Combination of docetaxel and cetuximab for penile cancer: a case report and literature review

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Guidelines on the treatment of metastatic squamous cell carcinoma of the penis are limited to a few prospective trials. Cisplatin-based regimens represent the standard of treatment with promising activity of taxanes. Recently, epidermal growth factor receptor overexpression has been shown in these patients. We treated an elderly man with a docetaxel–cetuximab combination after failure of the cisplatin regimen. We observed a necrosis of the inguinal lymph nodes and a reduction of ^{18}F-fluorodeoxyglucose uptake at PET/CT scan. Only mild mucositis and skin toxicity had been detected. Our case report, the first in the literature, shows that this combination is active and well tolerated in penile squamous cell carcinoma.

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Introduction

Squamous cell carcinoma (SCC) of the penis is a rare disease that represents less than 0.4% of all malignancies in men in the US, with a modest incidence also in China and the UK, whereas it is relatively common in South America, Africa, and India [1].

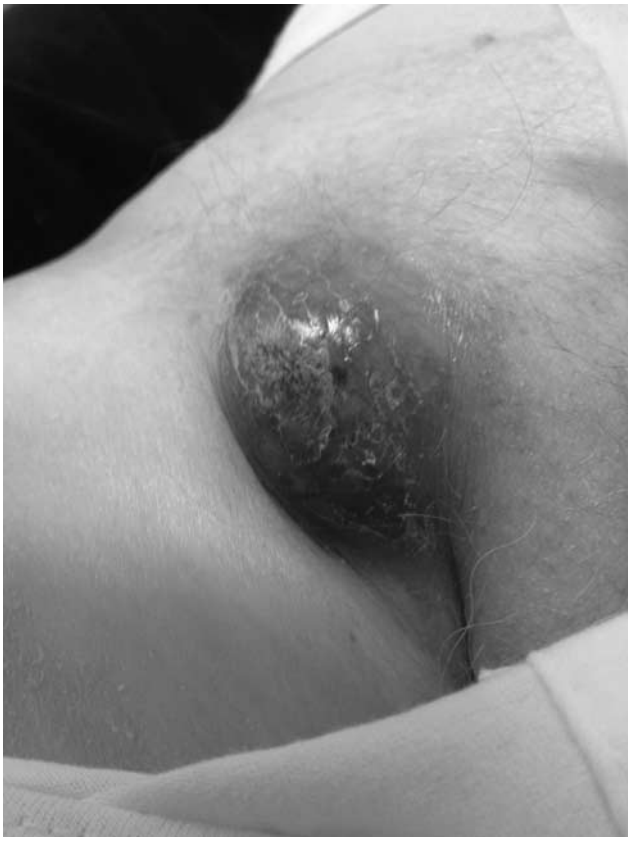
Exposure to the human papillomavirus, lack of neonatal circumcision, and use of tobacco have been recognized as the most common etiologic risk factors of this malignancy [2].

Local treatments are suitable for carcinoma *in situ* and grade 1–2 T1, whereas for grade 3 T1 and invasive tumors (T2), partial or total penectomy is the standard therapy. Lymphadenectomy is the treatment of choice for patients with inguinal lymph node metastases [2].

For metastatic or recurrent disease, the treatment strategy is a chemotherapeutic approach. Because of the rarity of this cancer, few trials have been published and the majority of them are limited by a retrospective nature and small number of patients [2].

The similarity to head–neck cancers in terms of the natural history and response to chemotherapy has propelled treatment of metastatic SCC of the penis with the same drugs used to treat the former, such as the 5-fluorouracil (5-FU)–cisplatin [3] or methotrexate–bleomycin–cisplatin (CMB) combinations [4]. The response rates were 25–32% for both combinations, with high and limiting toxicity for the CMB regimen.

Fig. 1



Pink cutaneous nodular lesion with a hard-elastic consistency in the right groin before cetuximab–docetaxel.

