Immediate post-operative hypersensitivity reaction to Cetuximab in patients pre-operatively treated by the monoclonal antibody : what's wrong ?

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To the Editor,

Cetuximab, an anti-Epidermal Growth Factor Receptor (EGFR) monoclonal antibody, has been considered for years as an effective drug in metastatic colorectal cancer (mCRC). Three patients, median age 65, were treated in our institution for rectal well-differentiated adenocarcinoma associated with synchronous liver-only metastatic disease. Pre-operative treatment consisted in 6 cycles of FOLFOX (Oxaliplatin 85 mg/m^2 day 1, Elvorine 200 mg/m^2 day 1, bolus 5-Fluorouracil 400 mg/m^2 day 1 and continuous infusion 5-fluorouracil 2.4 g/m^2 for 46 hours, administered every 2 weeks), combined with Cetuximab given weekly (first dose 400 mg/m^2 in a 2-hours infusion, next doses 250 mg/m^2 in 1-hour infusion, with Dexamethasone and anti-histamine drugs given as pre-medication). Chemotherapy was followed by short course radiation therapy (25 Gy in 5 fractions). Primary tumour and liver metastases were then completely removed and followed by 6 other cycles of FOLFOX-Cetuximab. Whereas no reaction to Cetuximab were observed during the first 12 administrations, the 3 patients developed a very acute allergic reaction combining generalized pruritus, skin and palmo-plantar rash (Fig. 1) as well as dyspnea during first post-operative cetuximab administration, despite adapted therapy with corticosteroids and anti-histamine drugs. Cetuximab was immediately stopped leading recovery from the side effects. Skin reactions recurred during the next 2 administrations, leading to definitely suspend Cetuximab infusion in one patient. The 2 other patients completed their scheduled post-operative treatment. When reviewing patients' files, no history of allergy was found. On the other hand, all patients had positive Gram negative bacterial infection during the immediate post-operative time, efficiently treated with antibiotics.

It is well recognized that infusion reactions related to Cetuximab occur during the first administration in almost all treated patients, with less than 5% of critical hypersensitivity reactions (HIRs) (1).

Chung *et al*. recently demonstrated a strong correlation between HIRs to Cetuximab and the presence of IgE antibodies against galactose-α-1,3-galactose (α-gal), an oligosaccharide present on both Fab segments of the molecule (2). The IgE antibodies sensitize mast cells located on cutaneous and mucosal surfaces as well as on circulating basophils, inducing the clinical symptoms encountered when allergic reactions occur (3). They demonstrated that most of the HIRs to Cetuximab were observed in patients having such IgE antibodies before treatment with Cetuximab. The reason why patient develop IgE antibodies against the oligosaccharide is not well established. The triggering mechanism might be infectious, as hypothesized by Chung *et al*. (2). O'Neil *et al*. also believed that the pre-existing antibodies might arise from cross-reactivity with a plant or pollen antigen since they found a strong relationship between HSRs and a prior allergy history (4).

It is of interest that most of observed allergic reactions described in the literature occurred during first Cetuximab administration, contrasting with our cases where patients developed their allergic reactions when the drug was reintroduced after surgery (13th administration).

Based upon Chung hypothesis, and founded on our findings, we assume that our patients have been exposed to gram negative intestine bacterial translocation during the peri-operative time, leading to α-gal exposure to masts cells producing anti- α-gal IgE, responsible for the high IgE levels associated with clinical hypersensitivity reaction observed in our patients.

Some authors support the hypothesis that bacterial products can be translocated from the intestinal tract into the circulation. One such study demonstrates serologic evidence that IgG and IgM antibodies to peptidoglycan are elevated in the sera of rheumatoid arthritis and juvenile rheumatoid arthritis patients, suggesting that immunogenic bacterial peptidoglycan complexes can be systemically translocated in humans (5).

Furthermore, Hamadeh *et al*. demonstrated that gram negative bacterial gut translocation could lead to de novo expression of the α-gal on human red blood cells, leading to their senescence (6).

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Submission date : 11/01/2011
Acceptance date : 07/07/2011

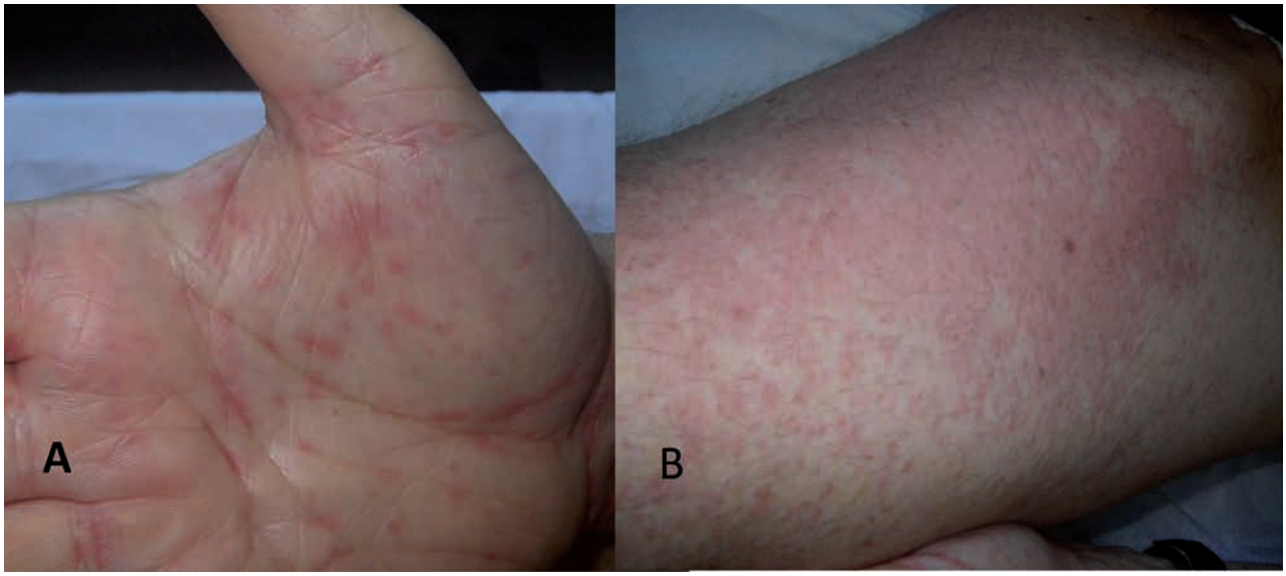

Fig. 1. — Palmoplantar (A) and cutaneous (B) rash when Cetuximab was re-administered after surgery

Based upon these observations, we recommend to clinicians to be extremely cautious when prescribing Cetuximab post-operatively, especially when Gram negative infection during the peri-operative time has been demonstrated.

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