

Cavernous sinus syndrome secondary to trigeminal nerve invasion by cutaneous squamous cell carcinoma: A case report and brief review

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ABSTRACT

Objectives: Cutaneous squamous cell carcinoma (cSCC) has a broad clinical spectrum, especially when it affects the head and neck. Given the possible presentations, there is perineural dissemination, with an unfavorable prognosis and involvement of less differentiated tumor cells. A possible outcome is cavernous sinus syndrome (CSS), which encompasses the cavernous sinus, an anatomical structure that includes the oculomotor, trochlear, abducens nerves and the V1 and V2 branches of the trigeminal nerve.

Methods: We present a 62-year-old white man who manifested unilateral progressive ptosis, binocular diplopia and supraorbital pain in the right eye.

Results: The relevant history of skin neoplasms on the head raised the diagnostic hypothesis. Neuroimaging evaluation demonstrated nerve infiltration of the trigeminal nerve with tumor expansion at the level of the ipsilateral cavernous sinus.

Discussion: The concomitance between cSCC and CSS correlates with the participation of the neural growth factor and the overexpression of programmed cell death protein 1 (PD-1), with dermatological and neurological manifestations. In this context, the standard treatment used is cemiplimab, an immunotherapy used in unresectable and metastatic tumors and recently emerging as neoadjuvant therapy in surgical cases. The present report illustrates the association of such entities with the use of the described monoclonal antibody.

Practical implications

We raise the spectrum of differential diagnosis of unilateral cavernous sinus syndrome with perineural infiltration of skin tumors in the head, especially when there is facial pain included in the clinical syndrome, which infers a high suspicion of trigeminal nerve involvement.

Introduction

cSCC is the second most prevalent skin neoplasm, with a favorable clinical course after diagnosis and appropriate management, although its incidence has been increasing in recent years. Risk factors include low Fitzpatrick's phototypes, advanced age, immunosuppression, and exposure to ultraviolet radiation [1]. However, the rate of metastases

can reach 5 %, with aggressive behavior and a poor prognosis in specific cases, especially when there is perineural invasion [2,3]. In this context, the overall survival rate of patients with locally advanced disease or metastases, estimated at 5 years, ranges from 51 to 64 % [1].

Secondary metastatic nerve involvement can lead to CSS, with consequences resulting from the cranial nerves involved. The trigeminal and facial nerves are characterized by a long path, passing through soft tissues and bone structures. There are often ophthalmological manifestations, as well as pain, such as ocular and facial pain and headache, in addition to hypoesthesia in the trigeminal branches topography. It has a prolonged course, initially asymptomatic and deep dissemination, leading to diagnostic postponement [2–4].

Perineural invasion is correlated with head-and-neck cSCC in approximately 2.5–14 % of general cases. Higher incidences are associated with the location status of the cSCC, for e.g. periocular sites,

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which could represent about 36 % of perineural invasion affection [4]. This process is mediated by neurotrophic factors and complex intracellular signaling cascades with remodeling of the microenvironment. This behavior indicates a higher risk of locoregional recurrence, especially when the invasion is extratumoral, multifocal, and involves nerve tissue larger than 1 mm. In these cases, the prognosis is worse when compared to intratumoral involvement of the nerve tissue alone [5].

When locally advanced, the neoplasia often requires adjuvant therapy. Immunotherapy is emerging as a promising alternative in metastatic and unresectable cSCC [6].

Case report

A 62-year-old white man presented a history of progressive ptosis in the right eye. In a neurological evaluation, he reported that the signs and symptoms began about eleven months ago, with the onset of supra-orbital pain in the right eye. The pain was intense, had stabbing and shock patterns, and had a low response to common analgesic drugs. After two months from onset, binocular diplopia, ophthalmoplegia and ptosis surged in the ipsilateral eye. Emergency care was required, with the use of carbamazepine, amitriptyline and corticosteroids without any improvement. About five months from onset, visual acuity began to decrease (20/80 to 20/200) in the right eye for a trimester.

Past medical history includes numerous cutaneous neoplasms on the head, followed up as outpatients by the dermatology department for 20 years, with previous excisional biopsies revealing squamous cell carcinoma (SCC) and basal cell carcinoma (BCC).

