Case Report

Unresectable metastatic colorectal cancer patient cured with cetuximab-based chemotherapy: a case report with new molecular insights

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Abstract: Here we report the case of a 20-year-old patient who was diagnosed in 2002 with a metastatic colorectal cancer (CRC). He achieved a complete response under cetuximab-based therapy and remains without disease recurrence until now while chemotherapy was discontinued in 2009. The tumor exhibited high level of epidermal growth factor receptor (*EGFR*) amplification, no mutation in *KRAS*, *NRAS* or *BRAF* genes and a microsatellite-stable (MSS) phenotype. Intriguingly this young patient was carrying a monoallelic germline mutation of *MUTYH* that was associated with an inactivation of the second allele by loss of heterozygosity on tumor DNA. Moreover, this mutation was associated with a specific mutational signature on tumor level characterized by C > A single base substitutions and a higher mutational load than usually observed in MSS neoplasms. This case report paves the way for further researches on *MUTYH*-associated cancers' sensitivity to anticancer therapies.

Keywords: Epidermal growth factor receptor (*EGFR*); *MUTYH*; colorectal cancer (CRC); targeted therapy

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Introduction

Cetuximab-based chemotherapy is a standard of care for patients with RAS wild-type metastatic colorectal cancer (CRC) (1). However, it is not used as curative intent and the disease generally relapses or get progressive. Here we report the case of patient who remains in complete remission nearly 10 years after cetuximab discontinuation.

Case presentation

A 20-year-old Asian man, without a family history of cancer, was diagnosed in January 2002 with a locally advanced CRC. The evolution of his disease and treatments is summarized in *Figure 1*. In February 2002, he underwent a rectosigmoid resection and a lymphadenectomy of the aorto-iliac bifurcation. The pathological analysis found a poorly to moderately differentiated adenocarcinoma; sixteen nodes were collected, of which eight were metastatic with capsular rupture for five of them. The tumor was classified as pT4, N2, M0 with positive mesosigmoid sections. Twelve cycles of adjuvant chemotherapy with 5-fluorouracil (5FU) and oxaliplatin (i.e., FOLFOX) were administered from March to August 2002. At the end of treatment, carcinoembryonic antigen (CEA) and computerized tomography scan (CT scan) were normal.

In February 2003, the CT scan showed evidence of a hepatic and node recurrence: there was one 2 centimeters (cm) liver lesion (segment VII) and one adenopathy along the left iliac axis measuring 2.8 cm with node infiltration up to the origin of the external iliac artery. The patient

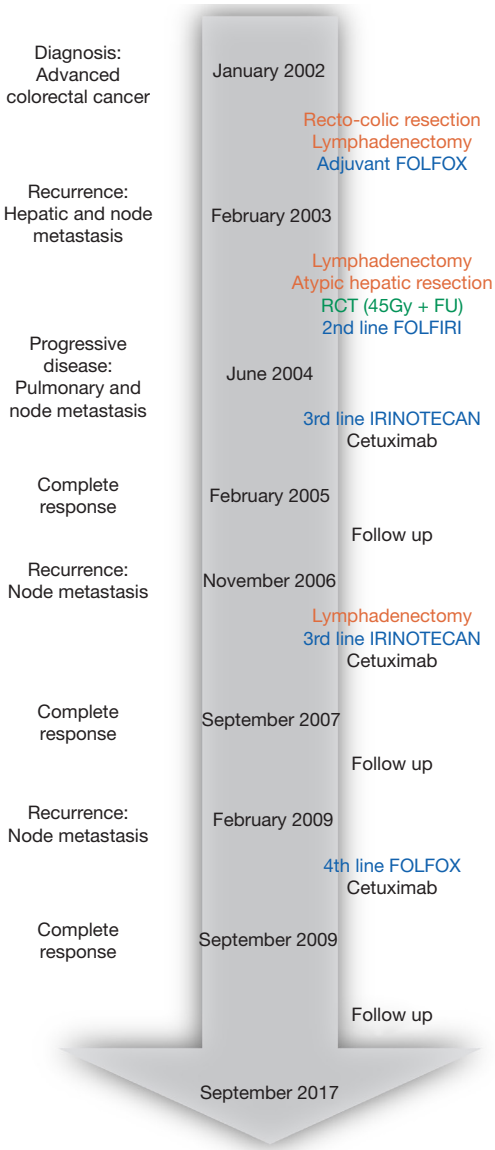

Figure 1 Timeline of the disease evolution. RCT, radiochemotherapy.

underwent a left ilio-inguinal lymphadenectomy with epiplo-plasty, and an atypic hepatic resection. The pathological analysis reported several metastatic lymph nodes and assessed the diagnosis of hepatic recurrence. Then, the patient had a radiochemotherapy from April to May 2003: 45 Gy on the left inguino-iliac volume, with additional 10 Gy to the tumor bed. Concurrent chemotherapy with 5FU as a continuous infusion was performed throughout the radiation treatment. Second-line chemotherapy with 5FU and irinotecan (i.e., FOLFIRI) was subsequently scheduled but discontinued after 4 cycles because of severe digestive side effects.

