Received: 25 July 2022 | Revised: 2 December 2022 | Accepted: 12 April 2023

DOI: 10.1002/ccr3.7266

CASE REPORT

Clinical Case Reports Open Access WILEY

Eosinophilic, polymorphic, and pruritic eruption associated with radiation therapy in two patients diagnosed with prostate cancer

Maria Alexandra Barbu[1,2] | **Rodica Maricela Anghel**[1] | **Gabriel Ricu**[2] | **Tiberiu Tebeica**[3] | **Raluca Patru**[4] | **Alexandru Michire**[1]

[1]Department 8—Radiology, Oncology, Hematology, Faculty of Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

[2]MedEuropa Center of Oncology and Radiation Therapy, Bucharest, Romania

[3]Leventer Center- Department of Dermatopathology, Bucharest, Romania

[4]Coltea Hospital- Oncological Department, Bucharest, Romania

Correspondence
Gabriel Ricu, MedEuropa Center of Oncology and Radiation Therapy, Bucharest, Romania.
Email: gabriel.ricu@medeuropa.ro

Key Clinical Message: We report 2 cases of EPPER diagnosed in patients who received radiation therapy and hormonal therapy for locally advanced prostate cancer. Both our patients developed this rare late toxicity, but early diagnosis and treatment of this adverse event offers a good prognosis, with no unnecessary interruptions of oncological treatment required.

Abstract: Acute and late adverse events are a major problem for patients receiving radiation therapy. We describe two cases of eosinophilic, polymorphic, and pruritic eruption associated with radiotherapy (EPPER) syndrome, a very uncommon toxicity that affects cancer patients. Both our cases were men diagnosed with localized prostate cancer and were treated with radiotherapy and hormonal therapy. They developed EPPER during and after completing the total radiation dose. Multiple tests and skin biopsies were performed in order to find a superficial perivascular lymphohistiocytic infiltrate, confirming EPPER. The patients received corticotherapy and fully recovered after this treatment. There are a few more cases of EPPER reported in the literature, but the pathogenic mechanism is still unknown. EPPER is an important side effect of radiation therapy and it is probably underdiagnosed, due to its occurrence (usually after completing the oncological treatment).

KEYWORDS
eosinophilic eruption, prostate cancer, radiation therapy

1 | INTRODUCTION

Eosinophilic, polymorphous, pruritic eruption associated radiotherapy (EPPER) syndrome was first mentioned by Rueda et al in 1999.[1] This syndrome typically appears during radiation therapy, or after a while following the treatment completion. It is characterized by generalized erythematous and pruritic skin papules or vesicles, bullae and nodules. The eruption is not limited to the irradiated areas and the lower and upper extremities are often affected. The biopsy findings of these lesions includes a perivascular lymphohistiocytic infiltrate with eosinophils.[1,2]

There are only a few clinical cases reported in the literature on this topic. According to these reports, the syndrome appears in patients diagnosed with cervical cancer, breast cancer, or lymphoma and can occur up to nine and a half months after radiation therapy.[1–7]

We describe two atypical clinical cases of EPPER diagnosed in our institution. The patients are men, treated for prostate cancer with radiation therapy and hormonal therapy. They developed the syndrome after completing radiation treatment.

2 | CASE PRESENTATION 1

A 72-year-old man, diagnosed in January 2021 with stage IIIA prostate cancer, presented in our clinic for oncological treatment. He had no comorbidities, he was ECOG 0 and because of his high-risk stage group we started radiation therapy and androgen deprivation therapy (ADT) in July 2021. He was referred to a radiation oncologist and he performed external beam radiation therapy, volumetric modulated arc therapy (VMAT) up to a total dose of 54 Gy in target volume prostate, seminal vesicles, regional lymph nodes, followed by a boost to a total dose of 78 Gy in target volume—prostate and involved lymph nodes. 10 days before finishing radiation treatment, the patient developed papular rash all over his body, especially on the legs (Figure 1). The allergist suspected a postmedication eruption and the patient started corticotherapy (CRT) for 2 weeks (decreasing dose of prednisone with inhibitory proton pump protection). Apart from the popular pustular dermatological reaction, no other signs or symptoms were described by the patient.

For differential diagnosis, he also denied any exposure to sun or to biting insects or new drug ingestion.

