Successful Use of Inhaled Steroids For the Management of Radiation Pneumonitis in an Infant: Case Repot

Radyasyon Pnömonisinin Tedavisinde İnhale Steroidlerin Bir Süt Çocuğunda Başarı ile Kullanımı

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ABSTRACT Radiation pneumonitis and subsequent pulmonary fibrosis are among the serious complications of thoracic irradiation and can have severe implications on patients' quality of life. Systemic corticosteroids are commonly used agents to treat radiation pneumonitis. However, the potential adverse effects of systemic corticosteroids, particularly in growing children, are considerable. An infant with lung metastatic Ewing sarcoma developed severe radiation pneumonitis following chemoradiotherapy. Systemic prednisolone was started first. However, due to the prolonged need for corticosteroid therapy, inhaled budesonide was administered with reduced systemic corticosteroid dose in an attempt to avoid the adverse effects of systemic corticosteroid treatment. The treatment was then continued exclusively with budesonide with a good clinical response. To our knowledge, this is the first pediatric case reported to benefit from inhaled steroids for severe radiation pneumonitis. This response suggested that inhaled steroids might serve as a adjunct or even an alternative to systemic corticosteroids in radiation pneumonitis.

Key Words: Radiation pneumonitis, child, budesonide, pulmonary fibrosis

ÖZET Radyasyon pnömonisi ve ardından gelişebilen akciğer fibrozisi, toraksa yönelik radyoterapinin ciddi komplikasyonlarından olup, hastanın yaşam kalitesini önemli oranda etkileyebilmektedir. Radyasyon pnömonisinin tedavisinde sistemik kortikosteroidler sıklıkla kullanılan ajanlardır. Ancak sistemik kortikosteroidlere bağlı potansiyel toksik yan etkiler özellikle gelişmekte olan çocuklarda ciddi bir sorundur. Skapula primerli ve akciğere metastatik Ewing sarkomu tanısı ile kemoradyoterapi alan bir süt çocuğunda ağır radyasyon pnömonisi gelişti ve sistemik prednizolon tedavisi başlandı. Ancak uzun süre kortikosteroid kullanma gereksinimi doğunca, sistemik tedavinin olası yan etkilerinden kaçınmak amacı ile, hastaya sistemik steroidlere ek olarak inhale steroid tedavisi eklendi. Daha sonra tedaviye sadece inhale budesonid ile devam edildi ve iyi bir klinik yanıt alındı. Bildiğimiz kadarıyla bu olgu, radyasyon pnömonisinin tedavisinde inhale steroid tedavisinden yarar gördüğü bildirilen ilk pediatrik olgudur. Bu hastadaki yanıt, inhale steroidlerin radyasyon pnömonisi tedavisinde sistemik kortikosteroidlere ek ve hatta alternatif olarak kullanılabilecek ajanlar olduğunu düşündürmüştür.

Anahtar Kelimeler: Radyasyon pnömonisi, çocuk, budesonid, akciğer fibrozisi

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Radiation pneumonitis (RP) is a well known complication of thoracic irradiation.[1-5] Systemic steroids have been widely used for the management of this complication.[1-3] However, the adverse effects of systemic corticosteroids, particularly in growing children are considerable. Inhaled steroids are being increasingly used in a variety of pulmonary diseases in children. These drugs may particularly be useful for the management of RP because these patients usually receive multiagent cytotoxic

chemotherapy that inevitably cause many other adverse effects. To our knowledge, there is only one adult patient with RP reported in English literature that benefited from inhaled steroids.[6] Here; we report the successful use of inhaled steroids as an adjunct with oral steroids in a 20-month-old boy with Ewing sarcoma who developed RP after receiving bilateral lung irradiation in addition to multiagent systemic chemotherapy.

CASE REPORT

A 20-month-old boy presented with Ewing sarcoma originating from his right scapula. He also had a metastatic nodule in the inferior lobe of the right lung during initial presentation. He was started on chemotherapy including ifosfamide, carboplatinum, etoposide (ICE) alternating with vincristine, adriamycine and cyclophosphamide (VAC). After three ICE alternating with two VAC courses, reevaluation imaging studies showed some regression in the primary tumor, but a new pleura-based nodule appeared just adjacent to the right costaphrenic sinus. Therefore, local treatment with radiotherapy (RT) was started. He received bilateral whole lung (12 Gy) and right scapular (53,4 Gy) RT with 150 cGy fractions, using 6 MvX photon beam encompassing bilateral lungs, without any lung correction. During RT, he only received weekly vincristine injections. The patient did well for three weeks after the completion of RT. Then he presented with fever (38°C), cough and respiratory distress. On physical examination, he was apparently cyanotic, tachypneic (respiratory rate 70 per minute), and dyspneic. Pulmonary auscultation revealed bilateral moist rales. Oxygen support was started immediately. On complete blood count and differential, there was no finding to support an infectious etiology and C-reactive protein was negative. Chest X-ray showed diffuse alveolar infiltration in both lungs and thoracic computerized tomography (CT) revealed that the infiltration was more prominent at the primary tumor area which was irradiated with an additional boost dose of RT (Figure 1). He was started on parenteral broad spectrum antibiotics since an infectious etiology could not be ruled out. He became increasingly dyspneic at the second day of parenteral antibiotics. With a presumptive diagnosis of RP, a thorax CT was performed and the radiologic findings supported the diagnosis of RP. Prednisolone 2mg/kg/day IV was started while he was on broad spectrum antibiotics. Repeated blood cultures and viral, mycoplasmal, and fungal serology were negative. Starting from the fourth day of treatment, a gradual clinical improvement was observed. During the clinical course, our several attempts to taper the corticosteroid dose had resulted in flare up of clinical symptoms. One month later, prednisolone dose was tapered to 1mg/kg/day and he was started on inhaled budesonide (0,25mg q 12h). After two months of the treatment, thorax CT showed a significant regression of alveolar infiltration. Systemic and inhaled steroids were continued. The anticancer treatment was restarted after a two months delay due to this severe complication. The dose of systemic corticosteroid was decreased at the third month of the treatment; however cough and respiratory distress worsened. Because of this flaring up, the dose of systemic steroid was slowly tapered and had to be continued till the end of seventh month of treatment. Inhaled budesonide (0,25 mg q 12h) was given for one year in order to control respiratory symptoms. Three months after cessation of the systemic steroid therapy, an attempt to decrease inhaled budesonide to 0,25 mg/day had failed. The dose of inhaled budesonide was again increased to 0,5 mg/day because of recurring cough. Thorax CT performed one year after the diagnosis of RP reve-

