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Case Report

Tolerance and Long Term Efficacy of Cetuximab in Metastatic Squamous Cell Carcinoma of the Penis: Case Report and Literature Review

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Abstract: Squamous cell carcinoma of the penis is rare in daily practice. Epidermal growth factor receptor is widely overexpressed in this type of cancer. In a metastatic situation, chemotherapy has modest efficacy. Agents targeting this receptor, including Cetuximab, are effective as monotherapy or in combination with chemotherapy. The finding was fortuitous in the anatomopathological analysis of a resection specimen for phimosis. It progressed first to the inguinal lymph nodes 3 months after surgery and then rapidly to the lungs and liver after the first line of chemotherapy. Cetuximab monotherapy in the second line of therapy was well tolerated and showed a complete response after 6 months of treatment. This response has been maintained for 5 years of treatment. The efficacy of agents targeting the Epidermal Growth Factor Receptor in squamous cell carcinoma of the penis opens the way to therapeutic optimization.

Keywords: Squamous cell carcinoma, penis, Epidermal growth factor receptor, EGFR, Cetuximab, Case Report, Orleans, France.

BACKGROUND

Penile cancer is a rare disease in developed countries and France. The most common histological type is squamous cell carcinoma [1], with a moderately high level of EGFR expression [2]. Given the limited efficacy of chemotherapy, recent scientific data have demonstrated an interest in anti-EGFR agents, in particular Cetuximab. We, therefore, report the only case of squamous cell carcinoma of the penis treated in our Medical Oncology Department at the Regional Hospital of Orleans. It is a long responder and complete remission under Cetuximab after an early progression post-radio-chemotherapy followed by first-line treatment with the TIP protocol (Paclitaxel + Ifosfamide + Cisplatin).

CASE PRESENTATION

This is a 59-year-old patient with a cardiovascular history of stroke, abdominal aortic aneurysm and stented coronary syndrome, child-pugh A alcoholic cirrhosis, and non-insulin-

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dependent diabetes. He is married with three children.

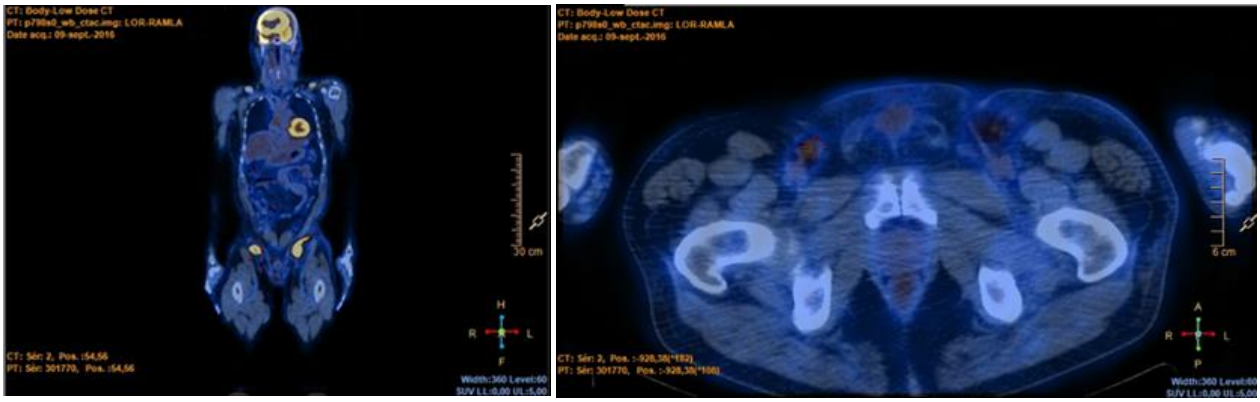
He was operated on, on 01/03/2016 for phimosis with in-Sano excision. Anatomo-pathological examination revealed a squamous cell carcinoma of the prepuce. The extension workup, done by a thoracic-abdominal-pelvic CT, did not reveal any secondary lesions. It was decided to monitor the patient postoperatively.