In June 2004, a second metastatic recurrence with lung metastasis and retroperitoneal lymph nodes was diagnosed on abdominal pain. Epidermal growth factor receptor (*EGFR*) expression was assessed in the recto-sigmoid tumor and in the node metastases and its expression was high. A third-line treatment with cetuximab was started in August 2004 at 400 mg/m^2 for the first injection, then 250 mg/m^2 every week (qw), associated with irinotecan 180 mg/m^2 every 2 weeks (q2w). Irinotecan was responsible for grade III diarrhea and was lowered to a 150 mg/m^2 dosing. Complete radiological and biological response was obtained in February 2005 and the treatment was stopped at this date, after 12 courses of cetuximab and irinotecan.

In November 2006, a disease progression of the retrocaval and lombo-aortic nodes was observed. Irinotecan (150 mg/m^2 q2w) and cetuximab (250 mg/m^2 qw) were started again from January 2007 using. After 5 cycles, the patient achieved a partial response, with complete regression of lung metastasis. In May 2007, a lombo-aortic and illiac lymphadenectomy was then performed. The pathological analysis found node metastases from colon cancer. CT-scan and CEA were normalized, and chemotherapy was discontinued after 3 post-operative courses in September 2007.

In February 2009, the patient was diagnosed with a fourth recurrence located in lombo aortic and pelvic nodes only. A FOLFOX regimen combined with cetuximab (250 mg/m^2 qw) was started from March 2009. After 5 cycles, there as evidence of partial response, and the treatment was continued with LV5FU2. By September 2009, the patient achieved complete response and treatment was stopped.

The last evaluation with clinical examination, CT scan and CEA dosing performed in September 2017 found no evidence of recurrence.

Extensive molecular characterization

An extensive molecular characterization of the patient's cancer was performed given its rare and dramatic sensibility to *EGFR*-targeted therapy. We performed whole exome sequencing from fresh frozen tumor sample and adjacent normal tissue. We also assessed the microsatellite status of the tumor cells using Pentaplex panel. Finally, we determined the copy number variation of tumor cells of the primary tumor and the metastatic iliac lymph node by genotyping 250,000 single nucleotide polymorphisms

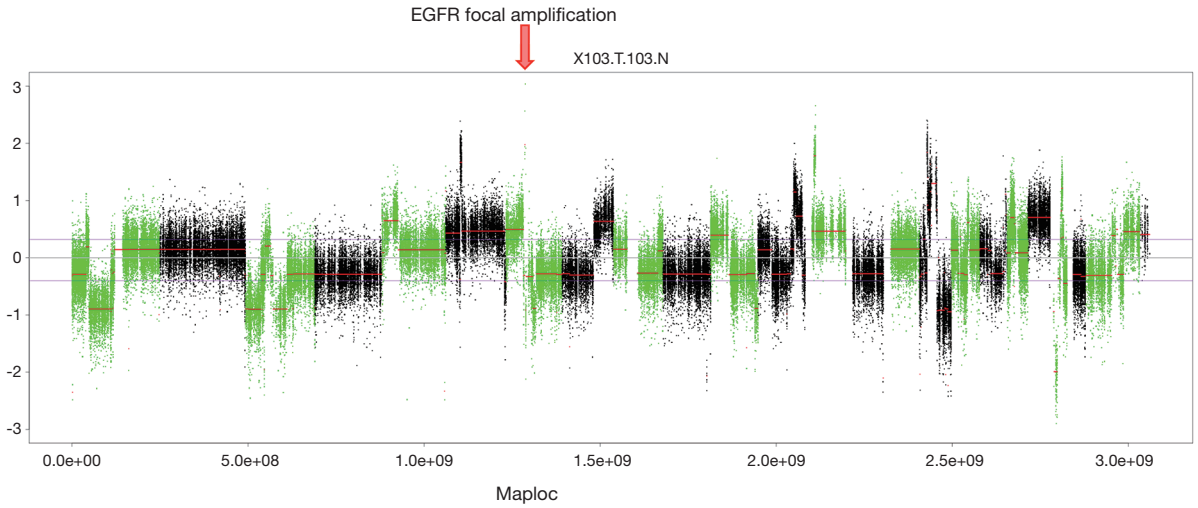

Figure 2 Copy number variation of single-nucleotide polymorphisms detected in patient between tumor to normal DNA. Red arrow shows the focal amplification of *EGFR* gene.

(SNPs) on tumor and normal DNA using GeneChip Human Mapping 250K Sty Array (Affymetrix, Santa-Clara, CA, USA).

The patient tumor was found *KRAS*, *NRAS*, *PIK3CA* and *BRAF* wild-type with a microsatellite-stable (MSS) phenotype. Extended SNPs genotyping revealed that *EGFR* gene was highly amplified (more than 70 copies) (*Figure 2*). No difference in copy number variation was observed between the primary tumor and the iliac lymph node resected two years later.

