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CASE REPORTS
PRIKAZI SLUČAJEVA

PERINEURAL METASTASIS OF CUTANEOUS SQUAMOUS CELL CARCINOMA OF THE NOSE AND PERIOCULAR REGION – A CASE REPORT

PERINEURALNO METASTAZIRANJE KUTANOG SKVAMOCELULARNOG KARCINOMA NOSA I PERIOKULARNE REGIJE – PRIKAZ SLUČAJA

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Abstract

Introduction. Cutaneous squamous cell carcinoma is the second most common malignant skin tumor and predominant affects the head and neck region. Although most cases have a favorable outcome following surgical excision, high-risk tumors—particularly those exhibiting perineural invasion—are associated with aggressive behavior, local recurrence, and metastatic spread. **Case Report.** We present the case of a 66-year-old woman with high-risk cutaneous squamous cell carcinoma of the nose and glabellar region. Clinical examination and computed tomography demonstrated full-thickness involvement of the nasal pyramid, with destruction of the cartilaginous septum and the right nasal bone. The patient underwent total nasal amputation with R0 resection and local reconstruction. Histopathological analysis revealed a keratinizing squamous cell carcinoma with marked perineural invasion. Although adjuvant radiotherapy was indicated, the patient declined further treatment. Three months after surgery, she developed an orbital metastatic lesion manifesting by ptosis and periorbital swelling. The patient subsequently died due to acute intracranial hemorrhage. **Conclusion.** This case illustrates the aggressive nature of high-risk cutaneous squamous cell carcinoma with perineural invasion and its potential for rapid metastatic progression despite complete surgical resection. Early identification of histopathological risk factors and timely implementation of adjuvant oncologic therapy are crucial for improving outcomes in patients with perineural invasive cutaneous tumors.

Key words: tumori kože; skvamozni karcinom; nos; metastaza; invazivnost tumora; faktori rizika; ishod lečenja

Sažetak

Uvod. Skvamocelularni karcinom kože je drugi najčešći maligni tumor kože, sa dominantnom lokalizacijom u regiji glave i vrata. Iako većina tumora ima povoljan tok nakon hirurške ekscizije, visokorizične forme, naročito one sa perineuralnom invazijom, pokazuju sklonost ka lokalnoj recidivnosti i metastaziranju. **Prikaz slučaja.** Prikazana je pacijentkinja starosti 66 godina sa visokorizičnim skvamocelularnim karcinomom kože nosa i glabelarne regije. Kliničkim i radiološkim pregledom kompjuterizovanom tomografijom, tumor je zahvatao punu debljinu nosne piramide sa destrukcijom hrskavičavog septuma i desne nosne kosti. Učinjena je totalna amputacija nosa sa R0 resekcijom i lokalnom rekonstrukcijom. Patohistološki je potvrđen keratinizujući planocelularni karcinom sa izraženom perineuralnom invazijom. Iako je adjuvantna radioterapija bila indikovana, pacijentkinja ju je odbila. Tri meseca nakon operacije razvila je metastatsku leziju orbite sa kliničkom slikom ptoze i periorbitalnog otoka. Kratko nakon toga preminula je usled akutne intrakranijalne hemoragije. **Zaključak.** Ovaj slučaj ilustruje agresivan tok visokorizičnog skvamocelularnog karcinoma kože sa perineuralnim metastaziranjem i brzom progresijom bolesti uprkos kompletnoj resekciji. Rano prepoznavanje histoloških faktora rizika i sprovođenje adjuvantnog onkološkog lečenja od suštinskog su značaja za poboljšanje ishoda kod pacijenata sa perineuralno invazivnim tumorima kože.

Ključne reči: Skin Neoplasms; Carcinoma, Squamous Cell; Nose; Neoplasm Metastasis; Neoplasm Invasiveness; Risk Factors; Treatment Outcome

Introduction

Cutaneous squamous cell carcinoma (cSCC) is the second most common skin malignancy, with more than 80% of cases occurring in the head and neck region. It belongs to the group of non-melanoma skin cancers, which collectively account for approximately one-third of all malignant tumors worldwide [1,2]. The most important etiological factor is cumulative damage from chronic ultraviolet (UV) radiation exposure. Advanced aid and immunosuppression significantly increase the risk of disease development and progression [1,3].

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Abbreviations

AJCC – American Joint Committee on Cancer
BWH – Brigham and Women's Hospital (prognostic staging system for cSCC)
cSCC – Cutaneous Squamous Cell Carcinoma
CT – computed tomography
HG1 – Histologic Grade 1 (well-differentiated carcinoma)
IMRT – intensity-modulated radiotherapy
MRI – magnetic resonance imaging
NCCN – National Comprehensive Cancer Network
PD-1 – Programmed Death-1 (immune checkpoint receptor)
PNI – perineural invasion
R0 – complete surgical resection with negative margins
VMAT – Volumetric Modulated Arc Therapy

Case Report

A 66-year-old woman presented with a *de novo* tumor lesion on the skin of the nose that had first appeared approximately seven months earlier. Since its onset, the lesion had progressively enlarged and was associated with intermittent bleeding. Three months after the initial lesion development, the patient noticed a second, similar lesion on the skin of the nasal root above the right eye. Her medical history was notable for surgically treated –uterine adenocarcinoma 13 years earlier, without evidence of recurrence. She denied alcohol consumption, tobacco use, or exposure to psychoactive substances. The patient was retired, but had previously worked in agriculture, with long-term occupational exposure to ultraviolet radiation.

