

Perineural tumour spread from colon cancer, an unusual cause of trigeminal neuropathy - a case report


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ABSTRACT

Malignant trigeminal neuralgia due to perineural spread along the branches of the trigeminal nerve, is known to commonly occur secondary to squamous cell carcinomas, lymphomas and adenoid cystic carcinomas in the head and neck region. Rarely metastases to the trigeminal nerve have been reported in breast cancer, prostate cancer and colon cancer. To the best of our knowledge trigeminal neuropathy due to skull base metastases and perineural spread along the maxillary (V2) and mandibular (V3) branches of the trigeminal nerve, secondary to colon cancer, has not been previously reported. The diagnosis in our index case was made on magnetic resonance imaging, and patient was treated accordingly by fractionated stereotactic radiotherapy, with subsequent relief of her pain.

CASE REPORT

CASE REPORT

Clinical History

A forty six year old lady, who was a known treated colon cancer patient, presented with clinical signs of trigeminal neuralgia since 1 month. Her main complaint was severe burning type of pain and numbness along the distribution of the trigeminal nerve branches V2 (maxillary) and V3 (mandibular) on the left side of the face in the cheek and jaw. The pain was unresponsive to conventional analgesics and badly affected the patient's quality of life. There was weakness of the muscles of mastication on her left side as well. There were no other cranial nerve abnormalities. She also had left sided ear pain. The patient was initially referred for a dental checkup, which was unremarkable. Subsequently an oncologic consultation suspected neoplastic trigeminal neuralgia as a cause of her pain and accordingly magnetic resonance imaging (MRI) of the brain and skull base was requested. The patient's

past history was significant for a sigmoid colon moderately differentiated adenocarcinoma, pT3N0M0 for which she underwent surgery three years ago followed by adjuvant chemotherapy completed six months later. After a period of six months, she was evaluated for dyspnea and cough, computed tomography (CT) scan showed a right hilar mass and pulmonary nodules with mediastinal lymphadenopathy. Fine needle aspiration cytology (FNAC) was suggestive of metastatic adenocarcinoma. She received radiation therapy and chemotherapy over a period of 2 years to which there was a partial response. The latest CT chest scan done one month prior to presentation showed that the disease had stabilized.

Imaging Findings

A magnetic resonance imaging (MRI) scan of the brain and skull base showed abnormal T2 bright signal intensity (SI) and post contrast T1 enhancing soft tissue in the region of the left pterygoid plates, and along the course of V2 and V3

branches of the left trigeminal nerve in the region of the foramen rotundum and the foramen ovale respectively, with intracranial extension into the floor of the middle cranial fossa, inferior most aspect of the cavernous sinus as well as the Meckel's cave (Figures 1,2). Abnormal T2 high signal intensity and contrast enhancement was also noted within the left levator veli palatini and to a lesser extent along the pterygoid muscles, the latter being best appreciated on T2 and apparent diffusion coefficient (ADC) map, suggestive of sub acute denervation changes (Figure 3). T2 hyper intense signal was also noted in the left mastoid air cells, probably as a result of secondary Eustachian tube dysfunction (Figure 3).

Diagnosis

Imaging (including MRI and PET-CT) was negative for any primary malignancy in the head and neck region. Clinical and endoscopy evaluation was also negative for malignancy in the upper aero digestive tract and the salivary glands. In view of the past history of colon cancer, the diagnosis of skull base metastatic disease with perineural spread along V2 and V3 branches of the left trigeminal nerve and resultant sub acute denervation changes of the above described muscles was considered. Histopathological confirmation was not possible as the patient refused a biopsy]

Management

The patient underwent palliative fractionated stereotactic radiosurgery to the skull base lesion, which resulted in considerable improvement in her pain.

