

Incidence and Risk Factors of the Secondary Skin Infections in Patients with Radiodermatitis

Radyodermatitli Hastalarda Sekonder Deri İnfeksiyonlarının İnsidansı ve Risk Faktörleri

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Abstract

Objective: The aim of this prospective study was to investigate the incidence and risk factors of secondary infected radiodermatitis in patients receiving radiotherapy and to determine isolated microorganisms' resistance profiles to different antimicrobial agents.

Materials and Methods: The study comprised 62 patients admitted to the Regional Training and Research Hospital from January 2009 to January 2010. Radiodermatitis was graded according to the National Cancer Institute's Common Toxicity Criteria version 3.0. Potential risk factors for secondary infection were recorded and evaluated by univariate and multivariate analyses.

Results: In 62 patients, grade 1, 2, 3 and 4 radiodermatitis were observed in 33 (53.2%), 11 (17.7%), 8 (12.9%) and 10 (16.2%) patients, respectively. Skin infection secondary to radiodermatitis occurred in 14 patients (infected patients), 21.4%, 21.4% and 57.2% of whom had grade 2, 3 and 4 radiodermatitis, respectively. Forty-eight patients were found to be colonized with microorganisms (colonized patients). In the univariate analysis, concurrent endocrine therapy and radiodermatitis grade differed significantly between infected and colonized patients ($p<0.05$). Multivariate analyses showed that the radiodermatitis grade was an independent risk factor for the acquisition of infection ($p<0.05$). The microbial pathogens isolated from patients with skin infection were seven methicillin-resistant coagulase-negative *Staphylococcus* (MRCNS) strains, three methicillin-resistant *Staphylococcus aureus* (MRSA) strains, two *Candida* sp., one methicillin-sensitive coagulase-negative *Staphylococcus* (MSCNS) strain and one methicillin-sensitive *S. aureus* (MSSA) strain. *Staphylococci* strains were more resistant to beta-lactam antibiotics. No glycopeptide resistance was found.

Conclusion: The results of this study indicate that high-grade radiodermatitis leads to an increased risk for secondary infection of the skin with pathogens.

Key Words: Colonization, Radiodermatitis, Risk factors, Secondary skin infection

Özet

Amaç: Bu prospektif çalışmada; radyoterapi alan hastalarda radyodermatite sekonder olarak gelişen infeksiyonların insidansı ve risk faktörleri ile izole edilen mikroorganizmaların antibiyotiklere karşı direnç profillerinin araştırılması amaçlandı.

Gereç ve Yöntem: Çalışmaya; Haziran 2009 ile Haziran 2010 tarihleri arasında, Erzurum Bölge Eğitim ve Araştırma Hastanesi'ne başvuran 62 hasta dahil edildi. Radyodermatitler, National Cancer Institute's Common Toxicity Criteria version 3.0'a göre derecelendirildi. Sekonder infeksiyonlar açısından potansiyel risk faktörleri kaydedilerek, univariate ve multivariate analiz ile değerlendirildi.

Bulgular: Altmış iki hastanın; %53.2'si grade 1, %17.7'si grade 2, %12.9'u grade 3 ve %16.2'si grade 4 radyodermatit olarak derecelendirildi. 14 hastada (infekte hastalar) ise radyodermatite sekonder gelişen deri infeksiyonu saptandı. İnfekte hastaların %21.4'ü grade 2, %21.4'ü grade 3 ve %57.2'si grade 4 radyodermatite sahipti. 48 hastada izole edilen mikroorganizmalar kolonizasyon olarak değerlendirildi (kolonize hastalar). Univariate analizde; infekte ve kolonize hastalar arasında eş zamanlı endokrin tedavi uygulaması ve radyodermatitin derecesi anlamlı oranlarda farklı bulundu ($p<0.05$). Multivariate analizde ise; radyodermatitin derecesi sekonder infeksiyon için bir risk faktörü olarak saptandı. İnfeksiyonlu hastalardan; 7 metisiline dirençli koagülaz negatif *Staphylococcus*, 3 metisiline dirençli *Staphylococcus aureus*, 2 *Candida* sp., 1 metisiline duyarlı koagülaz negatif *Staphylococcus* ve 1 metisiline duyarlı *S. aureus* izole edildi. Tüm stafilokok suşlarının en dirençli olduğu antibiyotik grubu beta-laktam antibiyotikler olarak tespit edilirken, glikopeptidlere karşı bir direnç saptanmadı.

Sonuç: Çalışmanın sonunda yüksek grade radyodermatitin, sekonder deri infeksiyonları için bir risk faktörü olduğu saptanmıştır.

