PERINEURAL SPREAD IN INVASIVE FUNGAL SINUSITIS: UNDERRECOGNIZED COMPLICATION OF HEAD AND NECK INVASIVE FUNGAL INFECTION

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ABSTRACT

Background: Peri-neural spread of fungal infection is a potentially fatal condition. Identification of the major risk factors, as well as rigorous analysis of clinical features and radiological findings, may improve the chances of prompt diagnosis and better patient outcome.

Aim of the work: In this study we pursue to investigate perineural spread in patients with invasive fungal infection.

Patients and Methods: An institutional Review Board (IRB) approved retrospective study was conducted between April 2021 and October 2022 on 17 patients (10 male and 7 female) presented with clinical concern of fungal sinusitis and suspected perineural spread. The patients have performed contrast enhanced MRI and CT examination to evaluate sites of peri-neural extension, the involved cranial nerves, and the anatomical location. Histopathological data were obtained through surgically excised specimens in all cases.

Results: In our study, the peri-neural spread was found with involvement of pterygopalatine fossa (PPF) (16 cases) (94.1%), foramen rotundum (FR) (13 cases) (76.5%), vidian canal (VC) (two cases) (11.8%), Meckel’s cave (MC) (10 cases) (58.8%), cavernous sinus (CS) (8 cases) (47%), main trigeminal nerve till pons (two cases) (11.8%), 16 out of 17 cases (94.1%) showed involvement of maxillary division of trigeminal nerve (V2) and to lesser extent ophthalmic division of trigeminal nerve (V1) (only 1 case) and mandibular division (V3) (6 cases) at infra-temporal fossa.

Conclusion: Peri-neural spread can occur in invasive fungal infections, and most commonly along the anatomical distribution of trigeminal nerve and its branches "especially V2".

Keywords: perineural spread, fungal sinusitis, pterygopalatine fossa, trigeminal nerve.

INTRODUCTION:

Malignant neoplasms of the head and neck, such as adenoid cystic carcinoma, squamous cell carcinoma, rhabdomyosarcoma, and lymphoma, are known to spread along the endoneurium or perineurium to a noncontiguous region, a condition known as perineural disease spread. Malignant perineural spread frequently occurs along the trigeminal nerve and its branches[1].

Perineural invasion (PNI) describes neoplastic invasion of the nerves, which is a common pathologic finding in head and neck cancers and usually associated with poor outcomes. PNI is a histologic finding of tumor cell infiltration and is distinct from
perineural tumor spread (PNTS), which is macroscopic gross tumor infiltration and spread along a nerve extending from the primary tumor, a condition - by definition – is more advanced, being radiologically or clinically apparent[2].

Perineural spread, however, is not limited to cancer and can be associated with benign conditions such as infections, granulomatous diseases, and benign tumors such as meningioma[3].

Invasive or noninvasive fungal infections can impact the orbits and paranasal sinuses. Noninvasive fungal infections are confined to the sinuses, manifest as allergic sinusitis or mycetoma, and are more prevalent in immunocompetent individuals, it may result in bony expansion, but there is no tissue invasion or bone destruction. On the other hand, invasive infections can spread rapidly[4]. Deep face soft tissue infiltration and obliteration of normal fat planes in the preantral and retromaxillary fat, pterygopalatine fossa, infratemporal fossa, and pterygomaxillary fissure are frequent. Spread can occur along the foramen rotundum into the maxillary division of the trigeminal nerve, and extends perineurally up to the pons, and from the orbit into the cavernous sinus[4].

Paraesthesia or anaesthesia in the region of the trigeminal nerve distribution is one of the first symptoms of perineural extension. Despite the fact that there aren’t many articles available on fungal perineural extension, a large series found that 7% of mucormycosis patients had facial numbness as their initial symptom. Paraesthesia was highlighted by the authors as a lesser-known but early sign of a fungal infection[5].

The detection of perineural spread is possible with both CT and MR imaging. Despite the fact that MR imaging is favored because of its greater soft-tissue contrast[6]. On an MRI, perineural spread can be seen as widening/excessive enhancement in the pterygopalatine fossa, Meckel's cave, or cavernous sinus, as well as enlargement, irregularity, and excessive enhancement of either a cranial nerve or its branch (either within the cisternal portion or within a canal or foramen)[7].