Subsequently, the patient consulted in June 2016, three months post-op, due to the appearance of inguinal adenopathy.

On physical examination, a large lymph node mass of 10cm fistulated to the skin was found on the left. On the right, there was also a 5cm fixed adenopathy. There was no macroscopic lesion of the penis.

The left inguinal lymph node was resected on 22/08/2016 confirming the secondary location of his penile squamous cell cancer.

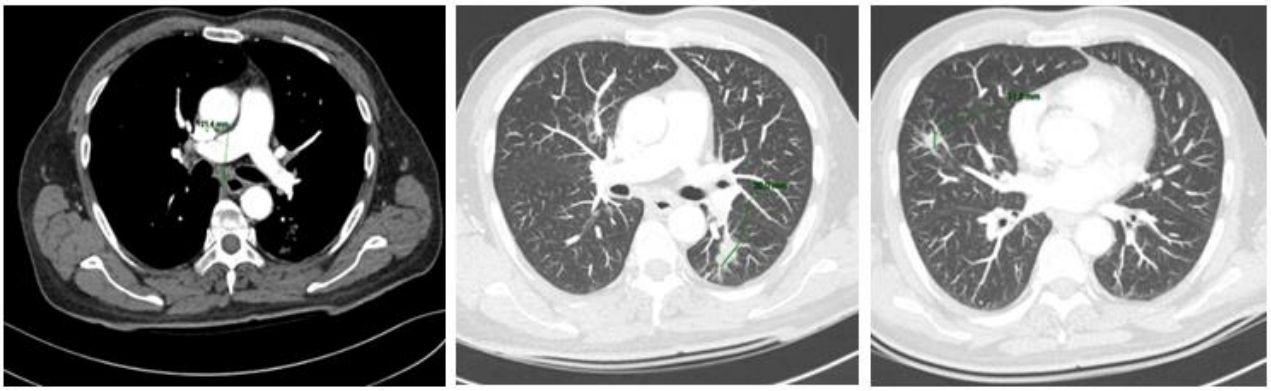
A PET scan on 08/09/2016 described secondary lesions only in the bilateral inguinal region.

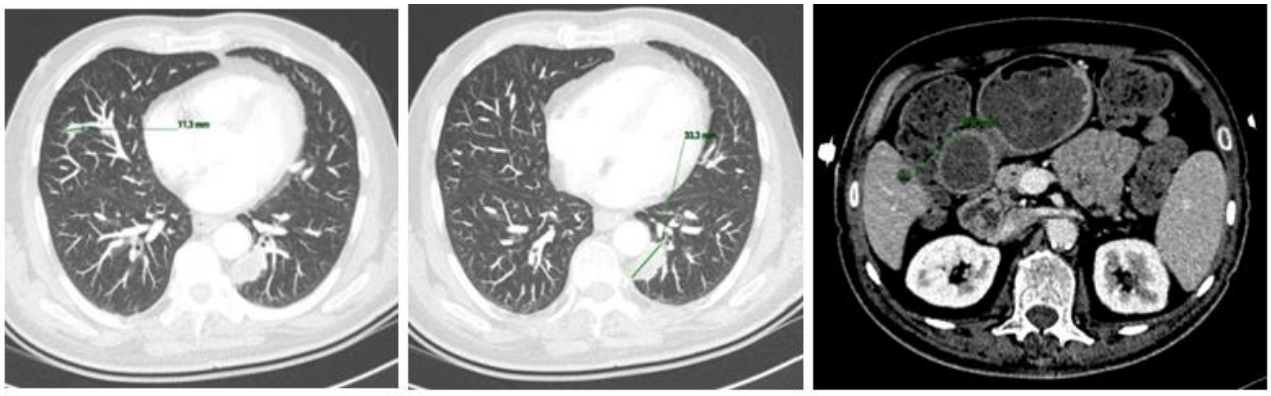


He then received radiochemotherapy from 03/10/2016 to 23/11/2016. He was delivered 45 Gray in the right and left ilioinguinal areas, with overexposure up to 63 Gray in the right and left inguinal adenopathies fistulized to the skin. Three courses of well-tolerated concurrent chemotherapy were given at week 1, week 4, and week 7. She received Cisplatin (15mg/m2 or 29mg per day over four days) and 5FU (800mg/m2 or 1550mg/day over four days).

