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CASE REPORT

Erlotinib-Induced Episcleritis in a Patient with Pancreatic Cancer

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ABSTRACT

Context Erlotinib is a relatively new anilinoquinazoline indicated for treatment of pancreatic cancer in combination with gemcitabine. It is a tyrosine kinase inhibitor that specifically targets epidermal growth factor receptor (EGFR), which is commonly overexpressed and/or mutated in solid tumors. Active competitive inhibition of adenosine triphosphate, inhibits downstream signal transduction of ligand dependent EGFR activation. EGFR kinase inhibitors are less toxic than conventional chemotherapy as they are relatively specific for tumor cells. Common side effects include acneiform (papulopustular) rash, diarrhea, edema, pruritus, dry skin and alopecia.

Case report This article reports the case of a 55-year-old Caucasian female with recurrent pancreatic cancer who developed episcleritis after seventeen days of treatment with erlotinib. Symptoms completely resolved four weeks after drug discontinuation.

Conclusions To our knowledge, erlotinib-induced episcleritis has not been previously described.

INTRODUCTION

Pancreatic carcinoma is an unusually lethal disease with an annual incidence rate almost identical to the mortality rate. Cancer of the exocrine pancreas is the fourth most common malignancy in the United States. Gemcitabine, the current standard of care in first line treatment, was approved based on a relatively dramatic improvement in clinical benefit response (24% *versus* 5%) but median survival was only modestly improved from 4.4 months to 5.6 months [1]. Unfortunately, combination therapy with other cytotoxic agents has either failed to provide significant benefit or has done so at the expense of intolerable toxicities. The epidermal growth factor receptor (EGFR) is known to be over-expressed in pancreatic cancer and there are data to suggest that this molecular characteristic may be a poor prognostic factor as it may denote a more aggressive form of the disease. Current therapeutic modalities to target the EGFR include monoclonal antibodies directed against the extracellular domain of the receptor as well as tyrosine kinase inhibitors that disable the activating portion of the receptor. The combination of gemcitabine and one of the tyrosine kinase inhibitors, erlotinib, is the first combination therapy to demonstrate survival benefits in pancreatic cancer in a phase III study [2]. Although the gain in survival was statistically significant, it is unclear whether the modest, two-week improvement in survival is clinically meaningful. Erlotinib is a relatively new anilinoquinazoline indicated for treatment of pancreatic cancer in combination with gemcitabine. It is a tyrosine kinase inhibitor that specifically targets EGFR, which is commonly overexpressed and/or mutated in solid tumors [3]. Active competitive inhibition of adenosine tri-phosphate (ATP) inhibits downstream signal transduction of ligand dependent EGFR

activation [4]. EGFR kinase inhibitors are less toxic than conventional chemotherapy as they are relatively specific for tumor cells. Common side effects include acneiform (papulopustular) rash, diarrhea, edema, pruritus, dry skin and alopecia [5]. This article reports the case of a 55-year-old Caucasian female with recurrent pancreatic cancer who developed episcleritis after seventeen days of treatment with erlotinib. Symptoms completely resolved four weeks after drug discontinuation. To our knowledge, erlotinib-induced episcleritis has not been previously described.

CASE REPORT

A 55-year-old Caucasian female with past medical history of hypertension presented with obstructive jaundice and was found to have pancreatic head mass at the beginning of 2006. She underwent Whipple surgery and was staged as T1N1 with 3/13 lymph nodes positive. Both perineural and lymphovascular invasion were identified and the lesion was felt to be infiltrative and in very close proximity to the retroperitoneal margin. As an adjuvant therapy, the patient received gemcitabine plus oxaliplatin (GemOx) but developed sensory neuropathy. Therefore, regimen was switched over to gemcitabine-capecitabine. The patient finished a total of 12 cycles, with no further severe side effects to the chemotherapy. One year after diagnosis, her CA 19-9 was increasing, and an MRI confirmed several enhancing lesions along the surface of the liver, as well as in the peritoneum, with the largest in Morrison's pouch, measuring 2 cm. She was restarted on chemotherapy with single-agent docetaxel at 25 mg/m^2. Two months later, the patient had a CT scan which showed disease progression. She was started on erlotinib in addition to docetaxel. Erlotonib was increased from 100 mg to 150 mg daily after two weeks due to lack of rash (a sign of response).

Three days following dose increase, the patient developed a localized area of erythema and tenderness at the peripheral aspect of the right eye. Closer examination revealed patches of white sclera interspersed with radially coursing, dilated episcleral vessels (Figure 1). Scleral hue was absent and there was no involvement of the palpebral conjunctiva. The patient denied severe ocular pain, photophobia, morning crusting, or severe discharge. There was no history of ocular medications, granulocyte-macrophage colony-stimulating factor (GM-CSF) therapy or exposure to irritants/allergens. Pupils, visual fields, visual acuity, motility, and fundus examination were otherwise within normal limits.

