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# Effective treatment of a platinum-resistant cutaneous squamous cell carcinoma case by EGFR pathway inhibition

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**Abstract.** Cutaneous squamous cell carcinoma (cSCC) is the second most common type of non-melanoma skin cancer. Platinum-based regimens have been an integral part of palliative care for patients with locally advanced or metastatic disease. There is no evidence of efficacy for later lines of chemotherapy and no targeted therapy has been introduced as 'standard of care'. Here we report on the case of an elderly cSCC patient, resistant to conventional therapy, however successfully treated with anti-epidermal growth factor receptor (EGFR) agent (Cetuximab) in addition to a daily dose of Curcumin phospholipid. The patient responded to treatment and experienced no recurrence for 11 months with only minor skin-related toxicity. To our knowledge, this is the first report of clinical evidence that an anti EGFR targeted therapy with a daily oral dose of Curcumin phospholipid is well tolerated and results in a highly effective disease control in a heavily pretreated cSCC patient.

## Introduction

Cutaneus Squamous Cell Carcinoma (cSCC) is a common malignancy in elderly, representing nearly 25% of non-melanoma skin cancers. Its incidence is continuously rising due to aging population and increased ultraviolet exposure (1).

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Platinum-based combination therapies demonstrated high efficacy in the locally advanced or metastatic settings. However, they are not always able to guarantee durable responses (2), highlighting the need to assess new therapeutic options, especially for the recurrent disease no more amenable to surgery.

So far, no targeted therapy has been introduced as 'standard of care' for cSCC. However, multiple studies have reported deregulation of the EGFR-signaling cascades (RAS-MAPK and PI3K-AKT-mTOR axes) and/or other pathways (i.e., Notch, p53, CDKN2A) (3,4). A recent comprehensive genomic profiling of 315 cancer genes in 122 cSCC cases showed that 88% harbored at least one clinically relevant mutation, with an average of 2.5 actionable genomic alterations per patient (5). Thus, conventional and unconventional deregulated pathways eventually amenable for therapeutic intervention are being found also in cSCC. In example, anti-EGFR monoclonal antibodies have been used in platinum-resistant advanced cSCC patients with clinical benefit and improved toxicity profiles (6).

Curcumin is a dietary polyphenol derived from the root of the plant Curcuma Longa, which has been shown to possess anti-inflammatory and anti-cancer activities both *in vitro* and *in vivo* (7,8). *In vitro*, it causes cell growth inhibition and/or apoptosis in multiple cancer cell models (9) and has been reported to inhibit several cancer-related pathways such as PI3K-AKT-mTOR and EGFR axes (10). In particular, Curcumin demonstrated to reduce the invasion and adhesive abilities of cSCC A431 cells by the inhibition of Signal Transducer and Activator of Transcription 3 (STAT3) activation (11). Furthermore, Phillips *et al* reported that Curcumin was able to significantly reduce cSCC tumor progression *in vivo* by inhibiting S6 phosphorylation and, as a consequence, the mTOR pathway (12).

Here we report the first description of an elderly cSCC patient, resistant to conventional treatments, but successfully responding to an anti-EGFR pathway inibition with a 'chemo-free' combination of Cetuximab with a daily oral dose of Curcumin phospholipid supplement.

### Data collection methods

*DNA extraction*. DNA was extracted from Formalin-Fixed and Paraffin-Embedded (FFPE) tumor tissue, obtained by skin lesion biopsy. Xylene was added once and ethanol was added twice to remove all paraffin from the tissue sample. The DNA was extracted using QIAamp DNA FFPE Tissue kit (Qiagen GmbH, Hilden, Germany) according to the manufacturer's instructions (13). Eluted DNA was quantified with Qubit 2.0 Fluorometer (Thermo fisher).

*IT-PGM sequencing and variant calling*. Approximately 10 ng of DNA was required to construct the barcoded and adaptor-ligated library using the Ion AmpliSeq Library Kit 2.0 (Thermo fisher). The sample was analysed using the Ion AmpliSeq Colon and Lung Cancer Research Panel V2 containing a single primer pool to amplify hotspots and targeted regions of 22 cancer genes frequently mutated in CRCs and NSCLCs (https://www.ampliseq.com). Templated spheres were prepared using 100 pM of the library using the Ion One Touch 2.0 machine. Template-positive spheres were loaded into Ion chip 314 and sequenced by IT-PGM machine (Thermo fisher). Sequencing data were finally analysed with Coverage Analysis and Variant Caller plugins available within the Ion Torrent Suite software. Variants with a quality <30 were filtered out. Sequence reads were finally visualized with IGV tool using HG19 as reference genome to direct inspection of mutations.

