Perineural spread in head and neck tumors

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Abstract Perineural spread is the dissemination of some types of head and neck tumors along nervous structures. Perineural spread has negative repercussions on treatment because it requires more extensive resection and larger fields of irradiation. Moreover, perineural spread is associated with increased local recurrence, and it is considered an independent indicator of poor prognosis in the TNM classification for tumor staging. However, perineural spread often goes undetected on imaging studies. In this update, we review the concept of perineural spread, its pathogenesis, and the main pathways and connections among the facial nerves, which are essential to understand this process. Furthermore, we discuss the appropriate techniques for imaging studies, and we describe and illustrate the typical imaging signs that help identify perineural spread on CT and MRI. Finally, we discuss the differential diagnosis with other entities.

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Perineural spread in head and neck tumors

Tumores Nervios Craneales/Auxiliares; Neoplasias Cabeza y Cuello/Diagnóstico; RM; TC; Imagen Multimodal

Introduction

Perineural spread is how some types of tumors spread from head to neck through nerve sheaths. Jean Cruveilheir was the first to talk about this way of tumor spread in 1835, so it is not a new way of neoplasm spread due to changes in behavior thanks to the advances in medical care. However it often goes unnoticed in such a way that it does not usually show up in radiological reports.

Perineural spread, perineural spread, perineural macroscopic invasion, perineural affectation, small or big nerve affectation are terms that can be used indiscriminately in literature yet they show very different processes. Perineural invasion (PNI) or small-caliber nerve invasion (SCNI) is the macroscopic affectation of nerve fascicula that can be seen anatomopathologically and found where the main tumor rests. Perineural spread (PNS) or large-caliber nerve invasion (LCNI) is the macroscopic shape that can be seen in image studies or found clinically and is located beyond the main tumor lesion.

The goal of this article is get to know this kind of tumor spread, its meaning, its spread patterns and its radiological features in order to understand the condition and avoid false negatives in radiological reports.

Basic anatomical concepts

Peripheral nerves are made up of three layers called from the inside out epineurium, perineurium, and endoneurium (Fig. 1). In the epineurium both the most external component of the vasa nervorum and lymphatic channels can be found. Perineurium is the intermediate layer—one concentrically arranged multilayered structure of endothelial cells. Endoneurium is not a layer per se rather the laxus vascular connective tissue surrounding the Schwann cell-axon-complex making up the nerve fiber or small nerve. Various nerve fibers and the adjacent endoneurium gather around by the perineurium creating nerve fascicula. The cluster of several fascicula surrounded by the epineurium is what makes up the peripheral nerve or large nerve. Endoneurium is isolated from the extracellular compartment by the perineurium and from blood flow by the strong links of endothelial cells of endoneurial capillary. This is what is called hematoneural barrier. Its disruption allows the outflow of perineural contrast that in PNS patients is responsible for nerve pathological enhancement in image modalities.

Controversy on perineural affectation

There are several controversies in the actual literature on this type of tumor spread due to several reasons:

A. There is not a standard use of different terms. In most cases each publication uses a different term and does not specify on what grounds.

B. Not even among anatomopathologists there is a clear consensus on what PNI really means. Some authors define PNI as the malignant cells located in the perineural space with total or almost total affectation of nerve circumference in the tangential anatomopathological cutting. Others like tumor affectation of one third of nerve circumference or tumor cells in any of the component layers.

C. According to the American College of Pathologists PNI needs to be present in the reports filled out by anatomopathologists (present, absent or undetermined) and is conditioned by sampling methods, staining and immunohistochemical processing of tumor.

Studies show variable and contradictory results depending on the anatomopathological features and anatomical location of primary tumor:

- PNI has been reported in many tumor lineages but is more common in the cystic adenoid carcinoma (CAC) (20–80%) and in the squamous carcinoma (SC) (27–82%).

- PNS is rare in SC at the level of the mouth floor, tonsillar fossa, larynx, pharynx and in the presence of PNI in the primary tumor recurrence is also rare according to some authors. However, other authors claim that survival is worse when PNI is found in tongue tumors. It seems that in the CAC there are no differences in the incidence of PNS among those located in the major salivary glands or other regions. Also its repercussion on overall survival, or the very capacity of tumor to invade adjacent structures is not clear.

- Prognosis of PNI in mucoepidermoid carcinoma is poor even though it is not characteristically associated with this type of tumor.

