

Radiation Port Wart: A Distinct Cutaneous Lesion after Radiotherapy

Mine Genc, MD; Melek Yavuz, MD; Gülseren Cimsit, MD; Ümit Cobanoglu, MD; and Aydin Yavuz, MD
Konya and Trabzon, Turkey

Labeled Background: Radiotherapy may cause common cutaneous side effects such as acute and chronic radiodermatitis and also rare skin conditions.

Case Report: A 42-year-old woman who received radiotherapy for invasive breast carcinoma developed multiple, scaly, rough papules and nodules restricted to treatment fields six months after completion of the treatment. A relapse of the breast cancer and/or seborrheic keratosis was ruled out by histological confirmation of verruca vulgaris.

Conclusion: We report the first case of verruca vulgaris associated with radiation treatment.

Radiotherapists and dermatologists should be aware of this possibility and be able to differentiate it from other skin lesions associated with irradiation.

Key words: radiation ■ human papilloma virus ■ reactivation

© 2006. From the Department of Radiation Oncology, Selcuk University, Meram Medical Faculty, Akyokus, Konya, Turkey (Genc) and Department of Radiation Oncology (M. Yavuz, [A. Yavuz]; Department of Dermatology (Cimsit, associate professor); Department of Pathology (Cobanoglu), Karadeniz Technical University, School of Medicine, Trabzon, Turkey. Send correspondence and reprint requests for *J Natl Med Assoc.* 2006;98:1193-1196 to: Dr. Mine Genc, Department of Radiation Oncology, Selcuk University, Meram Medical Faculty, Akyokus, Konya, 42080, Turkey; phone: +90 332 2236602; fax: +90 332 2236182; e-mail: minegenc@yahoo.com

INTRODUCTION

Radiotherapy may cause common cutaneous side effects such as acute and chronic radiodermatitis^{1,2} and also rare skin conditions, beginning on or strictly limited to irradiated skin areas: acne, dermatophytosis, dyskeratosis, Grover's disease, subcutaneous pustulosis, cutaneous lichen, morphea, autoimmune bullous dermatosis and subacute cutaneous lupus erythematosus.²⁻⁴ We present here the clinical case of a woman exposed to ionizing radiation for the treatment of breast carcinoma in whom common warts (verruca vulgaris) developed within the area of irradiation six months after the end of the treatment. To our knowledge, this is the first reported case of verruca vulgaris as developed at the radiotherapy port in the English-language literature.

CASE REPORT

A 42-year-old female patient who had a modified radical mastectomy for invasive breast cancer received adjuvant treatment with six cycles of chemotherapy (cyclophosphamide 500 mg/m², methotrexate 40 mg/m², fluorouracil 500 mg/m², days 1 and 8, q 4 weeks), as well as radiotherapy to the right chest wall using 9-MeV electron beams (Saturne-43, linear accelerator) and to the axilla using photon beams (Alcyon-II, Cobalt-60 machine). Prescribed tumor dose was 48.6 Gy for all fields. Daily fractions of 1.8 Gy were applied. At the end of radiotherapy, there was a diffuse dry dermatitis involving most of the area in the treatment field.

Six months after completion of the treatment, she noticed multiple, single or grouped verrucous lesions on skin surfaces of the right chest wall and axillary regions (Figure 1) and was referred for a dermatological opinion. The patient gave no history of previous skin problems or family history of skin disease, and no mucosal involvement was found. Clinical examination revealed painless, firm, irregular, scaly rough-surfaced, light brown or grayish-black papules and nodules measured 1-7 mm in diameter (Figure 2). The irradiated skin, including the lesions, was mildly hyperpigmented. The lesions were limited precisely to the field of previous radiotherapy, and the rest of the skin outside the radiotherapy field was completely normal.

