Eosinophilic, Polymorphic, and Pruritic Eruption Associated With Radiotherapy

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Objective: To characterize the epidemiological, clinical, and histopathological features of patients with cancer who develop widespread polymorphic and pruritic skin lesions following radiotherapy.

Patients, Design, and Interventions: During phase 1, epidemiological and clinical features of 103 patients with cancer, 83 treated with radiotherapy (71 women and 12 men) and 20 controls who did not undergo radiotherapy (16 women and 4 men), were explored during 3 months (October 1995 to January 1996). During phase 2, in 30 additional patients with cancer who were treated with telecobalt or linear accelerator, 18 with skin lesions (15 women and 3 men) and 12 without lesions (10 women and 2 men), the following were investigated: (1) hematoxylin-eosin–stained sections for routine histopathological examination and direct immunofluorescence, and lymphocytic markers; (2) blood, skin, and primary tumor eosinophilia; and (3) the presence of antiepidermal autoantibodies. Patients were examined during 5 months (February 1996 to June 1996).

Setting: A dermatology department at a university hospital.

Results: During phase 1, 14 (17%) of the 83 patients undergoing radiotherapy developed an eruption. Acral excoriations, erythematous papules, vesicles, and bullae were the most frequent lesions. During phase 2, in 18 patients, a superficial and deep lymphocytic perivascular infiltrate with numerous eosinophils, intraepidermal and interstitial eosinophilic infiltrates, eosinophilic panniculitis, IgM and C3 perivascular deposits, and slightly predominant CD4+ cells were observed. No antiepidermal autoantibodies were found.

Conclusions: The clinical, histopathological, and immunopathologic features in patients with cancer undergoing radiotherapy are described. To our knowledge, this condition has not been well characterized. Because of its unique presentation, the denomination “eosinophilic, polymorphic, and pruritic eruption associated with radiotherapy” is suggested.

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Radiotherapy has frequently provoked local acute and chronic radiodermatitis.1-3 Generalized cutaneous eruptions during radiotherapy were reported as early as 1903;4 since then, various skin eruptions, frequently diagnosed as erythema multiforme5-10 (in most cases, without histological confirmation), generalized papuloerythematosous rashes,11 widespread and nonspecific skin eruptions,12,13 Stevens-Johnson syndrome,14 and bullous pemphigoid after radiation therapy,15 have been described.

Since 1975, a few closely related dermatoses characterized by sustained eosinophilia of an undetectable cause associated with hematologic, cardiac, and neurologic abnormalities have been described as the idiopathic hypereosinophilic syndrome; in some patients, response and survival improved when treated with chemotherapy.16-18

During the past few years, we have observed several patients with cancer, mostly women, who developed an intensely widespread, polymorphic, and pruritic eruption lasting several weeks or months, most of them while receiving telecobalt radiotherapy for their primary malignant neoplasm. Histological examination of the biopsy specimens of these patients disclosed a marked and noticeable tissue eosinophilia; to our knowledge, this eruption has not been previously described in a similar presentation.

Although this eruption shares some aspects of diseases in which eosinophils play an important role, our purpose is to describe the epidemiological, clinical, and histological features of this not well-characterized dermatological condition. We suggest the denomination “eosinophilic,
MATERIALS AND METHODS

Considering that several patients with cancer at our institution (Universidad del Valle, Cali, Colombia) developed the already described polymorphic eruption with skin eosinophilia when treated with radiotherapy, we decided to explore the possibility of a cause-effect relationship in our patients.

For this purpose, a 2-phase study was undertaken in patients with cancer who were undergoing radiotherapy from October 1995 to June 1996. Informed consent was obtained from every patient.

Phase 1 consisted of a cohort of 148 patients with cancer who were treated at the departments of radiotherapy and surgery, and referred to the dermatology outpatient clinic, where a prospective study was carried out from October 1995 to January 1996. From this group, 88 consecutive patients were enrolled, treated with radiotherapy, and followed up during the therapeutic intervention. The remaining 60 were consecutive control patients with cancer who were undergoing surgery or receiving chemotherapy or palliative therapy with pain medications, according to the tumor stage. Irradiated patients were examined before treatment, when half the radiation dose was delivered, and at the end of therapy; control patients were examined similarly. All patients developing acute radiodermatitis within the irradiated target or taking medications that could originate drug eruptions were not included in the protocol.