Follow-up

In view of the infiltrative and extensive neural involvement shown by imaging, surgery was not considered. Only palliative support by stereotactic radiosurgery was undertaken, which resulted in significant relief of the patient's symptoms. A follow-up MRI done two months after the completion of stereotactic radiosurgery showed no significant change in the intracranial component of the disease, and an increase in the extra cranial component, which was expected in view of the limited field of radiosurgery given. Repeat MRI and PET-CT was negative for any primary malignancy in the head and neck region.

DISCUSSION

Etiology & Demographics

Malignant trigeminal neuralgia due to perineural spread along the branches of the trigeminal nerve, is known to commonly occur secondary to squamous cell carcinomas, lymphomas and adenoid cystic carcinomas in the head and neck region. Rarely metastases to the trigeminal nerve have been reported in breast cancer, prostate cancer and colon cancer [1,2,3]. An extensive search through the literature revealed 2 case reports of colon cancer causing trigeminal neuralgia, which was due to metastases to bilateral trigeminal ganglions and cisternal segments of the trigeminal nerve in one case [4], and metastases to the Meckel's cave in another case [1]. This is the first case report so far, of metastatic colon cancer presenting as skull base metastases and perineural

tumour spread to the V2 and V3 branches of the trigeminal nerve.

Perineural spread of tumour most commonly occurs along the facial nerve and the branches of the trigeminal nerve [5]. Perineural tumour infiltration is often a form of direct primary spread of neoplasia. The areas of infiltration are microscopically continuous with the main focus of a tumour, although they may be macroscopically discontinuous. Perineural tumour spread has been demonstrated to occur in perineural or endoneural tissue planes along the path of least resistance [6]. Both antegrade and retrograde perineural tumour spread can take place. Besides arising due to direct contiguous spread from primary tumours in the head and neck, it can also occur as metastatic invasion of peri- and/or endoneurium from non-head and neck malignancies [7].

Clinical Findings

The trigeminal nerve is the largest cranial nerve, transmitting sensory information from the face and providing motor innervation to the muscles of mastication and the veli palatini muscles. Malignant trigeminal neuropathy manifests as pain and skin/mucosal dyesthesia (numbness, paresthesia) in the region innervated by the trigeminal nerve divisions, or as weakness of the muscles of mastication. It may represent a sign of relapse in patients with prior treated neoplastic processes and is associated with a poor prognosis.

Anatomy

The trigeminal nerve exits the anterior aspect of the lower pons, passes through the prepontine cistern to reach the Meckel's cave, a cerebrospinal fluid (CSF) cistern posterolateral to the cavernous sinus, where it relays in the Gasserian (trigeminal) ganglion and then trifurcates into ophthalmic, maxillary, and mandibular nerves within the Meckel's cave.

The ophthalmic nerve passes forward in the lateral wall of the cavernous sinus to gain access into the orbit via the superior orbital fissure to supply sensation to the eyeball, lacrimal glands, conjunctiva, part of the nasal mucosa, skin of the nose, upper eyelid, and forehead [8].

The maxillary nerve exits the skull base through the foramen rotundum ossis sphenoidalis inferolateral to the cavernous sinus, it then enters the pterygopalatine fossa where it gives off several branches, its main trunk continues anteriorly in the orbital floor and emerges onto the face as the infraorbital nerve to innervate the middle third of the face and upper teeth [8].

The mandibular nerve runs laterally along the skull base to exit the cranium by descending through the foramen ovale into the masticator space, where it divides into several sensory branches to supply sensation to the lower third of the face and tongue, floor of the mouth, and the jaw.

The motor root of the mandibular nerve innervates the four muscles of mastication, the mylohyoid, the anterior belly of digastric, the tensor muscle of the tympanic membranes, and the tensor muscle of velum palatinum [9].

Imaging Findings

Imaging of perineural spread of tumour is best accomplished with MRI, in light of its superior soft tissue contrast and multiplanar capability. High resolution non contrast T1 weighted images without fat suppression and contrast enhanced T1-weighted spin echo images with fat-suppression are often the most helpful for diagnosis [10].