Figure 1. Preoperative condition

Figure 2. Preoperative condition - profile

On physical examination, an exophytic, irregular tumor mass measuring approximately 4 cm in diameter was observed, completely covering the nasal pyramid and exhibiting surface ulceration **(Figures 1 and 2).** Endonasal examination revealed full-thick-

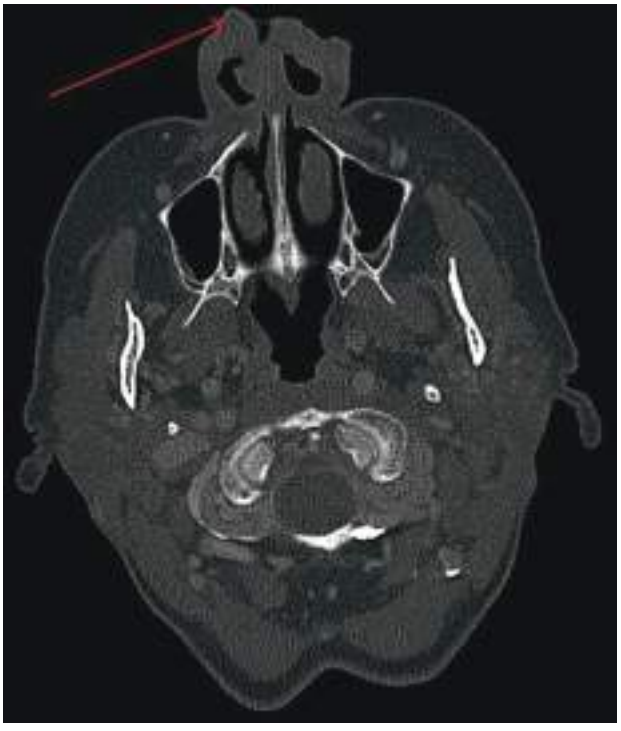

Figure 3. CT scan of the head - tumoral change and involvement of the soft tissues of the nose - indicated by an arrow

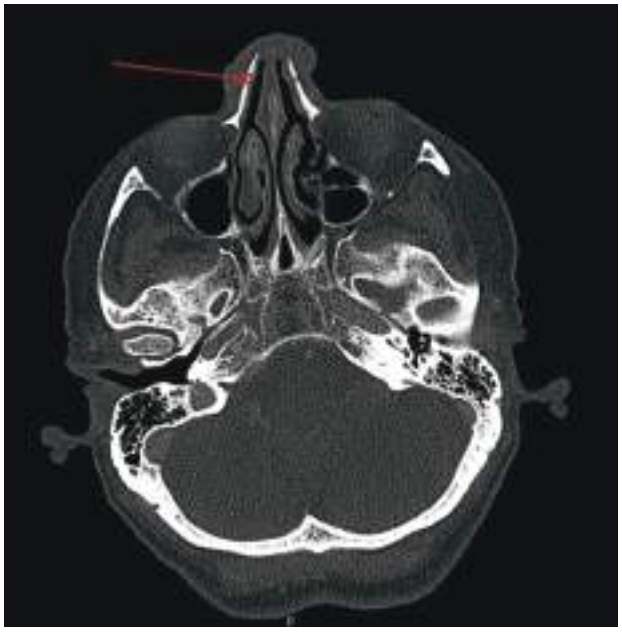

Figure 4. CT scan of the head - tumoral change and involvement of the bony structures of the nose - indicated by an arrow

Figure 5. Postoperative condition - 10 days after surgery

ness infiltration of the nasal alae and columella, with extension to the nasal mucosa and destruction of the cartilaginous septum, which was partially exposed on the dorsal aspect of the nose. Additionally, an oval tumor lesion measuring 12 mm in diameter was present in the glabellar region. This lesion was elevated above the skin surface, with undermined borders and central necrosis, and showed no continuity with the primary nasal tumor **(Figure 1).** Multislice computed tomography (CT) of the facial bones, paranasal sinuses, and brain demonstrated infiltration of the full thickness of the nasal skin, alae, columella, cartilaginous septum, and right nasal bone, without evidence of invasion into adjacent facial structures or