Phase 2 consisted of an exploratory comparative study from February 1996 to June 1996, with 30 additional patients divided into 2 groups: (1) 18 consecutive patients who developed EPPER, 16 of whom received telecobalt radiotherapy and 2 treated with linear accelerator; and (2) another group of 12 consecutive patients without any cutaneous eruption during radiotherapy. The same exclusion criteria as used in phase 1 were applied. Patients undergoing chemotherapy were not included.

The following equipment and parameters for radiotherapy were used: cobalt therapy (Theratron 780; Theratronics, Ottawa, Ontario), 1.5 MeV; source-axis distance, 80 cm; linear accelerator (6MB Class Mevatron; Siemens, Walnut Creek, Calif), 6 MeV; source-axis distance, 100 cm. There were 28 sessions (5 per week), and the radiation dose was 1.8 to 2.0 Gy per session. The isocentric technique was used.

HEMATOXYLIN-EOSIN STAIN, DIRECT IMMUNOFLUORESCENCE, AND IMMUNOPEROXIDASE STUDIES

Skin biopsy specimens taken at the beginning of the cutaneous eruption, or from normal skin in those patients without lesions, were submitted for routine hematoxylin-eosin histopathological studies. Frozen sections were obtained for direct immunofluorescence and immunoperoxidase studies. For immunofluorescence studies, 10 specimens were processed with fluorescein-labeled anti-IgG, anti-IgM, anti-IgA, anti-C3, or anti-C4 (1:100; Behringwerke AG, Marburg, Germany). As positive controls, previously diagnosed bullous pemphigoid and pemphigus foliaceus specimens were used.

For immunostaining, frozen sections of 8 patients were labeled with monoclonal antibodies L26 and common lymphocytic antigen (Leu3; 1:50; Dako A/S, Glostrup, Denmark); positive lymphocytic antigens were tested for helper and suppressor T lymphocytes (CD4+ and CD8+, 1:50; Beckton Dickinson, San Jose, Calif).

BLOOD AND SKIN EOSINOPHILIA

Eosinophils were investigated as follows: (1) Tumor-associated blood eosinophilia (TABE) was determined in peripheral blood samples before radiotherapy and at the time of the skin biopsy and expressed as number of eosinophils per liter. (2) Skin-associated tissue eosinophilia was determined per square millimeter in lesional and nonlesional skin by evaluating the percentage of the total inflammatory area of each biopsy specimen under ×2 magnification by using a calibrated standard scale (American Optical Scientific Instruments, Buffalo, NY); and the number of eosinophils in 1000 inflammatory cells was determined with the same scale within a known area of 0.04 mm², under ×40 magnification. Since 0.04 mm² of inflamed skin contains a mean of 325 inflammatory cells, 3 of these areas with approximately 1000 cells were determined; eosinophils per square millimeter in lesional and nonlesional skin were calculated.

PRIMARY TUMOR EOSINOPHILIA

Tumor-associated tissue eosinophilia was classified as marked (>200 cells), moderate (100-200 cells), slight (<100 cells), or none under ×40 magnification, according to the density of the stromal infiltrate as described previously.

TESTING FOR ANTIEPIDERMAL AUTOANTIBODIES

The serum samples of 10 patients with EPPER and 10 controls were tested for autoantibodies against epidermal antigens by indirect immunofluorescence and immunoblotting techniques, as reported previously. Briefly, cryosections of human skin and monkey esophagus were incubated with a 1:20 dilution of the test sera and the bound antibodies detected by fluorescein-labeled antihuman IgG (Cappel Laboratories, Durham, NC). The immunoblotting procedures were carried out using human sodium deoxycholate epidermal extracts and 7% polyacrylamide gel electrophoresis analysis. The fractioned proteins were transferred onto nitrocellulose paper and then incubated with the test sera. Immunoreactants were detected using iodine 125-labeled staphylococcus protein A and autoradiography. Positive serum samples included were from patients with pemphigus vulgaris and pemphigus foliaceus known to recognize desmogleins 3 and 1, respectively. In addition, serum samples from a patient with bullous pemphigoid who had autoantibodies against the hemidesmosomal proteins BP230 and BP180 were also included.

STATISTICAL ANALYSIS

The relative risk for developing EPPER and other variables (type of skin cancer, sex, and radiotherapy dose) were determined in patients with and without cutaneous lesions. Other variables (TABE, skin-associated tissue eosinophilia, and immunohistochemistry) were analyzed by average comparison (continuous variables), proportions comparison (categoric variables), and association among variables (4 × 4 tables, χ² test, and Fisher exact test), with a 5% significance level (%).
polymorphic, and pruritic eruption associated with radiotherapy” (EPPER), and we believe that this ailment falls within the spectrum of the eosinophilic dermatoses.

