Leukocytoclastic vasculitis during treatment with the oral EGFR tyrosine kinase inhibitor erlotinib

Erlotinib is a novel oral tyrosine kinase inhibitor targeting the epidermal growth factor receptor (EGFR). Skin reactions are a frequent side-effect of erlotinib therapy with various clinical manifestations such as papulo-pustular rash, xerosis, paronychia and hair changes [1]. We report two patients with advanced solid tumors who were diagnosed with a histologically confirmed cutaneous leukocytoclastic vasculitis occurring during treatment with erlotinib.

The first patient, a 67-year-old man with advanced hepatocellular carcinoma started treatment with single-agent erlotinib (150 mg daily) in February 2007 [2]. Previous treatment consisted of right hemihepatectomy, five cycles of transarterial chemoembolization treatment, radiotherapy and systemic chemotherapy with capecitabine. After 4 weeks of anti-EGFR treatment with erlotinib, the patient presented with purpuric lesions surrounding flat red-black areas of necrosis mostly located on his lower legs, clinically indicative of an immune complex vasculitis of the hemorrhagic-necrotic type (Figure 1A); no clinical signs of acneiform rash were obvious. A skin biopsy revealed a mostly perivascular lymphohistiocytic
infiltrate in the upper and lower plexus, mixed with many neutrophils, nuclear dust and some eosinophils as well as extravasal erythrocytes. Direct immunofluorescence revealed C3 complement and fibrinogen deposits around the vessels. Based on these findings, a histological diagnosis of leukocytoclastic vasculitis was made. Erlotinib was discontinued and oral prednisolone treatment (40 mg for 3 days and subsequently 30–20–10 mg from day 4 to 6) was started in combination with topical anti-infective therapy. The lesions cleared within 6 weeks without recurrence.

The second patient, a 70-year-old woman with metastatic pancreatic adenocarcinoma, started treatment with gemcitabine and erlotinib in February 2007 [3]. After 2 weeks on erlotinib (150 mg daily), an acneiform skin rash (limited to seborrhic areas like face and upper trunk) appeared. Another 3 weeks later, a different type of rash developed on both thighs, clinically indicative of allergic vasculitis (Figure 1B). Skin biopsy revealed leukocytoclastic vasculitis. Erlotinib was discontinued and the patient received the same treatment regimen with steroids as described above combined with topical therapy. The lesions cleared within 5 weeks without recurrence. Both patients did not show any sings of systemic vasculitis by clinical and laboratory examinations. An allergy work-up was offered, but both patients refused further diagnostic procedures.

Paraneoplastic vasculitis is a known phenomenon in patients with hematological and solid malignancies [4, 5]. Interestingly, both episodes of cutaneous leukocytoclastic vasculitis in our patients did not occur within (or even before) the first diagnosis of malignant disease, but during treatment with the anti-EGFR tyrosine kinase inhibitor erlotinib. Cutaneous drug eruptions develop frequently in patients receiving EGFR-targeting drugs [1], but we are unaware of any report on cutaneous vasculitis syndromes in association with erlotinib therapy to date. Based on the molecular mechanisms of EGFR-targeting agents and the observed correlation in time, a causal relationship between the leukocytoclastic vasculitis and erlotinib treatment appears probable in both patients. We therefore strongly recommend further preclinical and clinical investigation of this syndrome in order to improve the classification, diagnosis and treatment of erlotinib-associated skin reactions.

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Figure 1. (A) Hemorrhagic-necrotic type leukocytoclastic vasculitis in a patient treated with erlotinib for advanced hepatocellular carcinoma. (B) Leukocytoclastic vasculitis in a patient receiving treatment with gemcitabine and erlotinib for metastatic pancreatic cancer (right thigh).