### Case report

An 83 years old Caucasian male patient was admitted in our oncology department on March 2016 for recurrent cSCC of the supraclavicular region. The patient had been previously treated with a platinum-based chemotherapy regimen (Carboplatin AUC4-5-Fluorouracil, 750 mg day 1-5; q21-3 cycles) with neoadjuvant intent. After an early locoregional disease progression, he had debulking surgery followed by locoregional radiotherapy. More specifically, the patient underwent radical ipsilateral neck dissection with resection of the sternocleidomastoid muscle, the spinal accessory nerve, the whole collarbone and the internal jugular vein, required to remove the vast (m.d. 15x8 cm) lesion infiltrating the underlying tissue. The pathology report confirmed the diagnosis of poorly differentiated cSCC obtained at the time of first biopsy and revealed bone infiltration.

After 9 months, a head and neck MRI revealed a locoregional disease progression characterized by a 6.4x3.6 cm nuchal lesion and a 10.5x4.8 cm lesion in the supraclavicular region having a cranium-caudal extension of 15 cm. The tumor had also infiltrated the left paravertebral muscle, the left parotid gland and the lax cellular tissue of the supraclavicular region. An increase in cervical, submandibular and nuchal lymph nodes dimension was also detectable. Moreover, the supraclavicular 10 cm lesion appeared ulcerated at the medical examination (Fig. 1A).

Given the extent of disease and its lack of response to previous treatments, a new systemic therapy appeared

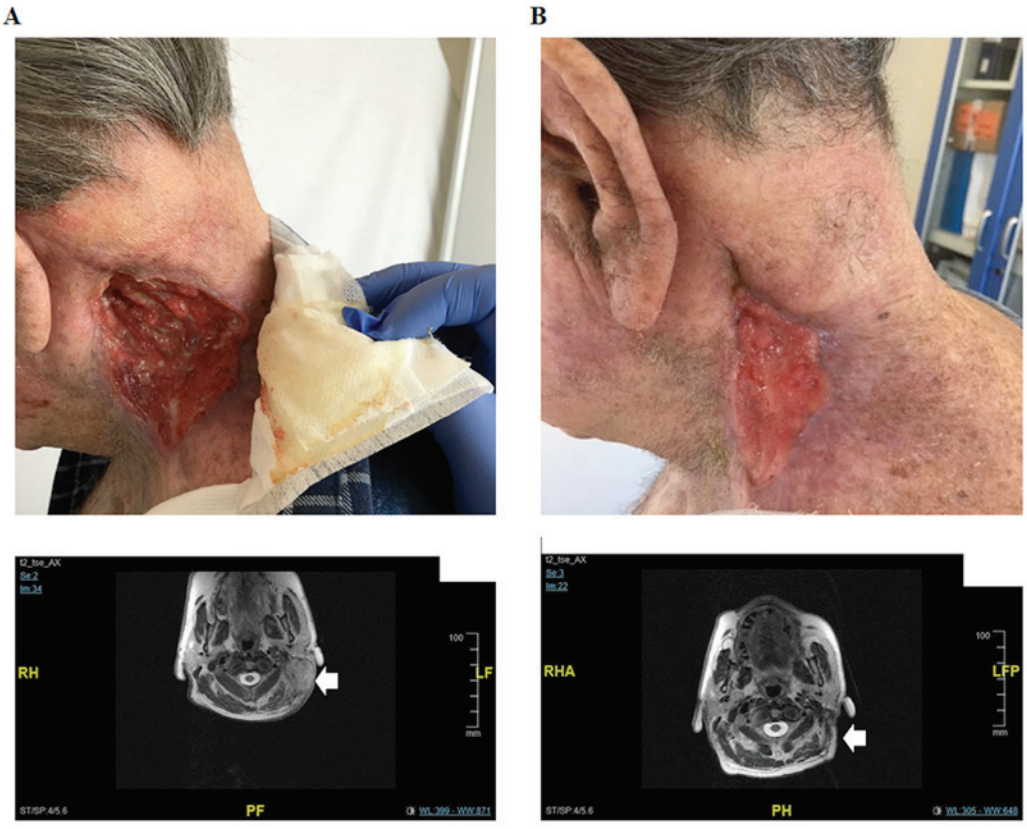


Figure 1. Lesion and MRI of the patient before and after cetuximab-curcumin treatment for recurrent cSCC of the supraclavicular region. Tumor masse (arrow) can be seen in the nuchal and supraclavicular regions of the patient before initiation of cetuximab-curcumin treatment. Moreover, the supraclavicular 10 cm lesion appeared ulcerated at the medical examination (A). The masse (arrow) became significantly reduced in size on MRI obtained 12 weeks after treatment (B), indicating good response to combination treatment.

