Hypertrophic cranial pachymeningitis and orbital apex syndrome secondary to infection of the eye: illustrative case

Tara Zielke, BS,2 Miri Kim, MD, PhD,1 Joshua E. Simon, MD,1 Ewa Borys, MD,3 Vikram C. Prabhu, MD,1 and Suguna Pappu, MD, PhD1,4

Departments of 1Neurological Surgery and 3Pathology, Loyola University Medical Center, Maywood, Illinois; 2Loyola Stritch School of Medicine, Maywood, Illinois; and 4Department of Neurological Surgery, Edward J. Hines VA Hospital, Hines, Illinois

BACKGROUND Hypertrophic cranial pachymeningitis is a rare inflammatory disorder characterized by thickening of the dura mater and multiple cranial neuropathies. Although an infectious etiology may be present, often no specific cause is discovered.

OBSERVATIONS The authors described a 71-year-old man with progressive right eye vision loss, ptosis, and complete ophthalmoplegia with imaging findings suggestive of hypertrophic cranial pachymeningitis. Extensive studies, including cerebrospinal fluid studies, showed negative results. Blood serum, cell-free evaluation, and paraffin-embedded dural tissue testing had positive results for Pseudomonas aeruginosa, which allowed treatment tailored to the organism and a salutary clinical outcome.

LESSONS The constellation of neurological and radiological findings may make a diagnosis difficult in an inflammatory setting. The most precise methodology for establishing a diagnosis involves sampling the dura and testing it for infectious pathology. However, if results are inconclusive, further cell-free serum sampling with next-generation sequencing is a viable option for identifying pathogens with infectious concerns. This case highlighted the importance of multimodality studies for identifying a targetable pathogen.

https://thejns.org/doi/abs/10.3171/CASE20168

KEYWORDS hypertrophic cranial pachymeningitis; orbital apex syndrome; Pseudomonas aeruginosa

Hypertrophic cranial pachymeningitis (HCP) is a rare condition characterized by diffuse or localized chronic inflammation and hypertrophy of the dura mater.1 Known etiologies include infectious, toxic, neoplastic, inflammatory, and traumatic origins. However, in many cases of HCP, no specific cause is found. These cases are categorized as idiopathic HCP, and the diagnosis is made by exclusion of other potential causes.2,3 The symptoms and signs of HCP vary widely based on the extent and location of dural involvement and can range from headache to cranial neuropathies, vision changes or loss, cerebral or cerebellar dysfunction, or radiculopathy.4–7 At times, the orbital apex may be involved, resulting in a complex neurological picture known as orbital apex syndrome. This syndrome results from dysfunction of cranial nerves II, III, IV, V, and VI, which are concentrated in this region.8 Symptoms and signs of orbital apex syndrome include vision loss, painful ophthalmoplegia, and pupillary abnormalities.9 Orbital apex syndrome may be caused by neoplastic, inflammatory, infectious, or vascular pathology. Orbital apex syndrome caused by Pseudomonas aeruginosa infection is extremely rare.10 An accurate diagnosis is essential because it guides treatment, which is vastly different for each cause. We present a case of orbital apex syndrome secondary to P aeruginosa infection of the eye that resulted in radiological findings suggestive of HCP.

Illustrative Case A 71-year-old, right-handed man with a known history of progressive advanced glaucoma in both eyes, type II diabetes mellitus, chronic kidney disease, and a gastrointestinal stromal tumor treated with a partial gastrectomy 3 years earlier presented with severe right-sided temporal headaches and vision changes over the course of

ABBREVIATIONS CRP = C-reactive protein; CSF = cerebrospinal fluid; HCP = hypertrophic cranial pachymeningitis; MRI = magnetic resonance imaging; PCR = polymerase chain reaction; rRNA = ribosomal ribonucleic acid.

INCLUDE WHEN CITING Published May 24, 2021; DOI: 10.3171/CASE20168.

