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Case report

Hand-Foot syndrome induced by sorafenib, a multitargeted tyrosine kinase inhibitor, in a patient with advanced renal cell carcinoma

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= Abstract =

Renal cell carcinoma (RCC) arising from epithelial cells of the renal tubules is a highly aggressive and malignant tumor in all ages; however, it rarely occurs in children. the standard treatment for RCC is radical nephrectomy with lymph node dissection when the tumor is localized and can be completely resected. Adjuvant chemotherapy, radiotherapy, and immunotherapy are used for pediatric patients with advanced RCC involving lymph nodes or metastatic lesions. Sorafenib is an oral, multikinase inhibitor that has recently been approved for use in metastatic RCC. Common toxicities that have been reported include dermatologic changes such as rash or desquamation and hand-foot skin reaction, diarrhea, fatigue, alopecia, and hypertension. In particular, hand-foot syndrome (HFS) an erythematous skin lesion of the palms and solesis most often caused by cytostatic chemotherapeutic agents. In this report, we have studied a 14-year-old female patient with hand-foot syndrome that occurred in association with sorafenib for the treatment of metastatic RCC. Furthermore, this case demonstrates that reversal of complications can be achieved by discontinuing the drug and intervention with topical steroids, vitamin E, and high-dose pyridoxine. **(Korean J Pediatr 2009;52:119-123)**

Key Words : Hand-Foot syndrome (HFS), Sorafenib, Renal cell carcinoma

Introduction

Sorafenib is an oral, multikinase inhibitor that was recently approved for use in metastatic renal carcinoma. Sorafenib was initially developed as an inhibitor of Raf kinase; however, it has broad spectrum activity against multiple tyrosine kinases, including angiogenic factors VEGFR (vascular endothelial growth factor receptor) and PDGFR (plate derived growth factor receptor)[1]. Oral sorafenib is being increasingly accepted into clinical practice for advanced renal cancer and in other tumor types as it permits convenient administration in a home-based setting. Sorafenib capsules are taken orally twice daily approximately 12 hours apart (after breakfast and after dinner) for 3 weeks, followed by a 1-week, treatment-free period. After this 1-week 'rest' period, the patient starts the next cycle of treatment. The normal recommended dosage is 400 mg/m^2 twice daily. At this dosage, sorafenib was generally well tolerated, with manageable side effects including rash (34%), diarrhea (33 %), fatigue (26%), and hypertension (11%)[2]. However, a dose reduction may be indicated at the onset of adverse events. One of common adverse events associated with its use in clinical practice is HFS, which is an erythematous skin lesion of the palma and sole, is most often caused by cytostatic chemotherapeutic agents. The pathogenesis of the HFS has not yet been sufficiently clarified and it is rarely serious and never life-threatening. However, HFS can significantly interfere with the activities of normal daily living[3].

Renal cell carcinoma (RCC) arising from epithelial cells of the renal tubule is a highly aggressive and malignant tumor in all ages. Although RCC accounts for 2% to 3% of all adult malignancies, it rarely occurs in children[4]. The incidence of this tumor in childhood is estimated to be from 0.1% to 0.3% of all childhood cancer[5], and from 2% to 6% of all malignant renal tumors[6]. It is initially asymptomatic, but clinically overt symptoms such as an abdominal mass

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The abbreviations used are: HFS, Hand-Foot syndrome, RCC, renal cell carcinoma, PPE, palmar plantar erythrodysaesthesia.

or hematuria may indicate late-stage disease and a poor prognosis. Standard treatment for RCC is radical nephrectomy with lymph node dissection and results in cure when the tumor is localized and completely resected. However, the role of adjuvant chemotherapy, radiotherapy and immunotherpy for pediatric patients with advanced RCC with lymph node involvement or metastatic lesion has not been defined. Because approximately 20% to 50% of patients will eventually develop metastatic disease after nephrectomy, patients with metastatic RCC face a dismal prognosis, with a median survival time of only 6 to 12 months and a 2-year survival rate of 10% to 20%[7].

In this article, we report on a patient with HFS that occurred in association with sorafenib for the treatment of metastatic RCC. And the review of current literature is included.