On admission physical examination (see Fig. 1), the patient presented isolated paralysis of the right frontal muscles, preserved direct and consensual photomotor reflexes in the left eye and absent in the right eye, medium-fixed pupil on the right, in addition to ophthalmoplegia and proptosis in the same eye. In addition, there was hypoesthesia in the territory innervated by the V1 and V2 branches of the trigeminal nerve on the right, preserving V3.

Magnetic resonance Imaging (MRI) of the skull and orbits (see Fig. 2) revealed an expansive mass extending from the subcutaneous tissue of the right supraorbital region, passing through the supraorbital foramen into the orbit, superior orbital fissure, cavernous sinus and cerebellopontine angle cistern on the same side, maintaining contact with

the optic nerve posteriorly. The right cavernous sinus was invaded and enlarged, with medial deviation of the internal carotid artery on this side, as well as Meckel's cave and foramen ovale, with local insinuation into the right masticatory space. The lesion followed the trigeminal path, in contact with the lateral face of the pons. Serum levels of the angiotensin-converting enzyme, IgG4 and ANCA showed a normal range.

Based on the histopathological analysis of the right supraorbital tissue, squamous cell carcinoma was observed invading the fibrous tissue locally, with no evidence of cervical or pulmonary metastases.

Given these findings, the patient was referred to a specialized oncology service, with a proposal for palliative radiotherapy. Initially, he underwent four chemotherapy sessions (with carboplatin and paclitaxel), thirty radiotherapy sessions focusing on the right eye lesion, and seventeen more radiotherapy sessions to address a left frontoparietal skin lesion that had appeared later. This initial approach demonstrated a partial tumor response, even a second-line treatment was instituted with immunotherapy, cemiplimab, for 18 applications in one year of follow-up.

The neuroimaging exams of the oncological follow-up after the end of immunotherapy did not demonstrate a satisfactory response to the treatment. It was shown by comparative CT scan exams that there was an increase in the dimensions of the expansive/infiltrating lesion in the infra-orbital topography, also showing eyelid thickening and lateral rectus extrinsic muscle and the optic nerve infiltration, causing compression, proptosis and medial deviation of the right eyeball. In light of the new findings, the oncology service decided to carry out chemotherapy re-exposure to carboplatin and paclitaxel (scheme q21d). The ophthalmology team decided to enucleate the right eye due to recurrent refractory orbital pain and a non-functional organ.

Actually, he continues a follow-up by a multidisciplinary team. Until this final report on neoplastic stability.

Discussion

Perineural invasion of the trigeminal and facial nerve territories is not uncommon in malignant head and neck tumors, due to superficial subcutaneous nerve plexuses connected to these nerves, and the neoplasms that most commonly invade secondarily are the cavernous sinus



Fig. 1. (A) Isolated right frontal muscle palsy associated with right eyelid ptosis. (B) Multiple cutaneous neoplastic lesions associated with scars from previous excisional biopsies.

