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Neurological improvement of perineural and leptomeningeal spread of squamous cell carcinoma treated with intrathecal chemotherapy and systemic EGFR inhibition

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Squamous cell carcinoma (SCC) is a common cancer of the skin. Risk factors include fair skin, excessive sun and ultraviolet light exposure, and history of xeroderma pigmentosa. Perineural invasion (PNI), an uncommon manifestation of SCC, involves microscopic tumor cells invading various layers of the nerve sheath. It is associated with a poorer prognosis. Standard treatment for PNI includes radiation therapy. Here, we describe a case an older gentleman with a history of SCC with PNI successfully treated with erlotinib and intrathecal chemotherapy.

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Keywords: cutaneous squamous cell carcinoma • EGFR inhibitors • leptomeningeal metastasis • perineural invasion

Practice points

- Perineural invasion (PNI), an uncommon manifestation of squamous cell carcinoma (SCC), is associated with a poor prognosis.
- Findings of cranial neuropathy in clinical examination of patients with SCC may suggest PNI.
- MRI PNI findings may include enlargement or abnormal enhancement of the nerve.
- It is important to be observant of perineural spread for SCC and always consider the possibility of leptomeningeal metastasis.
- Adjuvant radiation therapy is considered one of the limited treatment options for SCC with PNI, particularly in patients where surgery is not a viable option.
- Intrathecal chemotherapy has become the mainstay of treatment in leptomeningeal metastasis.
- High expression of EGFR in cutaneous SCC makes EGFR inhibitors a rational choice in patients with advanced disease.

Cutaneous squamous cell carcinoma (SCC), the second most common skin cancer worldwide, has a substantial risk of metastasis in contrast to basal cell carcinoma, the most prevalent form that carries less risk of metastases [1]. Perineural invasion (PNI) is a rare pathologic feature associated with SCCs with a reported incidence ranging from 3 to 6% [2,3]. This under-recognized route of metastasis can account for distant tumor spread well beyond local invasion, especially leptomeningeal metastasis (LM). Although the pathogenesis remains incompletely understood, PNI seems to play a role in many different malignancies such as pancreas, colon, rectum, prostate and head and neck cancers [4].
**Case presentation**

A 68-year old Caucasian male with history of SCC in the left temple was seen in our clinic for evaluation of facial numbness. He has a history of hyperlipidemia, hypertension and a triple vessel coronary artery bypass graft for coronary artery disease. 2 years prior, he had left temple SCC treated with Mohs micrographic surgery with negative margins. He presents now with numbness on the left side of his face that includes the upper lip. The symptom was initially attributed to scar tissue. Shortly after, he developed a nodule in the left buccal area. A biopsy of the nodule revealed SCC that was immediately treated with local radiotherapy. 1 year later, another nodule appeared in the left temple area for which he completed another course of radiotherapy. A few months after radiotherapy, he started to experience horizontal diplopia and an eye exam showed medial deviation of his left eye. A neurological exam revealed trigeminal nerve paresthesia of the left face and paresis of the left abducens and facial nerve. He was prescribed dexamethasone 4 mg oral daily. MRI of his face and brain showed extensive perineural spread along the ophthalmic (V1), maxillary (V2) and mandibular (V3) branches of the left trigeminal nerve proximal to the left cavernous sinus, Meckel's cave and cisternal segment. There was evidence of denervation atrophy of the left muscles of mastication. The cancer spread around the left facial nerve and mild asymmetric, abnormal enhancement of the dura along the left middle cranial fossa (Figure 1A & B). Spinal MRI showed nonspecific 5-mm nodular thickening and enhancement within the left posterolateral thecal sac, which was highly suspicious of leptomeningeal neoplastic disease (Figure 1C). The lumbar puncture showed no malignant or atypical cells, but revealed elevated white blood cells of 48 (normal: 0–10 mm$^3$) and elevated total protein at 80 mg/dl (normal: 15–45 mg/dl).