RESULTS

PHASE 1

Incidence

Of the 88 patients treated by radiotherapy, 5 dropped out of the study and 83 (71 women and 12 men; mean age, 50.4 years) were seen at the first and second follow-up visits. In this group, none of the men and 14 of the women developed cutaneous lesions; hence, the incidence of EPPER was 17% (14/83). Of the 60 patients not exposed to radiation therapy, 40 dropped out and only 20 (16 women and 4 men; mean age, 49.6 years) were seen at the first follow-up visit. None of them developed EPPER, indicating that the incidence was 0% (0/20); 5 of them received chemotherapy, and 2 palliative therapy with codeine phosphate and morphine sulfate. This was considered the end point of observation for this group. No other patients were excluded from protocol. The total number of evaluable patients in phase 1 was 103.

Type of Tumor

Of 83 patients with cancer who underwent radiotherapy, 44 had cervix carcinoma; 9, breast carcinoma; and 30, other types of tumors. In the 20 control patients who did not undergo radiotherapy, 9 had breast carcinoma; 3, malignant melanoma; 3, non–Hodgkin lymphoma; and 5, other tumor types.

Of the 14 patients who developed EPPER during radiotherapy, 13 had cervix carcinoma and 1 had a meibomian gland sebaceous carcinoma, indicating that the former had a risk 11.7 times higher to develop this eruption when compared with other types of tumor ($P<.001$).

Radiotherapy Dose

Most patients developed EPPER when receiving a radiation dose between 26 and 67 Gy, the mean radiation dose at onset being 30 Gy. Therefore, patients had a 12.8 times higher risk of developing lesions of EPPER when treated by radiotherapy with a dose within the range of 25 and 57 Gy than within a range of 6 and 25 Gy ($P<.001$).

PHASE 2

No patients were withdrawn from the study. Radiotherapy in patients with cancer induced a unique dermatosis with the following characteristics.

Clinical Features

The most prominent symptom in all patients was severe generalized pruritus with no specific time presentation. Lesions were polymorphic, consisting mainly of numerous 3- to 10-mm round or oval erythematous papules and excoriations (Figure 1). Less frequently, patients developed wheals with typical “orange pitting” vesicles (Figure 2, top) or tense subepidermal bullae (Figure 2, bottom). Four patients had nodules suggesting panniculitis; residual hyperpigmented macules were also observed. Lesions affected mainly lower extremities (in 18 of 18 patients); upper extremities (in 9 of 18 patients); and, less frequently, the trunk, neck, or head. Palms, soles, or mucosae were not involved. Only 1 patient disclosed typical erythema multiforme. Some patients were observed after the study was completed, and they kept having lesions for several weeks, and a few for 3 to 6 additional months.

Tumor-Associated Blood Eosinophilia

Increased blood eosinophilia ($>0.5 \times 10^9/L$) was present in 5 of 12 patients with skin lesions (range, 0.68–3.85 $\times 10^9/L$) and in 4 of 11 patients without lesions (range, 1.02–3.45 $\times 10^9/L$) ($P = 1.0$).

Histopathological Features

Biopsy specimens from all patients showed an inflammatory pattern composed mainly of superficial and deep perivascular infiltrates of variable severity, in most cases confined to the dermis (Figure 3 and Table 1). Other findings included mild hyperkeratosis, moderate acanthosis, and some degree of spongiosis. No apoptosis or eosinophilic necrosis, as found in erythema multiforme, was observed. In the dermis, the most important finding was a lymphohistiocytic infiltrate with superficial and deep perivascular distribution. A prominent feature was the presence of eosinophils in 18 of 18 specimens. In 6 of the 9 patients who had less than 323

Figure 1. Multiple erythematous papules and excoriations mainly of acral distribution.
Eosinophils/mm², biopsy specimens showed at least greater than 10.4 eosinophils/mm² in lesional skin. Of the 9 patients in phase 2 who had greater than 323 cells/mm², 5 disclosed a massive eosinophilic infiltrate extending from the perivascular compartment to the reticular dermis and toward the epidermis (Figure 3 and Table 1); sometimes the infiltrate provoked spongiotic, intraepidermal vesicles with eosinophils and eosinophilic granules (Figure 4). Vesicles and subepidermal bullae histologically indistinguishable from bullous pemphigoid were seen in 8 patients (Figure 2, bottom). The extension of inflammatory infiltrates to the hypodermis in the form of eosinophilic panniculitis, with massive predominance of eosinophils infiltrating the septa and adipose lobules, was noted in 4 patients (Figure 3, Figure 5, and Table 1). Typical features of erythema multiforme were only observed in 1 patient disclosing epidermal necrosis, lymphocytic perivascular infiltrates, and adventitial edema without eosinophils. This patient was excluded from the EPPER statistical analysis.