Principal MRI features of perineural tumor spread include abnormal nerve thickening with peripheral or solid enhancement after intravenous (I.V.) contrast administration, concentric expansion and/erosion of skull base foramina and extra cranial bony nerve canals, obliteration of perineural fat pads, an enhancing mass in the Meckel's cave, lateral bulging of the cavernous sinus dura, and denervation atrophy of the innervated muscles.

Tumour extension through the foramen ovale and perineural spread into Meckel's cave is best appreciated on coronal T1- weighted images post I.V. gadolinium with fat saturation [11] whereas axial non-contrast T1-weighted images shows to advantage associated skull base marrow infiltration.

Denervation changes of muscles supplied by the affected nerve are classified as acute changes, which take place within a month following denervation. Sub acute changes are those that follow up to 12-20 months and chronic changes occur thereafter [12]. The superior soft tissue contrast of MRI facilitates the depiction of the progressive evolution from earlier acute and sub acute phases to a chronic phase of the denervated muscle or muscle group.

Acute denervation is characterized by T2 prolongation, increase in muscle volume and abnormal muscle enhancement. Sub acute denervation is characterized by continued abnormal enhancement and T2 prolongation, without increase in muscle volume. Early chronic denervation is characterized by mild fatty changes of the affected musculature without evidence of appreciable volume loss, T2 prolongation or abnormal contrast enhancement, whereas long standing chronic denervation is characterized by more extensive fatty infiltration and volume loss of the affected musculature [12,13,14].

Differential Diagnosis

The differential diagnosis of perineural enhancement on MR imaging includes many infectious, neoplastic and inflammatory processes. Invasive fungal infections such as Aspergillosis and Mucormycosis may extend along the cranial nerves to the skull base and may lead to nerve enlargement and enhancement, but usually affects only severely immunocompromised individuals. There may be associated signs of invasive fungal sinusitis, such as T2 hypo intense signal within the sinuses or along the nerves to suggest fungal infection [15].

Primary neural tumours such as schwannomas typically present as discrete well-circumscribed masses, but can extend in a more diffuse and infiltrative fashion as well, usually associated with neurofibromatosis [16].

Inflammatory meningeal conditions such as sarcoidosis or syphilis can also lead to enhancement of cranial nerves. Bilaterally symmetrical involvement of the nerves is a criterion to distinguish many of these non-neoplastic lesions from perineural spread of tumour, which is typically unilateral. However inflammatory processes may also be unilateral. Furthermore lymphoma may involve nerves in a bilateral and relatively symmetrical fashion [13].

Literature Search

Perineural tumour infiltration has been recognized pathologically in a wide variety of carcinomas involving the lung, uterus, breast, stomach, esophagus, rectum and prostate, and in tumors of the head and neck [17]. There are only a few published reports of trigeminal mono neuropathy caused by brain metastases in patients with malignant neoplasms.

Hirota et al reported a case of metastases to the Meckel's cave in a patient with a past history of breast cancer, who presented with facial pain and numbness as the only sign of a brain metastasis. She was successfully treated by microsurgery and radiotherapy [2].

Mastronadi et al reported a case of operated colo-rectal adenocarcinoma, who presented much later with trigeminal neuralgia, which was due to metastases to the trigeminal ganglion in the Meckel's cave [1]. The patient was treated by surgery and radiotherapy.

Fischbein et al reported a case of treated prostate cancer, with disease relapse many years later presenting as trigeminal neuralgia involving V3 segment. Imaging showed a mass in the right cerebellopontine angle (CPA) and Meckel's cave with perineural extension along V2 in the foramen rotundum and V3 in the foramen ovale, and also along the facial nerve mastoid and tympanic branches, probably spreading retrogradely from V3 to the seventh cranial nerve along the auriculotemporal nerve [3]. The patient was treated by palliative radiotherapy.

