Case Report
Olgu Sunumu

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Evaluation of hand-foot syndrome and hand-foot skin reaction: Case series

El-ayak sendromu ve el-ayak deri reaksiyonunun olgu serisi ile değerlendirilmesi

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Abstract

Hand-foot syndrome (palmoplantar erythrodysesthesia, palmar-plantar erythema, toxic erythema of the palms and soles, or Burgdorf's syndrome) is characterized by painful predominantly palmoplantar lesions with the association of different chemotherapeutic agents. More recently, hand-foot skin reaction has been reported to be associated with regimens using targeted agents, in particular the multikinase inhibitors. Hand-foot syndrome/skin reaction has a major impact on patient's quality of life, necessitating dose reduction or treatment interruption. In this article, hand-foot syndrome and hand-foot skin reaction were discussed through patients consulted our dermatology outpatient clinic.
Keywords: Hand-foot syndrome, hand-foot skin reaction, chemotherapy, multikinase inhibitors

Öz

El-ayak sendromu (palmoplantar eritrodizestezi, palmar-plantar eritem, avuç içi ve ayak tabanlarının toksik eritemi veya Burgdorf sendromu) başlıca palmoplantar bölgede ağrılı lezyonlarla seyreden, farklı kemoterapötik ajanlarla ilişkisi saptanmış bir deri reaksiyonudur. Son zamanlarda hedefe yönelik tedavilerin özellikle çoklu kinaz inhibitörlerinin kullanımı ile el-ayak deri reaksiyonu olarak adlandırılan yeni bir antite bildirilmiştir. El-ayak sendromu/deri reaksiyonunun, tedavi dozlarının kesilmesine veya azaltılmasına neden olarak hastaların yaşam kalitesi üzerine önemli etkileri bulunmaktadır. Burada deri ve zührevi hastalıklar polikliniğimize konsülte edilen olgular üzerinden el-ayak sendromu ve deri reaksiyonu tartışılacaktır.
Anahtar Kelimeler: El-ayak sendromu, el-ayak deri reaksiyonu, kemoterapi, çoklu kinaz inhibitörleri

Introduction

Hand-foot syndrome, also called palmoplantar erythrodysesthesia, palmar-plantar erythema, Burgdorf syndrome, or toxic erythema of palms and soles is a common skin reaction which develops due to chemotherapeutic agents[1]. The most common causative agents are doxorubicin, liposomal doxorubicin, docetaxel, 5-fluorouracil (5-FU), cytarabine, and capecitabine, while the syndrome can also be seen with the use of paclitaxel, hydroxyurea, methotrexate, 6-mercaptopurine, cyclophosphamide, cisplatin, daunorubicin, etoposide, vinorelbine, irinotecan, and epirubicin[2]. Recently, after the introduction of multikinase inhibitors in oncology, palmoplantar reactions that show specific clinical findings have been recorded and characterized as hand-foot skin reaction. The main causative drugs for this reaction are multikinase inhibitors, such as sorafenib, sunitinib, pazopanib, axitinib and regorafenib, and BRAF inhibitors such as vemurafenib and dabrafenib[1-3]. Here, hand-foot skin syndrome and hand-foot skin reaction are discussed based on the cases consulted physicians of the dermatology outpatient clinic.

Method and Results

Patients, who were receiving chemotherapy and had complaints of hand and/or foot reactions and were referred to the dermatology outpatient clinic between January 2016

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and June 2017, were clinically evaluated. Gender, age, type of cancer, the chemotherapeutic agent that the patient was receiving, the day, week or cycle of chemotherapy at the time of presentation and the grade of hand-foot syndrome/reaction were recorded. The informed consent forms of patients were obtained.

A total of 28 patients with a mean age of 60.9 years (36-81) were included. Seventeen (62.5%) patients were female and 11 (37.5%) were male. Almost half of the patients had breast cancer among the other types of cancer. The chemotherapeutics administered were as follows: paclitaxel in 5 patients, docetaxel in 5, capecitabine in 5, cetuximab in 4, capecitabine + lapatinib in 2, capecitabine + cetuximab in 1, capecitabine + paclitaxel in 1, sorafenib in 2, pazopanib in 1, panitumumab in 1, and clofarabine + cytosine arabinoside in 1 patient. Ten patients (35.7%) had grade 1, 12 patients (42.9%) had grade 2 and 6 patients (21.4%) had grade 3 hand-foot syndrome/skin reaction (Table 1).