Laboratory investigations like complete blood count, erythrocyte sedimentation rate and fibrinogen test were

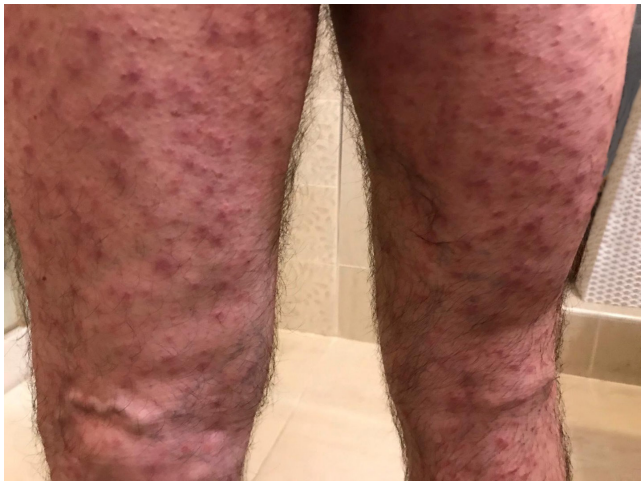

FIGURE 1 : Case 1. Papular rash developed on legs 10 days before finishing RT.

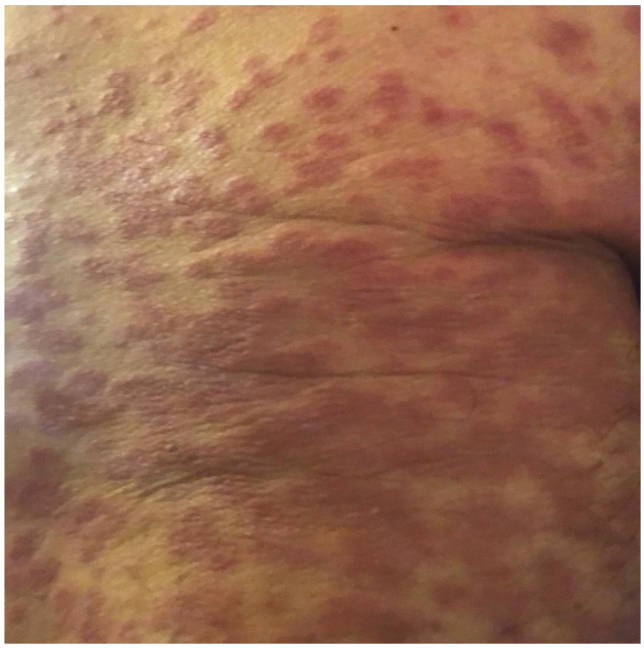

FIGURE 3 Case 2. Pruritic rash developed on thorax 2 months after RT.

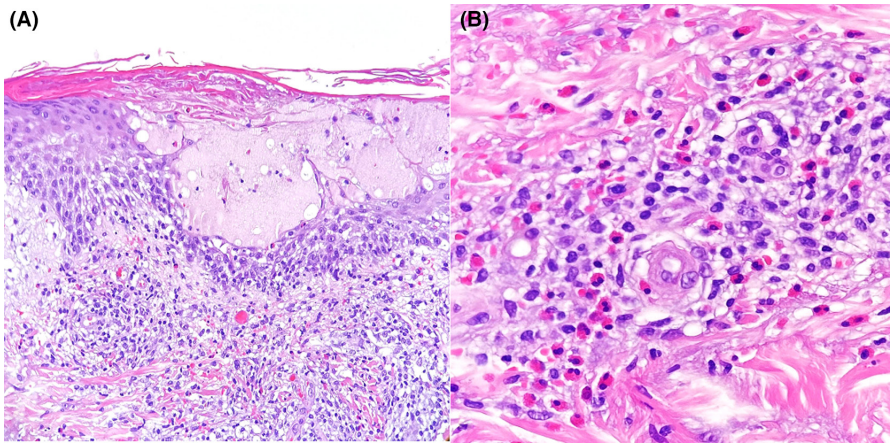

FIGURE 2 (A): Spongiotic intraepidermal vesicle; (B): Abundant eosinophilic, lymphocytic, and histiocytic infiltrate.

TABLE 1 Patients' characteristics and outcome described in published cases in the literature