The combination of the results from his spinal MRI and his cerebrospinal fluid (CSF) sample increased the clinical suspicion of LM. The decision was made to immediately start aggressive treatment with intrathecal chemotherapy consisting of cytarabine liposome injection (Depocyt$^\text{©}$) 50 mg and methotrexate (MTX) 12 mg every 2 weeks. In addition, radiotherapy to the left cavernous sinus and adjacent areas of involvement was delivered with 54 Gray in 30 fractions. Treatment with cetuximab (Erbitux$^\text{©}$), an EGFR inhibitor, was initiated after radiation at a loading dose of 400 mg/m$^2$, followed by a weekly standard dose of 250 mg/m$^2$. CSF sample taken before administration of his second dose of intrathecal chemotherapy showed large atypical cells. The patient tolerated the first three sessions with minimal side effects. Shortly after the fourth treatment, the patient experienced an episode of chemical meningitis after suffering from dehydration, a known side effect of the intrathecal chemotherapy agents. This event, and two subsequent cytologies that were negative for malignant cells, prompted a reduction of intrathecal chemotherapy treatments to once every month. A follow-up MRI of face and brain 3 months later showed overall mixed response. The previously described enhancement along the left medial middle cranial fossa and the trigeminal nerve decreased, however, new soft tissue enhancement was seen at the left lateral aspect of the maxilla, inferior alveolar nerve and external auditory canal. Due to the ambivalence of the MRI images, the patient was sent for a fluorine-18-fluorodeoxyglucose positron emission tomography scan of his head and body. This showed mild fluorine-18-fluorodeoxyglucose activity consistent with MRI findings, possibly reflecting treatment effect. The rest of the body showed no abnormal foci of uptake. Clinically, his neurological symptoms remained stable with notable improvement in his left facial movement. Treatment-related toxicities included minimal rash on his face and chest consistent with an anti-EGFR effect from the cetuximab.

There were two palpable small nodules in the subcutaneous tissue at the inferior aspect of the left lower eyelid that appeared to be increasing in size. The lesions were removed and cetuximab was discontinued. Pathology results revealed SCC with extensive PNI. The patient was switched to a daily regimen of erlotinib (Tarceva$^\text{©}$) 150 mg. Aside from a mild rash and diarrhea, he experienced no side effects. Restaging MRI scans showed a stable intracranial disease with a decrease in the previously described enhancement along the left medial aspect of middle cranial fossa (Figure 2). There were no new cutaneous malignant lesions noted during physical examination. Neurological exam showed resolution of his left abducens nerve palsy and diplopia. He showed evidence of radiographic and neurological clinical stability for more than a year after the initial diagnosis. However, he developed multiple medical complications and prolonged hospitalizations and erlotinib was held. He never recovered from his medical illnesses and eventually developed neurological progression confirmed on imaging of the brain and spine (Figure 3) and died of acute cardiorespiratory cause. An autopsy showed evidence of continued SCC in nerves and leptomeninges.

**Discussion**

PNI from SCC has been recognized as an important negative prognostic factor in overall survival [5]. Cutaneous SCCs have been sporadically described to cause neurological symptoms due to PNI. The majority of these patients...
Perineural and leptomeningeal spread of squamous cell carcinoma

Figure 1. T1 MRI of the brain and spinal cord postgadolinium. (A & B) Abnormal signal intensity in the cavernous sinus. (C) Abnormal signal intensity noted throughout spinal cord, especially in lumbosacral region.

present with cranial neuropathy, with possible extension to the skull base. The local control rate at this time remains at 25% [6]. LM in cutaneous SCCs with evidence of CSF involvement is extremely rare and has only been described in five cases [7–10]. At this stage of the disease, treatment remains palliative and stabilizing or diminishing neurological deficits. LM occurs when retrograde dissemination of malignant cells along the nerve cause tumor invasion of the meninges and CSF. This can be viewed as the most devastating consequence of PNI. Due to the blood–brain barrier (BBB), the cancer cells that reach the CSF will encounter relative protection from the host’s defensive immune system. As a result, they can freely migrate throughout the CNS and reattach by directly traversing the pial membrane into the spinal cord or nerves [11]. The prognosis is poor for patients diagnosed with LM and the median survival time of treated patients is only 4–6 months [12]. Due to the limited BBB penetration of systemic chemotherapeutic agents, intrathecal chemotherapy has become the mainstay of treatment in LM. Studies show that both liposomal cytarabine and MTX have individually treated LM effectively [13]. A general high expression of EGFR in cutaneous SCC makes EGFR inhibitors a rational choice in patients with advanced disease. Erlotinib has been approved for the treatment of non-small-cell lung cancer and pancreatic cancer [14]. Experience in aggressive
cutaneous SCC is limited but promising. Complete and partial responses were seen in patients who failed all other therapies in several case reports [15,16]. A literature review identified five cases of leptomeningeal dissemination of a primary cutaneous SCC with evidence of CSF involvement [7–10]. These cases have been summarized in Table 1. Due to the limited number of patients, no standard treatment exists. In most cases, treatment only consisted of radiotherapy [7–9], while one patient received concomitant intravenous MTX [7]. To the best of our knowledge, this is the first case description of a cutaneous SCC with LM spread successfully treated with intrathecal chemotherapy. These patients unfortunately have a poor prognosis. No patient survived beyond 6 months after diagnosing LM; however, our patient survived well over 12 months after his diagnosis. This excellent response might be partly attributable to the early diagnosis of LM. Contrary to other patients [13–16], our patient had not shown any clinical signs of widespread LM when diagnosis occurred. It is important to be observant of perineural spread for SCC and always consider the possibility of LM. This report shows that intrathecal chemotherapy with Depocyt (cytarabine liposome injection) and MTX, and systemic EGFR inhibitors could result in neurologic disease control in LM from SCC.
Table 1. Case reports of cutaneous squamous cell carcinomas with leptomeningeal metastasis.