Table I. Genetic variants found in the cSCC patient by IT-PGM sequencing.

| Gene[a] | Mutation[b] | AF[c] (%) | Relevance[d] | Prediction test[j] | (Refs.) |
|---|---|---|---|---|---|
| FGFR3 | c.1138G>A p.Gly380Arg (COSM24842) | 28.7 | Pathogenic[e,f] | | (23,24) |
| | c.1953G>A p.Thr651=(rs7688609) | 100.0 | Benign[e,g] | | |
| EGFR | c.1498+22 A>T (rs1558544) | 100.0 | NC[g,i] | NNSPLICE: Unchanged | |
| | c.2361G>A p.Gln787=(rs1050171) | 100.0 | Benign[e,g] | | |
| MET | c.534C>T p.Ser178Ser (rs35775721) | 67.2 | Benign[g] | | |
| MAP2K1 | c.174G>C p.Gln58His | 15.8 | Likely pathogenic[i] | PROVEAN: Deleterius; SIFT: Damaging; PolyPhen: Possibly damaging; CRAVAT: High pathogenicity cancer driver impact | |
| TP53 | c.743G>A p. Arg248Gln (COSM10662) | 21.1 | Pathogenic[e,f,h] | | (25-27) |
| | c.836_861del27 p.Gly279_Asn288delinsAsp | 31.1 | Likely pathogenic[i] | PROVEAN: Deleterius CRAVAT: High pathogenicity cancer driver impact | |
| | c.215 C>G p.Pro72Arg, (rs1042522, COSM250061) | 60.2 | Uncertain significance[e,f,i] | | (30) |
| | c.1-46C>T | 21.2 | NA | NNSPLICE: Unchanged | |

[a]The following 22 genes were analyzed: DDR2, NRAS, ALK, ERBB4, CTNNB1, PIK3CA, FBXW7, FGFR3, BRAF, EGFR, MET, FGFR1, NOTCH1, FGFR2, PTEN, KRAS, AKT1, MAP2K1, ERBB2, TP53, SMAD4, STK11. [b]Sequence variant nomenclature according to HGVS recommendations (http://varnomen.hgvs.org/); (COSMIC and/or dbSNP ID numbers). [c]AF: Variant allele frequency in the tumor sample. [d]Biological impact of the variant according to: [e]ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/); [f]COSMIC (http://cancer.sanger.ac.uk/cosmic); [g]dbSNP (https://www.ncbi.nlm.nih.gov/projects/SNP/); [h]IARC database (http://p53.iarc.fr/); [i]*In silico* prediction tests (see next column). [j]In silico prediction on the biological impact of the variant according to multiple software (PolyPhen-2, http://genetics.bwh.harvard.edu/pph2/; SIFT, http://sift.jcvi.org/; PROVEAN, http://provean.jcvi.org/index.php; CRAVAT, https://www.cravat.us/CRAVAT/; NNSPLICE, http://www.fruitfly.org/seq_tools/splice.html.

necessary for the patient. In order to consider alternative treatment opportunities dictated by tumor biology, we evaluated the mutational profile of the tumor at the time of the latest progression. DNA was extracted from FFPE tumor tissue, obtained by skin lesion biopsy. This was sequenced on an Ion Torrent PGM platform by the Ion AmpliSeq Colon and Lung research Panel V2. The tumor sample showed no mutation in most relevant EGFR signal transducers. In contrast, it harbored pathogenic mutations in the FGFR3 and TP53 genes and a likely pathogenic mutation in the MAP2K1 gene (Table I).

The lack of other established therapeutic alternatives, the positive results obtained by a recent phase II Study (14) employing Cetuximab and the absence of mutations on major components of the EGFR signal transduction pathway met the ethical constraints of a tailored therapy, and prompted us to propose an off-label Cetuximab-based combination treatment.

Based on its known anti-inflammatory and anti-tumor properties and in consideration of its ability to inhibit cancer-related pathways, in this particular case we added a daily supplementation of oral Curcumin phospholipid (Meriva, 500 mg orally once daily) to the conventional Cetuximab schedule (400 mg/mq, followed by subsequent weekly doses of 250 mg/mq). The protocol was approved by the institutional review board (Ospedale Sant'Andrea, Sapienza University of Rome) on March 2016, and the patient provided written informed consent. Already after 4 weeks of this treatment, a significant clinical benefit was reported by the patient. In particular, the lesion's bleeding stopped and a 5 cm reduction in size was reported at the medical examination. After 12 weeks, a head and neck MRI confirmed the clinical response and showed an ~50% reduction of the lesions. The infiltration of the left parotid gland was no longer detectable and a dramatic regression in cervical, submandibular and nuchal lymph nodes was evidenced (Fig. 1B). Thus, the patient responded to treatment and experienced no recurrence for 11 months. After 12 weeks, no major therapy-related toxicity had been observed. On the contrary, treatment regimen had been well tolerated and patient complained only for minor skin-related toxicity (maximum grade 2 according to CTCAE version 4.0).

