# Inflammatory Pseudotumor of the Cavernous Sinus and Skull Base

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**Abstract**

Inflammatory pseudotumor is a non-neoplastic process of unknown etiology characterized by a proliferation of connective tissue with an inflammatory infiltrate. Intracranial inflammatory pseudotumors classically involve the cavernous sinus but can also occur in the supratentorial or infratentorial compartments and spinal canal. Symptoms are dependent on location, and when present in the cavernous sinus, typically include cranial nerve palsies of those nerves in the cavernous sinus. These lesions are rapidly responsive to steroid therapy. Surgery is typically indicated for biopsy only, but complete resection may be justified for lesions outside the cavernous sinus.

Running Head: Skull base inflammatory pseudotumor

Key Words: Intracranial neoplasm, pseudotumor, skull base



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## Introduction

Inflammatory pseudotumor of the orbit was initially described in 1903 by Busse and Hochheim [21, 42], but it was not until 1980 that intracranial involvement was reported [80]. These lesions develop as a non-neoplastic process of unknown origin characterized by a proliferation of connective tissue with an inflammatory infiltrate [64]. The lung [7] and liver [4, 73] are the two most common sites of inflammatory pseudotumor, but the lesions have been described in the stomach [74], pancreas [2], heart [33], kidney [27], bladder [15, 20], and skin [40]. Central nervous system inflammatory pseudotumors are exceptionally uncommon and typically arise from the meninges [3]. Intracranial inflammatory pseudotumor involving the cavernous sinus with resultant painful ophthalmoplegia was classically described by Tolosa [77] and Hunt et al. [39], and is now referred to as the Tolosa-Hunt syndrome [38]. We present an illustrative case of a large inflammatory pseudotumor that involved bilateral cavernous sinuses and the clivus, and a review of the contemporary literature.

## Illustrative Case

This 28-year-old, previously healthy man developed headache, nausea, dizziness, and double vision one week after extensive dental work. At an outside institution, he was noted to have a right sixth cranial nerve palsy. The evaluation at that hospital included a magnetic resonance imaging (MRI) scan, which was interpreted as being consistent with cavernous sinus thrombosis, and a lumbar puncture that revealed cerebrospinal fluid with elevated protein and white cells. Subsequently, the patient was treated empirically with warfarin (Coumadin), steroids, and cephalosporin (Rocephin) for presumed sinus

thrombosis secondary to an infectious process. After initiation of treatment, the double vision, headache, and nausea, dizziness improved. A steroid taper was attempted after a full course of cephalosporin, but the same symptoms returned.

The patient was referred to our institution where his neuroradiological workup included MRI studies that revealed extensive meningeal thickening and enhancement primarily involving the bilateral cavernous sinuses, high posterior clinoid area, and distal petrous internal carotid artery canals (Fig. 1A-F). The differential diagnosis included meningioma and inflammatory pseudotumor. An endonasal transsphenoidal partial excision of the clivus lesion was performed to acquire a specimen for histopathological analysis. Intraoperatively, an erosive process of the clivus was observed with a lesion that was mucinous in character. The histopathological findings demonstrated nonspecific acute and chronic inflammatory fibrosis consistent with inflammatory pseudotumor (Fig. 2). No neoplastic process was identified. No organisms were cultured from the biopsy material.

The patient continued steroid treatment with 70 mg of prednisone daily after the diagnosis of inflammatory pseudotumor was established. His headaches continued but were diminished, and the diplopia completely resolved. No new symptoms have developed. A follow-up MRI one year after biopsy demonstrated near complete resolution of the pseudotumor (Fig. 1G). A steroid taper was initiated, which the patient tolerated without a return of symptoms. Still, one year after biopsy, he has continued on physiologic steroid doses due to symptoms consistent with systemic withdraw.