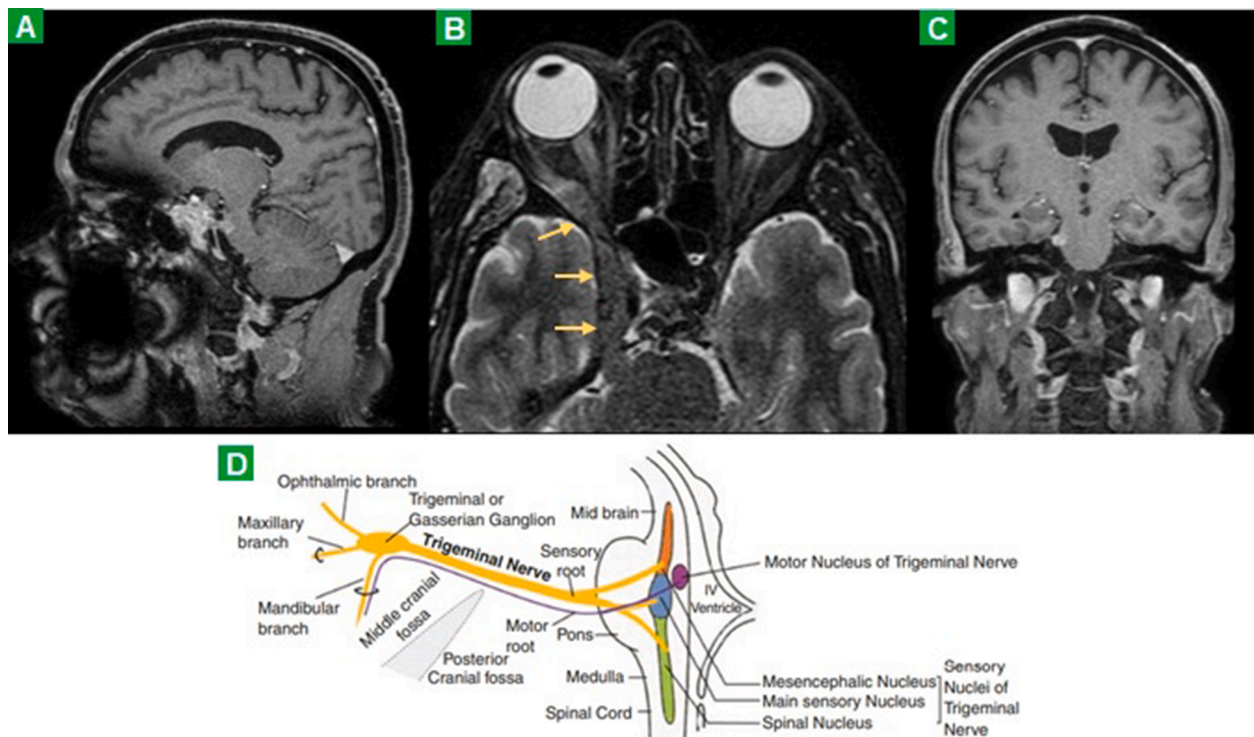


Fig. 2. MRI skull and orbits. (A) Sagittal T1-weighted gadolinium-enhanced section showing an expansile mass in the right orbital apex with irregular invasion into the preoptine cistern. (B) Axial T2 STIR section: arrows identifying an infiltrative lesion of the trigeminal nerve in the orbital apex transition, Meckel's cave, cavernous sinus, and trigeminal root emerging from the anterior pons. (C) Coronal T1-weighted gadolinium-enhanced section revealing involvement of the trigeminal nerve root on the right at its origin in the pons. (D) Anatomy of the trigeminal nerve to emphasize the path outlined in figures A, B, and C. Adapted from Singh GP. (2019). Anatomy of Trigeminal Nerve. Handbook of Trigeminal Neuralgia, 11–22. https://doi.org/10.1007/978-981-13-2333-1_2.

[7,8]. In these cases, there are reports of associated orbital involvement, due to the topography of the cranial nerves described. This behavior can cause CSS, with or without overlap with orbital apex and superior orbital fissure syndromes. There may also be dissemination of neoplastic lesions by contiguity through the foramen ovale [8,9]. Risk factors for this behavior are immunosuppression and desmoplasia associated with the growth of skin lesions [3]. cSCC neurotrophism correlates with interference of the neoplasm in the neural growth factor, a neurotrophin with a crucial role in neuronal development. There is also mediation of the neural cell adhesion molecule (N–CAM) [4]. The overexpression of immunological checkpoints, such as the programmed cell death receptor 1 (PD-1), causes the inactivation of T lymphocytes, with tumor cells escaping from the action of the immune system. It is worth remembering that perineural invasion confers a poor prognosis in cases of cSCC.

Noble formations pass through the cavernous sinus, such as the internal carotid artery, the oculomotor, trochlear, and abducens nerves, and the ophthalmic (V1) and maxillary (V2) branches of the trigeminal nerve. In SSC, the most affected nerve is the abducens (VI cranial nerve), followed by the oculomotor (III) [10].

