

## Case Report

**Steroid-resistant Tolosa–Hunt syndrome with a de novo intracavernous aneurysm: A case report**Hiroshi Takasuna, Rie Sasaki<sup>1</sup>, Makoto Shiraishi<sup>1</sup>, Masatomo Doi<sup>2</sup>, Daisuke Wakui, Hidemichi Ito, Kotaro Oshio, Yuichiro TanakaDepartments of Neurosurgery, <sup>1</sup>Neurology, and <sup>2</sup>Pathology, St. Marianna University School of Medicine, Kawasaki, Japan

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**Abstract****Background:** We report a case of steroid-resistant Tolosa–Hunt syndrome (THS) with recurrent bilateral painful ophthalmoplegia, accompanied with sphenoid sinusitis, pituitary abscess, and an aneurysm arising from the cavernous portion of the internal carotid artery.**Case Description:** A 53-year-old woman suffered severe left painful ophthalmoplegia. A magnetic resonance image (MRI) revealed thickness of the left cavernous sinus (CS). Steroid was administered under the diagnosis of THS, and the symptom transiently diminished. However, painful ophthalmoplegia fluctuated bilaterally after tapering the steroid. An MRI showed development of bilateral cavernous lesions associated with sphenoid sinusitis, pituitary abscess, and an aneurysm in the left C4 segment. Biopsy and drainage of the lesions were performed with an endoscopic transsphenoidal procedure. The histological examination showed nonspecific granulomatous inflammation. The methotrexate (MTX) was effective to reduce the CS and pituitary lesions; however, the aneurysm slightly increased and remained unchanged in size thereafter.**Conclusions:** To our knowledge, this is the first report of a growing de novo C4 aneurysm in THS. Surgical intervention and administration of MTX should be attempted in steroid-resistant THS. Careful observation with serial MRI and MR angiography is important to manage the complicated THS.**Key Words:** Aneurysm, cavernous sinus, pituitary abscess, sphenoid sinusitis, steroid, Tolosa–Hunt syndrome**Access this article online****Website:**[www.surgicalneurologyint.com](http://www.surgicalneurologyint.com)**DOI:**

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**Quick Response Code:****INTRODUCTION**

Tolosa–Hunt syndrome (THS) is a disorder related to nonspecific inflammation in the cavernous sinus (CS) and superior orbital fissure. Formation of aneurysm and pituitary inflammation are rare complications in THS, although there have been some reports of internal carotid artery (ICA) stenosis in the inflammatory CS.<sup>[6,16,22,23,25-27]</sup> We describe a patient who had an aneurysm arising from

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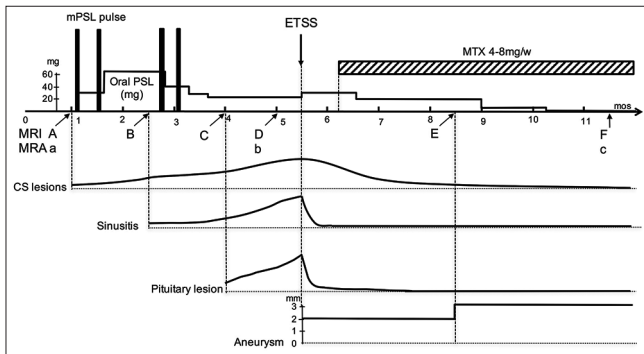
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the ICA in the CS affected by nonspecific inflammation of THS and a pituitary abscess.