Searching for a familial predisposition to cancer, the patient was found to carry a germline monoallelic inactivating *MUTYH* mutation at codon 156 (rs762307622, W156*, ExAC frequency in non-Finnish Europeans =0%); no mismatch repair gene germline mutation was found. Interestingly, following loss of the wild-type allele in tumor cells the mutation of the *MUTYH* gene became somatically homozygous. This biallelic *MUTYH* tumor mutation was associated with a mutational signature characterized by C > A single base substitutions and 164 non-silent single nucleotide variations (SNV).

Discussion

Here we report the case of a 20-year-old man who experienced a long-term complete response to cetuximab-based chemotherapy. The extensive characterization of his tumor revealed a high level of *EGFR* amplification, no mutation in *KRAS*, *NRAS*, *PIK3CA* and *BRAF* genes, but a monoallelic *MUTYH* germline mutation associated with an additional *MUTYH* inactivating mutation in tumor cells.

To the best of our knowledge, this is the first report of a nearly ten-years lasting complete response to cetuximab in a patient with metastatic CRC, even if several cases of complete responses to anti-*EGFR* therapy have been reported. Notably, Boudrias-Dalle *et al*. described the case of a patient with metastatic CRC who showed a complete response two years after panitumumab discontinuation; however no translational research for such a response was reported (2).

In 2004 cetuximab was demonstrated as clinically efficient in patients with CRC that expresses *EGFR* in both monotherapy and combination with irinotecan (3,4), given the rational for the use of cetuximab in our patient. *EGFR* expression using immunohistochemistry and *EGFR* gene copy number were initially suggested as potential biomarkers predictive for the efficacy of cetuximab (5). However, Lièvre *et al*. demonstrated that activating mutation in *KRAS* gene is the major mechanism of resistance to anti-*EGFR* antibodies, leading to the development of extended *RAS* mutational analysis (1,6). Nevertheless, it is worthy to note that an increased *EGFR* copy number was found in 3 patients among *KRAS*-wild type patients of Lièvre's cohort and that it was associated with an objective tumor response to cetuximab (P=0.04). Similarly, Yen *et al*. showed that *EGFR* overexpression remained predictor of clinical response among *KRAS* wild-type patients (7), maybe because of an enhanced ADCC (Antibody-Dependent Cell-mediated Cytotoxicity) (8). The complete long-term response observed in our patient might

be due to both the high-level amplification of *EGFR* and the absence of *RAS* mutation.

Our patient was found to carry a monoallelic mutation of *MUTYH* with an additional inactivation of the second allele by loss of heterozygosity in tumor cells. *MUTYH* is a DNA glycosylase involved in the repair of oxidative damage and has a role in base-excision repair system. Only a few data are published about monoallelic *MUTYH* germline mutation carriers. Notably there is no data about sensitivity of *MUTYH*-associated CRC to anticancer treatments. Biallelic loss-of-function *MUTYH* mutations predispose to familial CRC [i.e., *MUTYH* association polyposis (MAP)] through somatic G:C-T:A transversions in the adenomatous polyposis coli (APC) suppressive tumor gene (9). Lefevre *et al.* found that biallelic loss-of-function of *MUTYH* can lead to a loss of function of *MLH1* and a microsatellite instability (MSI) cancer phenotype (10). Moreover c.34G > T *KRAS* mutation is highly associated with *MUTYH*-associated CRC, through G:C-T:A transversions in *KRAS* exon 2 (11,12). In accordance to this work, we found that *MUTYH*-associated cancers are defined by a specific mutational signature characterized by an enrichment of C > A transversions and relatively high mutational load (also inferior to mutational burden of MMR-deficient tumors (13-15). Interestingly, our patient's tumor displayed a homozygous *MUTYH* mutation without *KRAS* or *MLH1* mutation, while he was carrying a monoallelic *MUTYH* mutation. To our knowledge this loss of heterozygosity phenomenon has never been reported in *MUTYH* monoallelic carriers. Although the literature is dramatically poor about the chemosensitivity and the immunogenicity of *MUTYH*-mutated CRC, we might hypothesize in the case of our patient that the elevated mutational burden participated to the impressive long-lasting remission through immune-mediated response.

Conclusions

We report the case of a young patient diagnosed with a metastatic CRC more than fifteen years ago who might have been cured by cetuximab-based chemotherapy, as this treatment was discontinued more than 8 years ago. Overexpression of *EGFR* might be the reason of his dramatic response to cetuximab. Plus, while little is known the clinical impact of *MUTYH* mutations, it may have contributed to such a chemosensitivity. Our report paves the way for further researches on both *MUTYH*-associated cancers chemosensitivity and immunogenicity.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Informed Consent: Written informed consent was obtained from the patient for publication of this Case Report and any accompanying images.

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