This study's goal was to investigate the prevalence of perineural spread in patients with invasive fungal infection and importance of MRI in early detection of such findings.

PATIENTS AND METHODS:

This is retrospective descriptive study, that included patients with imaging features suggesting peri-neural spread of invasive fungal sinusitis and are proven pathologically as well. The study was conducted from April 2021 to October 2022.

Ethical Consideration

An institutional Review Board (IRB)-approval of the study was obtained from National Liver Institute, Menoufia University Academic and Ethical Committee with registration number (00413/2022). Written informed consent of the participants' patients was waived out as this is a retrospective study.

Study Population:

This study included 17 patients (10 male and 7 female), subjected to head and neck imaging for suspected fungal sinusitis and possible perineural spread that was suspected by the clinical manifestations of the patients such as facial pain, diplopia, cranial nerve deficits and focal neurological deficits. All patients underwent MRI examination, which included standard sequences, diffusion-weighted MRI, and post-contrast MRI evaluation. CT of the paranasal sinuses was performed in 11 cases as well. Finally, diagnosis of fungal sinusitis was confirmed in all cases by histopathological assessment.
Inclusion criteria:

Included patients with histopathological proven invasive fungal sinusitis with clinical features suspicious of perineural spread and underwent MRI evaluation.

Exclusion criteria:

Patients who performed surgical debridement before doing MRI evaluation and patients who did not undergo MRI evaluation were excluded.

Technique:

A 1.5 T MRI scanner was used (Optima 450 W GEM suite MRI; GE Healthcare, Seattle, Washington, USA). The patient is positioned head first with the use of a head and neck surface coil. All patients underwent MRIs that included scans of their brains and para-nasal sinuses.

The scan took an average of 30 minutes to complete. The following sequences were used to investigate each case while supine:

- Axial T1 Weighted-Image; axial and coronal T2 Weighted-Images and axial STIR.
- Axial DWI and ADC map:
  - Diffusion-weighted MR imaging was produced utilizing a multi-section single-shot echo planar imaging sequence with b values of 0, and 1000 s/mm2.
  - ADC maps were generated automatically by the MRI software for axial DWI.
- Post-contrast MRI sequences were produced utilizing fat-suppressed T1-weighted gradient echo sequences in the axial, coronal, and sagittal planes. The contrast study was carried out following a manual bolus injection of 0.1 mmol/kg body weight of Gd-DTPA.

Imaging interpretation:

Imaging studies of all cases were assessed by two different blinded radiologists (A.Y. and S.A.) with experiences in head and neck imaging for 15 and 10 years respectively.

The studies were evaluated first for presence of signs of fungal sinusitis including opacification of one or more of the para-nasal sinuses, intermediate to hyperintense signal on T1WI and hypointense signal on T2WI, hyperattenuating sinus content on non-contrast CT images, presence of fungal ball within sinus lumen, and distention of the sinus and destruction of its bony boundaries.

The imaging studies then were evaluated for signs of peri-neural spread of the fungal infection including thickening and excessive enhancement of the involved cranial nerve, widening of the skull base foramen presumed to be involved by the fungal spread, presence of features of fungal spread at sites of presumed peri-neural spread e.g., Meckel’s
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cave, pterygopalatine fossa, orbital extension as well as presumed intra-cranial course of trigeminal nerve, indirect signs including motor denervation of the muscles supplied by the affected cranial nerve.

The following points were fulfilled/evaluated in each patient: site of peri-neural extension; the involved cranial nerve and the anatomical location, presence of obvious cranial nerve enhancement, presence of obvious cranial nerve thickening, foraminal widening in CT studies, and presence of subsequent motor denervation.

Data Analysis:

Descriptive data analysis regarding the mentioned imaging features in all enrolled patients. SPSS version 21 was used to compile and analyze all data (SPSS Inc., Chicago, IL). The continuous variables such as age were represented by mean and standard deviation and were compared using either the student’s t-test or the Mann-Whitney (t) test according to test of normality. Whereas categorical variables were represented by percentages, and were compared using the Chi-squared test (X2). P value ≤ 0.05 was considered statistically significant.