**Discussion**



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Inflammatory pseudotumor has been referred to by several names in the literature, including plasma cell granuloma [7, 18, 49], inflammatory fibrosarcoma [54], inflammatory myofibroblastic tumor [63, 71], inflammatory myofibrohistiocytic proliferation [76], fibrohistiocytoma [52], xanthomatous pseudotumor [14], and plasma cell–histiocytoma complex [72]. The multiple terms given to this single pathologic entity reflect the variable compositions of inflammatory pseudotumor. The pathologic specimen in the illustrative case demonstrated a combination of fibrous stroma, acute and chronic inflammatory processes, and a lymphoid infiltrate composed of both B- and T-cells. All of these components are typical of an inflammatory pseudotumor, but the degree of fibrous stroma and specific inflammatory cells involved can vary greatly [8, 48, 70]. Plasma cells frequently predominate, but they may be outnumbered by lymphocytes [76]. Other cellular constituents can include histiocytes, macrophages, and eosinophils [14, 26, 40]. The polyclonality of the plasma cells, demonstrated by the presence of both kappa and lambda light chains with immunohistochemical staining, distinguishes inflammatory pseudotumor from monoclonal processes such as plasmacytoma and lymphoma [3, 64]. A subset of inflammatory pseudotumors have monoclonal plasma cells, but this has only been described in two cases [37, 79].

*Etiology*

The etiology of inflammatory pseudotumor is unknown, but it has been associated with a number of diseases processes including Sjögren's disease [17], Epstein-Barr virus [5, 6, 34], human immunodeficiency virus [75], polymyositis [3], and neuro-Behçet's disease [32, 62]. al-Sarraj et al. [3] proposed that inflammatory pseudotumor is the result


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of an exaggerated immunological process, which is supported by evidence of the elevation of serum immunoglobulins [12]. The immunological response could potentially be triggered by a viral or bacterial infection [30]. Viral infections appear to be a more likely culprit, because Epstein-Barr virus has been associated with up to 40% of inflammatory pseudotumor cases [6], whereas histopathological evaluation does not demonstrate bacteria [64] (as in the illustrative case). In other cases, the immunological response may not need to be triggered *per se* but instead may result from an autoimmune disorder, given the association between inflammatory pseudotumors and several autoimmune diseases.

*Location and Presenting Symptoms*

The location of the mass has a significant impact on which symptoms are produced by intracranial inflammatory pseudotumor. Cavernous sinus involvement typically causes painful ophthalmoplegia (i.e., Tolosa-Hunt syndrome), but painless ophthalmoplegia can also occur [29]. Stenosis of the intracavernous intracerebral artery can lead to transient ischemic attacks [10]. In rare instances, inflammatory pseudotumor has been reported to have an intrasellar component, resulting in hypopituitarism [31, 60] or to extend to Meckel's cave, causing facial pain [51, 60]. In the present case, the inflammatory pseudotumor extended to the clivus, where an abducens nerve palsy could potentially have been caused by compression of the nerve as it traverses Dorello's canal. Alternatively, the abducens palsy could have been caused by direct cavernous sinus involvement.


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Besides the sellar and parasellar areas, other intracranial locations of inflammatory pseudotumors have included the tentorium [80], falx [57], spinal cord meninges [26], lateral ventricle (choroid plexus) [12, 64], fourth ventricle [3, 59], and intraparenchymal regions [16, 76]. Lesions are usually solitary, but multiple intracranial inflammatory pseudotumors in the same patient do occur [16, 53].