SUBMITTED December 21, 2020. ACCEPTED December 30, 2020.
© 2021 The authors, CC BY-NC-ND 4.0 (http://creativecommons.org/licenses/by-nc-nd/4.0/).
tissue at the right orbital apex. A large piece of thickened dura and thickened tissue, with patchy yellowed discoloration and no frank purulence. Enhanced dural and orbital apex tissue. The dura was markedly thickened, with patchy yellowed discoloration and no frank purulence. An interval contrast-enhanced MRI scan obtained 1 week after steroids had been initiated demonstrated no significant change in the contrast-enhancing tissue at the right orbital apex.

As a result of the patient’s lack of response to steroids, inconclusive CSF studies, and persistent low-grade leukocytosis, he underwent a right-sided craniotomy and open biopsy of the right-sided enhancing dural and orbital apex tissue. The dura was markedly thickened, with patchy yellowed discoloration and no frank purulence. A large piece of thickened dura and thickened fibrous tissue from the orbital apex was resected to decompress the neural elements at the orbital apex and sent for routine and permanent studies.

Postoperatively, the patient reported significantly improved headache and pressure behind his right eye because the neural elements at the orbital apex had been decompressed. On postoperative day 2, the patient had reliable light perception of his right eye and slightly improved extraocular movements.

Pathological evaluation of the dura demonstrated chronic inflammation and meningotheelial proliferation that indicated an acute or chronic infectious process, but no evidence of a benign or malignant neoplastic process was noted. The peri orbital specimen was notable for fibrous tissue with granulation tissue and chronic inflammation, and areas of necrotic tissue revealed microabscesses consistent with an infectious process (Fig. 2). Further staining for microorganisms showed negative results for bacterial, mycobacterial, or fungal organisms. Because of the inconclusive nature of the studies and concern for an infectious process, the tissue was sent for polymerase chain reaction (PCR) studies.

With the concern for infection and persistent leukocytosis despite cessation of steroids, identification of a microbial organism was prioritized to establish an optimal antibiotic treatment regimen (Fig. 3). A lumbar puncture was repeated, but evaluation of CSF again failed to reveal evidence of an infectious process or malignancy, which prompted further analysis for identification of an occult microbial process. Simultaneous serum analysis through the next-generation sequencing serum test and PCR studies of the intraoperative pathology specimens were performed. The test identified *P. aeruginosa* on next-generation sequencing. Independently, 16S ribosomal RNA (rRNA) was extracted from the paraffin-embedded dural tissue and found to be positive for 16S rRNA of *P. aeruginosa*, which confirmed the diagnosis.

The patient was started on 2 g of cefepime every 8 hours with the intention of completing a 4- to 6-week course. However, because of significant neurotoxicity with acute onset of altered mental status approximately 72 hours after starting the cefepime, the antibiotic regimen was adjusted to 2 g of cefazidime every 12 hours for 4 weeks. The patient demonstrated marked improvement in mental status, with rapid resolution of headache and significant improvement of the ptosis; however, his extraocular movement remained severely restricted. He also showed resolution of the serum leukocytosis and a decrease in inflammatory markers (Fig. 3).

The patient completed a 6-week course of cefazidime, and follow-up MRI showed significant improvement in the dural enhancement of the right convexity dura and orbital apex lesion (Fig. 4A and B). After completion of his course of antibiotics, approximately 2 months...
postoperatively, the patient reported complete resolution of his headaches and return of light perception in the right eye. Six-month follow-up imaging demonstrated continued improvement in dural enhancement and stable clinical examination (Fig. 4C and D).

**Discussion**

HCP is characterized by inflammation and hypertrophy of the dura mater, with the three meningeal layers becoming fused by dense fibrotic membranes. It is a rare disorder with an array of causes and symptoms, including multiple cranial neuropathies, headache, and vision changes. In our patient, the optic nerve was involved, portending a poor visual prognosis. Our patient had known low vision before his infection, which led to complete loss of vision as his infection progressed. He demonstrated improved light perception in the right eye after a 6-week course of antibiotics as well as resolution of his pain.

The first documented case of HCP by Charcot and Joffory in 1869 reported it as having an infectious origin via syphilis. Several cases resulting from infectious causes have been reported, including syphilis, tuberculosis, Aspergillus, Candida, and Petriellidium boydii. Infectious HCP is commonly related to sinusitis and chronic otitis media, leading to skull base osteomyelitis. Other causes include traumatic, neoplastic, and inflammatory conditions such as rheumatoid arthritis and sarcoidosis. However, most cases of HCP remain idiopathic. Our patient did not have hearing loss, destruction of the clivus, immunosuppression, prior head or neck surgeries, inflammatory conditions, or a history of chronic otitis media or sinusitis.

