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# Cheek Numbness Caused by Perineural Tumor Invasion of the Infraorbital Nerve: A Review of 3 Diagnostically Challenging Cases

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Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
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**Conflict of interest:** None declared

## Case series

**Patient:** Female, 86 • Male, 58 • Male, 78  
**Final Diagnosis:** Squamous skin carcinoma  
**Symptoms:** Facial numbness • facial pain  
**Medication:** —  
**Clinical Procedure:** —  
**Specialty:** Otolaryngology

**Objective:** Challenging differential diagnosis





**Background:** Facial pain and numbness are common symptoms with a variety of causes; rarely, it is an initial sign of perineural infiltration of malignant tumors.

**Case Reports:** Here, we report 3 challenging cases, all presenting with pain and numbness of the cheek as the primary symptoms. Upon referral, there were neither signs of severe illness nor information about previous malignant diseases, while the diagnostic work-ups revealed additional involvement of the facial nerve in 2 of the cases. Surgical removal of the perineural tissue around the infraorbital nerve revealed perineural invasion by a squamous carcinoma. A more thorough review of their medical histories revealed that all 3 of the patients had had previous facial skin cancer.

**Conclusions:** Numbness or pain in the cheek may represent perineural invasion of a facial cutaneous carcinoma. This review of 3 cases addresses the necessity of identifying previous incidences of skin cancer in the medical history.

**MeSH Keywords:** Carcinoma, Squamous Cell • Facial Pain • Neoplasm Invasiveness • Neuralgia • Skin Neoplasms

**Full-text PDF:** <https://www.amjcaserep.com/abstract/index/idArt/907034>

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## Background

Facial pain, paresthesia, and motor deficits are commonly encountered in clinical practice, and can be caused by a variety of diseases [1,2]. The main causes of facial pain are dental problems and sinusitis [3], while other causes include temporomandibular joint disorders, trigeminal neuralgia, migraines, and post-herpetic neuralgia. The wide variety of causes makes this condition a diagnostic challenge; therefore, care is needed when diagnosing patients presenting with numbness of the face. Rarely, it is the sole sign of malignancy. Perineural invasion (PNI) has been observed in less than 5% of patients with cutaneous carcinoma, but the diagnosis is often delayed [1,4]. Here, we present 3 challenging cases presenting with facial pain and numbness. The diagnostic work-ups revealed that the lesions were caused by the spread of a tumor from previous facial skin cancer.