Case report

A 14-year-old female was admitted to Chonbuk National University hospital with 1 month-history of right flank pain and macroscopic hematuria. Her past history was unremarkable. There had been no weight loss, fever, or night sweats. On physical examination, a large, firm, non tender mass was palpated in right upper quadrant of the abdomen, and there was a knocking tenderness of right flank area. No evidence of lymph node enlargement was found. Urinalysis confirmed the hematuria. Blood and liver function tests were normal except for low hemoglobin (6.6 g/dL) and high lactate dehydrogenase (538 IU/L). The abdominal CT revealed a huge solid mass with the involvement of all parenchyma of the right kidney with multiple lymph node involvement at the regional retroperitoneal lymphatic chain (Fig. 1). On the parent's requests, the patient was transferred to another hospital for further evaluation. There, the patient underwent right radical nephrectomy and lymphadenectomy. Histological evaluation of the renal tumor revealed a RCC (Fig. 2). Intramuscular interferon (INF) injections were initiated after radiotherapy, consisting of 6 million IU/day of 5 times/2 weeks for 3 months, followed by INF injections of 5 times/2 weeks for another 6 months.

One year after the surgery, the patient was readmitted to our hospital because of multiple bone pain. Routine tests showed normal liver function, but a slight increase in C-reactive protein (CRP), and elevated erythrocyte sedimentation rate. A whole body bone scan and PET/CT demonstrated hypermetabolic bony metastasis at the left shoulder, right proximal humerus, iliac bone and thoracic vertebrae (T9, 12) and pulmonary metastases.

In view of the fact that the metastatic lesions had failed to respond to immunotherapy, the patient's parents elected to have a sorafenib only treatment without other chemotherapy. Treatment was initiated, consisting of a with 28-day cycle of sorafenib at 400 mg orally twice daily, for 21 days then the-7 days suspension of treatment to allow the patient to rest. Five days after the initial sorafenib administration, she developed paresthesia in her palms and soles, which became painful and erythematous. And well-demarcated bullae were formed in the palms, toes and periungual zones of distal phalanges (Fig. 3). The bullae gradually resolved

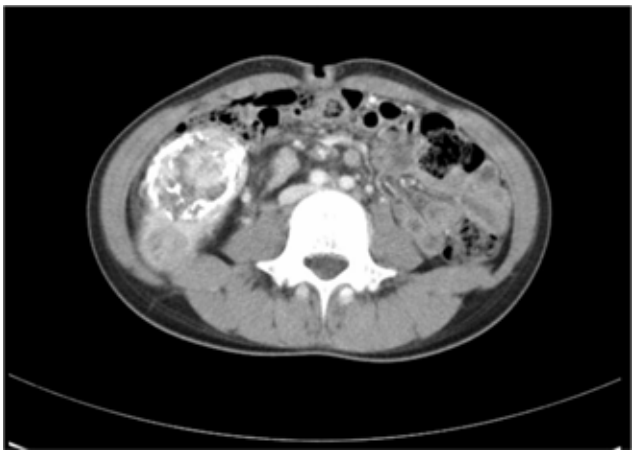

Fig. 1. Abdominal computerized tomography showing huge mass in the right renal parenchyma and multiple lymphadenopathies.

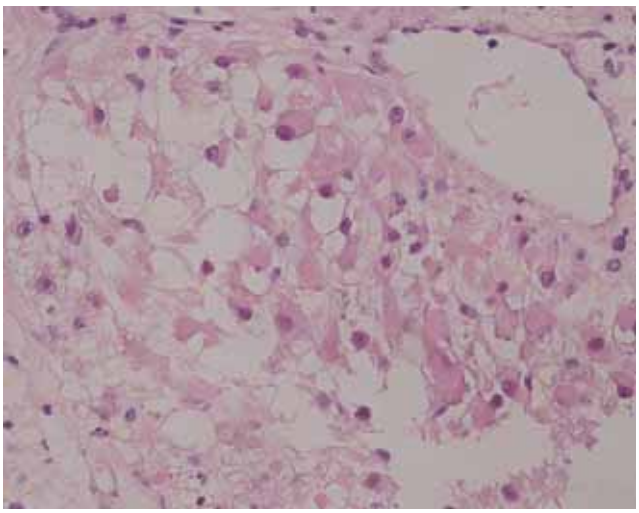

Fig. 2. Pathological diagnosis of the renal mass revealed renal cell carcinoma with clear cell and rhabdoid cell components (Hematoxylin and eosin staining, ×400 magnification).