Despite contradictions, it seems evident that PNS has a negative impact in treatment (more extensive surgical
Pathogenesis

The biological mechanism of pathogenesis is not fully understood. Former theories claim that the tumor spreads through endoneurial lymphatic channels while the lymphatic ones can be found in the outer layer of epineurium since they do not penetrate any further. Considering that certain types of tumors are associated with PNS while others—more aggressive—are not even in advanced stages the most widespread accepted theory is that of the reciprocal signals between the nerve and tumor cells that activate the signaling pathways. These pathways include trophic and chemotactic factors and adhesion proteins to the extracellular matrix. Several growth factors and adhesion proteins have been found. At the CAC-level the p75 neurotrophin receptor has been reported. During the development of the nervous system this receptor can be seen in the Schwann cells and its interaction with growth factor is capable of stimulating the migration of Schwann cells across the nerve. There might be a similar mechanism in PNI. In the PNI-related oropharyngal SC there is overexpression of the nerve growth factor and its receptor—tyrosine kinase A that can potentially be used as a marker to predict tumor progression. Between the adhesion molecules at CAC both the N-CAM—in 93% of PNI patients—and ICAM-5 (telencephaline) are expressed. In SC of head and neck the N-CAM is expressed in between 50% and 93% of all cases.

Anatomy of nerves of the facial region and patterns of spread

To be able to understand and define the PNS patterns we need to take into consideration facial nerves and regional classification. The nerves frequently associated with PNS are the cranial nerves V and VII since they have the largest regional spread and a closer relationship to those anatomical regions where tumors grow whose anatomicopathological type is most commonly associated with PNS (Fig. 2). Yet in the facial skeleton there is a rich network of anastomosis between cranial nerves and the cervical plexus so all nerves can potentially be affected (Tables 1 and 2).

Trigeminal nerve

In all cranial nerves there are five (5) different anatomical regions: nuclear, fascicular, cisternal, the skull base and the peripheral one. Even though spread can affect all segments the most commonly affected ones are the peripheral and the skull base segments.

In the cranial nerve V the region of skull base reaches out from Meckel’s cave where the Gasser ganglion is located towards the exit foramina of its three (3) peripheral branches—ophthalmic, maxillary and mandibular nerves.
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Figure 2  Scheme of the main branches of pairs V and VII. Anastomoses between both pairs are represented in red—the color of this figure can be seen in the electronic version of this article only. GSPN: greater superficial petrosal nerve. LDNP: large deep petrosal nerve. IDNP: lesser deep petrosal nerve. ATN: Auriculotemporal nerve. CTN: chorda tympani nerve. PP: pterygopalatine ganglion. SPN: Sphenopalatine nerve. Anastomosis (triple line) between the SPN and the lacrimal branch of V1.

Figure 3  Anatomy of cranial pair V. (A) T2-weighted axial MRI. Nuclear region of cranial pair V in the protuberance. In front of it at the prepontine cistern-level the cisternal segment can be found (long white arrow). (B) T1-weighted coronal MRI after gadolinium injection. (C) T1-weighted coronal MRI with fat saturation after gadolinium injection. (D) T1-weighted axial MRI after gadolinium injection. (E) T1-weighted axial MRI with fat saturation after gadolinium injection. The V1 branch can be seen (B) in the superior orbitary fissure (white silhouette), lateral to the anterior clinoid apophyss (‘); V2, (B) and (D), in the larger round bayonette-shaped foramen (white arrow point) to reach into the infraorbitary nerve canal (white line); V3, (C) and (E), in the oval foramen (white triple arrow) and descending to innervate the muscles of the chewing space (triple line).
Beyond the orifices the peripheral region can be found (Figs. 3 and 4).

The ophthalmic nerve (V1) arises from the Gasser ganglion anterior and medial region continuing through the lateral wall of cavernous sinus towards the superior orbital fissure. Just before penetrating in the fissure it is divided into three (3) terminal branches: lacrimal, frontal, and nasal.

The maxillary nerve (V2) reaches out from Meckel’s cave onwards crossing the major round foramen towards the pterygopalatine fissure. Then it reaches to the outside and looking down, this double angulation has a bayonette-shaped axial cutting to get into the infraorbital nerve canal.