The evolution was unfortunately marked by sepsis on the implantable chamber and spondylodiscitis L2-L3. He finished his antibiotic therapy on 21/04/2017 with the disappearance of the infectious syndrome and spinal pain.

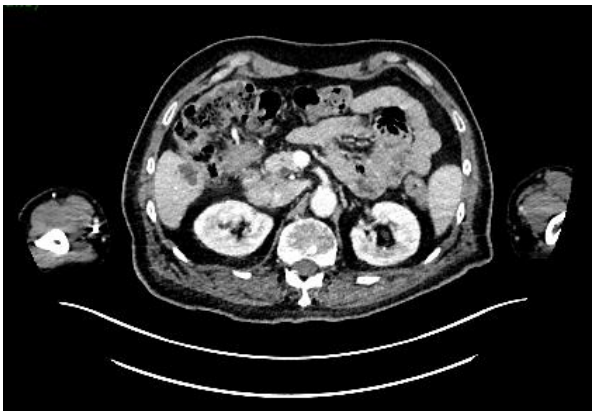
A CT scan on 24/04/2017 concluded that the tumor had progressed to the lung and liver, with a single segment V.





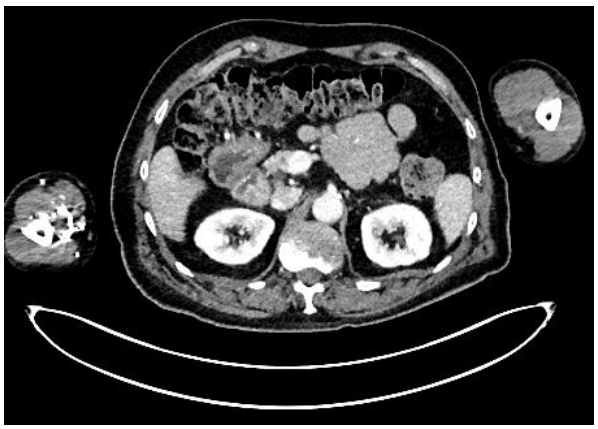
The first line of therapy was initiated according to the TIP protocol, every three weeks, combining Paclitaxel (175mg/m2), Ifosfamide (1200mg/m2 over three days), and Cisplatin (37.5mg/m2 on day1 and day2). In total, he was able to benefit from four courses of this protocol without inter-course toxicity including hematological, neurological, and renal toxicities.

The PET SCAN of 27/09/2017 describes a metabolic extinction of the pulmonary target lesions with unfortunately a progression of the single hepatic target lesion of segment V of 18 mm Vs 10 mm on a stable cirrhotic liver with no sign of decompensation.

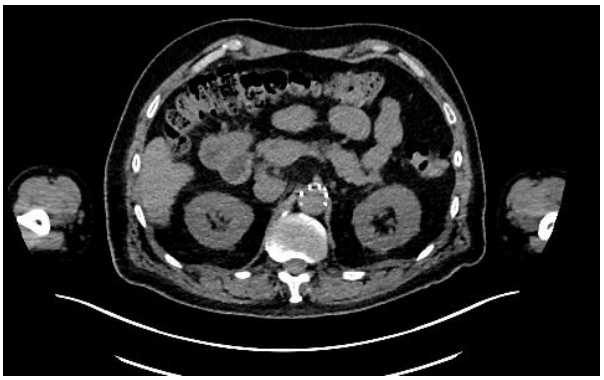


Additional molecular biology results were inconclusive. Unfortunately, the analysis of EGFR and KRAS genes was not interpretable due to a lack of quality and quantity of nucleic acids extracted from the sample.