*Radiographic Appearance*

In general, inflammatory pseudotumors have nonspecific neuroradiologic findings. Inflammatory pseudotumors are iso- to hypointense on T1-weighted MRI, hypointense on T2-weighted MRI, and homogeneously enhancing [12, 35, 48, 64]. They can be hypercellular, and therefore MRI spectroscopy cannot reliably distinguish these lesions from neoplasms [46]. Infrequently, bony erosion can occur [31, 48]. In this circumstance, distinguishing between an inflammatory pseudotumor and destructive neoplasm or infectious process is difficult without the aid of a biopsy [35]. Inflammatory pseudotumors can also be difficult to differentiate from meningiomas, because both lesions are generally homogeneously enhancing and are often associated with the meninges. The hypointensity on T2-weighted MRI can help differentiate inflammatory pseudotumors from other lesions of the skull base that are iso- or hyperintense on the same imaging sequence, including chordomas, chondrosarcomas, nasopharyngeal carcinomas, and metastatic malignant tumors [35].

*Treatment*


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Steroid therapy is the cornerstone of treatment for inflammatory pseudotumor, especially with involvement of the cavernous sinus. Cranial nerve palsies usually respond quickly to steroid therapy, and the diagnosis of inflammatory pseudotumor should be questioned if steroids do not help alleviate symptoms. The International Headache Society in 1988 defined specific criteria for diagnosing Tolosa-Hunt syndrome and included a response to steroids within 72 hours as one of those criteria [1]. One possible exception is when the lesion has a large fibrosis component, indicating a more chronic process, in which steroids are less effective [36, 67]. The optimal steroid dose and schedule for inflammatory pseudotumor of the cavernous sinus or skull base is unclear. For inflammatory pseudotumor of the orbit, two weeks of prednisone (1/mg/kg/d), or an equivalent steroid, followed by a taper over weeks to months is standard [24, 56, 66]. In case reports involving the cavernous sinus or skull base (Table 1), steroid doses varied greatly with treatment ranging from one to eight months. The steroid dose used for inflammatory pseudotumor of the orbit likely applies to lesions of the cavernous sinus and skull base, with the duration of treatment being titrated to clinical response.

Recurrence rates after steroid treatment are difficult to assess for intracranial inflammatory pseudotumors because most publications consist of single case reports. Of the 17 cases listed in Table 1 that received steroids, only two (12%) had progression or recurrence of symptoms, but it should be noted that several of those cases received multiple treatment modalities besides steroids, including radiation and surgery. Series of orbital inflammatory pseudotumor cases have found a recurrence rate of 25% to 77% [50,


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55, 56, 68, 78]. Rarely, recurrence can occur ten or more years after completion of steroid therapy [9, 11].

If recurrence does occur, then a longer course of steroids is indicated, and response to treatment may be monitored with serial imaging studies. For cases unresponsive to steroids, radiation treatment is a reasonable alternative. Doses between 2000 and 4000 rad have been delivered for intracranial inflammatory pseudotumor with a positive clinical response [22, 28, 44, 58]. When the cavernous sinus is involved, surgery may be indicated to perform a biopsy and confirm a diagnosis, but complete surgical resection is usually not an option because of the high risk of causing additional cranial neuropathies. Complete surgical resection is possible with lesions in other locations, such as the ventricles or infratemporal fossa.

For rare cases that are refractory to both steroid therapy and radiation therapy, other immunosuppressant or chemotherapeutic medications may be considered [43]. In a review of three patients who received the antimetabolite methotrexate for treatment of orbital inflammatory pseudotumor, because of contraindications or failure of steroid therapy, two of the patients had a reduction in inflammation whereas the third patient had no response [69]. Cyclosporine has also been effective in controlling orbital inflammatory pseudotumor when a patient with diabetes could not tolerate steroids because of poor glucose control [25]. Anecdotal reports have also suggested that azathioprine [23] and infliximab [82] can contribute to treatment regimens.

## Conclusion


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Inflammatory pseudotumor is a non-neoplastic proliferation of connective tissue with an inflammatory infiltrate that can occur throughout the brain. These masses should especially be considered when a lesion is homogeneously enhancing and is associated with the meninges in the sella or parasellar areas. Extension to surrounding structures, such as the clivus and Meckel's cave, can also occur. Symptoms, particularly cranial nerve palsies, are rapidly responsive to steroid therapy. Surgery is often required to acquire a biopsy specimen, but complete resection is usually not possible with the involvement of the cavernous sinus.