Discussion

A clinical entity named hand-foot skin reaction has emerged with the use of new targeted agents in cancer treatment. Its difference from the classical hand-foot syndrome has been established in terms of onset of the symptoms, clinical findings, location, and pathogenesis. In hand-foot syndrome, the palms, soles, dorsal surface of the hands, feet and the areas of occlusion, friction and pressure are affected. Symmetrical erythema and edema are seen in the palm and sole with accompanying neuropathic pain. It may progress to blistering with desquamation, erosion, and ulceration. Palms are involved more frequently compared to the soles. Histopathology reveals basal layer vacuolar degeneration or full-thickness necrosis, spongiosis, hyperkeratosis, and parakeratosis. Sweat gland-related toxicity may play a role in the pathogenesis. On the other hand, hand-foot skin reaction affects flexural and pressure-bearing areas, including fingertips, interdigital web spaces, heels, lateral aspect of the feet, and the joints. Soles are involved more frequently compared to palms. Localized tender lesions are seen on

Table 1. The clinicial features of patients with hand-foot syndrome/skin reaction

No	Gender	Age	Type of cancer	Chemotherapeutic	Cycle	Grade
1	F	60	Metastatic breast cancer	Capecitabine	52. cure	2
2	M	60	Metastatic colon cancer	Setuksimab	7. cure	1
3	F	61	Metastatic tiroid cancer	Sorafenib	10. day	2
4	F	42	Breast cancer	Paclitaxel	10. week	1
5	M	67	Metastatic colon cancer	Panitumumab	1. cure	3
6	M	75	Metastatic prostate cancer	Docetaxel	3. cure	2
7	F	65	Metastatic breast cancer	Capecitabine	2. cure	3
8	F	47	Metastatic breast cancer	Capecitabine + Lapatinib	5. cure	3
9	M	62	Metastatic colon cancer	Capecitabine + Setuksimab	5. cure	2
10	F	60	Metastatic breast cancer	Paclitaxel	16. week	2
11	M	59	Metastatic colon cancer	Setuksimab	5. cure	3
12	F	58	Metastatic breast cancer	Paclitaxel	12. week	1
13	M	61	Metastatic rectum cancer	Setuksimab	3. cure	2
14	F	66	Metastatic breast cancer	Capecitabine + Lapatinib	42. cure	2
15	F	56	Breast cancer	Docetaxel	1. cure	1
16	F	36	AML	Klofarabin + ARA-C	7. day	2
17	M	62	Metastatic prostate cancer	Docetaxel	3. cure	1
18	F	60	Breast cancer	Docetaxel	1. cure	2
19	F	66	Breast cancer	Paclitaxel	7. cure	1
20	F	66	Metastatic breast cancer	Capecitabine + Paclitaxel	3. cure	1
21	F	50	Metastatic tiroid cancer	Sorafenib	2 year	3
22	F	76	Breast cancer	Paclitaxel	12. week	2
23	M	60	Metastatic renal cancer	Pazopanib	1. month	2
24	M	63	Metastatic rectum cancer	Setuksimab	1. week	3
25	M	60	Rectum cancer	Capecitabine	25. day	1
26	M	61	Metastatic prostate cancer	Docetaxel	6. cure	1
27	F	81	Metastatic breast cancer	Capecitabine	25. cure	2
28	F	67	Colon cancer	Capecitabine	5. cure	1

F: Female, M: Male, AML: Acute myelocytic leukemia, ARA-C: Cytosine arabinoside

the areas exposed to friction and trauma. Lesions may appear as blisters or focal hyperkeratosis overlying an erythematous base. Well-demarcated dyskeratotic, discohesive keratinocytes are observed in histopathology. Vascular mechanisms are found to be responsible for pathogenesis[2,3].

Hand-foot syndrome is evaluated in 3 grades according to the National Cancer Institute criteria. Painless minimal skin changes (erythema, edema or hyperkeratosis) are seen in grade 1, while skin lesions (peeling, blister, bleeding, edema or hyperkeratosis) or pain are observed in grade 2. Painful and severe skin changes in addition to limited self-care activities are seen in grade 3[4]. The grades of the hand-foot syndrome/skin reaction in our patients are shown in Figures 1, 2 and 3.