## Case Reports

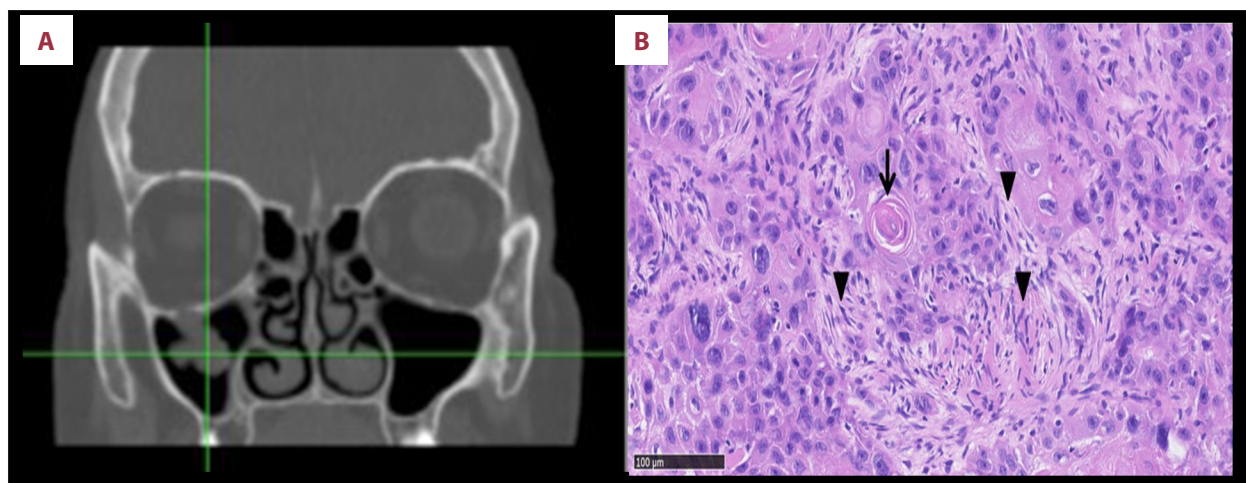
### Case 1

An 86-year-old woman was referred to our clinic with a 6-month history of numbness and pain in the right cheek, and chronic sinusitis was suspected. The ear, nose, and throat (ENT) examination did not reveal any abnormalities; therefore, a computed tomography (CT) scan was performed, showing a solid process in the right maxillary sinus in relation to the infraorbital nerve (Figure 1A). The tumor was removed via endonasal endoscopic surgery. The histology showed a well-differentiated squamous cell carcinoma (SCC) invading the infraorbital nerve and anterior wall of the maxillary sinus (Figure 1B). An extensive review

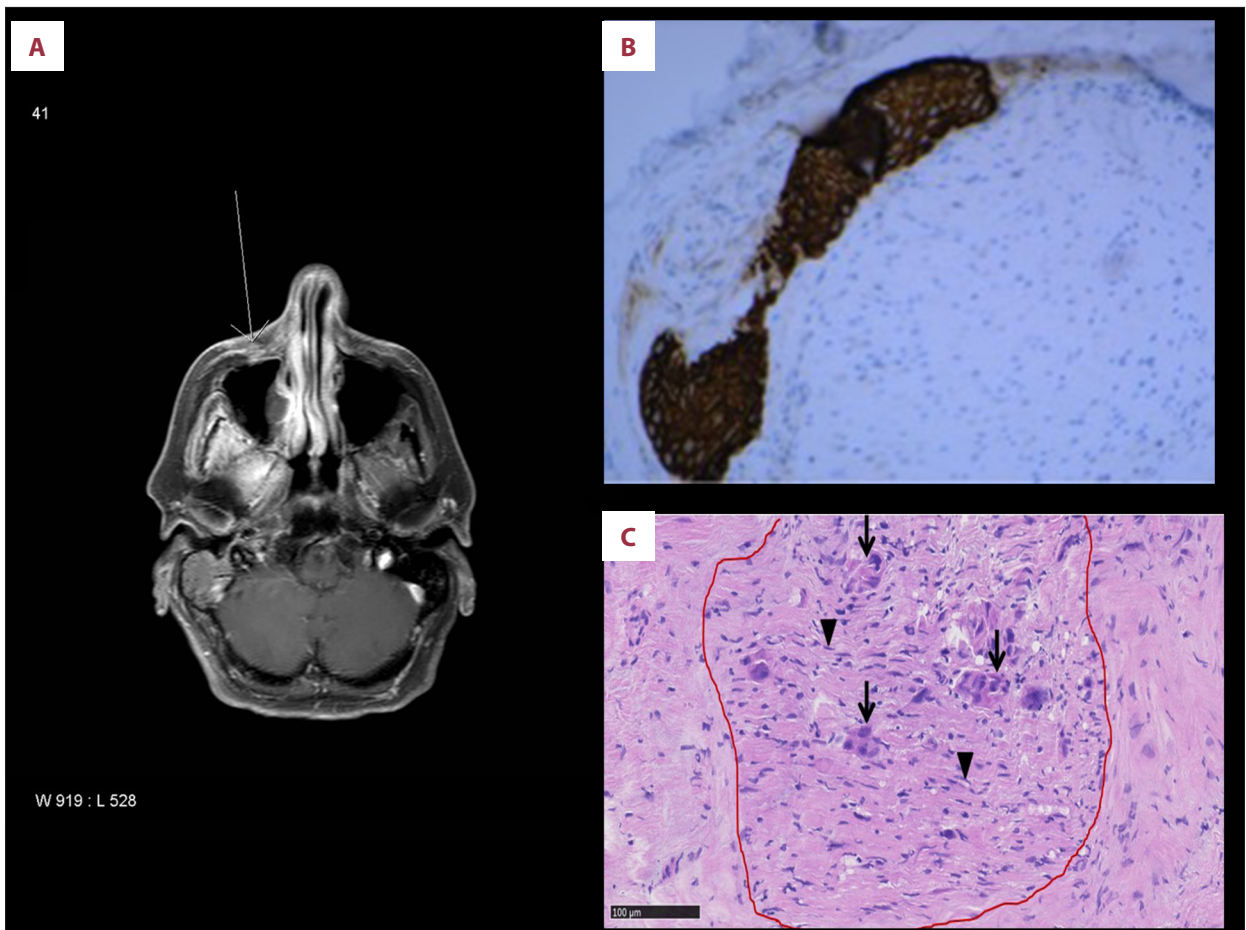
of her medical history revealed a well-differentiated SCC on the right cheek, diagnosed from a 2-mm punch biopsy taken 15 months earlier. The biopsy was 1.5 mm deep and entirely infiltrated by the carcinoma; however, no perineural invasion was found. The follow-up of the SCC at the Dermatology Department 9 months later was ended due to 2 negative control biopsies (each a 3-mm punch biopsy). At the time of referral to the ENT Department, there were no signs of recurrence of the facial skin cancer upon clinical examination. After sinus surgery, she completed radiation therapy of the right cheek and maxillary sinus. At the clinical control 3 months after the surgery, there was no sign of cutaneous recurrence.

