

CASE REPORT

Isolated Limb Perfusion for the Treatment of Unresectable In-Transit Metastases of Cutaneous Squamous Cell Carcinoma

Perfusão Isolada de Membro no Tratamento de Metástases em Trânsito de Carcinoma Espinocelular

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ABSTRACT – Squamous cell carcinoma (SCC) is the second most common non-melanoma skin cancer and its incidence has been increasing over the past decades. SCC in-transit metastases are rare and predict a poor prognosis.

We present the case of a 69-year-old patient with a right lower leg SCC, surgically excised with free margins. One month later, erythematous to violaceous, firm papules begin to erupt on the right lower leg, evolving to ulcerated nodules over a period of weeks. Homolateral inguinal and iliac nodal metastases were documented by percutaneous biopsy of an inguinal palpable lymph node and later documented by positron emission tomography – computed tomography (PET-CT). Given the unresectability of the disease, regional chemotherapy involving isolated limb perfusion (ILP) with melphalan and tumor necrosis factor-alpha (TNF α) was performed in order to avoid amputation. Macroscopic regression ensued, with complete resolution of all visible in-transit metastases 12 weeks after perfusion. However, a fatal outcome was observed 4 months later, due to systemic metastases.

ILP is an effective and well-established technique in the treatment of advanced tumors of the extremities. Its main indications are in-transit metastases of malignant melanoma and advanced soft tissue sarcomas. However, studies have shown its effectiveness in other tumors such as locally advanced SCC. Despite the unfortunate outcome, it was possible to avoid amputation of the limb, with complete local disease remission.

KEYWORDS – Amputation; Carcinoma, Squamous Cell; Extremities; Neoplasm Metastasis.

RESUMO – O carcinoma espinocelular (CEC) é o segundo cancro cutâneo não-melanoma mais comum e a sua incidência tem aumentado nas últimas décadas. A metastização locoregional é rara e, quando ocorre, associa-se a um pior prognóstico. Apresenta-se o caso de uma doente de 69 anos, com CEC da perna direita, invasivo, moderadamente diferenciado, totalmente excisado cirurgicamente. Após 1 mês, a doente refere o aparecimento de pápulas eritematovioláceas, de consistência dura, que evoluíram para nódulos de 3-4 cm, ulcerados, localizados na perna direita. A invasão ganglionar inguinal e ilíaca homolateral foi documentada através de punção aspirativa de conglomerado adenopático palpável a esse nível e posteriormente documentado por tomografia de emissão de positrões com TC (PET-TC). Dada a irressecabilidade cirúrgica da doença, foi realizada uma perfusão isolada de membro (PIM) com melfalan e fator de necrose tumoral (TNF α) para evitar a amputação. Foi observada resolução completa de todas as metástases em trânsito 12 semanas após a perfusão. No entanto, 4 meses depois, a progressão sistémica da doença culminou num desfecho fatal.

A PIM é uma técnica eficaz e bem estabelecida no tratamento de tumores avançados das extremidades. As suas principais indicações são as metástases em trânsito de melanoma maligno e sarcomas de partes moles. No entanto, estudos demonstram a sua eficácia no tratamento de outros tumores, como é o caso do CEC localmente avançado. Apesar de não ter alterado o prognóstico da doença, foi possível, com a abordagem instituída, evitar a amputação do membro, atingindo a remissão completa da doença localizada.

PALAVRAS-CHAVE – Amputação; Carcinoma de Células Escamosas; Extremidades; Metástase Neoplásica.

INTRODUCTION

Non-melanoma skin cancer (NMSC) represents the most common type of cancer in caucasians, with an incidence that has been steadily increasing worldwide. Basal cell carcinoma and squamous cell carcinoma (SCC) account for the majority of NMSC cases.^{1,2} The most commonly affected anatomic regions are sun-exposed areas like the head and neck, although a large proportion are located on the limbs.³ Extension of the disease will determine the most suitable treatment approach. Multiple treatment strategies are available for localized disease, from wide surgical excision - usually the

most common treatment - to Mohs micrographic surgery, cryosurgery or radiotherapy. However, when facing a locally advanced and/or widespread disease, with clinical and histopathological features associated with bad outcomes, surgical excision with adequate free margins may not be appropriate, leading to serious loss of limb function or even limb amputation.⁴

Isolated limb perfusion (ILP) is a well-established technique used for the treatment of unresectable tumors of the extremities.^{2,4} It was first introduced in clinical practice by Creech and Krentz, in 1957, in New Orleans, United States of America, in a patient with in-transit metastases of malignant melanoma, who achieved a complete

response.⁵ Nowadays, ILP is mainly used for the treatment of in-transit metastases of malignant melanoma and advanced soft tissue sarcomas of the extremities.^{4,6} However, recent studies have shown ILP's efficacy in rarer tumours confined to the extremities – locally advanced SCC, cutaneous lymphomas, Merkel cell carcinomas and desmoid tumors.⁷ ILP has proven to be a safe and effective limb-saving strategy without the systemic toxicity of conventional chemotherapy.⁴

CASE REPORT

We present the case of a 69-year-old female patient with a history of kidney transplant 10 years before, on immunosuppressive therapy with prednisolone, mycophenolate mofetil and everolimus.