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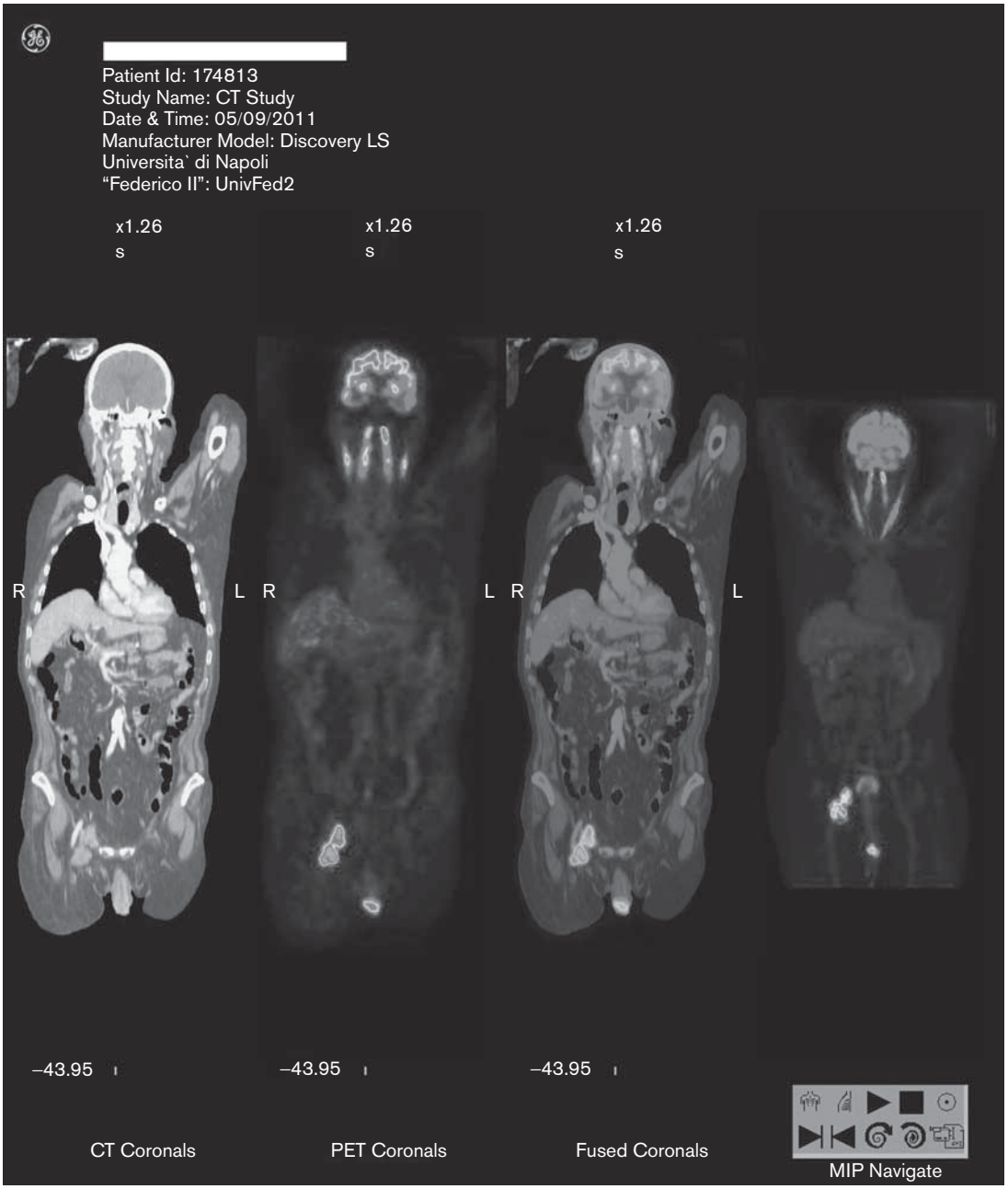
Fig. 2



PET/TC ^{18}F-fluorodeoxyglucose PET/CT scan revealed an increase in inguinal lymph nodes (60 × 45 mm) and uptake at inguinal right lymph nodes (SUV_{max} 16).

Most recently, the use of taxanes has been evaluated in a neoadjuvant and second-line setting [5–7].