Routine laboratory parameters were negative or within normal limits except for a leukocyte count of 3.2 x 10³/uL (normal, N: 4.8-10.8), a hemoglobin level of 10.2 gr/dL (N: 12-17) and a serum alkaline phosphatase level of 383 U/L (N: 91-258). All immunoglobulin levels were normal: IgG 979 mg/dL (normal, N: 800-1,700), IgA 246 mg/dL (N: 100-490), IgM 282 mg/dL (N: 50-300). Flow cytometric analysis of peripheral blood revealed a reversed helper/suppressor T-lymphocyte ratio of 0.48 (N: 1.0-2.0). The absolute lymphocyte count was 716/mm³, with 10% CD4 (N: 25-40%), 21% CD8 (N: 17-25%), 25% CD19 (N: 0-10%), 39% CD3 (N: 65-72%), and 18% CD16+56 (N: 5-10%). The results of the HIV serological test were negative.

A provisional diagnosis of local recurrence and/or

seborrheic keratosis was made, and serial biopsies were taken from the prominent lesions. Histologically, all the specimens presented the typical architectural features of verruca vulgaris with squamous epithelium exhibiting marked acanthosis, hyperkeratosis, papillomatosis and hypergranulosis (Figure 3). The granular layer cell contained keratohyaline granules, and the tips of the elongated rete ridges pointed radially toward the center of the lesion. There were chronic inflammatory infiltrates within the papillary dermis.

The lesions resolved partially during topical treatment with a solution containing 17% salicylic acid and 17% lactic acid and cryotherapy. However, over the following 24 months, episodic recurrences, not as severe as the initial lesions and always occurring within the radiation site, have been noted. Thirty months after the diagnosis of the breast cancer, palliative radiotherapy (30 Gy in 10 fractions with cobalt-60 photon beams) had to be given to the pelvis and lumbar vertebrae due to bone metastases. Six months later, similar lesions were again observed within the radiotherapy port. Another skin biopsy was performed, and histological examination again confirmed the diagnosis of verruca vulgaris.

DISCUSSION

Common warts or verruca vulgaris are asymptomatic, hyperkeratotic papillomas caused by infection with human papilloma viruses type 2, 4, 7 and 57.^{5,6} They manifest in different forms, have irregular verrucous surface

and keep on growing slowly with varying number from single to several hundred. They are localized mainly on the hands of children and young adults; however, they may appear elsewhere on the skin or mucosal surface, differing in morphological and histological features. In our case, the clinical findings and the histological criteria consisting of hyperkeratosis, acanthosis, papillomatosis and hypergranulosis with coarse keratohyaline granules suggested verruca vulgaris. The histologic differential diagnosis of verruca vulgaris include seborrheic keratosis. These lesions show papillomatous proliferation with prominent basaloid appearance and keratin-filled pseudocysts. Verruca vulgaris can usually be differentiated from seborrheic keratosis because verruca vulgaris usually displays coarse keratohyaline granule clumping and ectatic vessels within the papillary dermal tips. Although histopathology is compatible with verruca vulgaris, polymerase chain reaction (PCR) analysis of the tissue for the HPV DNA is essential. In the present case, we could not perform PCR analysis because of technical drawbacks.

It is proposed that the infectivity of the virus in an individual depends on the viral load and host immunity. Individuals with depressed cell-mediated immunity due to treatment with immunosuppressive drugs, Hodgkins' disease, malignant lymphomas, lymphocytic leukemia, AIDS and other malignancies are more likely to have an increased incidence and more widespread cutaneous warts.^{6,7} In our case, we determined a decrease in the pool of CD3+ and CD4+ cells, and consequent diminution of the CD4/CD8 ratio, suggesting an impaired T-cell-mediated cellular immunity, as well.

Transmission of the warts occurs by contact, either directly from person to person or indirectly via fomites left on surfaces. Infection via the environment is more likely to occur if the skin is macerated and in contact with roughened surfaces.^{5,6} Trauma that introduces breaks in the stratum corneum facilitates epidermal infection;⁶ thus, maceration of the skin with radiotherapy could have been a predisposing factor in our patient. The incubation period of human papilloma viruses averages about four months but varies from a few weeks to two years when inoculated experimentally.⁶ Reasonably, our patient's lesions developed six months after erythemogenic doses of radiotherapy.