Authors	Diagnosis	Number of patients	Treatment sequence	Onset	Outcome
C Garcia-Donoso	1. Invasive ductal carcinoma (T3N1M0) 2. Invasive ductal carcinoma (T1N0M0)	2	1. Neoadjuvant Doxorubicin, mastectomy with lymphadenectomy, adjuvant Doxorubicin, radiation therapy (50 Gy) 2. Mastectomy, adjuvant chemotherapy,	At the beginning of radiation therapy During RT reaching 30 Gy	1. No response to topical corticosteroids nor to antihistamines. Healing after 35 sessions of UVB exposure. 2. Eruption resolved after 1-month of topical mometasone furoate
Andrew E. Werchniak et al	Invasive ductal carcinoma (T1bN0M0)	1	Lumpectomy followed by adjuvant radiation (65 Gy to the tumor bed)	2 weeks after radiation-therapy completion	Topical triamcinolone with healing after 2 weeks of local treatment.
Jung Eun Lee et al	Invasive ductal carcinoma	1	Partial mastectomy and adjuvant RT (59 Gy)	2 days after RT completion	Healing after 10 days of oral prednisolone, antihistamine, topical corticosteroids
Miriama Delaibatiki et al	Invasive ductal carcinoma (T2pN2aM0)	1	Mastectomy, lymph-node dissection, adjuvant tamoxifen, adjuvant RT (50 Gy)	During RT at 36 Gy	Responded to antihistamine after 2 weeks of treatment.
Dong Jun Lee, You Chan Kim	Glioblastoma	1	Surgical resection, adjuvant RT (39.2 Gy)	Eruption developed after 3 days to the start of RT	Systemic antihistamines, topical corticosteroids with healing in 2 weeks
Marloes S. van Kester, Koen D. Quint	Invasive ductal carcinoma (T1bN0M0)	1	Lumpectomy, adjuvant RT (55.86 Gy)	2 months after finishing RT	Betamethasone valerate with healing in a few weeks
L. Lobelenz et al	Merkel cell carcinoma	1	Surgical excision, adjuvant RT (50.4 Gy)	14 days after the start of RT	Healing after 3 months of treatment with topical corticosteroids and phototherapy using UVB
Yuka Masuno et al	Anaplastic large cell lymphoma	1	Radiotherapy for relapse (10 fractions of 3 Gy electron beam irradiation)	After RT completion	Dexamethasone with healing in a few days
H-X Lam Cham Kee	Endometrial cancer	1	Radical hysterectomy with pelvic lymphadenectomy, adjuvant RT (50 Gy)	Immediately after RT completion	Topical corticosteroid but immediately interrupted. Lesion subsided without treatment.

within normal limits. Because the lesions did not improve, we performed a punch biopsy that described perivascular and interstitial intradermic lymphocytes, histocytes and a large number of eosinophils (Figure 2). The patient completed the radiation therapy treatment, continued ADT and CRT for the EPPER syndrome and, in 4 weeks, the lesions subsided. At his next follow-up, in January 2022 (4 months from EBRT), the patient was ECOG 0, PSA level undetectable and the eruption resolved.

3 | CASE PRESENTATION 2

A 71-year-old man diagnosed with very high-risk prostate adenocarcinoma in 2020, started VMAT EBRT up to a total dose of 54 Gy in target volume prostate, seminal vesicles, regional lymph nodes, followed by a boost to a total dose of 78 Gy in target volume—prostate and hormonotherapy in March 2021. He completed 5 weeks of radiation therapy and continued gonadotropin releasing hormone analogue. In June 2021, he presented with generalized pruritic rash (neck, chest, arms, and legs), and he denied any new exposure to drugs or sun (Figure 3). He was referred to a dermatologist who did a punch biopsy (the histology was similar to first case described) and recommended topical corticosteroids and systemic corticotherapy. The patient received as topical treatment a corticosteroid cream, applied on the affected skin twice daily.

The histopathological exam confirmed EPPER and after 10 days of oral dexamethasone, the rash disappeared. At his recent visit to our clinic (*9 months after the radiation therapy late toxicity diagnosis*), the patient had a good performance status and the PSA level was undetectable.

In both our cases, patients received the complete oncological therapies for their diseases. The papular pustular rash was diagnosed and treated while the patients were following the oncological treatment, with no unnecessary interruptions of their protocols needed.

4 | DISCUSSION

Rueda was the first to describe EPPER syndrome in 1999 when he examined for 3 months (phase one) 103 cancer patients, 20 in the control arm and 83 treated with radiation therapy. In second phase, he enrolled 30 additional patients who performed radiation therapy for their malignancies and examined them for 5 months. Fourteen patients in phase one and 18 patients during phase two developed a skin reaction which he named, considering the clinical presentation and histopathological results, "eosinophilic, polymorphic and pruritic eruption associated with radiotherapy" (EPPER).[1] Since then, other cases have been presented in literature, mostly in female patients with cervical cancer, endometrial cancer, breast cancer and anaplastic large cell lymphoma.[1–7] Generally, the lesions subsided with corticotherapy, antihistamines and UVB light. All these patients' characteristics and outcome after diagnosis are noted in Table 1.