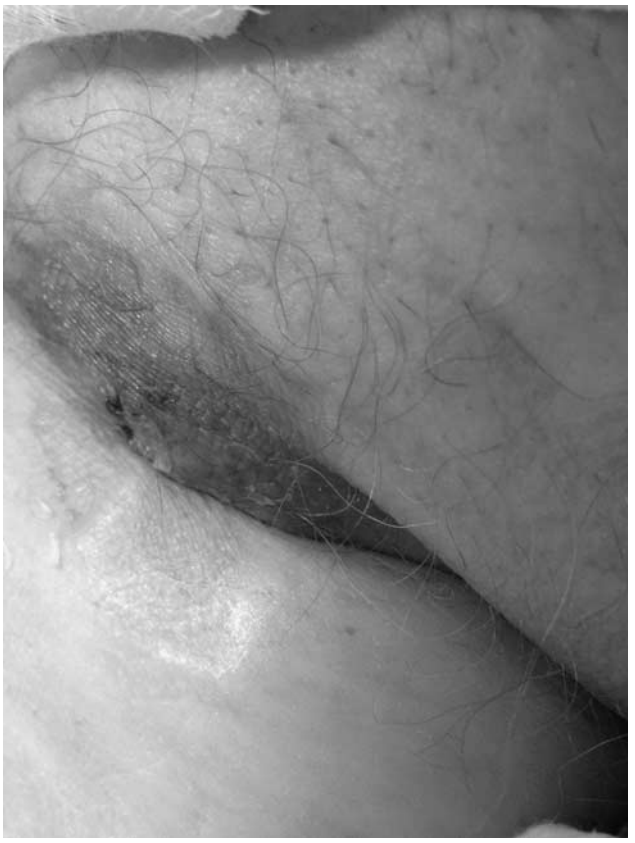
The discovery that epidermal growth factor receptor (EGFR) is involved in penile cancer [8] has led to evaluation of the potential benefit of anti-EGFR monoclonal antibody [9,10].

Here, we describe a case of metastatic SCC of the penis that was treated with a docetaxel–cetuximab combination after a cisplatin-based regimen.

Case report

A 75-year-old white man had been diagnosed with penile SCC in January 2011 by an excisional biopsy of glans lesion. At clinical examination, the penis appeared stiff and woody, and a huge mass of six for 2 cm was detected at the inguen, which was compatible with nodal package. Consequently, a ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT scan was performed. It revealed uptake at the penile region [standardized uptake value $(SUV)_{max}$ 15.3], at the

Fig. 3



Nodular lesion disappeared and persisted only as an eritematous patch after the chemotherapy.

inguinal right lymph nodes (SUV_{max} 21.8), and at the external lymph nodes of the left iliac region (SUV 5.3).

In March 2011, on the basis of a histologic examination and unresectable disease, we decided to treat the patient with a combination of cisplatin 100 mg/m^2 on day 1, and 5 days of a continuous infusion of 5-FU 1000 mg/m^2 every 21 days according to the institutional protocol, using a prophylaxis with pegylated filgrastim [granulocyte colony-stimulating factor (GCSF)]. After three courses, another PET/CT scan was carried out. It revealed a decrease in inguinal lymph node uptake (SUV 10.4 vs. 21) and size (2.6 vs. 6 cm). Penile and left iliac nodal regions did not show uptake. A total of six courses were administered, at the end of which stable disease was achieved. Treatment was well tolerated, except for renal injury and irreversible hypercreatininemia; the patient began a follow-up program after completion of therapy in July 2011. In September 2011, the patient presented an extensive disease relapse, involving a huge inguinal nodal right nodular mass (60×50 mm) that was fixed and painful. Figure 1 shows a pink cutaneous nodular lesion with a hard-elastic consistency in the right groin before cetuximab–docetaxel. A new PET/CT scan was performed. It showed uptake of ^{18}F-FDG at the inguinal region (SUV_{max} 16) (Fig. 2), increase in inguinal lymph nodes (60×45 mm), and nonspecific uptake at the penile shaft. Review of the slides confirmed the diagnosis of SCC and immunostaining was strongly positive for the EGFR (3 +), with an absence of *KRAS* mutations on molecular analysis. Because of disease progression, we decided to start a second-line treatment with docetaxel 75 mg/m^2 plus cetuximab 400 mg/m^2 as a loading dose and 250 mg/m^2 as a maintenance dose on days 1 and 8 every 21 days, with a prophylaxis of GCSF, after receiving approval from our institutional review board and obtaining informed consent from relatives. After two courses, the nodular component disappeared and the patient reported a reduction in pain. Figure 3 shows that the nodular lesion disappeared and persisted only as an eritematous patch. After four courses, another PET/CT scan was carried out. Nodal right package increased (70 mm) for the increasing necrotic component but ^{18}F-FDG uptake decreased (SUV_{max} 6) (Fig. 4). The pain was reduced and performance status was improved. We detected only grade 1 mucositis and skin toxicity. To date, the patient has received six cycles and is still continuing the treatment.