**Observations**

Investigative measures to determine a diagnosis and specific cause of our patient's HCP included blood samples, CSF collection, contrast MRI, and dura mater biopsy. The dura mater biopsy identified chronic inflammation and microabscesses, which raised concern for an infectious process over a malignancy. Preliminary evaluation of the CSF and dural biopsy produced negative results for any bacterial, mycobacterial, or fungal organisms through culture or stains. Because of the inconclusive nature of staining studies, the samples were subsequently sent for sequencing of the paraffin-embedded dural tissue, which ultimately showed positive results for 16S rRNA of *P. aeruginosa*. Simultaneous cell-free serum studies obtained via next-generation sequencing analysis supported the diagnosis of a *P. aeruginosa* infection. That blood test uses next-generation sequencing of microbial cell-free DNA to identify bacterial, fungal, viral, and parasitic pathogens.
Our patient had an enhancing lesion along the orbital apex that involved the optic nerve. Repeat ophthalmological evaluation demonstrated improved motility deficits of the right eye and improved plosis of the right eye; however, because of the patient’s inability to consistently detect light in the right eye, formal visual fields were not indicated. Without significant improvement in vision of the right eye, the ophthalmology service deemed that his visual prognosis was poor. Our patient did note resolution of his headaches and improved light perception at his most recent follow-up appointment a few weeks after his ophthalmology examination.

**Lessons**

Currently, no standard modalities are available to identify underlying pathogens for HCP. Additionally, there is no established protocol regarding the length of antibiotic treatment for infectious HCP once a pathogen is identified. In our patient, antibiotic treatment with ceftazidime for 6 weeks led to a declining trend in white blood cell values, reduced inflammatory markers (erythrocyte sedimentation rate and C-reactive protein [CRP]), and significant improvement in the patient’s symptoms with durable radiographic outcomes. The natural course of HCP is not well understood. However, after a course of antibiotic treatment, our patient was monitored with interval imaging studies after the clinical presentation for recurrence of symptoms. The next-generation serum test is an important tool in the case of occult infection, and it is able to identify pathogens without providing significant information regarding antibiotic sensitivities. *Pseudomonas* has been demonstrated to harbor varying amounts of antibiotic resistance, primarily in studies of pneumonia. Thus, understanding the local antibiogram as well as historical resistance is important for optimizing antibiotic treatment in patients with intracranial involvement. With a multidisciplinary team approach for targeting optimal treatment, the patient was started on antibiotics. He had a good long-term durable response and no evidence of recurrence 6 months after intervention.

This is the first documented case of HCP with orbital apex syndrome secondary to *P. aeruginosa* infection of the eye. Most cases of HCP are labeled as idiopathic after negative test results for malignancy, inflammation, and infectious processes. We used next-generation serum sequencing and PCR of the paraffin-embedded dural tissue to obtain a final diagnosis. This strategy should be used before assigning a designation of idiopathic etiology. With more diagnostic options, more tailored treatments can lead to better clinical outcomes.