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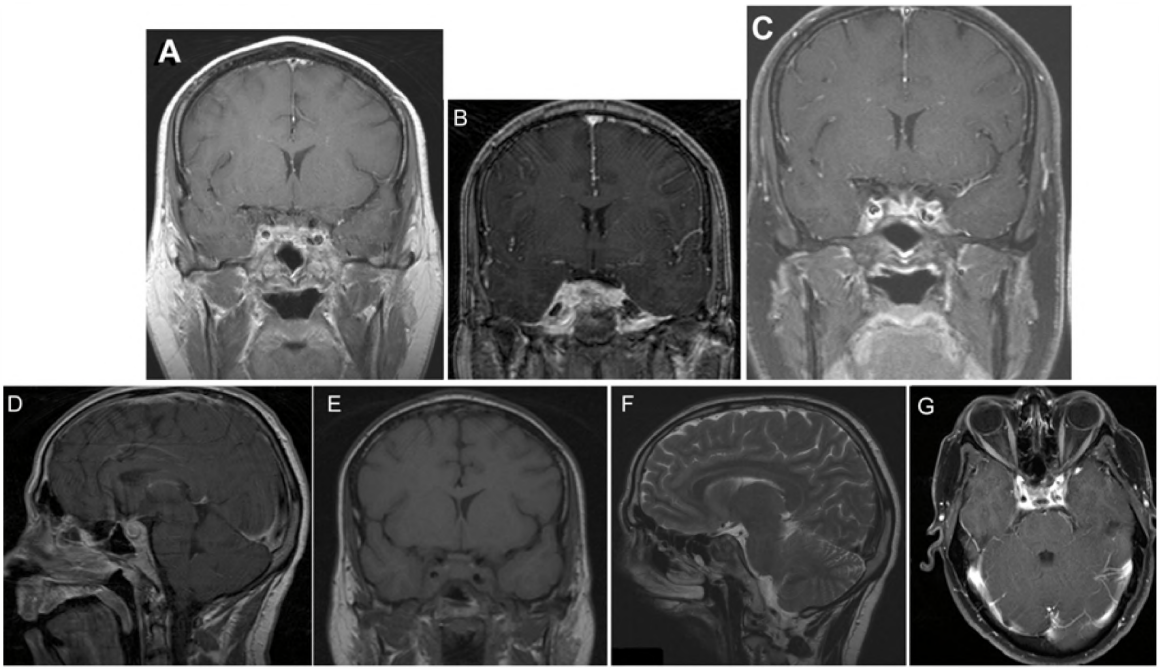


**Figure 1:** Magnetic resonance images demonstrating extensive meningeal thickening and enhancement primarily involving the bilateral cavernous sinuses, superior clivus region, and distal petrous internal carotid artery canals. The lesion is enhancing of post-gadolinium T1-weighted sequences (A-D), isointense on T1-weighted sequences without gadolinium (E), and hypointense on T2-weighted sequences (F). (G) Post-gadolinium T1-weighted MRI one year after biopsy, with near complete resolution of the lesion.