Discussion

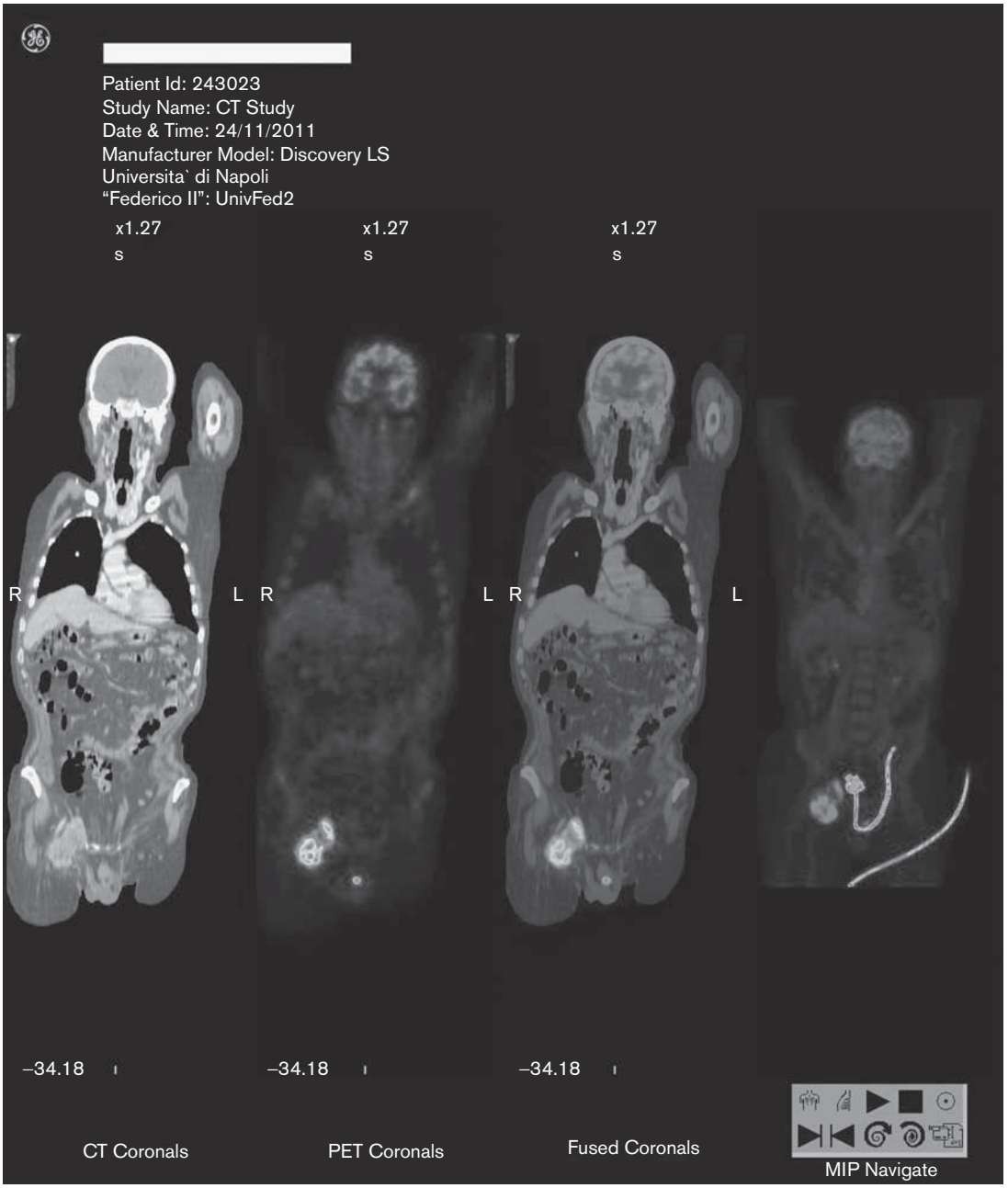
Penile cancer is a squamous epithelial neoplasia with a high mortality and only a few large prospective studies have addressed the role of systemic treatment in advanced disease. Established regimens are characterized by high toxicity and poor efficacy. Considering the relative paucity of data, recommendations and guidelines on the treatment of metastatic penile carcinoma are vague and derive from studies on head and neck cancers. For these reasons, a combination of cisplatin and 5-FU remains the standard regimen for metastatic SCC of the penis [2].

