

# A case of grade 3 squamous cell carcinoma successfully treated with methotrexate

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## Abstract

Cutaneous squamous cell carcinoma (cSCC) is a non-melanoma skin cancer whose lesions mostly arise on light-exposed sites. Patients with compromised immunity, Fitzpatrick I or II skin phototype, and previous burn scars or radiations are more at risk of developing it. The treatment of choice for cSCC is surgery; however nonsurgical options are generally reserved for patients who refuse a very invasive treatment or cannot tolerate a surgical procedure. We report a case of cSCC successfully treated with intralesional methotrexate.

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## Case Report

A 92-year-old woman from Benevento, Italy, with no significant medical history, presented in March 2022 with a 5-cm tumor on the left side of the cheek, extending close to the left lower eyelid. It was indurated and covered by a yellowish crust and blood. The lesion had been growing for more than 12 months (Figure 1).

A punch biopsy showed a poorly differentiated grade-3 squamous cell carcinoma (SCC) with tumor necrosis. Important nuclear and cytoplasm pleomorphism, typical and untypical mitosis were present (Figure 2).

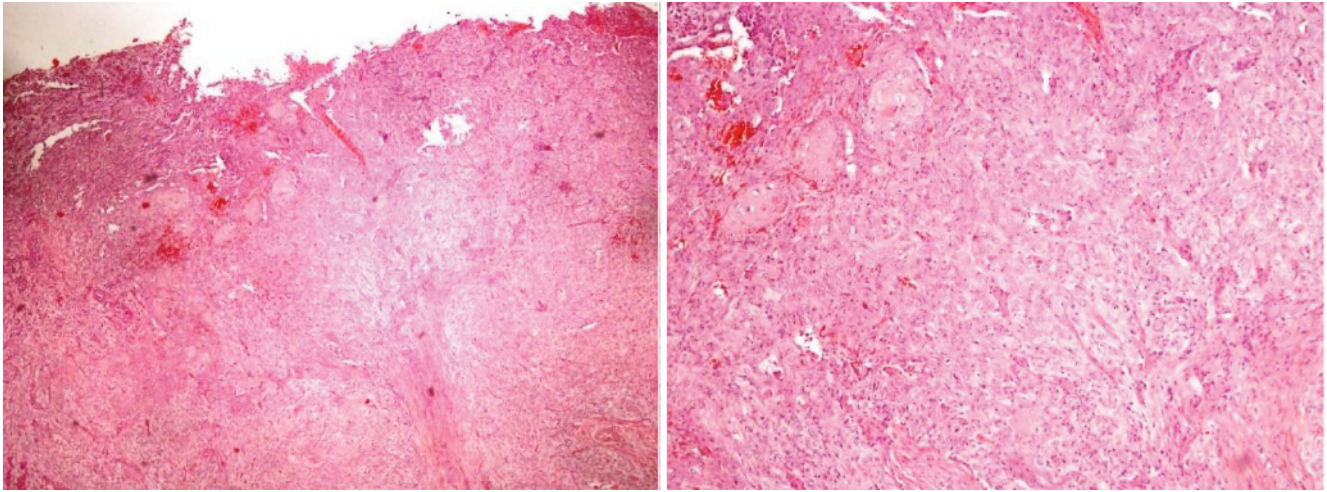
The primary aim is the complete removal with good cosmetic results. Surgery is the most common and effective treatment; however, it is necessary to maintain adequate margins (standard 4-5 mm). Some tumors are truly inoperable, due to the patient's rejection to undergo removal or reconstruction, either because of the size or the anatomic location of the tumor.

Surgical treatment was declined by the patient and her family members because of her age and also because of the large size of the required excision, so it was decided to treat her with intralesional methotrexate.

Methotrexate is a chemotherapy agent: it's a folic-acid analog that irreversibly inhibits the enzyme dihydrofolate reductase, blocking the synthesis of tetrahydrofolate and, ultimately, nucleoside thymidine, required for DNA synthesis; furthermore, methotrexate promotes caspase activation and apoptosis of cutaneous SCC (cSCC) cells.



**Figure 1.** Pre-treatment clinical photograph showing a large, indurated tumor with crust and blood.



**Figure 2.** Area of neoplasia with irregular contour, with different cell characteristics, partial squamous and partial basaloid.



**Figure 3.** Post-treatment clinical photographs showing resolution of squamous cell carcinoma on the left cheek.



Methotrexate, with a dose of 25mg/ml per session, was injected subcutaneously every 2 weeks proceeding from the periphery of the lesion toward the center. The clinical evolution of the lesion was weekly evaluated. Folic acid supplementation, with a dose of 5mg, was taken the day after each methotrexate administration.

The patient had an excellent clinical response with a complete resolution after 3 months (Figure 3). No recurrence was observed at the last follow-up (October 2022).

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## Discussion and Conclusions

CSCC represents around 20-30% of non-melanoma skin cancer and can reach enormous size if neglected. The invasiveness of the tumor depends on the size, anatomical location, and histological subtype. Surgery is the mainstay of treatment even in giant tumors.

In this clinical case, where surgery was set aside because of the size of the cSCC and the old age of the patient, methotrexate was chosen due to its inhibition of the enzyme dihydrofolate reductase, DNA synthesis, and cell replication.

Methotrexate has no side effects, is well tolerated with good compliance, has a quick response, and is easily administrated at a low cost.

The cons: it's an off-label therapy and there's local pain. In addition to this, it's important to highlight that the efficacy of methotrexate depends on how much it remains within the limits of the lesion, not spreading outside.

In literature, there is scarce data about its application for non-

melanoma skin cancer. We think it could be an alternative treatment for non-surgical patients. Methotrexate could be considered a neo-adjuvant therapy to decrease the size of the cSCC and subsequently facilitate surgery.

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