Colon adenocarcinoma with metastases to the bones in the head and neck and trigeminal neuralgia are extremely rare. An intensive search through the literature revealed very few case reports. Babu et al reported a patient of colon cancer with metastases to the mandible, who presented with pain in the jaw [18]. A similar case was reported by Naylor et al [19].

Treatment & Prognosis

The presence of perineural invasion is a poor prognostic factor with high recurrence rates and decreased survival, and has implications for the treatment approach, indicating the need for wider resection and an expanded radiation field [20].

Treatment of trigeminal neuralgia could vary from medications such as tranquilizers or neuroleptics. In the advent of failure of medications, patients become candidates for stereotactic radio surgery (SRS) or needle rhizotomy [21]. Radio surgery, either Lineac based or with Gamma knife, acts by denervation of the nerve with hypo fractionated radiation, with maximal level of pain relief typically achieved within one month [22]. Another treatment option is radiofrequency electro

coagulation (RFE). The advantages of SRS or RFE are decreased motor trigeminal denervation, diplopia and cheek hematoma [23]. The optimal SRS dose range for treatment of trigeminal neuralgia, which most centers use, is 80Gy applied to the trigeminal nerve a few millimeters proximal to its entry into the brain stem [23].

Patients who experience recurrent pain during long term follow up after the initial SRS dose; can be treated with a second SRS procedure, with a generally safe interval of six months between subsequent SRSs. The target of the second SRS is placed so that 50% of its target volume envelopes the first target and the dose is usually less than 50Gy.

Conclusion

Facial pain and numbness can be the only sign of distant brain metastasis, due to perineural tumor spread, which carries a poor prognosis.

Although trigeminal perineural tumour spread occurs far more commonly as a result of squamous cell carcinomas and adenoid cystic carcinomas in the head and neck region, it can rarely occur due to metastases from a primary tumour located elsewhere in the body, which in our index case, was a colon cancer.

The knowledge of the anatomy of the cranial nerves and the patterns of perineural spread is essential in the diagnosis of perineural neoplastic involvement, which is essential in planning appropriate SRS treatment field.

TEACHING POINT

Trigeminal neuralgia is a rare manifestation of colon cancer, which can occur secondary to skull base metastatic disease. The imaging modality of choice is high resolution MRI with contrast, which accurately depicts perineural tumour spread as abnormal thickening and enhancement along the anatomic distribution of the trigeminal nerve branches, along with denervation changes in the affected muscle groups.