### Case 2

A 58-year-old man was admitted to the Neurology Department due to pain and numbness of the right cheek, which had been going on for 4 months. Furthermore, the patient had facial palsy grade II as rated by the House Brackmann Classification [5]. An MRI showed pathological enlargement of the infraorbital nerve (Figure 2A). The patient was referred to the ENT Department, and the tissue around the nerve was resected from the right maxillary sinus via the Caldwell-Luc procedure. The histology showed an SCC invading the infraorbital nerve (Figure 2B, 2C). The patient's history was discussed at a multidisciplinary meeting. After addressing the patient's medical history, it became evident that he had been treated 5 times within the last 12 years for recurrent basal cell carcinoma (BCC) and actinic keratosis in the right temporal area, either by curettage or excision. Two of these older specimens from the right temporal area showed BCC and were curettage material. One specimen with BCC from the right temporal area was 2 mm deep with free resection margins. The last



**Figure 1.** (A) Case 1. Coronal CT of the sinuses used for image guidance during endoscopic surgery. A pedunculated tumor attached to the floor of the orbit in the right maxillary sinus is demonstrated. (B) Case 1. Biopsy from the infraorbital nerve. The nerve is almost entirely replaced by a squamous cell carcinoma. The arrowheads indicate the rest of the nerve, with small and often wavy nuclei. The arrow shows keratinization centrally located in a tumor island. Hematoxylin and Eosin (HE) stain.



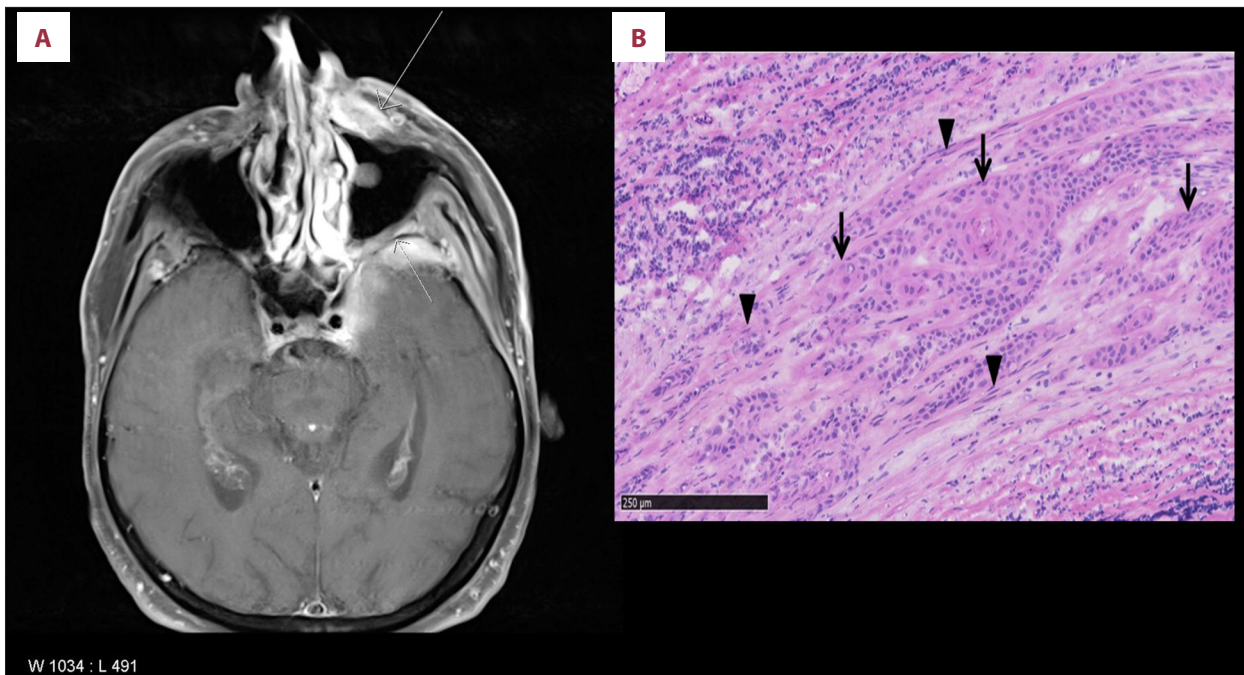
**Figure 2.** (A) Case 2. MRI, axial plane, showing enlargement around the infraorbital nerve on the right side, indicated by the arrow. (B) Case 2. Perineural invasion of the infraorbital nerve visualized by immunohistochemical staining for Cytokeratin 5. Original magnification  $\times 200$ . (C) Case 2: The contour of a nerve branch is highlighted in red. The arrowheads show the small nuclei of the nerve, and the arrows point to the large polygonal tumor cells from the squamous cell carcinoma. Hematoxylin and Eosin (HE) stain.