Patients should be informed of the possibility of having hand-foot syndrome/skin reaction prior to the initiation of chemotherapy. Patients should refrain from mechanical trauma to the skin such as pressure, friction, and heat. Regular use of moisturizers is recommended. Thick cotton gloves and socks can be used to protect palms and soles from damage and to keep them dry[5]. In the treatment of grade 1, moisturizing creams, keratolytic creams, and cushioning of the affected regions with gel or foam-based shock absorber soles and soft shoes are recommended. Treatment is maintained at the same dosage. In the treatment of grade 2, potent topical corticosteroids are applied for seven to ten days additionally. A dose reduction of 50% should be considered. Local antiseptic bath is used for the blisters and erosions in stage 3, in addition to the treatments used in stage 1 and 2. Treatment is interrupted at least for one week and started in a decreased dose after improvement of the condition to a level of grade 0 or grade 1 disease[6]. Among the patients in this case series, 10, 12 and 6 patients were found to have grade 1, grade 2 and grade 3 disease, respectively. The treatment was discontinued until the symptoms subsided in patients with grade 3. The incidence of hand-foot syndrome varies according to the causative drug. Capecitabine was the most frequently used chemotherapeutic drug in this case series. Capecitabine is an oral precursor of 5-FU. Approximately 54% of patients receiving this treatment may have hand-foot syndrome. This effect may be seen during each cycle or each dose of treatment applied. Dose reduction or interruption might be needed in about 15-25% of patients[7]. Another commonly used drug group in the cases presented here was taxane. Taxane is a group of chemotherapeutic drugs which exerts its activity by mitotic inhibition. Docetaxel and paclitaxel rank at the top of the agents in this group that can cause hand-foot syndrome[8]. The incidence of the syndrome has been reported to be 6-58% with docetaxel treatment[3].

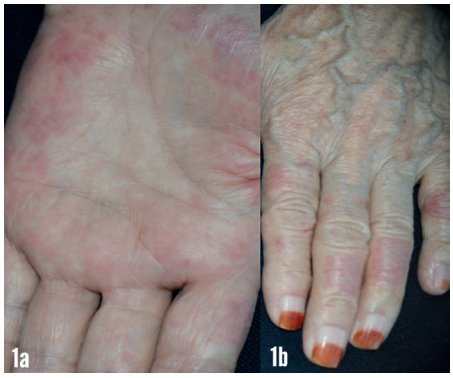

Figure 1. a, b) Erythema of the palms and dorsal hands in a female patient receiving paclitaxel (grade 1)

The severity of the syndrome caused by docetaxel, in general, is higher compared to paclitaxel, although cases of severe hand-foot syndrome induced by paclitaxel have been reported[8]. Combination treatment was also encountered among the cases presented here. The most frequent dermatological side effect associated with generally well-tolerated capecitabine and paclitaxel combination is hand-foot syndrome, due to long-term usage of cytostatic agents. The incidence of hand-foot syndrome was found to be 42% with mild to moderate severity in a study performed in patients receiving this treatment[9]. This rate was reported to increase up to 56-63% with the combination of another taxane, docetaxel plus capecitabine[2].

Multikinase inhibitors generally cause hand-foot skin reaction. In a study, the incidence was reported to be 12% in patients on sunitinib, pazopanib, axitinib and sorafenib (tyrosine kinase inhibitors) of whom 58% required no treatment, while 34% needed pharmacological treatment, 4% non-pharmacological treatment and 4% required

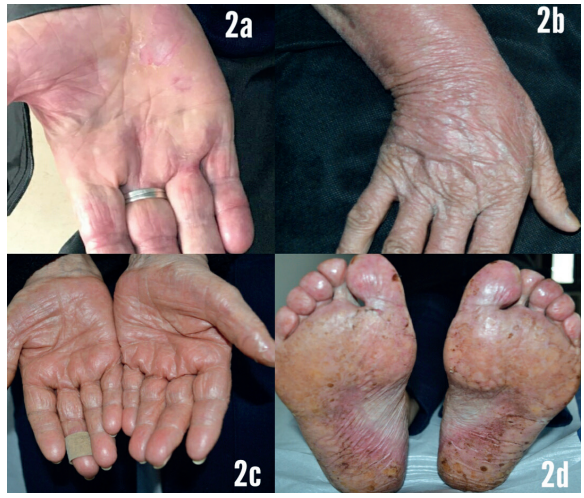

Figure 2. a) Erythema and desquamation in male patient receving pazopanib (grade 2), b) painful erythema in a female patient on paclitaxel therapy (grade 2), c) erythema of the palms in a female patient on capecitabine therapy (grade 2), d) difuse erythema, mild desquamation and crusted lesions in a patient receiving capecitabine (grade 2)