Figure 6. Postoperative condition - 10 days after surgery - profile

intracranial extensions **(Figures 3 and 4).** Ultrasonography of the regional lymph node basins revealed no enlarged or morphologically suspicious lymph nodes. The patient underwent total nasal amputation with resection of the involved portions of the right nasal bone and cartilaginous septum, as along with excision of the glabellar lesion using a 10-mm safety margin. Reconstruction of the glabellar and infraorbital defects was performed using local V-Y advancement flaps, while the defect created by removal of the nasal pyramid in the region of the piriform aperture was left to heal by secondary intention (*per secundam intentionem*) **(Figures 5 and 6).** The postoperative course was uneventful, apart from minor periorbital hematomas. Two weeks after surgery, complete wound healing was achieved, with progressive marginal epithelialization of the piriform aperture defect. Histopathological examination revealed *carcinoma planocellulare keratodes exulceratum et infiltrativum* involving the skin and fibrous, adipose, muscular, chondroid tissues, as well as the perineural space (HG1). All resection margins were free of tumor tissue, confirming an R0 resection) Adjuvant radiotherapy was recommended postoperatively, but the patient declined further treatment. Three months later, she developed swelling in the region of the right medial canthus accompanied by ptosis of the right upper eyelid. Magnetic resonance imaging (MRI) of the head revealed a metastatic lesion involving the orbital roof, with infiltration of the eyeball and eyelid. Two weeks thereafter, the patient died from acute intracranial hemorrhage. Autopsy

confirmed the presence of a 14-mm metastatic tumor in the right orbit, which had extended into the anterior cranial fossa, eroded the ophthalmic artery, and caused fatal intracranial bleeding. Histopathological analysis confirmed the lesion as a metastasis of squamous cell carcinoma.

Discussion

Surgical excision remains the gold standard in the treatment of cSCC. Despite generally favorable outcomes following complete excision, local recurrence occurs in approximately 3–5% of cases, metastatic disease develops in 3-16%, and disease-specific mortality ranges from 1.5–7.7% [3]. Tumors located on the ear, nose, lips, and temporal region exhibit higher rates of both metastasis and local recurrence. Histopathological parameters defining low- and high-risk tumor types include resection margin status, tumor size, depth of invasion, degree of differentiation, and the presence of perineural invasion [1,3,4]. According to both the AJCC and BWH staging systems, the tumor presented patient in this case fulfilled multiple high-risk criteria, including tumor diameter greater than 2 cm, thickness exceeding 2 mm, invasion of subcutaneous fat, cartilage and bone involvement, and extensive perineural invasion [1]. Although surgical margins were negative and consistent with European guideline recommendations for cSCC management [5], the cumulative presence of these adverse features indicated an aggressive tumor phenotype with a high probability of metastasis and local recurrence, associated with reduced overall survival [3,4,6,7]. Given the high-risk features, adjuvant radiotherapy was indicated postoperatively in accordance with National Comprehensive Cancer Network (NCCN) guidelines [7]. Perineural invasion (PNI) represents a particularly ominous histopathological finding and is defined as tumor cell infiltration with the perineural space, typically involving at least one-third of the nerve circumference. Immunohistochemical staining with pancytokeratin and S-100 protein is instrumental in confirming even subtle PNI, which may otherwise be misinterpreted as perineural inflammation on routine hematoxylin-eosin staining [8]. A distinctive and clinically significant characteristic of perineural spread is its discontinuous pattern: tumor cells may skip nerve segments, leaving intervening regions apparently uninvolved while progressing proximally along neutral pathways [4]. This biological behavior explains the use of adjuvant radiotherapy in high-risk tumors with PNI, even after R0 resection. Tumors of the periocular and eyelid region are associated with particularly aggressive behavior, demonstrating higher rates of lymphatic dissemination and perineural spread [9]. While adjuvant radiotherapy significantly improves local control and disease-free survival in high-risk cSCC, its use in the periocular region must be carefully balanced against the potential risk of vision impairment [8]. Modern conformal radiotherapy techniques, such as intensity modulated radiotherapy (IMRT) and volumetric-modulated arc therapy (VMAT), allow for excellent sparing of adjacent organs and minimize risk of exposure to radiation of organs at risk [10,11]. Proton therapy, in particular, is recommended for head and neck malignancies due to the close proximity of organs at risk, and provides even better result [12,13]. These treatment options should be thoroughly discussed with patients in the adjuvant setting, given the strong evidence supporting their role in high-risk disease. In the present case, therapeutic options became limited due to rapid disease progression and the patent's refusal of adjuvant treatment. According to current standards, immunotherapy with PD-1 inhibitors represents the treatment of choice for unresectable, locally advanced, or metastatic cSCC. Cemiplimab and pembrolizumab are the two approved agents in this setting, with cemiplimab most commonly used as first-line therapy. These agents have demonstrated durable responses and significant survival benefits in cSCC [6,8,14,15]. Unfortunately, in this patient, further oncological treatment was declined due to severe psychological distress and loss of therapeutic motivation.

Conclusion

This case illustrates the markedly aggressive clinical behavior of cutaneous squamous cell carcinoma of the nose with perineural invasion and metastatic spread, despite complete surgical excision with negative margins. The presence of extensive perineural invasion and deep tissue infiltration underscores the critical importance of identifying high-risk histopathological features and implementing adjuvant oncologic therapy when indicated. Early recognition of aggressive tumor variants, multidisciplinary treatment planning, and close postoperative surveillance are essential to improving outcomes in patients with high-risk cutaneous squamous cell carcinoma.

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