RESULTS:

Mean patients’ age in the studied 17 cases was 43.5 (ranged from 15–73 years) years with men preponderance (1.4:1).

Headache, facial pain, papilledema, diplopia, cranial nerve deficits, focal neurological deficits, convulsions “according to site of affection”, nasal stuffiness, anosmia, and nasal discharge were among the clinical manifestations. In cases of orbital affection, ophthalmoplegia, diplopia, proptosis, and loss of vision were observed. Some patients with pre-maxillary extension experienced malar swelling.

I. Sino-nasal affection: -

The extent of sinuses involvement was variable in different cases; all paranasal sinuses were involved in two cases (11.8%), isolated maxillary sinus involvement in two cases (11.8%) “one right-sided and one left-sided affection”, maxillary and ethmoid sinuses in four cases (23.5%) “two right-sided and two left-sided affection”, right side maxillary, ethmoid and sphenoid affection in two cases (11.8%), unilateral maxillary and sphenoid in one case (5.9%), bilateral maxillary and sphenoid in one case (5.9%), posterior group affection “ethmoids and sphenoid” in four cases (23.5%), the last case showed affection of all left side sinuses.

All cases showed typical imaging features of the invasive fungal sinusitis.

CT imaging findings:

- Opacification of the involved sinuses, showing iso-to hyperdensity relative to muscle tissue.
- Variable expansion of sinuses “most appreciated in maxillary and sphenoid sinuses”.
- Mottled lucencies or irregular bone destruction. Bone destruction was variable “extensive to very subtle; spread through intact bone via microvascular invasion”.
- Nasal septal ulceration.
- Fat stranding outside the sinus confinement; “intra-orbital fat, periantral fat, lacrimal sac, naso-lacrimal duct, masticator space, pterygopalatine fossa”.
- Bone erosion in the area of extra-sinus extension.
- Extra-sinus soft tissue density component.
- Bony sclerotic changes in the walls of the affected sinuses denoting chronic disease.
**MRI imaging findings:**
- T1: intermediate to hypointense signal.
- T2: hypointense signal lesion with fungal mass of intermediate to low signal, associated with fluid or hemorrhagic changes in some cases.
- T1 C+ (Gd): loss of normal sinus mucosal enhancement “denoting necrosis”, enhancing extra-sinus soft tissue.

**II. Extra-sinus / peri-neural extension:**

All enrolled cases showed variable degrees of extra-sinus and peri-neural extension to different anatomical zones suggesting / indicating peri-neural spread as following:

Involvement of pterygopalatine fossa PPF (16 cases) (94.1%), foramen rotundum FR (13 cases) (76.5%), vidian canal VC (two cases) (11.8%), Meckel’s cave (MC) (10 cases) (58.8%), cavernous sinus (CS) (8 cases) (47%), main trigeminal nerve till pons (two cases) (11.8%). The involved sites showed similar imaging findings “signal and enhancement pattern” to the originally involved sinuses (Table 2) (Figure 1).

### Table 2: Socio demographic data and perineural extension locations among the studied cases (N=17).

<table>
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<tr>
<th>Variables</th>
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<tr>
<td>FR</td>
<td>13 76.5</td>
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<tr>
<td>VC</td>
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<tr>
<td>Main V till pons</td>
<td>2 11.8</td>
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Diagram: Percentage of perineural extension to different anatomical zones among the studied cases (N=17).

In 16 out of 17 cases (94.1%), involvement of maxillary division of trigeminal nerve (V2) was noticed with obvious involvement of PPF with variable degrees of maxillary nerve thickening and enhancement.

Out of the mentioned 16 cases of V2 affection; 13 cases (81.3%) showed retrograde peri-neural spread “from peripheral to central course of the nerve”, (Fig. 1) one case (6.3%) showed only antegrade spread “from central to peripheral
course of the nerve” and two cases (12.5%) showed both patterns displaying retrograde spread on one side and antegrade spread on the other side.