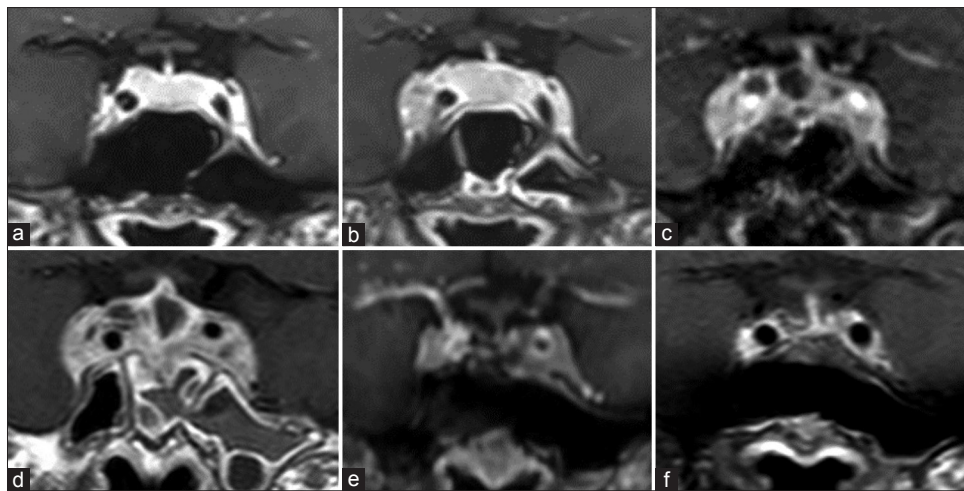
### CASE DESCRIPTION

A 53-year-old woman presented with severe left retro-orbital pain and diplopia for 1 month [Figure 1]. Neurological examination performed on admission in a local hospital revealed left abducens nerve palsy. A magnetic resonance image (MRI) revealed an enlargement of the bilateral CS, in which the left side was dominant [Figure 2a]. Biochemical analysis of the blood and cerebrospinal fluid revealed no systemic or neuronal inflammation. A presumptive diagnosis of THS was made. Neurological symptoms were relieved by two sessions of steroid pulse therapy with methylprednisolone (mPSL, 1000 mg/day for 3 days). She began receiving regular corticosteroid therapy with 30 mg/day of oral mPSL. However, right retro-orbital pain and right abducens nerve palsy developed over a

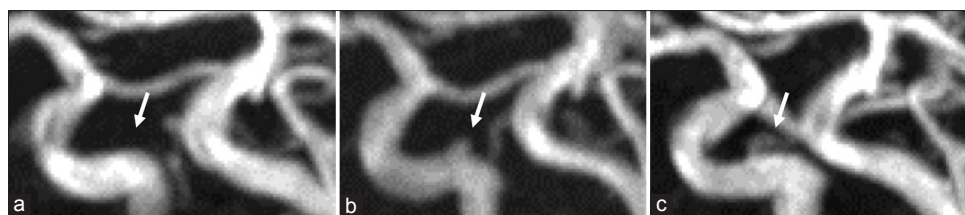
period of 3 weeks in spite of the steroid administration. Therefore, the oral mPSL was increased to 60 mg/day. Her symptoms worsened, and she was transferred to the neurological department in our hospital for further examination and treatment. There were leukocytosis, a slightly high level of C-reactive protein, and an increased erythrocyte sedimentation rate. The blood coagulation function, autoimmune test, infection examinations, and tumor markers were normal. The patient had bilateral retro-orbital pain and right oculomotor and bilateral abducens nerve palsy. An MRI showed noticeable enlargement of the right CS [Figure 2b]. The serum level of the pituitary hormones was within normal limits. Additional mPSL pulse therapies were introduced twice. The left abducens nerve palsy disappeared, and the right oculomotor and abducens nerve palsy were ameliorated. A gadolinium-enhanced T1-weighted MRI revealed multiple low-intensity lesions in the pituitary gland and the bilateral CS. Mucosal thickening and fluid collection in the sphenoid sinus were also seen [Figure 2c]. The amount of steroid was gradually decreased, and her orbital pain became worse. An MRI taken 1 month later showed that the inner membrane of the bilateral CS had become unclear. Hypertrophic dura mater around the sellae was also observed, and the sphenoid sinusitis had worsened [Figure 2d]. A tiny aneurysm was discovered to have arisen from the C4 portion of the right ICA as revealed by MR angiography (MRA) [Figure 3b]. This aneurysm was not apparent on the initial MRA [Figure 3a]. The follow-up hormonal examinations indicated total anterior hypopituitarism. Clarithromycin and carbocisteine (400 mg/day and 1500 mg/day, respectively) were administered for the diagnosis of bacterial sinusitis. An endoscopic endonasal transsphenoidal surgery was