Eventually at the end of the canal it emerges through the infraorbital hollow dividing into three (3) terminal branches. All along its itinerary it sprouts collateral branches of which two (2) are worth mentioning here: sphenopalatine and pharyngeal nerves. The sphenopalatine nerve sprouts from the V2 in the pterygopalatina fossa. Right there it contacts the pterygopalatine ganglion located in front of the vidian nerve canal to which it is also connected (Figs. 5 and 6). It has sympathetic branches to innervate the buccal-pharyngeal

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**Table 1** Connection of the V cranial pair.

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<td>Lingual nerve (V3)</td>
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<td>Chorda tympani nerve</td>
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<td>( V ) Pair</td>
<td>Cavernous sinus</td>
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<td>( V ) Pair</td>
<td>Sphenopalatine nerve (V2)</td>
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**Table 2** Connection of the VII cranial pair.

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<td>( \gamma ) Pair</td>
<td>Lingual nerve (V3)</td>
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<td>( \gamma ) Pair</td>
<td>Cervical branches</td>
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<td>Greater auricular nerve</td>
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<td>Greater superficial petrosal nerve</td>
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<td>( \gamma ) Pair and sympathetic plexus</td>
<td>Large deep petrosal nerve</td>
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<td>( \gamma ) Pair and sympathetic plexus</td>
<td>Vidian nerve</td>
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**Figure 4** Perineural spread in the three (3) branches of pair V. (A) and (B) CT in axial and sagittal planes. Spread through the left V1 branch (black arrow) in one patient with cutaneous epidermoid carcinoma. (C) and (D) T1-weighted axial and coronal MRI after gadolinium injection in one patient with perineural spread along the right V2 branch (white double arrows) due to nasal melanoma. Nerve is thickened and contrast-enhanced, yet it is never as hyperintense as the normal fat of the normal pterygopalatina fossa (“evil gray”) (white arrow points). Compare it to the normal V2 left branch in the infraorbital canal (discontinuous arrow). (E) and (F) T1-weighted axial and coronal MRI after gadolinium injection without (E) and with fat saturation (F) in one patient with cavum carcinoma. The left V3 branch is augmented and completely contrast-enhanced (white double arrow). It is evident when we compare it to the normal right nerve that only shows the peripheral enhancement of venous plexus (round white arrow). PNS reached Meckel’s cavum and consequently zone 2 (white asterisk) and also spread along the V2 branch (open white arrow points) and the vidian nerve (white arrow point).
**Figure 5** Obliteration of fat pads. (A) and (B) CT and (C) T1-weighted axial MRI. Obliteration of fat from left pterygopalatine fossa (long black arrows) in one patient with cavum carcinoma (compare it to the healthy right side; discontinuous black arrow). Invasion of the vidian nerve canal (black arrow point) too. Even though the obliteration of fat seen is that of the pterygopalatine fossa it can also be seen in other locations like in the patient of the inferior line. (D) and (E) CT with perineural spread through the left inferior alveolar nerve (white long arrow) secondary to one cystic adenoid carcinoma of left submandibular gland. Compare it to the normal fat of the right side (discontinuous white arrow).

**Figure 6** Patient underwent surgery due to cystic adenoid carcinoma of right maxillary sinus. T1-weighted axial MRI with gadolinium without (B) and with fat suppression (A), (C), (D) and (E) and T1-weighted coronal MRI with gadolinium without fat suppression, (F). Perineural spread along the right V1, bilateral V2, and right V3 branches of the right inferior alveolar nerve (discontinuous black arrow), palatine nerves bilateral in the palate (black arrow points) and palatine foramina (white arrow points) of the right auriculotemporal nerve (discontinuous white arrow), right greater superficial petrosal nerve (white long arrow) and vidian nerve (white double arrow). Affectation of Jacobson’s nerve IX pair (black curved arrow) probably from the vidian nerve and of the large deep petrosal nerve of the right carotid sympathetic plexus (white discontinuous circle). Affectation of the III pair (white curved arrow) due to connection with V1 branch in the cavernous sinus.
Figure 7  (A) Axial CT. (C) and (D) Oblique sagittal CT. (B) T1-weighted axial MR after gadolinium injection. Patient with cystic adenoid carcinoma at the palate and perineural spread along the right greater superficial petrosal nerve (discontinuous white arrows/white bar). This nerve sprouts from the geniculate ganglion (G) and anastomoses with the V2 branch. In this patient there is affection of the V pair in the oval foramen (discontinuous circle). Perineural spread disseminated across all segments of the VII pair: canicular C, labyrinthic L, trans tympanic TT and mastoideus M. Compare bone widening and intense asymmetric enhancement of the geniculate ganglion and the various segments of facial nerve with perineural spread in the right side and compare it to the healthy left side (*).

mucosa and the lacrimal gland–this last one anastomoses with the lacrimal nerve of V1. The palatine nerve is also born inside the pterygopalatine fossa and moving through the palatine canal towards the palate. When it reaches the palate it divides itself into greater and lesser palatine nerves reaching through the mucosa through the greater and lesser palate foramina (Fig. 6).

