulted in a resolution of her disease and PCT, and close management with frequent follow up is required to ensure that all toxicities that may occur are appropriately managed.

Patient consent

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient/parent/guardian/relative of the patient.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

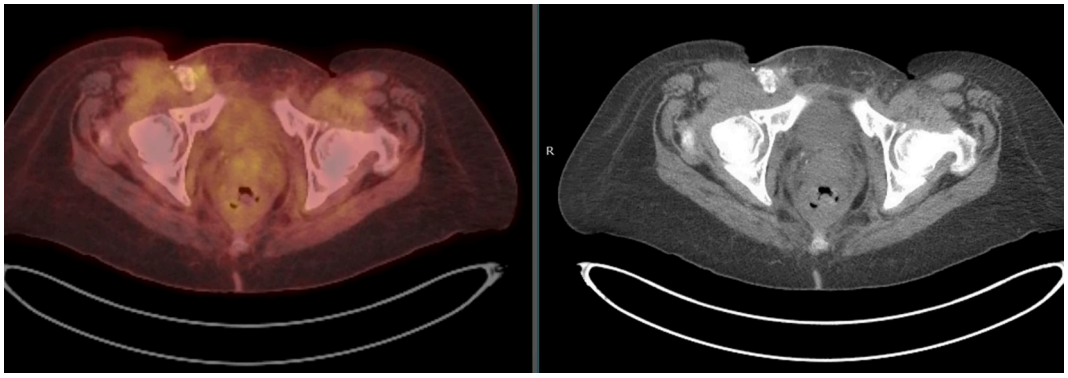

Fig. 3. Positron-emission tomography/computed tomography (PET/CT) 20 months after completing radiation shows mildly FDG avid soft tissue thickening with effacement of the intermuscular fat planes, likely related to biopsy proven radiation related myonecrosis that resolved with steroids.

Author contribution

All authors contributed to the writing and editing of this manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Elder, G.H., Smith, S.G., Herrero, C., Lecha, M., Mascaro, J.M., Muniesa, A.M., et al., 1981. Hepatoerythropoietic porphyria: a new uroporphyrinogen decarboxylase defect or homozygous porphyria cutanea tarda? Lancet 1 (8226), 916–919.

Egger, N.G., Goeger, D.E., Payne, D.A., Miskovsky, E.P., Weinman, S.A., Anderson, K.E., 2002. Porphyria cutanea tarda: multiplicity of risk factors including HFE mutations, hepatitis C, and inherited uroporphyrinogen decarboxylase deficiency. Dig Dis Sci. 47 (2), 419–426.

Anderson, K., 2001. Disorders of heme biosynthesis: X-linked sideroblastic anemia and the porphyrias. The metabolic & molecular bases of inherited disease, 2991–3062.

Lim, H.W., Poh-Fitzpatrick, M.B., Gigli, I., 1984. Activation of the complement system in patients with porphyrias after irradiation in vivo. J. Clin. Invest. 74 (6), 1961–1965.

Gunn, G.B., Anderson, K.E., Patel, A.J., Gallegos, J., Hallberg, C.K., Sood, G., et al., 2010. Severe radiation therapy-related soft tissue toxicity in a patient with porphyria cutanea tarda: a literature review. Head Neck. 32 (8), 1112–1117.

Rhomberg, W., Offner, F.A., 2005. Porphyria and radiotherapy: yet a constellation of risk? Strahlenther. Onkol. 181 (6), 401–404.

Schaffer, M., Schaffer, P.M., Panzer, M., Wilkowski, R., Duhmke, E., 2001. Porphyrias associated with malignant tumors: results of treatment with ionizing irradiation. Onkologie. 24 (2), 170–172.

Scarlett, J.D., Corry, J., Jeal, P.N., 1995. Cytotoxic chemotherapy and radiotherapy in a patient with breast cancer and variegate porphyria (VP). Aust. N Z J. Med. 25 (6), 742–743.

Love, L.A., Leff, R.L., Fraser, D.D., Targoff, I.N., Dalakas, M., Plotz, P.H., et al., 1991. A new approach to the classification of idiopathic inflammatory myopathy: myositis-specific autoantibodies define useful homogeneous patient groups. Medicine (Baltimore). 70 (6), 360–374.

Targoff, I.N., 2002. Laboratory testing in the diagnosis and management of idiopathic inflammatory myopathies. Rheum. Dis. Clin. North Am. 28 (4), 859–890 viii.