In all cases, it is difficult to assess whether radiation therapy is the main culprit as there might be other factors such as hormonal therapy, any other drug reaction or viral infection. Trying to clarify the problem, Kim et al. did an experiment on 6 pigs using cobalt therapy with 1-cm bolus applied to the skin up to a total dose of 50 Gy with a 5 × 5 cm field. They found that all irradiated pigs developed EPPER in the irradiated area and concluded that the pig model might be used for studying EPPER. Infiltration of the skin with eosinophil started after 35 days after irradiation.[8] The pathogenic mechanism of appearance is currently unknown; however, the authors of previous case reports tried to describe two possible mechanisms of action: 1—response to type 1 hypersensitivity reaction, mediated by Ig E and 2—delayed type 4 hypersensitivity reaction, with an aberrant Th2 presence.[1,4]

Most of the cases presented in literature have occurred in female patients treated with radiation therapy for cervical cancer or endometrial cancer or breast cancer, while we described two additional atypical cases of EPPER that appeared in men treated with EBRT plus hormone therapy. Given that most cases involve tumors that have hormonal susceptibility, it is possible that the sexual hormones may play a role in the pathogenesis.[9] For example, it was shown that estrogen signaling can modulate allergic inflammation by influencing eosinophil migration, adhesion and survival.[9] It would also be useful to assess whether the radiation technique might influence the outcome as well as the addition of a skin bolus as it was done in animal models.[8]

AUTHOR CONTRIBUTIONS

MARIA BARBU: Conceptualization; data curation; investigation; methodology; project administration; resources; visualization; writing – original draft; writing – review and editing. **Rodica Maricela Anghel:** Project administration; supervision; validation. **Gabriel Ricu:** Conceptualization; supervision; validation. **Tiberiu Tebeica:** Data curation; investigation; resources. **Raluca Patru:** Data curation; visualization; writing – original draft. **Alexandru Michire:** Conceptualization; data curation; formal analysis; investigation; writing – original draft.

FUNDING INFORMATION

This article received no specific grant from any funding agency.

CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONSENT STATEMENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

ORCID

Maria Alexandra Barbu https://orcid.org/0000-0001-9177-3305

REFERENCES

1. Rueda RA, Valencia IC, Covelli C, et al. Eosinophilic, polymorphic, and pruritic eruption associated with radiotherapy. *Arch Dermatol*. 1999;135:804-810.
2. Charra-Brunaud C, Cuny JF, Reigneau M, Vogin G, Peiffert D. Case report of EPPER syndrome (eosinophilic polymorphic pruritic eruption associated with radiotherapy) in a patient treated against endometrial cancer. *Cancer Radiother*. 2013;17:54-57.
3. Werchniak AE, Perry AE, Dinulos JG. Eosinophilic, polymorphic, and pruritic eruption associated with radiotherapy (EPPER) in a patient with breast cancer. *J Am Acad Dermatol*. 2006;54:728-729.
4. García-Donoso C, Tardío JC, Arias D, Romero A, Borbujo JM. Eosinophilic, polymorphic and pruritic eruption associated with radiotherapy (EPPER) in two patients with breast tumour. *J Eur Acad Dermatol Venereol*. 2007;21:1102-1104.
5. Kim S-H, Jang B-S, Kim B-S, et al. A case of eosinophilic, polymorphic, and pruritic eruption associated with radiotherapy in a patient with breast cancer. *Korean J Dermatol*. 2007;45(1):79-81.
6. Lee DJ, Kim YC. A pustular form of eosinophilic, polymorphic, and pruritic eruption associated with radiotherapy. *J Am Acad Dermatol*. 2011;65:e51-e53.
7. Masuno Y, Matsumura Y, Katoh M, et al. Eosinophilic, polymorphic, and pruritic eruption associated with radiotherapy (EPPER) mimicking bullous pemphigoid in a patient with anaplastic large cell lymphoma. *Eur J Dermatol*. 2011;21:421-422.
8. Kim JS, Jang WS, Bae MJ, Park S, Lee SS. Radiation-induced eosinophilic, polymorphic, and pruritic eruption in a pig skin model. *Lab Anim Res*. 2015;31:204-208.
9. Keselman A, Heller N. Estrogen signaling modulates allergic inflammation and contributes to sex differences in asthma. *Front Immunol*. 2015;6:568. doi:10.3389/fimmu.2015.00568

How to cite this article: Barbu MA, Anghel RM, Ricu G, Tebeica T, Patru R, Michire A. Eosinophilic, polymorphic, and pruritic eruption associated with radiation therapy in two patients diagnosed with prostate cancer. *Clin Case Rep*. 2023;11:e07266. doi:10.1002/ccr3.7266