The mandibular nerve (V3) passes under the Gasser ganglion coming out of the skull through the oval foramen. Then it gives rise to one motor-wise small anterior trunk and another sensitive-wise posterior trunk. The motor trunk innervates the chewing muscles. The posterior trunk divides into three (3) branches: auriculotemporal, lingual, and alveolar inferior nerves (Figs. 5 and 6). The auriculotemporal nerve passes through the parotid gland located behind the mandibular condyle. At the parotid gland it anastomoses with branches from the facial nerve (Figs. 2 and 6). The lingual nerve runs under the lingual espace. It connects to the chorda tympani—one facial nerve branch with parasympathetic innervation of the submandibular and sublingual glands (Fig. 2).

Facial nerve

In this cranial pair the skull base region is structured into four (4) segments. The canicular segment runs from the acoustic porous through the anterosuperior compartment of the internal auditory canal (IAC) and towards the fundus: the labyrinthic segment that runs between the fundus and the geniculate ganglion; the tympanic segment running—in a bony canal at the medial wall of the tympanic box from the geniculate ganglion to the second elbow; the last segment or mastoideus running from the second elbow towards the stylomastoid orifice. The peripheral region starts at the cranial exit through the stylomastoid orifice. From this location it runs through the parotid gland dividing into five (5) terminal branches responsible for the motor innervation of facial muscles.

All along its itinerary the facial nerve produces two (2) important branches: the greater superficial petrosal nerve (GSPN) (Fig. 7) and the chorda tympani. The GSPN emerges from the geniculate ganglion, moves forward and then anastomoses with the large deep petrosal nerve (LDPN) to make up the vidian nerve that reaches into the sphenopalatine ganglion to then make contact with the sphenopalatine nerve (Figs. 5 and 6). The chorda tympani sprouts from the VII cranial pair before it exists the stylomastoid orifice to then make contact with the lingual nerve.

Other cranial pairs and cervical plexus

The cervical plexus is a structure made up of the aforementioned division for the four (4) first cervical nerves. It innervates the postarticular region (greater auricular nerve) and the anterosuperior region of the neck giving
rise to numerous branches for the deep muscular structures like the cervical loop and the phrenic nerve.

A branch sprouts from the glossopharyngeal nerve—the tympanic nerve (nerve of Jacobson). Through the tympanic canaliculus it enters the tympanic form a plexus over the cochlear promontory (Fig. 6). It receives branches from the carotid sympathetic plexus making up the LDPN and the lesser deep petrosal nerve (IDPN). In the IDPN it anastomoses with the LDPN making up the vidian nerve (Figs. 2–5 and 7). The IDPN connects to the ATN (arculotemporal nerve).

The vagus nerve gives rise to one branch—Arnold’s nerve located in a separate canal that anastomoses with the mastoid segment of facial nerve.

The hypoglossal nerve in its cisternal segment establishes connections with cranial pairs IX and X.

Regional classification

It allows us to describe the anatomical spread of PNS on the MRI by segments of affectation. This system determines the spread of surgical, subcranial or skull base resection, and has proven to be a predictor of overall survival. It is all about three (3) regions whose limits are defined by the affected cranial pair (V or VII) and by the different branches of cranial pair V (V1, V2, or V3) (Table 3).

Clinical manifestations

Up to 45% of the patients with PNS are asymptomatic even with extensive affectation. And there are patients with clinical data suggestive of PNS showing no alterations in image modalities.

Overall the clinical manifestations of PNS are late and present subtle and unspecifically. We must be suspicious in the presence of an insidious affectation of cranial pairs slowly progressive and not coming back to normal function after six (6) months of therapy or if several cranial nerves are affected on one side only—Garcin’s syndrome.