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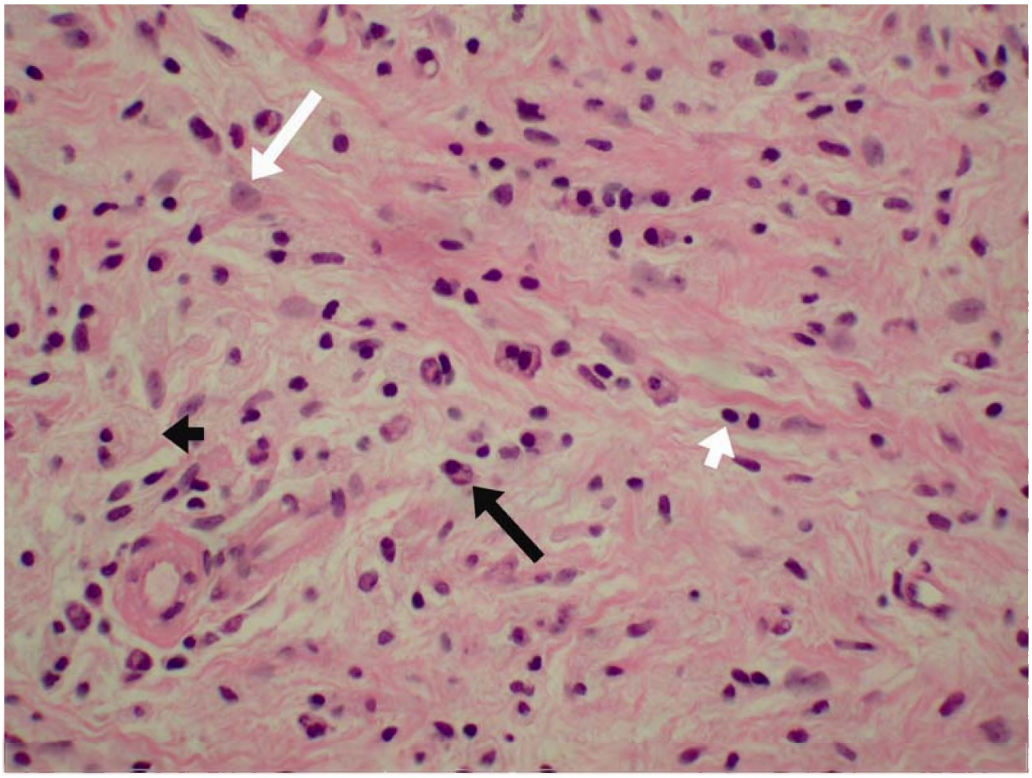

**Figure 2:** Histopathology demonstrating nonspecific acute and chronic inflammatory changes, including plasma cells (long black arrow), lymphocytes (short white arrow), foamy cells (short black arrow), and fibroblasts (long white arrow). The diverse population of inflammatory cells is in contradistinction to a lymphoma, which has a homogeneous population of lymphocytes.



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**Table 1:** Summary of reported cases of inflammatory pseudotumor or plasma cell granuloma involving the cavernous sinus or skull base identified by a PubMed search. Lesions involving the cavernous sinus are typically treated non-operatively due to the high risk of surgical morbidity. Steroids, with or without radiation, are usually effective in completely treating or stabilizing inflammatory pseudotumor, with only two reported cases of disease progression or recurrence during follow-up ranging from two months to four years. Steroid dosing and duration of treatment were highly variable. Other locations such as the infratemporal fossa can be amenable to surgical to resection.



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| Publication (Case#) | Age (years) | Gender | Diagnosis | Location | Treatment (besides steroids) | Steroid (dose) | Steroid duration | Treatment response | Follow-up | Recurrence |
|---|---|---|---|---|---|---|---|---|---|---|
| Roche et al., 2004[65] | 20 | Female | Biopsy | Infratemporal fossa | None | Dexamethasone (1mg/kg/d) | 2 mo | Symptoms: resolved Radiographically: resolved | 4 yr | No |
| Buccoliero et al., 2003[13] | 70 | Male | Biopsy | Parasellar & skull base | Radiation (30 Gy) | Dexamethasone (16 mg/d, tapered) | N/A | Symptoms: stable but persists Radiographically: lesion stable but persists | 14 mo | No progression |
| Williamson et al., 2003[81] | 49 | Male | Biopsy | Infratemporal fossa | Surgical resection | Unspecified (1 mg/kg/d, tapered) | 10 weeks | Radiographically: improved | 6 mo | No |
| Pallini et al., 2002 (1)[61] | 49 | Female | Resection specimen | Occipital condyle | Surgical resection | None | N/A | Symptoms: partially improved (cranial nerve palsies persist) Radiographically: complete resection | 5 yr | No |
| Pallini et al., 2002 (2)[61] | 46 | Female | Resection specimen | Occipital condyle | Surgical resection | None | N/A | Symptoms: partially improved (cranial nerve palsies persist) Radiographically: partial resection | 2 yr | No progression |
| Cho et al., 2001[19] | 62 | Male | Biopsy | Petrous apex | Radiation (total 5000 cGy divided among two fields | Prednisolone (60 mg/d, tapered) | 14 d, then 38 d | Symptoms: partially improved with steroids, returned after taper Radiographically: | N/A | Yes |

