References

[1] Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007;356:115–24.

[2] Figlin RA, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Négrier S, et al. Overall survival with sunitinib versus interferon (IFN)-alfa as first-line treatment of metastatic renal cell carcinoma (mRCC). Oral (abstract 5024). Presented at the 44th American Society of Clinical Oncology Annual meeting, Chicago, USA, May 30–June 3, 2008.

[3] Demetri GD, van Oosterom AT, Garrett CR, Blackstein ME, Shah MH, Verweij J, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: A randomized controlled trial. Lancet 2006;368:1329–38.

[4] Schmidinger M, Zielinski CC, Vogl UM, Bojic A, Bojic M, Schukro C, et al. Cardiac toxicity of sunitinib and sorafenib in patients with metastatic renal cell carcinoma. J Clin Oncol 2008;26:5204–12.

[5] Force T, Krause DS, Van Etten RA. Molecular mechanisms of cardiotoxicity of tyrosine kinase inhibition. Nat Rev Cancer 2007;7:332–44.

[6] Chu TF, Rupnick MA, Kerkela R, Dallabrida SM, Zurakowski D, Nguyen L, et al. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. Lancet 2007;370 (9604):2011–19.

[7] Cardinale D, Colombo A, Sandri MT, Lamantia G, Colombo N, Civelli M, et al. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. Circulation 2006;114:2474–81.

[8] Pfizer Inc. SUTENT, Summary of Product Characteristics. January 2008. Accessed 23/04/2008. http://emc.medicines.org.uk/emc/industry/default.asp?page=displaydoc.asp&documentid=18531

[9] Porta C, Szczylik C, Bracarda S, Hawkins R, Oudard S, Lee SH, et al. Short- and long-term safety with sunitinib in an expanded access trial in metastatic renal cell carcinoma (mRCC). Oral (abstract 5114). Presented at the 44th American Society of Clinical Oncology Annual meeting, Chicago, USA, May 30–June 3, 2008.

[10] Cooney MM, van Heeckeren W, Bhakta S, Ortiz J, Remiack SC. Drug insight: Vascular disrupting agents and angiogenesis–novel approaches for drug delivery. Nat Clin Pract Oncol 2006;3:682–92.

[11] Joensuu H. Cardiotoxicity of sunitinib. Lancet 2007;370: 1978–9.

Spontaneous regression of renal cell carcinoma lung metastases in a patient with psoriasis

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To the Editor

Spontaneous regression of metastases is a rare outcome of neoplastic disease. Although instances of spontaneous regression have been documented across the spectrum of malignant disorders, most cases have been documented in malignant melanoma or renal cell carcinoma (RCC) [1]. RCC is a tumor of peculiar biological behavior characterized by great variations in the clinical course, including, on the one hand, spontaneous regression of metastases or indolent course of metastatic disease, and, on the other hand, rapidly fatal metastases, paraneoplastic syndromes, or metastases in unusual sites. The mutation or epigenetic changes in the von Hippel-Lindau gene, that are present in most cases of RCC, result in increased production of vascular endothelial growth factor (VEGF) that could be responsible for some of the biological peculiarities

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of RCC [2]. In RCC, many instances of spontaneous regression have been observed after nephrectomy. The pathogenesis of spontaneous regression remains unknown. Different theories have been proposed to explain this rare phenomenon, and in most hypotheses the pathogenesis of spontaneous regression is thought to involve the activation of the host immune system [1]. We present here a patient who had spontaneous regression of lung metastases of RCC after nephrectomy associated with a flare of psoriasis.

A 68-year-old female with a history of hypertension, diabetes mellitus and psoriasis presented in December 2004 with a cough. Multiple lung metastases were detected on chest x-ray, and confirmed by CT scan. Subsequent investigations identified a tumor in the right kidney. The patient underwent right nephrectomy on February 16, 2005. Histologic examination of surgical specimen revealed clear cell carcinoma of the kidney. Therapy with interferon-alpha was planned, and for response evaluation, a control CT scan was performed that revealed a substantial regression of lung metastases. Subsequent CT scan demonstrated a complete regression of lung metastases. Because of complete regression of metastases, originally planned therapy was deferred. About one month after nephrectomy and simultaneously to regression of lung metastases, a flare of psoriasis was observed with psoriatic lesions appearing first in the nephrectomy scar and subsequently spreading to the back, extremities and the head. Local therapy including dexamethasone was prescribed. Because of persistent psoriasis complicated by psoriatic arthritis the therapy with oral methotrexate was started in October 2005 leading to regression of skin lesions. The patient was well until March 2006. In late March 2006, the patient presented with left pleural effusion. At that time, only few psoriatic lesions were present on the skin of the back. The therapy with oral methotrexate was interrupted. A bloody exudate was evacuated during repeated pleurocenteses. Administration of interferon-alpha (9 MU 3 times per week) was initiated in May 2006. The therapy was followed by an almost complete regression of pleural effusion on control CT in September 2006. The regression of metastases was again accompanied by a flare of psoriasis with lesions appearing on the trunk and extremities. Because of toxicity associated with therapy, the dose of interferon-alpha was reduced to 6 MU 3 times per week in September 2006 and subsequently interrupted in December 2006. In March 2007 the patient complained about dyspnea. CT scan in April 2007 revealed multiple lung metastases involving both lungs and a tumor mass in left pleural space the infiltrated the abdominal cavity and ribs. No psoriatic lesions were observed. Because of general status, only symptomatic therapy was possible. The patient died on June 26, 2007. An autopsy was not performed.