Anahtar Kelimeler: Kolonizasyon, Radyodermatit, Risk Faktörleri, Sekonder deri infeksiyonu

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Introduction

Radiation therapy (RT), employed as monotherapy or in combination with surgery or with chemotherapy and surgery, has been reported as an effective regimen for tumor treatment [1]. However, the use of RT also affects normal tissues adjacent to the cancer. Radiation injury to the skin is one of the most common adverse effects of radiation therapy [2]. Following a cumulative radiation dose exceeding 10 Gray, exposed skin often develops an intense local inflammatory reaction within 2 days to 1 week. The reaction peaks at 48 hours and subsequently subsides, only to be followed by a second phase of intense erythema with edema and vesiculation beginning 1 week after exposure and lasting up to 1 month. Erosions, pustules, and ulcerations may also develop in association with secondary infection [3].

We performed a prospective study to estimate the incidence and risk factors of secondary infected radiation dermatitis following radiotherapy among inpatients admitted to the Radiation Oncology Unit of the Regional Training and Research Hospital in Erzurum, Turkey. We also aimed to determine the microbiological profile and antibiotic resistance patterns of the causative pathogens.

Materials and Methods

Patients

The study population consisted of 31 women and 31 men with a mean age of 57.6 ± 13.3 years (range 14 to 83 years) who received RT at the Regional Training and Research Hospital from January 2009 to January 2010. The different pathological diagnoses of the patients were as follows: squamous cell carcinoma in 25 patients, invasive ductal carcinoma in 9, adenocarcinoma in 8, small-cell cancer in 4, non-small cell cancer in 3, invasive mucinous carcinoma in 2, non-Hodgkin's lymphoma in 1, mesothelioma in 1, basal cell carcinoma in 1, mucinous carcinoma in 1, metatypical carcinoma in 1, Ewing's sarcoma in 1, esthesioneuroblastoma in 1, mucoepidermoid carcinoma in 1, Hodgkin's lymphoma in 1, liposarcoma in 1, undifferentiated carcinoma in 1 patient. The location of the tumor was esophagus in 17 of the patients, lung in 13, breast in 11, stomach in 6, skin in 4, prostate in 1, bone in 1, larynx in 1, nasal cavity in 1, tongue in 1, salivary gland in 1, anal canal in 1, lymph nodes in 1, rectal canal in 1, soft tissue in 1, and nasopharynx in 1. Radiation therapy was delivered by cobalt-60 gamma rays with 1.25 MeV photons. Radiodermatitis was graded according to the National Cancer Institute's Common Toxicity Criteria (CTC) version 3.0 by the investigators [4]. Grade 1 changes included faint erythema and dry desquamation. Grade 2 changes consisted of persistent tender or edematous erythema that in some cases

progressed to focal loss of the epidermis and moist desquamation in the skin folds. Grade 3 dermatitis was characterized by confluent moist desquamation in locations other than the skin folds and pitting edema. Grade 4 changes can progress to ulceration and bleeding. We are often consulted to evaluate cancer patients who have developed secondary infected radiodermatitis following local radiation. These patients have generally experienced the process for several weeks, accompanied by intensely bright red skin, superficial erosions or pustules, pain, and spread of the lesions to areas outside of the local field [5].

Isolation, identification and susceptibility

Culture samples were collected with the sterile cotton swabs. The swabs were placed in modified Stuart medium and were sent to the laboratory and plated on blood agar and Mc-Conkey's and Sabouraud's dextrose agar media. After incubation for 18-48 h at 37°C, the isolates were identified using a conventional protocol or using commercial identification kits [6]. Antibiotic sensitivity tests were performed according to the criteria of the Clinical and Laboratory Standards Institute (CLSI) by the disc-diffusion method [7].

Statistical analysis

A statistical package (SPSS) was used in all analyses. Potential risk factors for skin infection were identified by univariate analysis. The chi-square test or Fisher's exact test were used for categorical variables, and Student's t-test or the Mann-Whitney U-test was used for continuous variables. Variables for which the p value was <0.05 in bivariate analysis were included in a multivariate logistic regression analysis model for multivariate analysis. All tests were two-tailed, and $p < 0.05$ was considered to be significant.

Results

Out of 62 patients investigated, 48 (77.4%) were found to be colonized with microorganisms (colonized patients), and 14 patients (22.6%) had a secondary skin infection (infected patients). Among the infected patients, the median RT dose received was 20.7 ± 9 (range 12 to 42 Gray); in colonized patients, this value was 22.7 ± 8.4 (range 8 to 50 Gray). According to the CTC, the skin toxicities among the 62 radiotherapy patients were as follows: 53.2% were grade 1, 17.7% were grade 2, 12.9% were grade 3 and 16.2% were grade 4. Of 14 infected patients, 21.4%, 21.4% and 57.2% had grade 2, 3 and 4 radiodermatitis, respectively.