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FIGURES

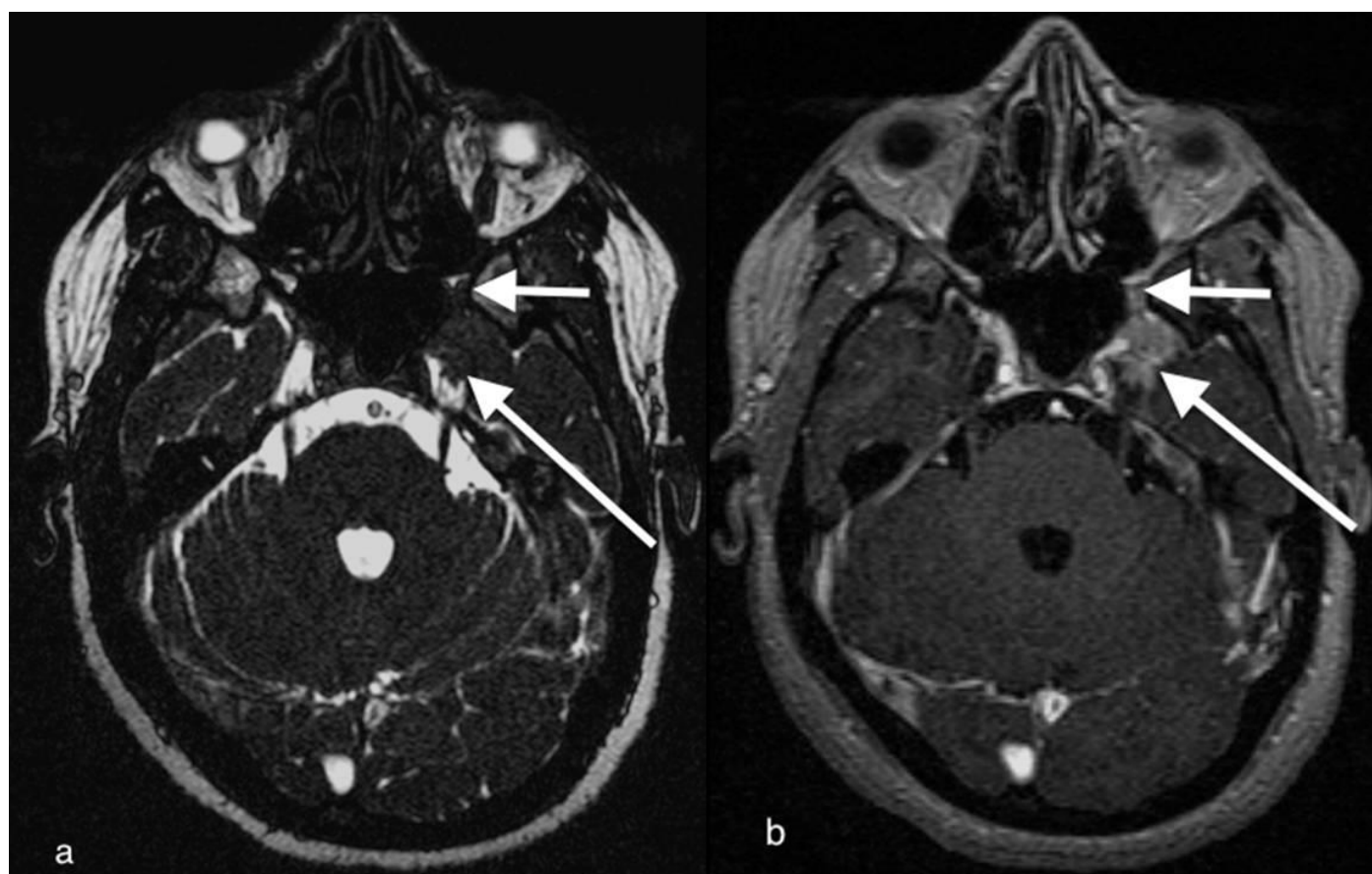


Figure 1: 46 year old known colon cancer female patient with perineural tumour spread along maxillary(V2) branch of the left trigeminal nerve, intracranial extension and involvement of the trigeminal ganglion.

FINDINGS: Axial 3D T2 weighted (CISS) image (a) and 3D T1 weighted (FLASH) post I.V. administration of Contrast medium cm (gadolinium; gadopentate dimeglumine chelate) (b), at the level of the skull base shows abnormal enhancing soft tissue in the region of the left foramen rotundum (short white arrow), suggestive of perineural tumour spread along the V2 branch of the trigeminal nerve, with extension into the middle cranial fossa and the Meckel's cave, shown as replacement of normal Meckel's cave CSF signal on T2 and enhancement on post I.V. cm (long arrow).

TECHNIQUE: Axial MRI, 1.5Tesla, 0.7mm slice thickness, 3D T2 weighted CISS(TR=6.06ms TE=2.76ms), 3D T1 weighted FLASH(TR=14ms TE=4.76ms) with I.V. cm gadopentate dimeglumine chelate 12ml.

