



# HOLY C.O.W.!

**IT'S...**

**Clinical Question of the Week #5  
July 28th, 2008 through August 4th, 2008**

Please e-mail your answers to Kuo, Tim, Wendy, and Kevin ([klian@mednet.ucla.edu](mailto:klian@mednet.ucla.edu); [tprovias@mednet.ucla.edu](mailto:tprovias@mednet.ucla.edu); [wsimon@mednet.ucla.edu](mailto:wsimon@mednet.ucla.edu); [kbreger@mednet.ucla.edu](mailto:kbreger@mednet.ucla.edu)) by 0800 on Monday, August 4<sup>th</sup>, 2008. The resident or intern with the most correct answers at the end of each month will receive a prize!

**Case:** A 50-year-old man presents with new onset of rash appearing over his chest, back, and face which has been worsening over the past several weeks (Figures 1a, 1b, and 1c below). The rash has also been associated with burning sensation and intense itching. A neighbor had recently seen the patient working in the yard on his garden, and told him to be evaluated because she thought he "had the pox." The patient's medical history is notable for metastatic colon cancer which was refractory to the first-line FOLFOX regimen, but had responded to second-line therapy, as well as a history of hernia repair. He smokes four cigarettes weekly, but does not drink. He had traveled recently to Bakersfield, but had not recently changed his soaps, shampoo, or detergent.



**Figure 1a**



**Figure 1b**



**Figure 1c**

A similar 50-year-old man with a similar story who also had an ancillary procedure as part of his treatment had the following rash (Figure 2).



**Figure 2**

However, a third 50-year-old man with a similar story had received a different protocol and ancillary procedure and had a different rash appearance (Figure 3).



**Figure 3**

#### **Questions:**

**1. What is the cause of the rash? What is unique regarding the extent of the rash?**

The patient received cetuximab (Erbix, an EGFR inhibitor in the form of a chimeric monoclonal antibody) as part of his second-line therapy for his colon cancer. Cetuximab specifically binds to the EGFR on tumor and healthy cells, thus inhibiting the binding of epidermal growth factor and other ligands.

Because EGFR is expressed constitutively in many healthy epithelial tissues, particularly skin and hair follicles, dermatologic toxicity in varying degrees is quite common with administration of the drug, occurring in up to 50-90% of patients receiving the drug. The eruption is an acneiform rash, named as such for the erythematous papulopustular eruption, but actually has nothing to do with acne or a prior history of acne as it has no relation to infection of follicles. Areas affected include the face, scalp, upper chest, and upper back, and resolve with cessation of the drug.

Eruption usually occurs in the first two weeks after initiation of therapy, and may have a waxing and waning course. The severity of the rash has been demonstrated to positively correlate with tumor response, a finding that has also been demonstrated with erlotinib (Tarceva) and to a lesser extent gefitinib (Iressa), both small molecules that inhibit EGFR. Notably, it has also been demonstrated that the rash may have a very profound impact

on the patient resulting in depression, low self-image, and social isolation. (0.5 for ID cause, 0.5 for tumor correlation).

**2. Name three associated symptoms/signs.**

Additional dermatologic effects of cetuximab include the possible development of paronychia, a painful inflammation of the proximal and lateral nail folds of toes and fingers, with the thumbs and great toes more commonly affected. Unlike the skin rash, this condition does not abate with continued therapy, and for some individuals, the areas do not completely heal for several months after the discontinuation of cetuximab. Xerosis and painful skin fissures are common with therapy.

Hair changes may occur 2-3 months after initiation of therapy, with thinning and dry, brittle texture. Trichomegaly, increased hair growth of the eyelashes and eyebrows, is rare but may occur and may also result in corneal irritation if ingrowing. Telangiectasia is noted to occur, as is nasal mucositis. Finally, ocular irritation including dry eyes and irritation of the eyelid follicles resembling blepharitis can occur. (1)

**3. How is the condition treated?**

While a grading system exists for rash severity, it is not entirely clinically relevant. Treatment of mild rash may include topical emollients and moisturizers. The use of benzoyl peroxide and retinoids has been debated, as has the use of topical corticosteroids, which may be used in settings of severe inflammation. Antipruritics are used for pruritis associated with the rash. Antibiotic ointments, such as those used in the treatment of acne do not have effect. If there is overlying superinfection of the skin, often a tetracycline is given. Sun exposure should be limited. Dose reduction is used in severe forms of the rash. (0.5)

**4. What is the cause of the varying findings in the three different patients depicted above?**

Radiation therapy given concomitantly with cetuximab may result in severe exacerbation of radiation dermatitis combined with the pustular eruption related to the drug.

Interestingly, however, when a previous area has received radiation in the past, sparing of the rash may occur. The mechanism of this phenomenon is unclear, but may have to do with drug delivery to the irradiated area or possibly with the sensitivity of skin EGFR. It is also unclear if the correlation with tumor reduction is altered by this phenomenon. Notably, this phenomenon has also been observed with erlotinib as well. (0.5)