**Skin-Associated Tissue Eosinophilia**

Eosinophils in inflamed skin were greater than 323.30 cells/mm² in 9 of 18 patients (range, 3.10-7780 cells/mm²) \( (P = .005) \).

**Tumor-Associated Tissue Eosinophilia**

Primary tumors were reviewed in 11 patients, and slight tissue eosinophilia (<100 cells) was seen in only 1 patient.

**Immunoperoxidase Studies**

The T-cell infiltrate was positive for common leukocytic antigen (Leu3) in all 5 patients, in contrast with a negative reaction for B-cell marker (L26). There was a predominance of CD4+ vs CD8+ cells (Figure 6, left).

**Immunofluorescence**

Direct immunofluorescence was performed in 10 specimens (7 patients and 3 controls). In 5 patients, IgM and C3 deposits were present in a superficial perivascular distribution (Figure 6, right). One patient had only IgM deposits, and the remaining one had negative findings. No basement membrane deposits were observed at the der-
moepidermal junction. Immunofluorescence results were negative in all control patients without skin lesions.

Antiepidermal Autoantibodies

Patients with EPPER did not show antiepidermal autoantibody activity. The serum samples of all 10 patients with EPPER and the 10 control serum samples did not recognize epidermal antigens by indirect immunofluorescence and immunoblotting techniques.

COMMENT

The clinical, histological, and immunopathologic features of this cutaneous eruption associated with radiotherapy in patients with cancer have not been appropriately characterized previously. Our patients disclose a distinct clinicopathological, eosinophilic eruption consisting of a generalized pruritic rash with excoriations (in 18 of 18 patients); erythematous papules (in 17 of 18 patients); and, less frequently, wheals (in 9 of 18 patients), vesicles (in 6 of 18 patients), tense bullae (in 5 of 18 patients), and nodules (in 4 of 18 patients), affecting predominantly lower and upper extremities, much different from previously described eosinophilic dermatoses.²² The eruption is triggered by radiotherapy mostly in patients with noncutaneous cancer (Table 2); in addition, EPPER has not been detected in patients with other types of cancer therapy. A chronic course during several weeks or months has been observed, similar to the papular pruritic eruption of acquired immunodeficiency syndrome.²³ Chronicity and polymorphism of this clinical picture is not in favor of drug reactions in our patients; furthermore, these are usually dermatoses of shorter duration. Also, negative stool test results in 7 of 9 patients with EPPER and positive results in 3 of 8 patients without EPPER speak against intestinal parasites as a causal factor. The incidence of this condition in our series was 17%; most patients had cervix carcinoma (13 of 14 in phase 1 and 14 of 18 in phase 2). Other malignant neoplasms, such as prostate carcinoma, seminoma, meibomian sebaceous gland carcinoma, rectal adenocarcinoma, and retroperitoneal carcinoma of unknown origin, were also seen, indicating that this condition is not limited to neoplasia derived from stratified squamous epithelia (Table 2). The high incidence of EPPER in our patients with cervix carcinoma could be possibly related to the high incidence of this neoplasia in developing countries,²⁴ although by improving cervical cytology programs, the incidence of cervix carcinoma has decreased by 40% at our institution (Population Cancer Registry, Universidad del Valle, 1998). The relative risk of developing EPPER is dose dependent, but it can occur with low doses. Although most patients received telecobalt therapy, 2 of them were treated with a linear accelerator, indicating that this type of radiation therapy is also involved in EPPER.

Well-documented erythema multiforme,¹⁰ Stevens-Johnson syndrome,¹⁴ subacute radiation dermatitis (graft-vs-host–like disease),²⁵ and bullous pemphigoid¹⁵ in association with radiotherapy have been reported, but these dermatoses are different from EPPER in many aspects. Erythema multiforme has clinical similarities with EPPER, but the latter spares palms, soles, and mucosae and targets lesions. The presence of more than 10.4 eosinophils/mm² in lesional skin in 6 patients with EPPER, the prominent eosinophilic component of the infiltrate (>323 cells/mm²) in another 12 of 18 patients, and the absence of dyskeratosis or eosinophilic epidermal necrosis in severe cases differentiate this condition from erythema multiforme.