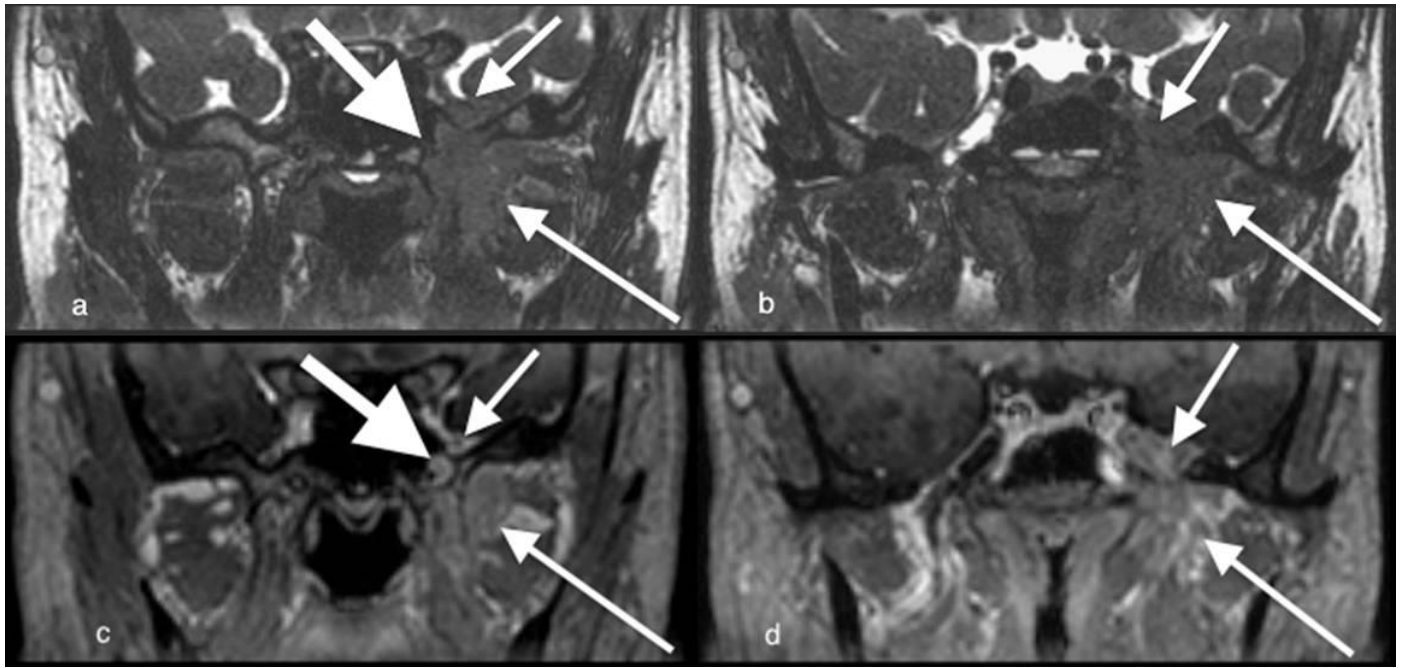


Figure 2: 46 year old known colon cancer female patient with skull base metastases and perineural tumour spread along maxillary(V2) and mandibular(V3) branches of the left trigeminal nerve, intracranial extension and involvement of the trigeminal ganglion.

FINDINGS: Reconstructed Coronal 3D T2 weighted CISS image (a) and coronal 3D FLASH T1-weighted image post I.V. administration of Contrast medium cm (gadolinium; gadopentate dimeglumine chelate) (c) at the level of the pterygopalatine fossa, show abnormal enhancing soft tissue replacing the marrow of the pterygoid body and the floor of sphenoid sinus on the left side, indicating skull base metastases, with infiltration of the vidian nerve canal (thick short arrow), foramen rotundum (thin short arrow) and the pterygopalatine fossa (long white arrow). More posterior section reconstructed coronal 3D T2 weighted CISS image (b) and coronal 3D FLASH T1 weighted post I.V. cm (d) show extension of the abnormal enhancing soft tissue along the left foramen ovale (long white arrow) which is widened, and in the Meckel's cave(short white arrow).