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| Igarashi et al., 1997[41] | 40 | Female | Biopsy | Cavernous sinus & temporal lobe | Surgical resection (temporal lobectomy) & radiation | Unspecified | N/A | N/A | 3 yrs | No |
| de Jesús, et al., 1996[22] | 16 | Female | Biopsy | Infratemporal fossa | Surgical resection & Radiotherapy (2000 rad) | Prednisone (160→40 mg/d) | > 15 mo | Symptoms: partially improved (progressed with steroids alone) | N/A | N/A |
| Ganesan et al., 1996 (1)[29] | 13 | Male | MRI | Cavernous sinus & skull base | None | Prednisolone (2 mg/kg/d, tapered) | 1 month | Symptoms: resolved | N/A | No |
| Ganesan et al., 1996 (2)[29] | 11 | Male | MRI | Cavernous sinus | None | Prednisolone (2 mg/kg/d, tapered) | 5 weeks | Symptoms: resolved | 6 mo | No |
| Han et al., 1996 (1)[35] | 38 | Male | Biopsy | Cavernous sinus & infratemporal fossa | None | Unspecified | > 1 mo | Symptoms: stable (cranial nerve palsy) | N/A | N/A |
| Han et al., 1996 (2)[35] | 30 | Male | Biopsy | Clivus | None | Unspecified | > 1 mo | Symptoms: stable (cranial nerve palsy) | N/A | N/A |
| Han et al., 1996 (3)[35] | 36 | Male | Biopsy | Cavernous sinus, clivus & infratemporal fossa | None | Unspecified | > 1 mo | Symptoms: stable (cranial nerve palsy) Radiographically: lesion stable but persists | 6 mo | No progression |

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| Han et al., 1996 (4)[35] | 57 | Male | Biopsy | Cavernous sinus & infratemporal fossa | None | Unspecified | > 1 mo | Symptoms: stable (cranial nerve palsy) | N/A | N/A |
| Han et al., 1996 (5)[35] | 25 | Male | Biopsy | Cavernous sinus & infratemporal fossa | None | Unspecified | > 1 mo | Symptoms: stable (cranial nerve palsy) | N/A | N/A |
| Le Marc'hadour et al, 1994 (1) [47] | 40 | Male | Resection specimen | Cavernous sinus | Surgical resection (concern for meningioma) | Unspecified | 2 mo | Symptoms: persist; CN III palsy Radiographically: partial resection | 2 yr | No progression |
| Le Marc'hadour et al, 1994 (2)[47] | 30 | Male | Biopsy | Cavernous sinus & petrous apex | None | Unspecified | 2 mo | Symptoms: resolved | 2 mo | No |
| Kodsi et al., 1993[45] | 40 | Male | Biopsy | Cavernous sinus | None | Prednisone (100 mg/d for 5 days in 3-week cycles) | 6 mo | Symptoms: resolved Radiographically: improved | 18 mo | No |
| Olmos et al, 1993[60] | 64 | Female | Biopsy | Cavernous sinus | Radiation (1400 cGy) | Prednisone (40→15 mg/d) | 8 mo | Symptoms: resolved | 8 mo | No |