There was a discussion on the value of local management of single hepatic metastasis by surgery, radio-embolization, or external radiotherapy. As squamous cell carcinomas of the penis are known to have a high level of EGFR expression, the medical oncology consultation meeting decided to initiate an anti-EGFR agent.



The second line of treatment was proposed with Cetuximab (500mg/m2 every fortnight). With this well-tolerated molecule, a complete remission of the disease was observed 6 months of treatment (on 27/03/2018) and maintained for 5 years.



At the last evaluation in August 2022, the patient was in good general condition with no tumor recurrence on his PET scan.

The side effects were more pronounced during the first 6 months. He experienced grade 2 nausea and grade 1 diarrhea after the first two courses, which improved with symptomatic treatment. Grade 1 transaminase elevation was already present at the initiation of treatment with Cetuximab. This liver toxicity worsened after the

third course of treatment to a grade 2. The liver function then gradually corrected and was normalized by the tenth course.

DISCUSSION

In daily practice in urological oncology, penile cancer remains a rare disease with a relatively low incidence in Europe. Worldwide, the incidence varies between 0.4 and 0.6% of cancers in men. The glans and prepuce are the preferred sites for this type of cancer and squamous cell carcinoma (95%) is the most common histological type with preferential extension to the inguinal nodes [1].

Several risk factors have been listed in literature such as lack of circumcision, lack of local hygiene (balanoposthitis-lichen), chronic inflammation due to maceration, risky sexual behavior (multiple partners, early first intercourse), phimosis, lichen sclerosis, smoking, obesity and a history of pelvic radiotherapy [1].

The search for HPV (Human Papilloma Virus) infection is essential because of its involvement in penile carcinogenesis and the clinical consequences in terms of increased risk of recurrence. It is negative in papillary squamous cell carcinomas. It should be noted that, as in head and neck cancers, HPV+ squamous cell carcinomas of the penis have a better prognosis [1, 2].

The discovery of penile cancer in our patient was fortuitous on the anatomopathological analysis of a resection specimen for phimosis. Three months after surgery, he presented with a resected lymph node recurrence with a new early unresectable inguinal lymph node recurrence of 10 cm for the most voluminous and fistulated to the skin.

Surgery with peri-operative chemotherapy involves managing squamous cell carcinoma of the penis (SCC) with inguinal lymph node involvement. When patients are not eligible for surgery, as in our patient, therapeutic success has been reported with definitive radiotherapy or radio-chemotherapy reserving surgery as a salvage option [3, 4].

In the metastatic setting, rather modest but important results of platinum-based multidrug therapy have been reported. These include the triplets Bleomycin + methotrexate and cisplatin (BMP) [2,5], Paclitaxel + Ifosfamide and Cisplatin (TIP) [6], Docetaxel + 5-Fluorouracil and Cisplatin (TPF) [7]. Improved safety has been evaluated with doublets combining Cisplatin with Irinotecan or Gemcitabine [8].

The phase II trial by Pagliaro and al evaluating the TIP protocol in 30 patients in the neoadjuvant setting reported an objective response of 50% with 22 patients who could be operated on. Progression-free and overall survivals were 8.1 months and 17.1 months respectively. Despite these results and all previous research, the study by Pagliaro et al recommended the TIP protocol as the standard of care in this location. In our patient treated with 4 courses of the TIP protocol, a discordant response was observed with metabolic extinction of the secondary pulmonary targets but a progression of the single hepatic lesion.

In the absence of standard second-line treatment and especially due to the early progression, the exploration of other therapeutic options in the era of targeted therapies and immunology has been evoked.