The unusual feature in our patient was the restriction of the warts to the irradiated skin. In fact, the literature neither mentioned the skin trauma with ionizing radiation as a predisposing factor of wart nor reported wart as being among the skin

Figure 1. Numerous, single or grouped verrucous lesions on the right chest wall and the axilla that clearly demonstrates the radiotherapy fields



reactions associated with radiotherapy. Although no obvious cause was identified in our case, it is conceivable that the virus was present in the basal layer of the epidermis and the keratinocyte stem cells in the hair follicle in a latent

state, and that it became activated by breakdown of the papilloma virus-specific immunity of the host by radiation therapy. Mechanisms of reactivation are not clearly defined. However, activation of HPV latent infection by

Figure 2. A close-up view of papules and nodules on the irradiated skin

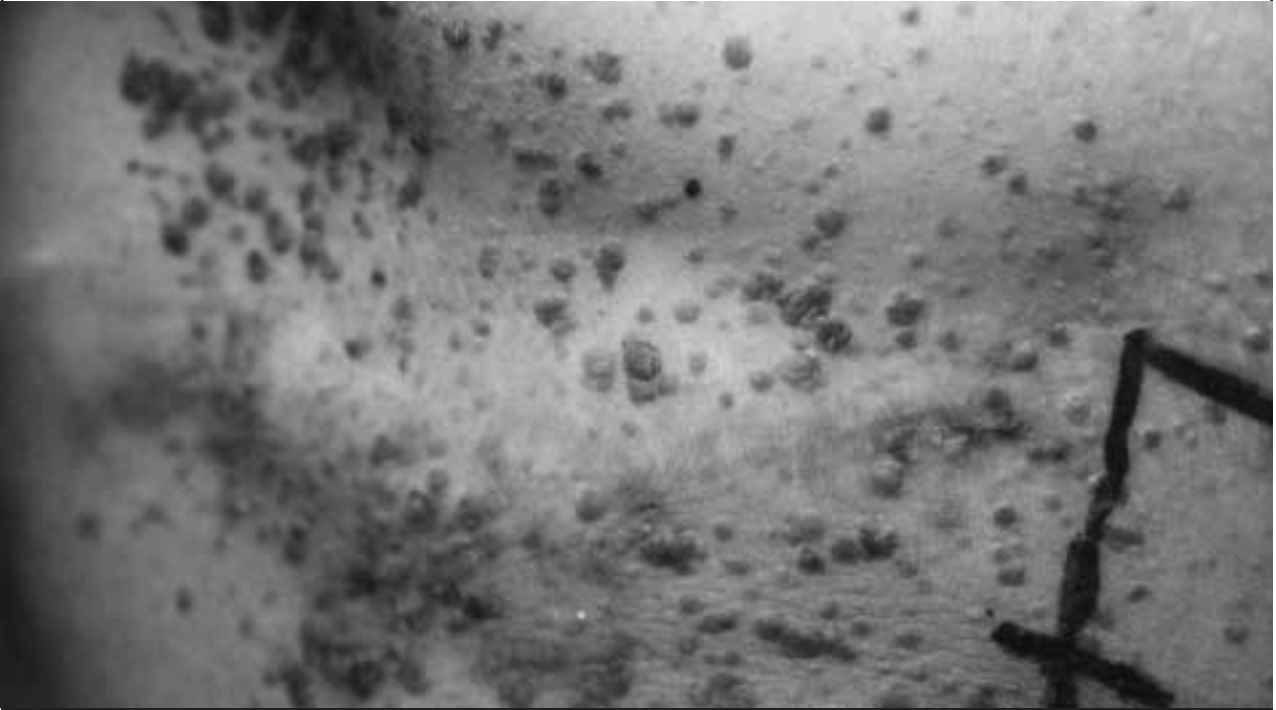
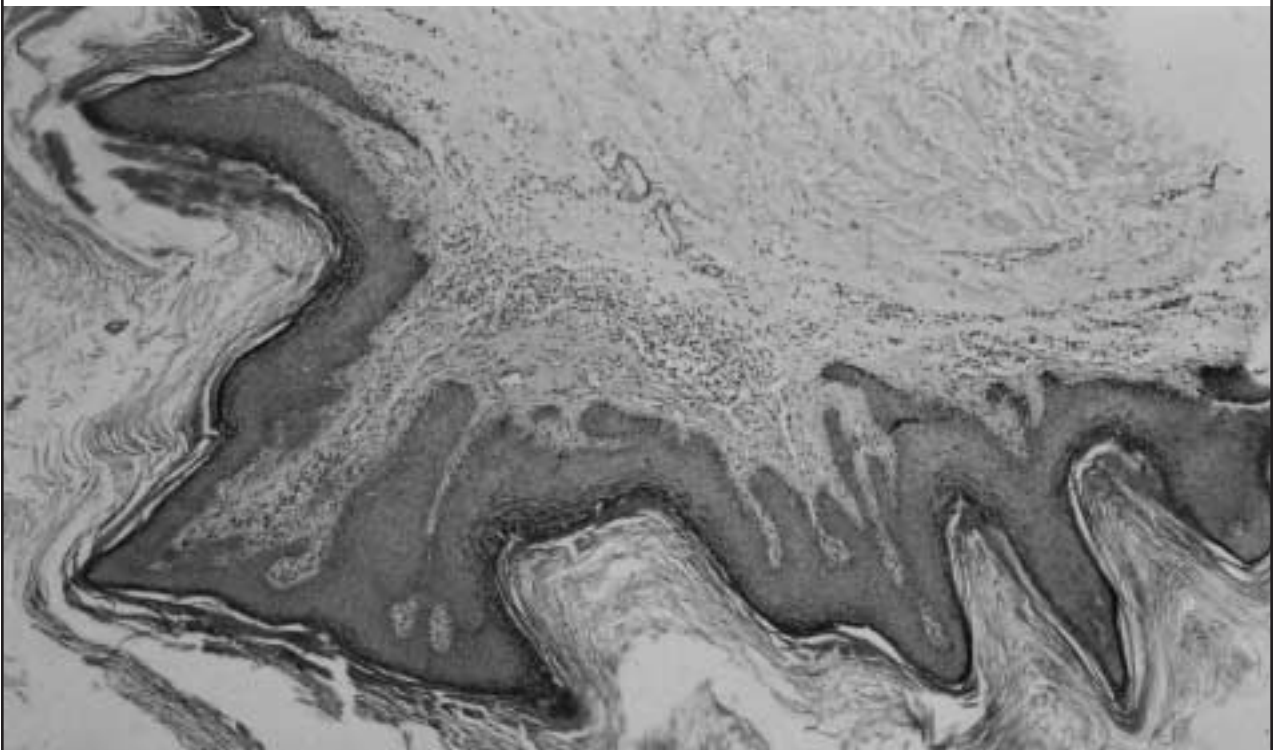