specimen that showed BCC from the right temporal area that was 5 mm deep and had free resection margins; however, it was  $<1$  mm from the base. The most recent specimen from the same area showed actinic keratosis and was removed by curettage. A positron emission tomography and a computed tomography scan (PET/CT) did not reveal any primary tumor. Subsequently, the patient underwent Caldwell-Luc surgery, in which the infraorbital nerve was removed up to the infraorbital foramen, including the bone and mucosal membrane in the maxillary sinus. Due to the non-radical resection, the patient underwent additional radiation therapy. Despite radiation therapy, the symptoms progressed, with increased numbness of the right facial side, partial facial palsy, tinnitus, and right hearing loss. A follow-up MRI showed metastasis in the right cerebellopontine angle, which was treated with stereotactic radiosurgery. Fifteen months after the referral to the ENT Department, the patient became psychotic, and an MRI showed a tumor in the frontal lobe of the brain. He was referred for

palliative treatment, and died of advanced cancer 18 months after the onset of symptoms.

### Case 3

A 78-year-old man presented to our clinic with severe left facial pain, paresthesia, and hypoesthesia of the left cheek. Prior to the referral, he had been treated for atypical headaches in the Neurology Department, and was evaluated with an MRI scan, PET/CT scan, and lumbar puncture. The MRI showed a process between the hard and soft palates. The patient's symptoms were discussed at a multidisciplinary meeting at which neurosurgeons, an otolaryngologist, and head and neck oncologists were present. The suspected tumor area in the palate was surgically removed, and the histology showed a collapsed retention cyst with atrophy of the surrounding salivary gland acini and fibrosis. Concurrently, the patient was treated for a recurrent actinic keratosis on the left side of his nose in the Plastic



**Figure 3.** (A) Case 3. MRI, axial plane, showing pathological enlargement around the infraorbital nerve and in the back of the maxillary sinus, highlighted by arrows. (B) Case 3: Biopsy from the infraorbital nerve. Visualized longitudinally cut peripheral nerve branch, with the infiltrating SCC splitting up the nerve fibers. Perineural inflammatory infiltrate is visible in the left upper and right lower corners of the picture. The arrowheads indicate the small nuclei of the nerve and the arrows point to the large polygonal tumor cells from the squamous cell carcinoma. Hematoxylin and Eosin (HE) stain.

Surgery Department. Although previously treated by curettage, the nasal lesion was excised shortly after the debut of neurological symptoms. The resected specimen showed SCC. The specimen was 4 mm deep and the margins were without SCC. Due to progressive neurological symptoms, the patient was referred for further treatment at the Neurology Department. A new MRI showed enlargement of the infraorbital nerve, extending from the maxillary nerve into the cavernous sinus and medial cranial fossa, and retrograde perineural invasion was suspected (Figure 3A). A deep submucosal biopsy from the infraorbital nerve showed a moderately differentiated SCC invasion (Figure 3B). Subsequently, the patient underwent radiation therapy of the skull base and the posterior wall of the maxillary sinus. Unfortunately, 1 year after radiation therapy, the patient died due to several comorbidities.