## Discussion

In recent years, given the limited efficacy of standard-of-care chemotherapy and radiotherapy for patients with locally advanced or systemic disease, several investigators have begun to study the genomic background of cSCC looking for novel actionable targets. In particular, the widespread employment of NGS techniques allowed to identify a large number of potentially actionable driver genes (15,16). As previously recognized for other tumors of epithelial origin, the

RAS-RAF-MEK-ERK and the PI3K/AKT branches acting downstream of RTKs such as EGFR are very frequently mutated/deregulated also in cSCC (17). Nonetheless, no targeted therapy options have entered the routine and wide use for patients with cSCC, yet (18,19). EGFR inhibitors should, in principle, be considered a valid therapeutic option also for cSCC, since EGFR seems to be overexpressed in a high proportion of primary tumors of this type, which acquire a metastatic phenotype (20). The absence of mutations in most relevant RTK-signal transducers revealed by our molecular profiling allowed us to offer the patient a therapeutic intervention based on Cetuximab (chimeric mouse-human anti-EGFR IgG1 monoclonal antibody). Initially approved for the treatment of advanced colorectal cancer, and subsequently employed in advanced or platinum-refractory Head and Neck Squamous Cell Carcinoma (HNSCC), Cetuximab monotherapy has also proved its efficacy and low toxicity profile in advanced and metastatic cSCC, as described in several case reports or case series (21,22).

In particular, in a recent prospective phase II trial carried out by Maubec *et al*, comprehensive of 36 patients, a 67% rate of 6-weeks disease control supported the use of single agent Cetuximab as first-line treatment for unresectable cSCC (14).

Nonetheless, the activation of alternative intracellular networks involved in the maintenance of the malignant phenotype could also limit the benefit of anti-EGFR treatment.

In our specific case, genetic profiling of the tumor tissue showed pathogenic mutations in FGFR3, TP53 and MAP2K1 genes. The p.Gly380Arg FGFR3 mutation has been reported in patients affected with achondroplasia, the most common form of human dwarfism (23), and in cancer patients (24). It causes an increased and ligand-independent phosphorylation of FGFR3 leading to constitutive activation of the downstream pathway, largely accounted for by MAPK and PI3K/AKT activity. Two different TP53 mutations coexisted in our cSCC case: The p.Arg248Gln is a known gain of function p53 mutation (25-27), while the p.Gly279_Asn288delinsAsp is a previously undescribed in-frame deletion which is predicted to be highly pathogenic. The low allelic frequency of both TP53 mutations suggests that both alleles of this gene might be destroyed in the tumor tissue. The MAP2K1 p.Gln58His mutation is also previously undescribed, but multiple prediction tools indicate it is most likely pathogenic (Table I). In principle, both the FGFR3 and the MAP2K1 mutations could have impaired the effect of anti-EGFR treatment, in this patient.

Interestingly, Curcumin is endowed with potent antinflammatory and cancer chemopreventive and therapeutic properties. Although the precise molecular mechanism of Curcumin action is far from being completely understood, it regulates the expression of several genes involved in cytokines production, cellular proliferation and cell survival (28), part of which are known TP53 targets.

Recent studies have pointed out that pharmacological doses of Curcumin can inhibit EGFR pathway in different squamous malignancies (8). Moreover, it has also been shown to enhance the inhibitory effect generated by drugs directly targeting EGFR, while also improving their toxicity profile (9). Preclinical evidences further indicated its ability to overcome anti-EGFR therapy resistance (29). All of these observations provided the rational for its use in combination with Cetuximab in the reported case. While we are aware that the description of a single cSCC case does not allow us to draw major conclusion on the possibility that Curcumin phospholipid oral supplement might potentiate the efficacy of the anti-EGFR treatment, it is important to notice that this strategy was well tolerated and resulted in a highly effective control of the disease in a heavily pretreated cSCC patient.

Based on our preliminary observation, we believe that the benefit of a combined anti-EGFR/Curcumin treatment on molecularly stratified cSCC patients should be further addressed with a specific clinical trial.

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**Availability of data and materials**

All data generated or analyzed during this study are included in this published article.

**Authors' contributions**

CC, CP, GG, MF and PM were involved in patient recruitment. FB, MP, VC, AT and AC were involved in sample preparation and sequencing. CC, FB, MS, PM, GG were involved in data analysis. CC, FB, MF, CP, MP, VC, AT, MS, AC, GG, and PM were involved in manuscript writing and editing.

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Written informed consent was obtained from the patient for the publication of this case.

**Competing interests**

The authors declare that they have no competing interests.

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