A total of 62 samples collected yielded 74 microorganisms (14 were from infected patients and 60 from colonized patients; Figure 1). MRCNS (50%) was the most prevalent isolate from infected patients. The results of antibiotic sus-

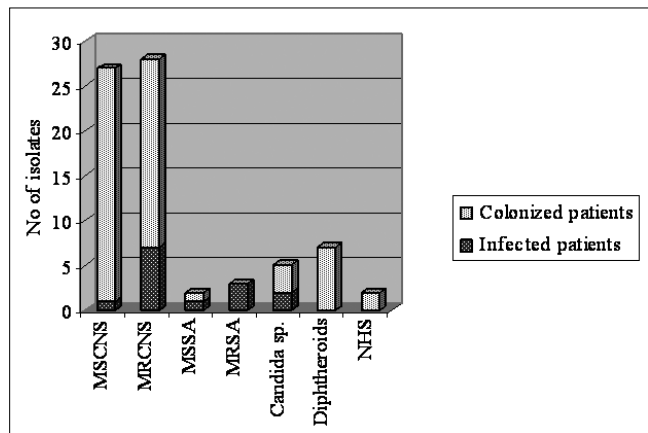


Figure 1. Microorganisms isolated from patients with radiodermatitis. MSCNS: Methicillin-sensitive, coagulase-negative *Staphylococcus*. MRCNS: Methicillin-resistant, coagulase-negative *Staphylococcus*. MRSA: Methicillin-resistant *Staphylococcus aureus*. MSSA: Methicillin-sensitive *Staphylococcus aureus*. NHS: Non-hemolytic streptococci.

ceptibility testing for coagulase-negative staphylococci and *Staphylococcus aureus* strains are shown in Figures 2 and 3, respectively. In general, the resistance rates of strains isolated from infected patients were higher than those of strains in colonized patients.

The results of univariate analysis are shown in Table 1. In the univariate analysis, concurrent endocrine therapy and a grade of radiodermatitis showed significant differences between infected and colonized patients ($p < 0.05$). In multivariate analysis, the grade of radiodermatitis was an independent risk factor for the acquisition of infection ($p < 0.05$) (Table 2).

Discussion

Radiation can affect all cells within its treatment field, thereby making irradiated tissue more susceptible to trauma, infection, and irritation. Disruption of the skin barrier that normally prevents invasion by microorganisms is associated with an immediate barrier defect, due to the removal of extracellular lipids from the stratum corneum. The epidermis is colonized at a higher rate by potentially pathogenic microorganisms. Colonizing microorganisms are commonly derived from the patient's body flora, as well as from the hospital environment, and may produce exogenous erythrotoxins or harbor plasmids expressing superantigens [8-10].

In this study, we evaluated the microbial colonization and infection of the skin area affected by radiation therapy. We also investigated the antibiotic resistance patterns of frequently isolated microorganisms. Staphylococci (mainly CNS) were isolated most frequently. Coagulase-negative staphylo-

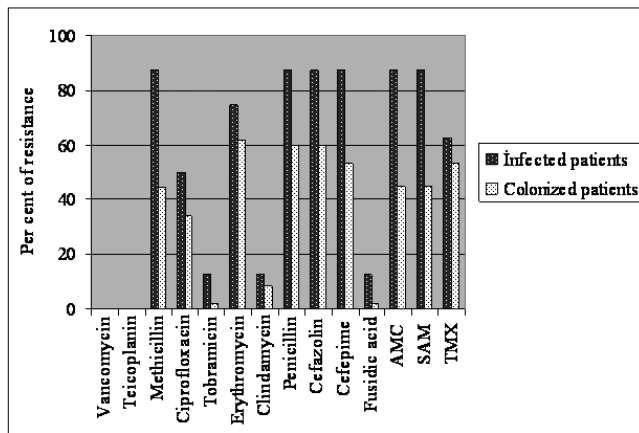


Figure 2. The resistance of coagulase-negative staphylococci to antimicrobial agents. AMC: Amoxicillin/clavulanic acid, TMX: Trimethoprim/sulfamethoxazole, SAM: Ampicillin/sulbactam.

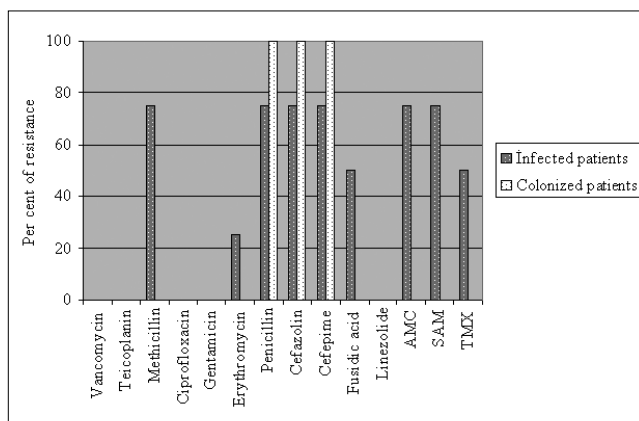


Figure 3. Resistance of *Staphylococcus aureus* strains to antimicrobial agents. AMC: Amoxicillin/clavulanic acid, TMX: Trimethoprim/sulfamethoxazole, SAM: Ampicillin/sulbactam.