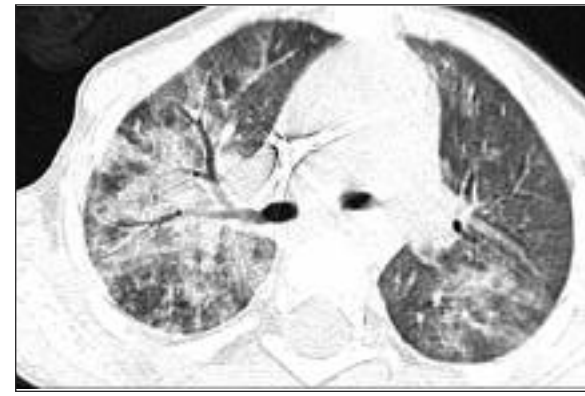

FIGURE 1: Bilateral alveolar infiltrations were more intense on areas near the primary tumor that high radiation dose was given.

aled diffuse fibrotic changes in the upper lobe of right lung. Now, 18 months after the completion of anticancer therapy, he is in complete remission for the tumor and has no respiratory symptom.

DISCUSSION

The clinical manifestations of radiation-induced lung injury may lead to two clinical syndromes; radiation pneumonitis and fibrosis. The acute inflammatory and late fibrosing stages of radiation injury do not represent separate pathogenetic entities but both clinical manifestations are the parts of a continuous pathogenetic process.[1-3,7] The underlying pathogenetic mechanisms for this process are complicated.

The differential diagnosis of RP, particularly from pulmonary infections, can be quite difficult during the acute phase. At the initial evaluation, we could not definitely exclude an infectious etiology. However, the clinical and radiological findings were suggestive for RP early in the clinical course. The lag time between RT and the symptoms together with characteristic chest X-ray findings are helpful in differential diagnosis. Acute RP usually occurs within two to six months after completion of radiotherapy.[1-4] The clinical symptoms are usually dominated by dry and unproductive cough, progressive dyspnea and, occasionally a low-grade fever.[1-3] Our patient developed an early onset RP with a severe clinical course. The early onset of symptoms implies a more severe and protracted disease.[3] The chest CT is more sensitive than the chest radiograph in detecting alveolar and interstitial opacifications in the radiation port.[1,7] Sometimes symptoms may develop before radiographic changes.[3]

Some chemotherapeutic agents may potentiate radiation-induced pulmonary injury. The best characterized is bleomycin, but others like doxorubicin, epirubicin, dactinomycin, cyclophosphamide, and to a lesser extent, vincristine may also enhance the toxicity of thoracic irradiation.[3-5,8,9] Our patient received doxorubicin, cyclophosphamide and vincristine before RT as well as concomitant vincristine during RT. These agents might be additional risk factors for the development of this early severe pneumonitis.

Although there are no prospective, controlled trials evaluating the efficacy of systemic corticosteroids, they remain the mainstay of treatment and response rate can be as high as 80%.[1-3] When steroids are effective, the reversal of symptoms can be dramatic, but recrudescence of symptoms may be problematic during dose tapering.[1] We needed to use a prolonged course of systemic steroid with gradual dose tapering because of flare-ups during this severe clinical course. In an attempt to avoid the well known complications of systemic corticosteroids, we added inhaled budesonide to be able to reduce the dose of oral prednisolone. He could finally tolerate discontinuation of systemic steroid after seven months and we then continued with only inhaled budesonide for one year.

Inhaled steroids, that have minimal systemic adverse effects, have been used in the treatment of several pulmonary disorders, however, there is very limited experience concerning the use of these agents for the management of RP. There has been only one case report of the successful use of inhaled corticosteroids after tapered systemic corticosteroids in an adult patient with RP.[6] A study in adults with RP showed that inhaled steroids were more effective than oral steroids for the prophylaxis of RP.[10]

Inevitably, most cases of RP progress to some degree of fibrosis.[1] It has been shown that the tissue mast cell and fibrotic responses were suppressed during systemic corticosteroid therapy but the ultimate fibrosis could not be altered.[11] Although this boy benefited from steroid therapy, he is still under the risk of developing lung fibrosis. Therefore, prophylaxis of this serious complication is a critical issue.

To the best of our knowledge, this is the first pediatric case report in English literature on the use of inhaled steroids in RP after initial treatment with systemic corticosteroids. Inhaled steroids may serve as an adjunct or even an alternative to avoid the adverse effects of prolonged use of systemic steroids, but prospective randomized clinical studies are needed to evaluate the effectiveness of these agents both for the prophylaxis and the treatment of this serious complication.

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