Some patients have lesions clinically and histologically indistinguishable from Wells disease²⁶ or eosinophilic panniculitis.²⁷ In addition, eosinophilic cellulitis with flame figures has been observed in association with anal carcinoma²⁸ and also in nasopharyngeal carcinoma following radiotherapy,²⁹,３⁰ but the clinical manifestations are more polymorphic in EPPER. Direct immuno-
fluorescence showed no linear deposits of IgG or C3 at the dermoeidermal junction in the patients with tense subepidermal bullae suggesting bullous pemphigoid. The finding of perivascular IgM and C3 is consistent with perivascular dermatitis, as in other inflammatory dermatoses. The negative findings of antiepidermal autoantibodies in the serum samples of 10 patients with EPPER and 12 controls against well-characterized epidermal antigens associated with bullous pemphigoid rule out this condition in EPPER.

The pathogenic mechanism of EPPER is unknown. We believe that cutaneous eosinophilia could be elicited by 2 mechanisms: First, it could be elicited in response to a type 1 hypersensitivity reaction mediated by IgE with production of interleukins 4 and 5, the last one recognized, along with granulocyte-macrophage colony-stimulating factor and interleukin 3, as an inducer of eosinophil.31 Second, it could be elicited as the result of a delayed type 4 hypersensitivity reaction in the milieu of an aberrant Th2 dominancy as observed in atopy, diabetes, and human immunodeficiency virus infection32 or in relation to the clonal expansion of Th2 cells, as reported in a patient with hypereosinophilic disease.33 Eosinophilic major protein, cationic eosinophilic protein, and/or neurotoxin derived from eosinophils could also be involved in the pathogenesis of this condition as proposed for the idiopathic hypereosinophilic syndrome.34,35

Tumor-associated tissue eosinophilia has been frequently described as a good prognostic sign in cervix carcinoma,36-38 where tissue eosinophilia has been postulated to occur because of the formation or transformation of an antigen from the tumor due to radiotherapy, eliciting an immune dysregulation from the host.39 Concerning blood eosinophilia, a higher TABE in patients with late stages (III and IV) of cervix carcinoma has been reported; a TABE increase in association with radiotherapy is frequent in early stages (I and II) of cervix carcinoma, and it has been claimed to represent a good pronostic sign (>50% regression).40 However, in our patients, TABE findings were not significant; moreover, blood eosinophilia may be related to radiotherapy itself.38

Table 2. Description of Clinical and Laboratory Findings of Patients With EPPER (Phase 2)*

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y†</th>
<th>Type of Tumor/Stage</th>
<th>HIV Test Result</th>
<th>Stool Examination Result‡</th>
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<td>Patients With Lesions (EPPER) (n = 18)</td>
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<td></td>
</tr>
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<td>2/M/69 Prostate cancer/NA</td>
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<td>Neg</td>
<td></td>
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<td>Patients Without Lesions (n = 12)</td>
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<td>30/F/65 Cervix/IIB</td>
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*EPPER indicates eosinophilic, polymorphic, and pruritic eruption associated with radiotherapy; HIV, human immunodeficiency virus; Neg, negative; NA, not available; and ND, not determined.
†Patients 1 and 17 underwent linear accelerator therapy; all others underwent telecobalt therapy.
‡Neg indicates negative for ova and parasites.
Skin-associated tissue eosinophilia in our patients with EPPER brings about some questions about prognosis; survival of these patients could characterize the value of EPPER as a prognostic indicator, as it occurs with tumor-associated tissue eosinophilia in cervical carcinoma.36-38

Topical corticosteroids, antihistamines, and UV-B light exposure have been helpful in some of our patients; interferon alfa has been reported as promising in the hypereosinophilic syndrome40-42 and could be tried in future studies.

Finally, the heterogeneity of the clinical and histopathological expressions observed in our patients suggests that, similar to what has been proposed by others in eosinophilic panniculitis27 and folliculitis,32 EPPER may represent a clinicopathological spectrum involving cutaneous immune reactions triggered by radiotherapy, originating a cascade of events mediated by different cytokines, specific T lymphocytes, or both, and leading to tissue damage by eosinophil proteins. Because of its unique presentation, the denomination EPPER is suggested.

Since the completion of this article, we have observed 3 additional patients with cervix carcinoma who developed EPPER while being treated with a linear accelerator (12 MV Mevatron; Siemens).

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