cocci (CNS) colonize human skin and represent a major part of the normal bacterial flora of healthy people. Although CNS bacteria have long been regarded as nonpathogenic, they have now been recognized as relevant opportunistic pathogens. CNS bacteria can be transmitted by hospitalized patients and healthcare workers, and they are often characterized by their resistance to many commonly used antibiotics, including methicillin [11]. In our study, a total of 55 CNS strains were isolated from the patients with radiodermatitis; 28 (50.9%) were methicillin-resistant, and 27 (49.1%) were methicillin-sensitive. Among the CNS bacteria, 7 MRKNS and 1 MSKNS strains were evaluated as infection agents. The rate of methicillin-resistant strains was 87.5% in infected patients. There was no vancomycin and teicoplanin resistance in any

Table 1. Univariate analysis of the clinical characteristics of infected and colonized patients with radiodermatitis

Characteristic	Frequency or mean±SD		Univariate analysis p value
	Infected patients (n=14)	Colonized patients (n=48)	
Age	54.9±21.0	58.4±10.1	0.07
Sex			
Male	4	27	0.06
Female	10	21	
T classification			
T1	0	0	0.28
T2	2	6	
T3	4	25	
T4	8	17	
Stage			
Stage 0	0	0	0.26
Stage I	3	6	
Stage II	5	29	
Stage III	6	13	
Concurrent endocrine therapy			
Yes	4	2	0.02
No	10	46	
Prior or concurrent chemotherapy			
Yes	8	25	0.5
No	6	23	
Total radiation dose	20.7±9	22.7±8.4	0.08
Grade of radiodermatitis			
Grade 1	0	33	0.00
Grade 2	3	8	
Grade 3	3	5	
Grade 4	8	2	

Table 2. Multivariate analysis of risk factors for skin infection in patients with radiodermatitis

Variable	p	OR	95% CI
Concurrent endocrine therapy	0.06	15.9	0.9-287
Grade of radiodermatitis	0.000	5.9	2.4-15.2

staphylococcus strain isolated. Similarly, Hill et al. [3] reported that two of their six patients developed radiodermatitis, due to a CNS superinfection.

S. aureus can cause more serious skin infections that can enter the bloodstream. Methicillin-resistant *S. aureus* (MRSA) strains are resistant to all currently available β -lactam antibiotics, including penicillins and cephalosporins [12]. In this study, a total of five (36.0%) *S. aureus* strains comprising three (75.0%) methicillin-resistant and two (25.0%) methicillin-sensitive strains were isolated. Three MRSA and 1 MSSA strains were obtained from infected patients. A similar observation was reported by another investigator. Dissemmond et al. [13] documented the bacterial colonization of 79 patients with chronic wounds: two patients had radiodermatitis. An *S. aureus* strain was isolated from one patient; the other patient exhibited colonization by *Proteus mirabilis* and *Escherichia coli*. Hill et al. [3] reported that 6 patients with severe radiodermatitis had wound cultures positive for abnormal microorganisms (enterococci, MRSA, MSSA and CNS).

Candida is a commensal human colonizer of the mucosal surfaces, the gastrointestinal tract and the skin. The disruption of epithelial barriers leads to deep-seated contamination by various pathogens from the environment or from the patient's own flora (e.g., *Candida sp.*) [14]. Our findings indicate that among the patients with radiodermatitis, two patients had candidal infections, and three patients were colonized with these microorganisms.

We have also investigated whether age, gender, T classification and tumor stage, concurrent endocrine therapy, prior or concurrent chemotherapy, total radiation dose and radiodermatitis grade influence the risk of infection in patients with radiodermatitis. In univariate analysis, sex, the mean age of patients, T classification, tumor stage and total radiation dose did not differ significantly between infected patients and the control group (Table 1, $p>0.05$). However, the rate of concurrent endocrine therapy and the grade of radiodermatitis were significantly higher in patients with infection than in the colonized group ($p<0.05$) in our study. Multivariate logistic regression analysis showed that there was a significant association between the grade of radiodermatitis and skin infection ($p<0.05$).

Although normal skin is not the primary target of ionizing radiation, in most cases, exposure of the normal skin is inevitable. The findings of this study suggest that the incidence of superinfection seems to be increased in patients with high-grade radiodermatitis. Taking control swab samples from the area of radiodermatitis can be a useful method for early diagnosis and the therapeutic treatment of infection.

Conflict of interest statement: The authors declare that they have no conflict of interest to the publication of this article.

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