In only one case of the 17 cases (5.9%); the V2 was spared, the process included sphenoid and ethmoid affection with further extension along V3 at infra-temporal fossa “sparing PPF” then extending through FO to CS and pre-pontine course of trigeminal nerve.

Combined involvement of both V2 and V3 was noticed in 5 cases (29.4%); with retrograde extension of V3 noticed in all cases.

The 6 cases of V3 affection (35.3%) showed extension at infra-temporal course and foramen ovale, involvement of inferior alveolar nerve and mental foramen noticed in one case, further spread to CS and para-sellar region was noticed in 4 cases.

Intra-orbital extension through SOF was noticed in one case (5.9%) with further anterograde spread along V1 (ophthalmic branch of the trigeminal nerve) (Fig. 2).

Involvement of the GSPN was noticed on one case (5.9%) with widened nerve canal however no further obvious extension along facial nerve (Fig. 3).

Fig. (1): A 53-years old female patient with histopathological proven AIFS showing right side retrograde perineural spread along V2. A, B, axial T2WI. C, D, coronal T2WI. E, axial T1WI MRI images. The images show mucosal thickening of the right maxillary sinus with hypointense soft tissue infiltration of the preantral fat (orange arrow) that extends into the infraorbital foramen (dashed white arrow), the floor of the orbit, along the infraorbital
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nerve (yellow arrow), into the pterygopalatine fossa (dashed orange arrow) then through the foramen rotundum into the Meckel’s cave (red arrow).

Fig. (2): A 45-years old male patient with histopathological proven AIFS showing left side antegrade perineural spread along V1&V2. A, B, axial fat saturated T2WI. C, D, E, coronal fat saturated T2WI. F, axial T1WI MRI images. The images show opacified sphenoid sinus (asterisk) showing intrasinus hypointense signal with hypointense soft tissue infiltration of the left cavernous sinus and left Meckel’s cave (orange arrow) that extends anteriorly along the ophthalmic nerve (V1) within the orbit (blue arrow) ending in a soft tissue infiltrating the upper eyelid (white arrow), from the Meckel’s cave it also extends through the foramen rotundum along the maxillary nerve (V2) (yellow arrow) into the pterygopalatine fossa (dashed white arrow).
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Fig. (3): A 60-years old male patient with histopathological proven AIFS showing left side retrograde perineural spread along left greater superficial petrosal nerve. A, axial fat saturated T2WI. B, C, D, axial fat saturated contrast enhanced T1WI MRI images. The images show hypointense mucosal thickening of the sphenoid sinus with heterogeneously enhancing hypointense soft tissue infiltration of the left cavernous sinus and left Meckel’s cave (orange arrow) that extends anteriorly through the foramen rotundum into the pterygopalatine fossa where it extends posteriorly along the left vidian nerve within the vidian canal to the left greater superficial petrosal nerve (yellow arrow) reaching the Genticulate ganglion of the facial nerve (arrowhead). On the right side heterogeneously enhancing soft tissue infiltration of the pterygopalatine fossa (red arrow) is noted.

DISCUSSION:

Perineural spread of fungal infection is uncommon, especially in immunocompetent individuals[8]. Despite the fact that it is a disease with a bad prognosis and an aggressive course, early diagnosis of fungal infection with intracranial extension and proper characterization of disease extent are extremely helpful in disease control and accepted prognosis[9].

We assessed the role of MRI in evaluating sites of peri-neural extension, the involved cranial nerves and the anatomical location in fungal sinusitis.

It should be noted that no published studies have specifically addressed the prevalence and the imaging features of perineural spread in cases of fungal sinusitis.

Regarding Sino-nasal affection:

The extent of sinus involvement varied from all paranasal sinuses to isolated single sinus involvement in different cases. According to Aribandi et al., non-contrast CT in fungal sinusitis typically shows mucosal thickening or soft-tissue attenuation within the lumen of the affected paranasal sinus and nasal cavity. Unilateral involvement of the ethmoid and sphenoid sinuses is more likely[9].