TECHNIQUE: Coronal MRI, 1.5Tesla, 0.7mm slice thickness, 3D T2 weighted CISS(TR=6.06ms TE=2.76MS), 3D T1 weighted FLASH(TR=14ms TE=4.76ms) with I.V. cm gadopentate dimeglumine chelate 12ml.

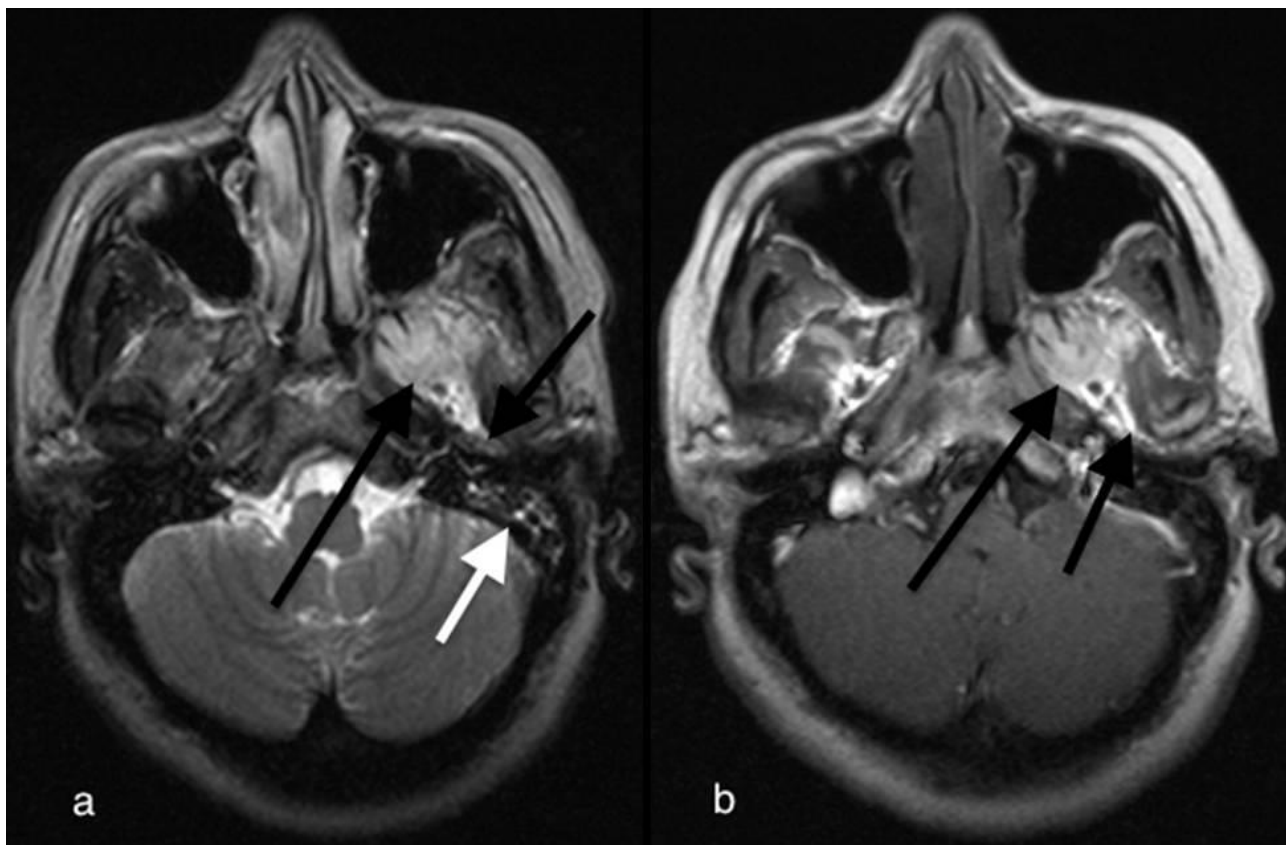


Figure 3: 46 year old known colon cancer female patient with sub acute denervation changes of muscles supplied by mandibular (V3) branch of the trigeminal nerve.