**Figure 1:** Pre- and postoperative clinical course. 0: Onset day, mos: Months, ETSS: Endoscopic transsphenoidal surgery



**Figure 2:** Serial magnetic resonance imaging (MRIs) in the pre- and postoperative course. (a) An initial MRI demonstrating enlargement of the left cavernous sinus (CS). (b) Enlargement of the right CS after two sessions of methylprednisolone (mPSL) pulse therapy. (c) Sphenoid sinus mucosal thickening after additional mPSL pulse therapy. (d) Further swelling of the bilateral CSs at 1 month after mPSL pulse therapy, unclear border between the CS and the pituitary gland, and the sphenoid sinusitis worsened. Cystic change is also seen in the pituitary gland. (e) The CS and the pituitary lesion decreased in size. (f) No recurrence of the CS or the pituitary lesions



**Figure 3: Serial magnetic resonance angiography (MRA) in the pre- and postoperative course. (a) No internal carotid artery (ICA) aneurysms revealed in the bilateral cavernous sinus (CSs) on the initial MRA. (b) A 2-mm de novo aneurysm arising from the right C4 portion of the ICA. (c) A 3-mm aneurysm with slight enlargement. White arrow: Aneurysm**

performed to exclude a CS tumor, such as a lymphoma, or a specific granuloma, as well as the possibility of an infectious disease; during the procedure, the sphenoid sinus and intrasellar contents were drained. A cream-like purulent content was discharged at the opening of the anterior wall of the sphenoid sinus. Mucosal thickening of the sphenoid sinus was also observed. The sellar floor was partially destroyed, and the dura mater was thick and hard. A biopsy of the hypophysis was performed. The pituitary gland was fragile, and the purulent discharge was similar to that from the sphenoid sinus. The dead space was irrigated with copious amounts of saline. Specimens were extracted from the left CS because the aneurysm was in the right CS. Histological examination of the CS showed granulomatous inflammation. This lesion consisted of eosinophilic foamy histiocyte-like cells that were positive for CD68 and negative for S100, CD1a, and inflammatory cells. The sphenoid sinus mucosa suffered from infiltration of lymphocyte and plasma cells in the edematous stroma. Inflammation was also seen in the hemorrhagic and necrotic pituitary gland. Neoplasms such as lymphoma, tuberculosis, and sarcoidosis were excluded. No bacterial growth was observed in the cultures of the drained contents. The severe painful ophthalmoplegia subsided immediately after the operation. She was diagnosed as having a steroid-resistant THS, and methotrexate (MTX, 4–8 mg/week) was administered. Clarithromycin and carbocisteine were continued for 3 months after the operation, at which time, decreased swelling of the bilateral CSs and no effusion in the sphenoid sinus were noted on the follow-up MRI [Figure 2e]. However, the aneurysm had slightly enlarged. Right ophthalmoplegia did not recur, and the aneurysm was carefully observed without any treatment. The mPSL was gradually decreased. MTX was maintained for 6 months, and the ophthalmoplegia disappeared. An MRI revealed the decreased size of the CS and pituitary lesions [Figure 2f]. However, the intracavernous aneurysm remained without change as revealed by MRA [Figure 3c]. Hormonal examination 3 months after the operation revealed still total anterior pituitary dysfunction. Hormone replacement therapy was started with hydrocortisone and levothyroxine sodium hydrate. Somatropin was also administered approximately 1 year after the operation.