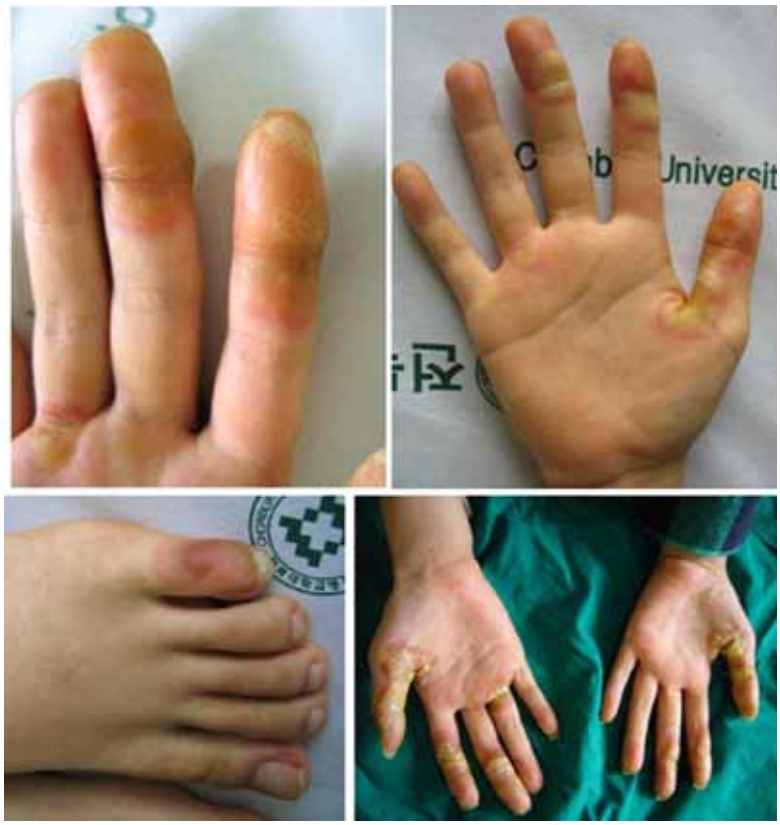

Fig. 3. Acral erythema and hyperkeratosis in the hand and foot of a patient treated with sorafenib.

over the next 2-3 days, after which palmar and plantar cutaneous desquamation occurred. Based on clinical findings, a diagnosis of HFS secondary to sorafenib therapy was made and managed with topical steroid, vitamin E (300 mg/day) and high dose pyridoxine (150 mg/day). The symptoms gradually resolved over two weeks.

Discussin

The term 'hand-foot syndrome' has been used for decades by hematologists to describe a painful swelling of the hands and feet in very young patients (e.g., age <18 months) with sickle cell disease[8]. In oncology the HFS was first described in 1984 as a pathologic process which is associated with several cytotoxic agents[9].

HFS, which is also known as palmar plantar erythrodysesthesia (PPE), is characterized by prodrome of dysesthesia (tingling sensations and intolerance to contact with hot objects) affecting the hands and feet, followed 3-4 days later by symmetrical swelling of the palms and soles of the feet, together with erythema and tenderness, particularly of the distal phalanges. It generally arises after 1-2 weeks of treatment with EGFR inhibitors. With continued drug therapy the swelling and erythema progresses and a central pallor develops over the tufts of the distal phalanges. Most reported case have resolved within 7 days of discontinuation of therapy[9], but tend to recur when therapy is re-instituted[10].

Histologically, tissues affected by HFS show general inflammatory changes with white blood cell infiltration, which include dilated blood vessels, edema and increased vascularity of the dermis, although nothing really stands out as a clear marker of the condition[11]. Consequently there is no standard diagnosis for HFS. In addition, HFS appears to differ according to the type of cytotoxic agent used[12]. Most patients with HFS induced by multiple kinase inhibitors seem to have more localized and hyperkeratotic lesions that are distinct from classic HFS that can arise with cytarabine, fluorouracil, capacitabine[13], or doxorubicin.