Topical steroids were initiated to reduce the inflammatory response. In an attempt to reduce toxicity, we reduced the erlotinib regimen from 150 mg to 100 mg daily. Symptoms improved with supportive care and

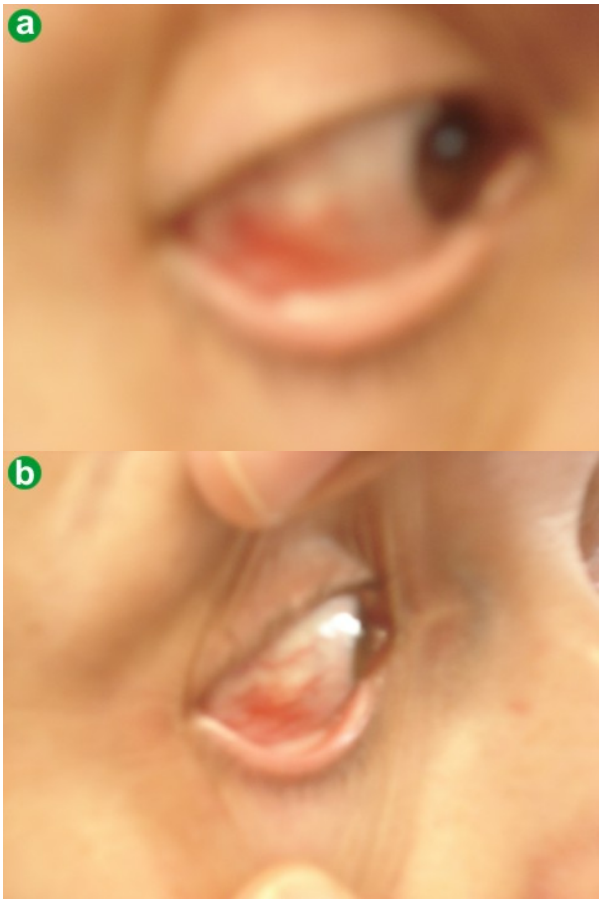

Figure 1. A detailed ophthalmologic examination revealed a visual acuity of 0.6 sine correction on both eyes. Ocular tension was 12 mmHg on the right eye and 10 mmHg on the left. The upper and lower eyelids were slightly swollen, the conjunctiva and episclera were locally reddened at 7 o'clock on both eyes (right more than left), and the cornea and other parts of the eyes were inconspicuous.

dose reduction. Erlotinib was again increased to 150 mg. She completed an additional cycle of 4 weeks with erlotonib and docetaxel with slight flare but no significant worsening of episcleritis. Restaging scans in August 2007 indicated progression of disease and docetaxel-erlotinib were discontinued. Topical steroid treatment was continued and ocular inflammation completely resolved within four weeks of drug cessation.

DISCUSSION

The mechanism by which erlotinib causes systemic or ocular side effects has not been fully characterized. Suppression of EGFR activity within normal tissue likely plays a central role, as side effects tend to affect sites where EGFR is known to be expressed. Sites include sebaceous glands, hair follicles, basal epidermal cells and the capillary system [6]. The episclera may be particularly susceptible due to the high concentration and resolution of the capillary system in this region.

Bilateral periorbital rash and eyelid ectropion has previously been reported with erlotinib. However, localized episcleral inflammation without systemic manifestation, as seen in our patient, has not been previously described [7]. Resolution of symptoms occurred with cessation of therapy. This is opposed to dermatologic side effects which typically respond to topical anti-inflammatory drugs or tetracyclines [8].

Docetaxel is a semisynthetic taxane indicated for the treatment of advanced breast, prostate, and non-small cell lung cancers; it is also used for the treatment of various other solid tumors. Myelosuppression, asthenia and peripheral neuropathy are the major toxicities [9]. Only known ophthalmic toxicity associated with docetaxel is epiphora - defined as excess tearing due to narrowing or blockage of the lacrimal outflow passages. Epiphora is associated with repeated weekly administration of docetaxel. Our patient has all clinical findings of episcleritis further excluding the role of docetaxel and strengthening the association with erlotinib [9].

Data suggest there is a positive relation between the development of a skin rash and treatment response. Further investigation of ocular response as an indicator of effectiveness and consequences of early termination will help maximize potential benefit from erlotinib use [6].

This case report describes a previously unrecognized ocular side effect of erlotinib. As a relatively new anti-neoplastic agent with increasing use for cancer therapy, it is essential to identify and manage its adverse effects. Episcleritis should be treated conservatively with topical anti-inflammatory drugs and cessation of erlotinib. Systemic treatment can be attempted if medication can not be discontinued.

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Abbreviations EGFR (alias: HER1, ErbB, ErbB1): epidermal growth factor receptor (erythroblastic leukemia viral (v-erb-b) oncogene homolog, avian) - *Homo sapiens*

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