## DISCUSSION

The etiology of THS remains unknown.<sup>[27,14]</sup> Pathological findings had idiopathic granulomatous inflammation in the CS and superior orbital fissure. This syndrome is defined as episodic orbital pain associated with paralysis of one or more of the oculomotor, trochlea, and/or the abducens nerves, that usually resolves spontaneously but tends to relapse and remit, as described in the international headache classification.<sup>[18]</sup> The diagnostic criteria were: 1. One or more episodes of unilateral orbital pain persisting for weeks if untreated; 2. Paresis of one or more of the third, fourth, and/or sixth cranial nerves and/or demonstration of granuloma by MRI or biopsy; 3. Paresis coincides with the onset of pain or follows it within 2 weeks; 4. Pain and paresis resolve within 72 h when treated adequately with corticosteroids; and 5. Other causes have been excluded by appropriate investigations.<sup>[12]</sup> The administration of corticosteroid is usually effective for THS. The diagnosis of THS is given based on both neurological course and radiological findings. Therefore, surgical intervention and pathological study of THS are relatively rare.<sup>[9,14,15,17]</sup> Our patient's symptoms fluctuated during the treatment with mPSL over 4 months. Although criterion No. 4 was not completely met, a biopsy of the cavernous lesion was performed to exclude other pathologies such as tumor and specific inflammation. Surgical intervention also aimed at confirmation and decompressive drainage for the pituitary and sphenoid sinus lesions.

THS usually improves with steroid therapy. However, in cases of insufficient efficacy of steroids or side effects, alternative therapies, such as immunosuppressant or radiation therapy, have been reported.<sup>[7,8,10,11,19-21,24]</sup> Azathioprine, MTX, and cyclosporine have been used as corticosteroid-sparing agents. Smith *et al.*<sup>[24]</sup> reported 14 patients with various noninfectious orbital inflammatory disease that two-thirds of the total patients experienced clinical benefits of MTX on a median maximum dose of 20 mg/week for a median of 25 months. In the present case, 8 mg/week of MTX was maintained for 6 months, after which the patient's retro-orbital pain and diplopia disappeared. In radiation therapy for THS, 4 of 5 reported cases had received

corticosteroid as an initial therapy, and radiation was added with doses from 20 to 50 Gy because of insufficient efficacy and/or side effects. The symptoms improved in all the patients without any recurrence or adverse effects related to the radiation. Therefore, immunosuppressant and/or radiation therapy are safe and effective options for steroid-resistant THS.

Pituitary abscess is purulent inflammation of the pituitary gland, of which more than 250 cases have been reported in the literature.<sup>[2,5,13,29]</sup> Pituitary abscess is very rare, with only 0.2–1% among all pituitary diseases. There are two types of pituitary abscesses. One type is caused by the hematogenous seeding of the pituitary gland or the coexisting lesions such as adenoma, craniopharyngioma, or Rathke's cleft cyst. The other type is the direct extension of an adjacent infection such as sphenoiditis, meningitis, and thrombophlebitis in the CS. Patients who are immunocompromised or have concurrent pituitary lesions may have increased risk. The most common clinical features are headache and visual deterioration. Pituitary insufficiency is not rare. Zhang *et al.*<sup>[29]</sup> reported 29 cases of pituitary abscesses in a single institute (70% anterior pituitary dysfunction and 40% diabetes insipidus). Pituitary abscess is demonstrated as a ring-enhanced cystic lesion. Surgical drainage and prolonged microbiology-guided antibiotic therapy are standard treatments for a pituitary abscess. The outcome reported in the literature shows that 60% of patients recovered completely, 30% recovered with hormonal or visual impairment, and 10% died after surgical and medical treatment. The present case of a secondary pituitary abscess had no systemic infectious disease or autoimmune disease. In the preoperative course, thickening of the mucosa and fluid collection in the sphenoid sinus gradually became apparent. A pituitary cystic lesion appeared after sphenoid sinusitis. Anterior pituitary function was also damaged during that period. Prolonged administration of high-dose mPSL and sinusitis possibly induced the pituitary abscess. The worsening of retro-orbital pain is caused not only by the inflammation of THS but also by sinusitis and abscess in the pituitary gland. The continuous administration of steroid made the patient a compromised host, and the lesion unexpectedly worsened. The negative cultures of the abscesses were attributed to the preoperative and intraoperative administration of antibiotics. Her symptoms, especially that of retro-orbital pain, were immediately alleviated after the operation because the internal pressure in the sphenoid sinus and pituitary fossa was reduced by transsphenoidal drainage.