We present here an observation of an apparent association between spontaneous regression of metastatic RCC and activity of psoriasis. The spontaneous regression of lung metastases was accompanied by the exacerbation of psoriasis, and remission of psoriasis was associated with tumor progression. The response of recurrent metastatic disease to the therapy with interferon-alpha was again accompanied with exacerbation of psoriasis, and during final progression the activity of psoriasis was low. The rare occurrence of spontaneous regression of metastasis in RCC precludes a systematic study of this phenomenon. The pathogenesis of spontaneous regression is still unknown. Many theories have been proposed, some of them based on anecdotal observation like the present case. RCC is resistant to virtually all cytotoxic agents. Therefore, biologic agents, including cytokines, and, more recently, targeted agents, were studied in metastatic RCC. Interferon-alpha and interleukin-2 have only a moderate effect on the natural course of metastatic RCC. In randomized clinical trials, administration of interferon-alpha resulted in survival benefit of few months [3]. The use of interleukin-2 in metastatic RCC is based on demonstration of a durable complete response in a minority of patients [4]. Targeted agents (multiple tyrosine kinase inhibitors sunitinib and sorafenib, anti-VEGF antibody bevacizumab and mammalian target of rapamycin inhibitor temsirolimus) were first introduced as second line agents in patients failing cytokine therapy, but have now also significant role in the first line setting.

Although tyrosine kinase inhibitors and bevacizumab may be superior to cytokines in efficacy in metastatic RCC, these agents are still not curative. Immune system may play an important role in determining the outcome of metastatic RCC. Durable complete response has been observed in patients treated with interleukin-2. Durable responses were also observed in patients treated with allogeneic non-myeloablative transplantation, and these responses could be maintained by donor lymphocyte infusions [5]. VEGF plays an important role in the pathogenesis of RCC, and most new agents used in metastatic RCC target also the VEGF pathway [2]. VEGF has an inhibitory effect on adaptive immune response. VEGF has been shown to inhibit the function of lymphocytes and dendritic cells, and anti-VEGF therapy has lead to augmentation of antitumor response in experimental animals [6].

Immune mechanisms also play a crucial role in the pathogenesis of psoriasis [7]. The exacerbations of psoriasis are known to be triggered by infections or medication. To our best knowledge the present case

could be the first description of a relation between the activation of psoriasis and spontaneous regression of metastases. Similar observation has recently been reported in a patient with rheumatoid arthritis and marginal zone B cell lymphoma treated with infliximab and methotrexate [8]. In that case spontaneous remission was noted after the withdrawal of infliximab and methotrexate. Allogeneic hematopoietic stem cell transplantation may be viewed as adoptive immunotherapy, and is frequently accompanied by graft-versus-host disease. A case of graft-versus-host disease manifesting as with psoriatic skin lesions has been described [9]. We can only speculate about the mechanism(s) of association between the course of psoriasis and metastatic RCC in the present patient. T lymphocytes isolated from psoriatic lesions exhibit cross reactivity to microbial and self antigens [7]. It is possible that similar cross reactivity exists between the putative tumor antigens responsible for tumor rejection and autoantigens in the skin, but this hypothesis remains speculative. The risk of cancer may be increased in patients with psoriasis, possibly as the result of therapy [10], but increased incidence of RCC has not been observed and RCC is a rare event in patients with psoriasis.

In conclusion, this case report presents further indication that immune response may play a role in spontaneous regression of RCC metastases after nephrectomy.

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References

[1] Lokich J. Spontaneous regression of metastatic renal cancer: Case report and literature review. Am J Clin Oncol 1997;20: 416–8.

[2] Rini BI, Small EJ. Biology and clinical development of vascular endothelial growth factor-targeted therapy in renal cell carcinoma. J Clin Oncol 2005;23:1028–43.

[3] Medical Research Council Renal Cancer Collaborators. Interferon-alpha and survival in metastatic renal carcinoma: Early results of a randomised controlled trial. Lancet 1999;353:14–7.

[4] Fisher RI, Rosenberg SA, Sznol M, Parkinson DR, Fyfe G. High-dose aldesleukin in renal cell carcinoma: Long-term survival update. Cancer J Sci Am 1997;3:S70–2.

[5] Yun T, Lee KW, Song EG, Na II, Shin HC, Yoon SS, et al. Non-myeloablative allogeneic stem cell transplantation for metastatic renal cell carcinoma. Clin Transplant 2007;21: 337–43.

[6] Gabrilovich DI, Chen HL, Girgis KR, Cunningham T, Meny GM, Nadaf S, et al. Production of vascular endothelial growth factor by human tumors inhibits the functional maturation of dendritic cells. Nat Med 1996;2:1096–103.

[7] Sabat R, Philipp S, Hoflich C, Kreutzer S, Wallace E, Asudullah K, et al. Immunopathogenesis of psoriasis. Exp Dermatol 2007;16:779–98.

[8] Thonhofer R, Gaugg M, Kriessmayr M, Neumann HJ, Erlacher L. Spontaneous remission of marginal zone B cell lymphoma in a patient with seropositive rheumatoid arthritis after discontinuation of infliximab-methotrexate treatment. Ann Rheum Dis 2005;64:1098–9.

[9] Matsushita T, Hasegawa M, Shirasaki F, Fujimoto M, Yamazaki H, Sato S, et al. A case of acute cutaneous graft-versus-host disease mimicking psoriasis vulgaris. Dermatology 2008;216:34–67.

[10] Hannuksela-Svahn A, Pukkala E, Laara E, Poikolainen K, Karvonen J. Psoriasis, its treatment, and cancer in a cohort of Finnish patients. J Invest Dermatol 2000;114:587–90.

The reverse side of the victory: Flare up of symptoms after discontinuation of sunitinib or sorafenib in renal cell cancer patients. A report of three cases

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