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<tr>
<td>Begemann et al. (2003)</td>
<td>72</td>
<td>Weakness hips</td>
<td>Malignant cells</td>
<td>MRI: nodular enhancement thoracic cord</td>
<td>Spinal lesions (3575 cGy in 13 Fr)</td>
<td>Three courses IV MTX (3500 mg/m²) every other week</td>
<td>6 months</td>
<td>[7]</td>
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<tr>
<td>Zhu et al. (2004)</td>
<td>70</td>
<td>Lower extremity paresis</td>
<td>Malignant cells</td>
<td>MRI: LM enhancement craniovertebral junction</td>
<td>Local Rx (dose not specified)</td>
<td>–</td>
<td>3 months</td>
<td>[8]</td>
</tr>
<tr>
<td>Sullivan and Smee (2006)</td>
<td>51</td>
<td>Leg paresis, paresthesia and pain</td>
<td>Malignant cells</td>
<td>MRI: enhancing cauda equina and nerve roots</td>
<td>Cranial base (3700 cGy) and lumbosacral spine (3650 cGy)</td>
<td>–</td>
<td>Not mentioned (hospice discharge after 1 month)</td>
<td>[9]</td>
</tr>
<tr>
<td>Skripuletz et al. (2010)</td>
<td>68</td>
<td>Mental changes, headaches and unstable gait</td>
<td>Malignant cells</td>
<td>MRI: multiple enhancing nodules cervical and lumbar spine</td>
<td>Whole spine Rx (35 Gy in 15 Fr)</td>
<td>–</td>
<td>4 months</td>
<td>[10]</td>
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CSF: Cerebrospinal fluid; CT: Computed tomography; IT: Intrathecal; IV: Intravenous; LM: Leptomeningeal metastasis; MTX: Methotrexate; Rx: Radiation; SCC: Squamous cell carcinoma.

Conclusion & future perspective

Although perineural spread is common in the setting of SCC, there exists a rare possibility of LM. In patients where surgery is not an option, radiotherapy is the widely accepted treatment. While prognosis for patients with LM remains poor, early recognition of LM may improve outcomes. Currently, radiotherapy and IT chemotherapy are used as standard treatments for PNI. Despite these treatments, prognosis remains poor. EGFR inhibitors, such as erlotinib, are being considered as alternative options for PNI. As mentioned above, our patient’s symptoms and neurological function improved after receiving erlotinib. More studies need to be completed to verify erlotinib’s effects in the treatment of PNI in patients with SCC.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Informed consent disclosure

An IRB approved retrospective chart review protocol was used to review records and to allow the inclusion of patient medical and treatment history within this case report. The authors state that they have obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

References

Papers of special note have been highlighted as: ● of interest

5 Provides clinical information about perineural invasion (PNI) in cancer patients.
Describes PNI in the setting of head and neck cancer, which is relevant to the patient presented.


- Describes PNI in the setting of head and neck cancer, which is relevant to the patient presented.


- Provides the background for the use of intrathecal chemotherapy as a treatment option for patients with PNI.


- Provides the background for the use of intrathecal chemotherapy as a treatment option for patients with PNI.


- Presents three patients with SCC of the skin who underwent treatment with erlotinib, similar to the patient presented here.


- Discusses erlotinib as a management option in patients with metastatic SCC.