Stenosis in the cavernous portion of the ICA has been reported in THS.<sup>[1,3,28]</sup> This change was likely caused by compression following the granulomatous inflammation and/or local periarteritis in CS.<sup>[6,22,23,25-27]</sup> Campbell *et al.*<sup>[4]</sup> described thickening of vessel wall by infiltration

of leukocytes, lymphocytes, plasma cells, and fibrin was found by autopsy. However, a de novo aneurysm arising from the cavernous portion of the ICA is rare in THS. To date, only 2 cases of cavernous portion aneurysms have been reported. Kambe *et al.*<sup>[15]</sup> first reported bilateral aneurysms in CS. A 58-year-old woman had right abducens nerve palsy and right retro-orbital pain. MRI showed an enlargement of hypophysis and bilateral CS. Cerebral angiography revealed stenosis of the left intracavernous ICA and aneurysms of the bilateral ICAs. The symptom recurred in spite of administration of prednisolone. MRI demonstrated an increase in the size of the hypophysis and cerebral angiography showed the right C4 aneurysm had decreased in size. However, the left C3 aneurysm remained unchanged after subsequent high-dose steroid therapy. The aneurysm was treated with Guglielmi detachable coils. A biopsy of the enlarged hypophysis was performed, and the specimen was noted to consist of inflammatory cells. A case with intracavernous carotid stenosis and a reversible dissecting aneurysm was reported by Zhou *et al.*<sup>[30]</sup> A 49-year-old woman had right oculomotor and abducens nerve palsy and right retro-orbital pain. Neuroimages showed an enlargement of the right CS and the right intracavernous carotid dissecting aneurysm. The symptom was alleviated immediately after administration of dexamethasone. Follow-up cerebral angiography revealed that the dissecting aneurysm had decreased in size. They speculated that inflammation had affected not only the CS but also the ICA; consequently, local vasculitis had developed. The dissection of the intracavernous ICA was directly induced by inflammation in THS. However, the possibility of the aneurysms being present prior to the illness in the two reported cases cannot be ruled out. In the present case, we could completely demonstrate serial MRA in THS; no aneurysms were seen at least on the initial MRA study. When the disease progression caused the severe bilateral enlargement of the CS and cystic changes in the hypophysis and the sphenoid sinusitis revealed on MRI, a small upper protruding aneurysm arising from the C4 portion of the ICA was clearly visible on the MRA. The aneurysm arose at the proximal half of the cavernous segment, and an inflammatory change was also seen at the posterior portion of the CS. This aneurysmal formation may be induced by rampant inflammation in THS. In review of the literature, including the present case, there were 3 cases with 4 aneurysms in THS [Table 1]. Aneurysms disappeared in 2 cases and were unchanged in 1 case, and only 1 aneurysm was treated with coil embolization. Aneurysm enlargement was only observed in the present case. There were no rupture cases. Disease progression of THS is worthy of special mention. Two of the 3 cases had recurrence of THS even with the steroid therapy. This might have suggested the potency of inflammation. Careful observation is needed in unfavorable courses of



**Table 1: Review of the aneurysm arising from internal carotid artery in cavernous portion with Tolosa-Hunt syndrome**

Author/year	Age/sex	Side	Location	ICA stenosis	Treatment	f/u (mos)	Change in size
Kambe/2006	58/F	Bilateral	C4	yes	ob		Decreased
			C3	yes	Coil Embolization		Treated
Zhou/2010	49/F	Right	C4	yes	ob	3	Decreased
Present case	53/F	Right	C4	No	ob	18	enlarged

treatment with steroids. To our knowledge, this is the first report of a de novo intracavernous aneurysm in THS.