Indeed, Epidermal growth factor receptor (EGFR) and k-Ras status have been extensively studied in recent years in this location. EGFR is overexpressed in variable proportions in more than 90% of SCC of the penis and its expression has been reported to be associated with early recurrence and a worse prognosis [2]. For example, Lavens and al. reported significant EGFR overexpression in 14 out of 17 patients evaluated with somewhat more moderate expression in the remaining 3; while Andersson and al found a somatic mutation in 39% (n=11) of 28 penile cancer patients, notably in the PIK3CA (29%), HRAS (7%) and K-ras (3%) genes [2]. The K-ras mutation leads to constitutive activation of the Ras pathway independently of the signaling cascade driven by EGF receptor activation, thus altering the efficacy of anti-EGFR drugs. It is therefore important to determine the K-ras status before the initiation of anti-EGFR drugs. It would be interesting to know the expression levels of EGFR to correlate them with the responses to Cetuximab as evaluated in the PENILANE trial.

Targeting this receptor, therefore, appears to be a promising therapeutic option. In this context, several anti-EGFR agents have been evaluated such as Cetuximab, Erlotinib, Gefitinib, and more recently Panitumumab, Nimotuzumab, and Dacomitinib [2].

At the time of progression under the TIP protocol, the drugs that had demonstrated efficacy and were available at that time were Cetuximab and Panitumumab.

Carthon *et al*., evaluated the efficacy of Cetuximab as monotherapy in 8 patients, in combination with a platinum salt (Cisplatin or Carboplatin) in 13 patients and in combination with

the TIP protocol in 3 patients. In monotherapy, Cetuximab was administered at 400mg/m2 as a loading dose and then at 250mg/m2 weekly. At the end of their study, they reported a partial response rate of 20% in the patients receiving Cetuximab monotherapy and 25% when combined with chemotherapy. The time to progression in the entire population was 2.6 months with a median overall survival of 6.9 months [9].

Necchi *et al*., reported a partial response rate of 9.1% (in one patient) and a complete response rate of 18.2% (in two patients) out of 11 patients. Progression-free survival was 1.9 months with increased overall survival of 9.5 months [10].

The efficacy of Cetuximab was spectacular in our patient noting complete remission after 6 months of treatment alongside a response maintained under treatment five years later. No serious toxicities requiring discontinuation or adaptation of treatment were observed in our patient.

CONCLUSIONS

Chemotherapy has limited efficacy in squamous cell carcinoma of the penis. Anti-EGFR drugs, including Cetuximab, are a major advance in this location. The treatment is well tolerated and effective even in cases of visceral metastasis with long-term tumor control or even complete remission. This result opens the way to optimizing therapeutic strategies.

List of abbreviations

EGFR: Epidermal growth factor receptor
TIP: Paclitaxel + Ifosfamide + Cisplatin
TEP Positron Emission Tomography
CT: Computed Tomography
HPV: Human Papilloma Virus
SCC: Squamous Cell Carcinoma
BMP: Bleomycin + methotrexate and cisplatin
TPF: Docetaxel + 5-Fluorouracil and Cisplatin

Declarations

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- Acknowledgements: Not applicable

Timeline

Profile	Married 59-year-old patient with three children and cardiovascular history of stroke, abdominal aortic aneurysm and stented coronary syndrome, child-pugh A alcoholic cirrhosis, and non-insulin-dependent diabetes
01/03/2016	In sano excision for phimosis with the fortuitous discovery of squamous cell carcinoma
22/08/2016	Histological confirmation of the secondary inguinal lymph node location of his squamous cell carcinoma of the penis
08/09/2016	Secondary inguinal node lesions only on baseline PET SCAN
03/10/2016 to 23/11/2016	Radiochemotherapy
24/04/2017	Remote tumor progression in the lung and liver on CT
18/05/2017 to 21/07/2017	Four courses of TIP protocol
27/09/2017	A metabolic extinction of the pulmonary target lesions with unfortunately a progression of the single hepatic target lesion of segment V
11/10/2017	Start of cetuximab in 2nd line
27/03/2018	Complete metabolic response
12/08/2022	Complete remission maintained after 05 years of treatment

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