The mechanism of HFS is unclear. One theory relating to sorafenib-associated HFS is that sorafenib may be eliminated by the eccrine secretion (sweat secretion), resulting in HFS caused by an as-yet unidentified mechanism relating

to the increased number of eccrine glands on the hands and feet[14]. HFS may also result from increased vascularization and increased pressure and temperature in the hands and feet. In addition, long-term alcohol intake and strenuous physical activity may increase the likelihood of developing HFS[12].

HFS seems to be dose dependent and both peak drug concentration and total cumulative dose determine its occurrence. Withdrawal or dose reduction of the implicated drug usually gives rise to amelioration of the symptoms and leads to recovery over several days/weeks, depending on the severity. Supportive treatments may help to relieve the pain and there are few supportive measures that have proven effectiveness at controlling symptoms. The use of topical emollients and creams would appear to be a prudent prophylactic and symptomatic treatment at the first signs of HFS[15]. Regular use of a topical petroleum-lanolin-based ointment with antiseptic hydroxyquinoline sulphate applied 3 times daily has been reported to alleviate the symptoms of HFS induced by various chemotherapeutic agents[16]. Nevertheless, dose interruption and, if necessary, dose reduction should remain the primary tool in HFS management. As a general recommendation[15], symptoms can often be relived by : 1) immersing the hands and feet in cool water, 2) avoiding extremes of temperature, pressure, and friction on the skin, 3) cushioning sore skin with soft pads, 4) topical wound care and consultation with a dermatologist for any blistering or ulceration.

For other treatments of HFS, Kara et al[17]. reported that treatment with vitamin E improved the symptoms of HFS without dose reduction and suggested that it could be of interest to consider vitamin E as a preventive drug when drugs with a strong association with HFS are going to be administered. Drake et al[18]. suggested oral dexamethasone as a treatment of HFS and reported that oral dexamethasone is effective in attenuating or eliminating HFS. The use of dexamethasone regimen prevents treatment delay and dose reduction. There also have been reported success using pyridoxin therapy[18] and topical DMSO[20] for the management of HFS. Because, in the case under discussion, we were not able to decide dose reduction or interruption, we used vitamin E and pyridoxin therapy together instead of dose management. By using those therapies our patient showed improvement in the symptoms of HFS.

Multitargeted tyrosine kinase inhibitors can induce a variety of dermatologic events, which require early recognition and effective management, in order to ensure continued life saving antineoplastic therapy.

한 글 요 약

진행된 신세포암 환아에게 sorafenib 투여시 발생한 Hand-Foot syndrome 1예

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신세포암은 소아에서는 드물지만 모든 연령에 걸쳐 신 세뇨관의 상피세포에서 기인하는 침습적 악성 종양이다. 종양이 국소화되어있다면 주위 림프절 절개와 함께 국소적 신절제술로 완벽히 제거될 수 있으나, 주위 림프조직을 침범한 경우나 전이 병변이 동반된 진행된 신세포암 에서는 보조 화학치료, 방사선치료 및 면역치료 등을 이용한다. Sorafenib는 경구, 다(多) kinase (multikinase) 억제제로서 최근 전이성 신장 암에 사용이 입증되었다. 그러나 설사, 피로, 탈모와 고혈압 등의 부작용과 발진이나 낙설 그리고 수족 피부 반응(hand-foot skin reaction)과 같은 피부변화 등이 보고되었다. 특히, 손바닥과 발바닥의 홍반 피부 병변을 보이는 수족 증후군(hand-foot syndrome, HFS)은 대부분 세포증식 억제 화학치료 약에 의해 야기된다. 손바닥 발바닥의 홍반성감각부전으로 알려진 수족 증후군은 저림과 고온의 물체에 대한 과민성 같은 감각이상의 전구증상 등을 특징으로 하며, 약 3-4일 후 원위 지관절에 홍반과 동통을 수반한 양측에 대칭적 손바닥과 발바닥의 부종이 생긴다. 저자들은 14세 여아의 전이성 신세포암 치료에 sorafenib 사용 시 나타난 수족 증후군과 그에 대한 치료를 경험하였기에 문헌고찰과 함께 보고하는 바이다.

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