## CONCLUSIONS

We reported a case of steroid-resistant THS. Pituitary abscess and sphenoid sinusitis were drawn by an immunocompromised condition due to long-term administration of high-dose steroids. When steroid therapy is not effective, immunosuppressant therapy or surgical intervention should be considered. Although the present case is only the third one reported with an intracavernous ICA aneurysm associated with THS, to our knowledge, this is the first case to show a de novo aneurysm and its development. This ICA aneurysm in the CS might have been induced by dissection due to inflammation in THS. Careful close observation with serial MRAs is important in cases of steroid-resistant THS.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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## Commentary

### ON THE TOLOSA–HUNT SYNDROME, CHIMERAS, AND DIAGNOSES

First, the authors are to be congratulated for their aggressive pursuit of diagnosis and dogged and, so far, successful management of this pathologically evolving paracavernous lesion.

The symptoms first seemed to be classic for the Tolosa–Hunt syndrome, as now understood, then morphed into a pituitary and sphenoid abscess, and then finally into a case whose radiopathophysiology was that of a de-novo, then stable, intracavernous aneurysm. What an evolution in the understanding of the necessary treatment of a single case!

In a very interesting manner, the evolution of understand in this case parallels not just the greater quest for the clarification of the uncertainty of diagnosis and treatment of all clinical problems but also reflects the evolution of both the pathophysiology and the very meaning of the Tolosa–Hunt Syndrome itself. Let me explain.

The first author of the index paper, William E Hunt, was always embarrassed by the very title of his paper, “Painful Ophthalmoplegia: Its relation to indolent inflammation of the cavernous sinus.” He felt that the words Painful and indolent (from the Latin *in-not* and *dolere*-pain) in the title were oxymoronic.

Perhaps he can be more easily forgiven an overwrought emotional response to the particulars of the publication when one realizes that the index case, VH, was his beautiful young wife and the mother of his three infant children. As a young attending at Ohio State, recognizing the seriousness of the anatomical localization of her symptoms, he took her back to the care of his mentor, Henry Schwartz, at the Barnes Hospital, where she underwent a (state of the art at the time) direct carotid stick hand-pulled 3-5 frame

angiogram, which she fortunately tolerated well. Steroid treatment was not known at that time.

He subsequently, perusing the literature, ran across the similar case of Dr. Tolosa, and Dr. Tolosa was kind enough to provide the pathological slides from his case. Unlike the case of Dr. Tolosa, “(o) ur cases lack only autopsy confirmation.” Even X-ray tomography was still in the future, and computed tomography and magnetic resonance imaging were not dreamed of. Subsequent cases presenting to the Ohio State University Hospital demonstrated the general utility of steroid treatment for this clinical syndrome of still unknown etiology. Importantly, the elegant clinical description of the syndrome and the precise clinicoanatomic correlation of the presentation are pathognomonic of the golden age of the queen of the clinical sciences.

Ultimately, the hallmark of the syndrome, as it was first described, is that it is a highly localized intracavernous occult inflammation without orbital mass effect or venous obstruction, generally self-limited, but sometimes relapsing, with variable relation to the onset of pain; routinely steroid sensitive, and differentiable by history, physical exam, and pathophysiology from the “ophthalmoplegic migraine” of Charcot and other vascular, neoplastic, and infectious lesions of the region.

As described in this paper, the “Tolosa–Hunt syndrome” has come to represent a much broader class of cavernous syndromes, or even multiple serial syndromes. Over time definitions, understanding, and meaning itself drifts, mutable and ephemeral as the patients we treat.

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