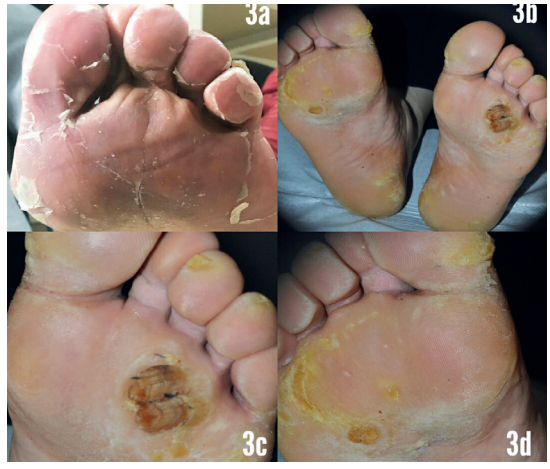

Figure 3. a) Diffuse painful erythema and desquamation in male patient on cetuximab therapy (grade 3), b-d) bilateral focal callus-like hyperkeratosis of the soles in a female patient receiving sorafenib therapy (Hand-foot skin reaction grade 3)

both[10]. In another study, hand-foot skin reaction was reported in 10-28% and 10-62% of patients receiving sorafenib and sunitinib treatments, respectively[3]. Pazopanib, an orally administered multi-targeted tyrosine kinase inhibitor, predominantly inhibits vascular endothelial growth factor receptor-1, 2 and 3, platelet-derived growth factor receptor-α and -β, and the stem cell factor receptor c-Kit. It is approved for the treatment of advanced renal cell carcinoma. The incidence of associated hand-foot skin reaction has been reported to be 6%. The rate of this adverse effect was observed to be lesser compared to that in patients receiving sunitinib[11]. On the other hand, lapatinib is the first dual-acting tyrosine kinase inhibitor which inhibits both human epidermal growth factor receptor type 2 (HER2/neu) and epidermal growth factor receptor. The most frequent adverse effect in patients with metastatic breast cancer receiving lapatinib and capecitabine combination treatment has been reported to be hand-foot syndrome with an incidence of 46.8%[12].

Cetuximab and panitumumab which are monoclonal antibodies inhibiting epidermal growth factor receptor are also used in the treatment of various cancer types. The incidence of skin toxicity has been reported to be 50-90% in patients receiving epidermal growth factor inhibitors. Papulopustular rash is the most frequent adverse effect. The second most common adverse effects are atrophic, sensitized skin, dryness and painful fissures in the palms and soles[13].

Acral erythema has been reported in patients with acute myelocytic leukemia receiving high-dose chemotherapy. Cytosine arabinoside treatment is among the most frequent causes of erythema[14]. One patient was found to receive this treatment in the case series presented here.

The risk of developing hand-foot syndrome depends both on the dose and drug[1,3]. Dosage and female gender have been defined as risk factors in the development of this syndrome, while risk factors of hand-foot skin reaction caused by multikinase inhibitors have been reported to be tumor type, normal pretreatment white blood cell count, female gender, good performance status, liver metastases, and the number of affected organs[3]. The onset of hand-foot skin reaction is usually within two to four weeks, however, it may occur in the first one-three months of the treatment. On the other hand, symptoms of the hand-foot syndrome may occur in 1-21 days after high-dose pulse treatment and in months in low-dose continuous treatment[2]. In the series presented here, we noticed that symptoms might be seen in different treatment periods and cycles in each patient and more than one syndrome were seen in one patient during the chemotherapy period. Individual genetic changes play a major role in the risk of development of this syndrome. Studies on genetic variations have recently been published in the literature. In their study, Mattison et al.[15] have reported that dihydropyrimidine dehydrogenase enzyme deficiency was seen to underlie the genetic tendency to capecitabine-induced toxicities and this deficiency affected Afro-Americans more frequently. It may explain the ethnic variations in hand-foot syndrome susceptibility. Also, in another study, the loss of rs3215400 allele in the cytidine deaminase gene was found to increase capecitabine-induced hand-foot syndrome risk[16].

Hand-foot syndrome and skin reaction can severely affect the physical, psychological and social lives of the patients. It may limit the antitumoral effect by causing dose reduction and cessation of the chemotherapy, although it has no direct effect on survival[5]. Patients should be informed about the development of this syndrome and recommendations prior to starting the drugs that can cause hand-foot syndrome/skin reaction. Early diagnosis and appropriate dermatological treatment are suggested to be important since the treatment is based on clinical appearance.

Ethics

Informed Consent: The informed consent forms of patients were obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.G.D., B.T.A., B.Y.A., Concept: H.G.D., Design: H.G.D., B.T.A., B.Y.A., Data Collection or Processing: H.G.D., B.T.A., B.Y.A., Analysis or Interpretation: H.G.D., B.T.A., B.Y.A., Literature Search: H.G.D., Writing: H.G.D.

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