The patient was admitted to the Dermatology Department with a 6-month history of a growing ulcerated nodule on her lower right leg, measuring 5 cm. Wide surgical excision was performed followed by closure with a full-thickness skin graft. Histopathology revealed a completely excised, invasive, moderately differentiated SCC, without perineural or lymphovascular invasion. Four weeks later, multiple erythematous-violaceous papules begin to erupt on the lower right leg in a linear pattern. Enlarged homolateral inguinal lymph nodes were also noticed on clinical examination. Skin and lymph node biopsies were performed and were positive for cutaneous and lymph node metastases of SCC, respectively. Staging PET-CT showed hypermetabolic activity in these locations. On re-evaluation, 4 weeks later, the lesions had evolved to 3-4 cm, exophytic, ulcerated, haemorrhagic nodules, located on the anterior and posterior surface of the lower leg (Fig. 1). Given the regional spread of the disease with locoregional metastases, the patient was treated with ILP, consisting of a combination of melphalan and TNF α . An iliac perfusion was performed with temperatures ranging from 39.5°C to 40°C, using 90 mg of melphalan (10 mg/L limb volume) and 1 mg of TNF α . Inguinal and ilio-obturator lymph node dissection was performed at the same time, without immediate interurrences. A total of 11 lymph nodes were excised, 10 of which had metastases from SCC.

As soon as 1 week after the procedure, partial disease regression was noticed, with a reduction in lesions size and erythema (Fig. 2A) with more significant reduction recorded at week 4 (Fig. 2B). Complete resolution of all in-transit metastases was observed at week 12, leaving



Figura 1 - Multiple erythematous and violaceous papulonodules covered with haemorrhagic crusts, located on the anterior (A, B), lateral and posterior (C) aspect of the right lower leg.



Figura 2 - One week post-procedure - reduction in size and erythema of the cutaneous lesions (A); Four weeks post-procedure – 1x1 cm erosion on the anterior aspect of the right lower leg with complete resolution of the remaining lesions (B).



Figura 3 - Twelve weeks post-procedure. Complete resolution of the cutaneous lesions with residual atrophic scarring.

only a residual scar on the anterior surface of the leg (Fig. 3). The patient did not experience any local or systemic toxicity. Nevertheless, 4 months later, systemic progression of the disease was reported on the PET-TC, showing hypermetabolic activity at multiple locations. Unfortunately, the patient died 4 months later.

DISCUSSION

SCC accounts for most non-melanoma skin cancer-related metastatic disease and deaths.⁸ Once an invasive/aggressive SCC is diagnosed, it must be staged as the risk for metastases is reported to be approximately 49 and 2 to 3 times higher in immunosuppressed individuals.¹⁰ Cutaneous in-transit and regional lymph node metastases are the most common metastatic presentation.⁸ Treatment modalities described for advanced SCC at any site include conventional cytotoxic chemotherapy, newer systemic therapies, radiotherapy and combinations of these modalities.⁴ The ILP technique has been extensively described. Its purpose is to allow local administration of high-dose chemotherapy while minimizing serious systemic side effects.^{3,11} Briefly, after heparinization, the surgeon identifies and cannulates the main vessels of the limb, in this case the right iliac vessels, which were clamped proximally. With the use of an extracorporeal circulation pump, chemotherapy with melphalan and TNF α is infused into the limb. The technique is based on the synergistic antineoplastic effect of chemotherapeutic drugs and high temperature,⁷ which should be maintained between 38°C and 40°C, measured with two thermometers placed in subcutaneous tissue and muscle. Systemic and regional toxicity should be assessed during perfusion with radiolabeled albumin infused on the systemic circulation and a gamma probe.^{2,7,11,12}

Several reports show excellent response rates with TNF α and melphalan-ILP for both malignant melanoma in-transit metastases or locally advanced soft tissue sarcomas.^{3,6,7} However, there is not much evidence on its efficacy when it comes to non-melanoma skin cancer, such as SCC. Veld et al recently reported a case series of 30 patients with locally advanced SCC treated with ILP. The overall response rate was 81%, with 16 patients having a complete response (59%). Limb salvage rate was 80% and the overall 2-year survival was 67%. The authors suggest that ILP should be considered as an option in patients with locally advanced SCC.⁴ Belgrano et al report two patients with SCC submitted to ILP, with disease stabilization in one patient and a complete response in the other. However, both experienced local progression of the disease within 4-7 months.⁷

In this case of a SCC with locoregional metastases, the regression of all in-transit metastases was considered an indicator of a successful outcome, mitigating the need for limb amputation. However, despite its regional efficacy, ILP is unlikely to have a great impact on survival, as shown in several large prospective studies on melanoma and locally advanced soft tissue tumors.^{6,13,14} The widespread disease observed later in this patient might have been a result of systemic metastases that were undetected by imaging and clinical evaluation.

In conclusion, in this patient, ILP was an effective and well tolerated limb-saving palliative treatment. However, it did not have any impact on the overall prognosis. This technique can be regarded as a therapeutic option in the management of multiple, locally advanced, drug-resistant tumors of the limbs, when surgical therapy is not feasible.

Presentations/ Apresentações

This case has been presented as a poster on "XIX Congresso Nacional de Dermatologia e Venereologia", Porto, 6-8th December of 2019.

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