FINDINGS: Axial T2-weighted image (a) and T1-weighted post I.V. administration of Contrast medium cm (gadolinium; gadopentate dimeglamine chelate) image (b) at the level of the nasopharynx demonstrates abnormal diffuse T2 high signal intensity and contrast enhancement in the left levator veli palatini muscle (long black arrow) and the pterygoid muscles, signifying subacute denervation changes. Abnormal T2 high signal intensity and contrast enhancement is also seen along the auriculotemporal nerve (short black arrow), note mastoid air cells show T2 hyper intense fluid signal (short white arrow) due to secondary Eustachian tube dysfunction.

TECHNIQUE: Axial MRI, 1.5Tesla, 5mm slice thickness, T2 weighted (TR=5580ms TE=100ms), T1 weighted (TR=431ms TE=9.5ms) with I.V. cm gadopentate dimeglamine chelate 12ml.

Etiology	Arises either due to direct contiguous spread to the perineurium or endoneurium, or due to metastatic invasion of the peri- and/or endoneurium, can spread in an antegrade or retrograde fashion.
Incidence	Extremely rare. There are only two case reports of colon cancer causing trigeminal neuralgia due to metastases to the trigeminal ganglion, and two case reports of colon cancer with metastases to the mandible.
Gender ratio	No gender predilection is known
Age predilection	No age predilection is known
Risk factors	Perineural tumour spread along the trigeminal nerve is more common in squamous cell carcinoma, adenoid cystic carcinoma and lymphoma in the head and neck region.
Treatment	Palliative only. Medical treatment like tranquilizers or neuroleptics. If medical treatment fails, then Stereotactic radiosurgery with Gamma knife or Lineac based can be used for pain relief, acts by denervation of the nerve using fractionated radiation.
Prognosis	Poor. Associated with high recurrence rates and decreased survival.
Imaging findings	MRI shows abnormal nerve thickening and contrast enhancement along the course of the branches of the trigeminal nerve with denervation changes in the corresponding muscles, widening of the skull base foramina, extension into the cavernous sinus or Meckel’s cave and loss of perineural fat pad.

Table 1: Summary table of perineural tumour spread secondary to colon cancer, presenting as trigeminal neuralgia.

Differential Diagnosis	MRI findings
Neoplasm (other than lymphoma)	Abnormal nerve thickening and contrast enhancement along the course of the branches of the trigeminal nerve with denervation changes in the corresponding muscles, widening or erosion of the skull base foramina, extension into the cavernous sinus or Meckel’s cave and loss of perineural fat pad. Usually unilateral. h/o primary malignancy, most common in the head and neck
Invasive fungal infections	Usually in immunosuppressed individuals. May be associated with signs of invasive fungal sinusitis, along with marked T2 hypo intense signal within the sinuses or along the nerve. Otherwise similar imaging findings to other etiologies.
Schwannoma	Typically present as discrete well-circumscribed masses, but can extend in a more diffuse and infiltrative fashion as well. Usually seen in neurofibromatosis.
Lymphoma	Typically bilateral and symmetrical. Otherwise imaging findings similar to other etiologies.
Meningeal inflammatory conditions	Typically bilateral and symmetrical. May be associated with leptomeningeal enhancement.

Table 2: Differential table for abnormal perineural enhancement on MRI.

ABBREVIATIONS

- ADC = apparent diffusion coefficient
- CSF = cerebrospinal fluid
- CT = computed tomography
- FNAC = fine needle aspiration cytology
- I.V. = intravenous
- MRI = magnetic resonance imaging
- RFE = radio frequency electro coagulation
- SI = signal intensity
- SRS = stereotactic radio surgery

KEYWORDS

trigeminal neuralgia; perineural spread; colon cancer; magnetic resonance imaging; skull base

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