## Discussion

We have presented 3 cases of hypoesthesia or pain in the cheek caused by the spread of facial skin cancer. In Denmark (population 5.6 million), non-melanoma skin cancer is diagnosed in more than 13 000 patients every year, and the age at diagnosis is usually >65 years [6]. It develops on sun-exposed sites, such as the head and neck, and is frequently treated with curettage [7]. It is often considered to be an indolent disease,

and might not be mentioned in the patient's medical history, which can lead to diagnostic challenges and delays in treatment.

In our first case, the patient had had a biopsy-proven SCC in an ulcer on the right cheek; however, the Dermatology Department ended the follow-up due to negative clinical findings and follow-up biopsies. The prior biopsies could not be reviewed because the specimens had been discarded. A thorough examination of the skin showed no other lesions and the patient did not present with any other symptoms suggestive of a different primary tumor. However, the MRI scan showed no connection to the site of the prior skin SCC and no additional abnormalities. However, it is impossible to conclude that the patient did not have a new primary tumor that was not detected by our diagnostic work-up. The diagnostic specimen was a 2-mm punch biopsy, not an intended curative resection. Possibly, the lesion was not adequately removed; however, at clinical examination the lesion had regressed. The second patient had multiple recurrences of BCCs and actinic keratosis, mainly treated with curettage; nevertheless, an SCC was found invading the nerve. Despite the thorough diagnostic work-up, including MRI and PET-CT scans, we were unable to detect any other primary tumor. Since a new primary tumor was ruled out, we hypothesize that some of the actinic keratosis, treated only by curettage, may have been SCC. Also, there is a possibility that one of the prior BCC's was actually basaloid SCC and

the squamous component of the tumor had metastasized and caused PNI. However, as the specimens had been discarded, we were unable to review the prior biopsies.

The possibility of spread and progression of a lesion diagnosed as pre-cancerous actinic keratosis, as demonstrated by the third case presented here, is a well-known complication [8]. Curettage is known to carry a significantly higher risk of recurrence than excision; therefore, it has been suggested that curettage should not be used for recurrent tumors [9]. Fragmented curettage material, in which the relationship to the surrounding stroma has not been properly visualized, is a diagnostic challenge, and can lead to misdiagnoses, such as a missed diagnosis of highly differentiated or basaloid SCC. This may have happened in the second case.

The pathogenesis of PNI has not been fully elucidated. Recent theories suggest that a cleavage plane between the perineurium and the nerve fiber provide a path of lessened mechanical resistance, allowing cancer cells to spread [1]. Furthermore, it has been suggested that some SCCs have a predilection for PNI, which are highly aggressive tumors with rapid and invasive growth [10].

PNI occurs in 3–14% of skin SCCs and are much more common than in BCCs. The initial symptoms are pain, numbness, and/or motor deficits. Most frequently, it involves the fifth and seventh cranial nerves [11]. Moreover, PNIs can be classified as either incidental or clinical [1,2]. An incidental PNI refers to the asymptomatic stage, in which only microscopic invasion is present. In a previous review, approximately 60–70% of the patients with PNIs were asymptomatic [1]. The symptomatic stage, when a patient presents with sensory or motor changes, is categorized as a clinical PNI; however, these symptoms

can often be misinterpreted, leading to a delay in diagnosis. A clinical PNI is relevant for prognostication since the local control rate is only 55%; furthermore, a clinical PNI exhibits more aggressive behavior, as observed in our 3 cases [12,13]. Recently, the 7<sup>th</sup> edition of the American Joint Committee on Cancer staging system for cutaneous skin cancers was updated, determining PNIs to be high-risk features [14].

The treatment of a PNI depends on the type and location. In a recent study, the best treatment strategy for a clinical PNI was suggested to be surgical resection and adjuvant radiotherapy [15]. In Denmark, a PNI is considered to be a high-risk feature requiring surgical removal with a resection margin of at least 6 mm, and in selected cases, adjuvant radiotherapy [16].

## Conclusions

Facial numbness and/or pain are common clinical symptoms, rarely caused by malignancy. However, common cutaneous SCC should be kept in mind, especially by otolaryngologists, when evaluating elderly patients with signs of facial numbness and pain, and a history of skin carcinoma.

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## Conflict of interest

None.

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