Figure 3. The biopsy specimen shows marked hyperkeratosis, acanthosis, papillomatosis, and hypergranulosis consistent with verruca vulgaris (H&E; original magnification, X 40).



UV light and trauma or mechanical irritation has been shown.⁸ Although there is no report of HPV reactivation by ionizing radiation, several viruses are known to be reactivated by radiation.⁹⁻¹¹ Radiation has been shown to alter the immune, nervous and endocrine systems.¹² Ionizing radiation induces an inflammatory response and the release of stress mediators such as glucocorticoids.¹³ Moreover, psychological stress may be associated with radiation exposure, and stress has been suggested to be associated with the reactivation of latent γ -herpes viruses.¹⁴ We also consider that, by direct or indirect mechanisms, radiation-induced vascular changes in the dermis or skin changes with subsequent compromise of epidermal integrity and increased cutaneous permeability may play a role in the decreased local cellular immunity and increased susceptibility to *verruca vulgaris* in the irradiated fields.^{1,2}

Our patient thus represents the first reported case of *verruca vulgaris* restricted to skin traumatized by ionizing radiation. Although it is extremely rare, we believe that this condition may be more common than it has been thought. Radiotherapists and dermatologists should be aware of this possibility and be able to differentiate it from other skin lesions associated with radiation therapy.

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