Hora and Houston[10] were the first to identify Aspergillosis of the paranasal sinuses, which can be either non-invasive or
invasive. A paranasal mass contiguous with their neighboring extension into the orbit or cranial cavity can be a symptom of the invasive type\cite{11}. The invasive type is typically described in immunocompromised patients, but nowadays, there has been a rise in these cases in otherwise immunocompetent individuals.

CT imaging is more sensitive in assessing bony changes. MR imaging is more sensitive in detecting intracranial and intra-orbital disease extension: Inflammatory changes in the retrobulbar fat and extraocular muscles, as well as proptosis, denotes intra-orbital fungal invasion\cite{12}. The most common, but non-specific, early CT finding is significant unilateral soft tissue thickening in the nasal cavity.

More extensive but late and infrequent changes include orbital or intracranial invasion, bone erosion, and inflammation of the retromaxillary fat pad\cite{12}.

Fungus balls often only affect one paranasal sinus and manifest as a mass within its lumen. The maxillary sinus and sphenoid sinus are the two sinuses that are most frequently affected\cite{9}.

**Extra-sinus / peri-neural extension:**

Peri-neural spread was once thought to be unusual. However, new research has shown that both macroscopic and microscopic peri-neural spread is possible. Despite being far from the initial site of infection, Sravani et al.\cite{13} showed peripheral peri-neural dissemination on biopsy specimens in 15 of 30 patients with ROCM. On large caliber nerves, other authors\cite{14, 15} revealed a macroscopic perineural spread that was clearly discernible on MRI imaging.

In our study, 16 of 17 cases with affection of the maxillary branch (V2) of the trigeminal nerve had obvious involvement of PPF with varying degrees of maxillary nerve thickening and excessive enhancement. Along the trigeminal nerve's three branches Margo et al.\cite{16} reported involvement of the ophthalmic branch (V1) of the trigeminal nerve in the anterior orbit in a patient with invasive MM.

In 13 cases retrograde peri-neural spread was noticed, one case shows only antegrade spread and two cases showed both patterns displaying retrograde spread on one side and antegrade spread on the other side. Retrograde involvement of maxillary nerve (V2) from the infraorbital nerve and spread to the pterygopalatine fossa through the inferior orbital fissure, as well as to the middle cranial fossa through the foramen rotundum, was also described by Parsi K et al.\cite{17}. Again, involvement of the cavernous sinus, Meckel's cave, as well as the cisternal segment of the trigeminal nerve has been described, with variable pontine localization\cite{17, 18}.

The strength of this study includes its specific study point of perineural spread of fungal infection as well as the pathological confirmation of diagnosis in all cases.

Our study has many limitations which have to be mentioned. The first one is the relatively small sample size, this is attributed to being a rare condition and also false negative clinical diagnosis of some cases due to non-specific clinical patterns as well as retrospective study design.

**Conclusion:**

Peri-neural spread of fungal infection is a potentially fatal condition. Identification of the major risk factors, as well as rigorous analysis of clinical features and radiological findings, may improve the chances of prompt diagnosis and better patient outcome.

Because peri-neural spread of fungal infection commonly occurs along the trigeminal nerve's and its branches' anatomical distribution, especially V2, knowledge of anatomical details and imaging signs of early pathological involvement is very helpful in proper radiological interpretation.
Conflict of interest:

The authors declare that they have no conflict of interest.

LIST OF ABBREVIATIONS

ADC: Apparent diffusion coefficient.
PNI: Peri-neural invasion.
PNTS: Peri-neural tumor spread.
CEMRI: Contrast enhanced MRI.
CT: Computed tomography.
DWI: Diffusion-weighted imaging.
MRI: Magnetic resonance imaging.
STIR: Short tau inversion recovery.
V: Trigeminal nerve trunk.
V2: maxillary branch of trigeminal nerve.
V3: mandibular branch of trigeminal nerve.
PPF: pterygopalatine fossa.
FR: foramen rotundum.
MC: Meckel’s cave.
CS: Cavernous sinus.
VC: Vidian canal.
GSPN: greater superficial petrosal nerve.
MM: Mucormycosis.

REFERENCES:


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