**References**

1. Riku S, Kato S. Idiopathic hypertrophic pachymeningitis. Neurpathology. 2003;23(4):335–344.
2. Goyal M, Malik A, Mishra NK, Gaikwad SB. Idiopathic hypertrophic pachymeningitis: spectrum of the disease. *Neuroradiology*. 1997; 39(9):619–623.
3. Hamilton SR, Smith CH, Lessell S. Idiopathic hypertrophic cranial pachymeningitis. *J Clin Neuroophthalmol*. 1993;13(2):127–134.
4. Dumont AS, Clark AW, Sevick RJ, Myles ST. Idiopathic hypertrophic pachymeningitis: a report of two patients and review of the literature. *Can J Neurol Sci*. 2000;27(4):333–340.
5. Hataano N, Behari S, Nagatani T, et al. Idiopathic hypertrophic cranial pachymeningitis: clinicoradiological spectrum and therapeutic options. *Neurosurgery*. 1999;45(6):1336–1344.
6. Kanamori M, Matsui H, Terahata N, Tsuji H. Hypertrophic spinal pachymeningitis. A case report. *Spine (Phila Pa 1976)*. 1997;22(15):1787–1790.
7. Mamelak AN, Kelly WM, Davis RL, Rosenblum ML. Idiopathic hypertrophic cranial pachymeningitis. Report of three cases. *J Neurosurg*. 1993;79(2):270–276.
8. Hedges TR, Leung LS. Parasellar and orbital apex syndrome caused by aspergillosis. *Neurology*. 1976;26(2):117–120.
9. Badakere A, Patil-Chhablani P. Orbital apex syndrome: a review. *Eye Brain*. 2019;11:63–72.
10. Kusunoki T, Kase K, Ikeda K. A case of orbital apex syndrome due to *Pseudomonas aeruginosa* infection. *Clin Pract*. 2011;4(e):e127.
11. Girkin CA, Penny JD, Miller NR, Reich SG. Pachymeningitis with multiple cranial neuropathies and unilateral optic neuritis secondary to *Pseudomonas aeruginosa*: case report and review. *J Neuroophthalmonol*. 1998;18(3):196–200.
12. Horiguchi T, Gotoh K, Yoshida K, Toya S. A successful case of hypertrophic cranial pachymeningitis treated by optic nerve decompression. *No Shinkei Geka*. 1996;24(3):281–285.
13. Charcot JM, Joffory A. Deux cas d’atrophie musculaire avec lesions de la substance grise et des faisceaux anterolateraux de la moelle epiniere. *Arch Physiol Norm Pathol*. 1869;2:354–367.
14. Gorell JM, Palutke WA, Chason JL. Candida pachymeningitis with multiple cranial nerve parapses. *Arch Neural*. 1979;36(11):719–720.
15. Mura H, Kira J, Kobayashi T, et al. Hypertrophic cranial pachymeningitis due to *Aspergillus flavus*. *Clin Neural Neurosurg*. 1992;94(3):247–250.
16. Schiess RJ, Coscia MF, McClellan GA. *Petriellidium boydii* pachymeningitis treated with miconazole and ketoconazole. *Neurosurgery*. 1984;14(2):220–224.
17. Brook I, Overturf GD, Steinberg EA, Hawkins DB. Acute sphenoid sinusitis presenting as aseptic meningitis: a pachymeningitis syndrome. *Int J Pediatr Otorhinolaryngol*. 1982;4(1):77–81.
18. Ishii A, Ohkoshi N, Nagata H, et al. A case of Garcin’s syndrome caused by pachymeningitis secondary to otitis media, responsive to antibiotic therapy. *Article in Japanese*. *Rinsho Shinkeigaku*. 1991; 31(8):837–841.
19. Fujimoto M, Kira J, Murai H, et al. Hypertrophic cranial pachymeningitis associated with mixed connective tissue disease: a comparison with idiopathic and infectious pachymeningitis. *Intern Med*. 1993;32(6):510–512.
20. Kupersmith MJ, Martin V, Heller G, et al. Idiopathic hypertrophic pachymeningitis. *Neurology*. 2004;62(5):686–694.
21. Yayan J, Ghebremedhin B, Rasche K. Antibiotic resistance of *Pseudomonas aeruginosa* in pneumonia at a single university hospital center in Germany over a 10-year period. *PLoS One*. 2015;10(10):e0139836.

**Disclosures**

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

**Author Contributions**

Conception and design: Pappu, Kim. Acquisition of data: Pappu, Zielke, Kim, Simon, Borys. Analysis and interpretation of data: Zielke, Kim, Prabhu. Critically revising the article: Pappu, Zielke, Kim, Borys. Reviewed submitted version of manuscript: Pappu, Zielke, Kim, Borys. Approved the final version of the manuscript on behalf of all authors: Pappu. Study supervision: Pappu, Kim.

**Correspondence**

Suguna Pappu: Loyola University Medical Center, Maywood, IL. suguna.pappu@gmail.com.