Image modalities

The image modalities used to diagnose this entity are MRI, CT and PET-CT. The MRI is the chosen one because of its greater contrast resolution and sensibility to discard “segmental” nerve affection. Despite its use being still not widespread, recent literature claims that the PET-MR can even be more accurate to diagnose PNS.

Magnetic resonance

Use T1-weighted high-resolution spatially isotropic volumetric sequences with or without fat saturation. Modalities with fat saturation allow us to define enhanced lesions that are close to espaces with fat like the orbits, the pterygopalatine fissure and neurovascular foramina. However, other authors prefer sequences without fat saturation because they think they can see very well those fat pads that are adjacent to foramina and distinguish them from those that obliterates pathologically due to tumor infiltration and because even after injecting gadolinium, the tumor never shows the same hyperintensity as fat does—the so-called “evil gray” (Fig. 4). Also not saturating fat avoids the susceptibility artifacts frequently observed in saturation sequences. In our institution the protocol consists of T1-weighted sequences without fat saturation before injecting the contrast and then T1-weighted sequences with fat saturation after injecting gadolinium. T2-weighted sequences are necessary for the study of cisternal, fascicular and nuclear segments of cranial pairs, when region 3 is affected. Also fat saturation can be useful to assess the inflammatory component associated with this entity above all where nerves are associated with fat pads.

Computed tomography

CT does a real good evaluation of both the shape and size of foramina and bone canals at the skull base-level. It allows us to distinguish between a rapidly destructive process usually associated with a speckled permeative pattern and another process with a slower and indolent course prone to remodeling and expansion.

PET-CT

It is very useful to diagnose head and neck cancers where it is superior to CT and MRI in the study ganglionic affectation

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IAC, internal auditory canal.
and to find residual or recurrent tumors. However, when it comes to PNS there are no accepted data on its sensitivity and specificity. Nevertheless any linear or curvilinear foci of abnormal FDG-uptake in the anatomical territories of cranial pairs must lead us to suspect PNS and correlate them with signs of MR to confirm diagnosis.

Radiological findings

1. Primary. They are associated with the direct affection of the nerve by the tumor.
   - Complete enhancement or complete uptake of the whole nerve circumference in T1-weighted gadolinium-enhanced sequences (due to rupture of hematoneural barrier) and thickening or enlargement of the nerve normal caliber. We must distinguish between the complete enhancement of the pathological nerve and the peripheral symmetric enhancement and variable thickness of the normal nerve (target appearance) (Figs. 3 and 4). Peripheral enhancement is due to the perineural venous plexus and it can be frequently seen in the foramina segments of the three (3) branches of the trigeminal nerve, in the geniculate ganglion, at the LDPN level and in the proximal part of the labyrinth segment of facial nerve.
   - Deletion or obliteration of juxtaforaminal fat pads due to tumor growth and the associated inflammatory component (Fig. 5).
   - Size increase of foramina and bone canals (Figs. 5 and 7).
   - Spread of intracranial compartment. It is associated with the infiltration of cavernous sinus, lateral wall dilating, dural thickening adjacent to the affected nerve segments and thickening or enhancement of cisternal and fascicular segments of the affected cranial pairs (Figs. 4E and 6C).

2. Secondary. Neural affection causes atrophy due to denervation. This finding is more frequent in both the chewing muscles (due to the affection of V3) and the tongue (due to affection of the hypoglossal muscle) and less common in the muscles of facial expression. The process of denervation has three (3) stages with different muscular signal patterns on the MRI. In the acute stage (1st month) the muscles are hyperintense in T2-weighted sequences and increase their size and enhancement in contrast-enhanced T1-weighted sequences. Hyperintensity is due to the increase of extracellular water volume and the reduction of the intracellular water one; the T2 of extracellular water is longer than the intracellular one. Enhancement is due to an increase in perfusion and accumulation of contrast in the extracellular space. In the subacute stage (up to 20 months) hyperintensity can still exist in T2 sequences while the signal in non-contrast-enhanced T1 sequences increases due to fat deposits; muscles keep their normal size though. In the chronic stage atrophy is general, the muscular volume diminishes and the signal increases in non-contrast-enhanced T1 sequences (Fig. 8).
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Figure 9  Zone classification 3. T1-weighted MR after gadolinium injection. (A) Axial image with fat saturation, (B) Axial image without fat saturation, and (C) coronal image without fat saturation. Patient with a history of right frontal cutaneous epidermoid carcinoma resection 7 years ago. He presented some time later with Tolosa-Hunt syndrome. (A) Inflammatory abnormalities in the orbitary vertex (white arrow point) and the cavernous sinus (white arrows). Corticoids were administered due to suspicion of inflammatory pseudotumor that resolved the clinical presentation partially. However in the control MR (not shown) abnormalities in the cavernous sinus persisted. Two (2) years later the patient presented with left Garcin syndrome. (B) and (C) The affectionation of left cavernous sinus and Meckel’s cavum is now more significant (asterisk) as well as the spread of the process towards the basal cisterns (discontinuous white arrows) and even towards the protuberance (black arrow). The biopsy of the affected ophthalmic nerve (not shown) was also positive for epidermoid carcinoma.