Metastases in cavernous sinus topography are mainly differentially diagnosed as meningioma. Other hypotheses that should be considered are lymphoproliferative and granulomatous diseases, immunoglobulin G4-related disease, Tolosa-Hunt syndrome, stroke and peripheral facial palsy [8–11]. Possible clinical presentations within the scope of the syndrome are: ophthalmoplegia, diplopia, headache, reduced visual acuity, chemosis, paresthesia along the trigeminal territories, and, more rarely, stroke events. The most common manifestation, according to previous studies, is headache [11,12].

The orbitofrontal pain sometimes reported results from micro-ischemic processes in nerve territories due to tumor dissemination in the vasa nervorum [6]. Facial palsy can be complete unilateral, when peripheral, or isolated in the lower part of the face, when central affection.

The patient reported in this case presents atypical right frontal muscle palsy, justified by tumor expansion in the corrugator supercilii area, with involvement of the temporal branch of the facial nerve. Lagophthalmos is frequently described. According to Rodge et al. [11], topographic analysis by MRI showed predominantly orbital involvement in cases of SSC not classified as Tolosa-Hunt syndrome. The use of gadolinium helps to identify perineural dissemination.

Radical surgery with negative margins to remove the tumor is the first-choice treatment, also including modalities such as cryosurgery and Mohs micrographic surgery. Low-risk cSCC can also be approached by means of electrodesiccation or curettage [13]. Other techniques used are topical approaches with imiquimod and 5-fluorouracil (5-FU). However, due to the sometimes unfavorable location, such as on the face and with orbital involvement, the presence of positive margins becomes frequent, with a relevant rate of locoregional recurrences. Chemotherapy has a limitation in reducing its serum concentration when passing through the blood-brain barrier, and in many cases, it has a partial effect. Radiotherapy acts in a cytoreductive manner, when indicated. The latter can be used in adjuvant therapy when there are positive tumor margins after tumor resection and in high-risk cases, such as perineural invasion [14].

Cemiplimab, a monoclonal antibody against PD-1 receptors, is also emerging as a therapeutic alternative in the context of SCC with a worse prognosis and metastatic spread without surgical proposal. Blocking PD-1 leads to better action of T and NK lymphocytes on tumor cells, as well as modulating the activity of innate lymphoid cells [15]. Ongoing pivotal studies have shown a response to the drug in approximately 40 % of the patients analyzed. It can also be used in neoadjuvant therapy in surgical cases. In this case report, it was decided to start immunotherapy as a second-line treatment, given the poor tumor responsiveness to the standard chemotherapy regimen, carboplatin and paclitaxel, in addition to the advanced staging of the metastatic tumor (unresectable). A delay in tumor progression was observed during the year of use of cemiplimab,

however, there was cumulative local advancement of orbital structures that, after common discussion by the oncology service, it was decided to re-exposure to palliative chemotherapy.

Conclusion

Non-melanoma malignant skin lesions, especially cSCC, although it may present indolent behavior, should raise suspicions regarding the possibility of a more aggressive nature, culminating even in perineural invasion. In this context, when head-and-neck cSCC is approached, there may be secondary involvement of noble structures, including the central nervous system. SSC is an example of this possibility, which requires an active stance regarding early intervention. In this sense, new lines of therapy have emerged, such as the use of immunobiologicals, in an attempt to manage metastatic diseases. Finally, immediate investigation of conditions such as the above-mentioned can mitigate unfavorable outcomes, with a positive impact on morbidity and mortality.

Ethical compliance statement

The study was carried out in accordance with the code of international and local Ethics (Declaration of Helsinki). This study was reviewed and approved by the local ethics committee of the Hospital Universitário Cassiano Antonio Moraes – HUCAM - Universidade Federal do Espírito Santo – UFES (Vitória, ES, Brazil). Research ethics committee approval under CAAE n° 77,649,124.8.0000.5071. The consent was obtained by the own patient. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of written consent is available for review by the Editor of this Journal.

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CRedit authorship contribution statement

Helena Alves de Andrade Ribeiro: Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Lucas Grobério Moulim de Moraes:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Conceptualization. **David Jamil Hadad:** Visualization, Supervision,

Methodology, Investigation, Conceptualization. **Vitor Fiorin de Vasconcellos:** Validation, Supervision, Methodology, Investigation, Data curation, Conceptualization. **Giselle Alves de Oliveira:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that there are no conflicts of interest relevant to this work.

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