Hussein and colleagues treated six patients with cisplatin and 5-FU as first-line therapy for metastatic penile cancer. These patients were treated with cisplatin on day 1, followed by 5 days of 5-FU infusion. Reported toxicities were mucositis, nausea, vomiting, and renal impairment. Five partial responses and one complete response were obtained [11]. Larger studies but in various settings of disease have been carried out by Haas *et al.* [4] and Theodore *et al.* [12].

The trial by Haas and colleagues enrolled 45 patients, who were treated with CMB. There were five complete and eight partial responses, yielding a 32.5% response rate. Five treatment-related deaths occurred and six patients had one or more life-threatening toxicities [4].

Theodore and colleagues treated 28 patients with cisplatin and irinotecan in a neoadjuvant or an advanced setting. The response rate was 30.8%. Grade 3 and 4 toxicities were diarrhea, neutropenic fever, and granulocytopenia [12].

Fig. 4



After four courses, PET/CT revealed an increase in the inguinal lymph node with a necrotic component but ^{18}F-FDG uptake was decreased (SUV_{max} 6).

Taxanes represent a class of agents with activity in head and neck, breast, and lung cancers. Limiting drug toxicities are neutropenic fever and irreversible neuropathy [13].

Regimens such as docetaxel–cisplatin–5FU (TPF) and placlitaxel, cisplatin, and ifosfamide combination showed activity in a neoadjuvant setting with a response rate of 50% and a pathologic complete response rate ranging from 10 to 13% [6,14].

Di Lorenzo and colleagues carried out a single-arm phase II study with paclitaxel in pretreated metastatic patients. The authors reported a partial response in 20% of cases, with a progression-free survival of 11 weeks and a median overall survival of 23 weeks. One patient had a grade 4 neutropenia, and grade 3 anemia and thrombocytopenia were seen in a minority of patients [7]. Thus, a regimen with a taxane appears to be a reasonable choice after progression from cisplatin-based therapy.

Recently, Lavens and colleagues showed EGFR overexpression in penile cancer. They studied 17 patients affected by SCC of the penis and all patients overexpressed EGFR with immnunohistochemistry (3+ in 14 cases and 2+ in three cases) [8].

On the basis of this knowledge, Carthon and colleagues studied the activity of cetuximab in patients with strong positivity for EGFR expression. For this subset of patients, he obtained a progression-free survival of 3.57 months and a median overall survival of 11.87 months. Acne was the most common toxicity; grade 3 and 4 events of cellulitis, thrombocytopenia, and tumor hemorrhage were also reported [10].

A recent case report has described the use of panitumumab as a single-agent therapy in a patient affected by recurrence of SCC of the penis. This patient started therapy with panitumumab after failure of adjuvant chemotherapy with a TPF regimen. He showed extensive disease recurrence consisting of cutaneous and subcutaneous nodules. After six administrations, pain decreased and nodules reduced in size and number [9].

Our case report represents the first in the literature to use a combination of targeted therapy and classic chemotherapy. This schedule appears to be active and well tolerated. The response was evaluated by reduction of ^{18}F-FDG uptake, necrosis of metastatic mass, and improvement in pain symptoms and performance status.

The only side-effects were neutropenia and skin toxicity. Neutropenia has been prevented by pegylated GCSF. Mild skin toxicity did not require anything other than dermatological creams. These results have encouraged us to continue treatment.

Conclusion

The results obtained with this original regimen are promising in terms of both efficacy and toxicity, especially in view of the very limited therapeutic options available for these patients. As a consequence, it appears important to investigate whether this regimen can be used on a larger sample of pretreated patients or whether it can be used as a first-line treatment for unfit patients.

However, the rarity of this disease, poor investment from large companies, and bureaucracy make the realization of a prospective trial difficult. Only international cooperation of independent clinicians would lead to success in clinical trials.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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