We must not forget that the signs of PNS can persist indefinitely yet despite clinical improvement. This is why we must be suspicious about relapse when the lesion deteriorates or symptoms grow worse.\textsuperscript{50} When a head and neck malignant tumor is stratified—especially those associated with PNS we must fully study the course of all cranial nerves. Due to the extensive network of connections all nerves can be potentially affected (Fig. 6). Nerve alteration can look discontinuous in the image ("’’skip’’ metastasis") though at the anatomopathological level it is continuous.\textsuperscript{3,57–59} Discrepancy is due to the fact that tumor load is variable all along the nerve and also to the fact that where discrepancy is lesser it might not be seen in radiological studies.\textsuperscript{9}

Differential diagnosis

The differential diagnosis of this entity is established with lesions of tumor, inflammatory, and infectious origin.\textsuperscript{50}

The affectionation of zone 1 (Fig. 4A–D)—peripheral usually is due to benign tumors of the nerve sheath like schwannomes and neurofibromes. In these lesions the tumor mass is located focally surrounding the nerve and even though its size is variable it is usually highly segmented not affecting all of its trajectory. Schwannomes are more common and usually originated in the junction between Schwann cells and glial cells and this is the reason why the usual location is zone 2. Even though it can be associated with any cranial pairs the VIII and V are the most common ones. Neurofibromes are usually peripheral and can be found isolated or in neurofibromatosis Type 1.

The affectionation of zone 2 (Figs. 4E and 9) is mainly represented by the affectionation of cavernous sinus.\textsuperscript{50} Among tumors meningiomas, schwannomes of pair V and metastasis are the most frequent lesions of all. Inflammatory psudotumors,\textsuperscript{11} granulomatose conditions,\textsuperscript{62} and infections are among non-tumor lesions. The clinical presentation of most of these processed has to do with the affectionation of oculomotor pairs—above all the VI cranial pair. However, in the PNS the affectionation of V pair is very common. Also in the image there are useful data like hyperostosis and the erosion of the adjacent bone that can lead us to meningiomas or metastatic processes, respectively. The dural tail that is more characteristic of meningiomas and inflammatory processes and one inflammatory process in the orbitary vertex is very suggestive both of inflammatory pseudotumors and the spread of an infectious sinusal process\textsuperscript{63–65} needs to be cautiously considered and followed for proper management (Fig. 9).

When the lesion is not continuous—though of variable size from zone 1 to zone 3 there are few processes that can be included. In these situations malignant lineage neural tumors,\textsuperscript{66} meningiomas and obviously PNS must be suspected.

The exclusive affectation of zone 3 is not a characteristic finding of PNS. It is now when we should think of
granulomatose inflammations like sarcoidosis, infections like neuritis of viral origin and tumors like leptomeningeal spread of extracerebral lymphoma.

Conclusion

Perineural spread is a type of metastatic spread more prevalent in certain types of tumors usually occurring in head and neck tumors. It is often misdiagnosed in image studies and yet it modifies the protocols of treatment and is associated with a higher rate of local recurrence and is also an independent prognostic factor of TNM classification of malignant tumors. Getting to know this association, the anatomical distribution of cranial pairs V and VII and their rich neural connection is essential. MRIs allow us to study the neural trajectory from the peripheral to the nuclear region in order to find thickness increases, complete enhancements and the obliteration of fat planes—which are all primary findings of this type of tumor spread.

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Ethical responsibilities

Protection of people and animals. Authors confirm that no experiments have been performed on human beings or animals.

Data confidentiality. Authors confirm that in this report there are no personal data from patients.

Conflict of interests

Authors reported no conflicts of interests.

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