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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, PhD[1,4]

Departments of [1]Neurological Surgery and [3]Pathology, Loyola University Medical Center, Maywood, Illinois; [2]Loyola Stritch School of Medicine, Maywood, Illinois; and [4]Department 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.

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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.

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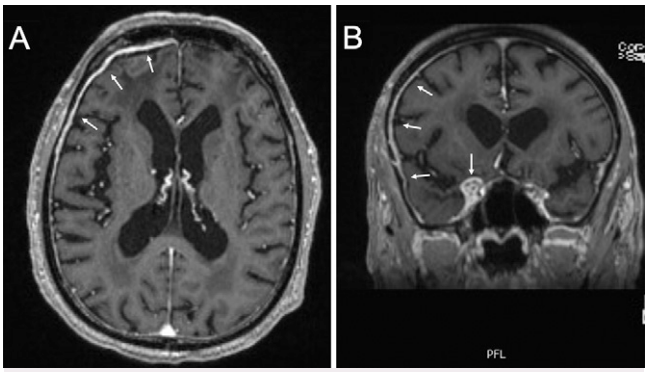

FIG. 1. T1-weighted post-gadolinium MRI scans of the brain in axial (**A**) and coronal (**B**) sections demonstrating diffuse right-sided dural enhancement (*arrows*).

approximately 1 month. The patient had a history of low vision, with the ability to perceive light and shadows with both eyes.

At the time of presentation, the patient was neurologically intact except for worsening of his poor vision, with stable light perception in the left eye and complete loss of vision in the right eye. He had associated right-sided ptosis, mild proptosis, and painful restriction of the right eye extraocular movements because of complete palsies of cranial nerves III, IV, and VI. He was also noted to have decreased sensation in the right face V1 distribution, which initially prompted an assessment for trigeminal neuralgia before neurosurgical evaluation. Magnetic resonance imaging (MRI) of the brain and orbit revealed a diffuse, homogeneously enhancing lesion at the right orbital apex involving the optic nerve sheath and dura of the right anterior hemicranium without evidence of other intracranial abnormalities (Fig. 1).

At the time of presentation, the differential diagnosis included lymphoma, sarcoid, malignancy, and infection. A lumbar puncture was performed, and cerebrospinal fluid (CSF) analysis showed normal red and white blood cell counts but decreased protein (29.4 mg/dL) and elevated glucose (70 mg/dL). The initial CSF culture results were negative for fungal or bacterial organisms, and a CSF viral panel result was negative. CSF cytology and CSF flow cytometry were also performed and were unremarkable for abnormal cells. CSF angiotensin-converting enzyme was also sent for evaluation of sarcoidosis; however, the results were also unremarkable. The patient was started on a brief course of dexamethasone at 4 mg every 6 hours but did not experience significant clinical relief of symptoms. 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 meningothelial proliferation that indicated an acute or chronic infectious process, but no evidence of a benign or malignant neoplastic process was noted. The periorbital 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 ribonucleic acid (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 ceftazidime 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 ceftazidime, 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

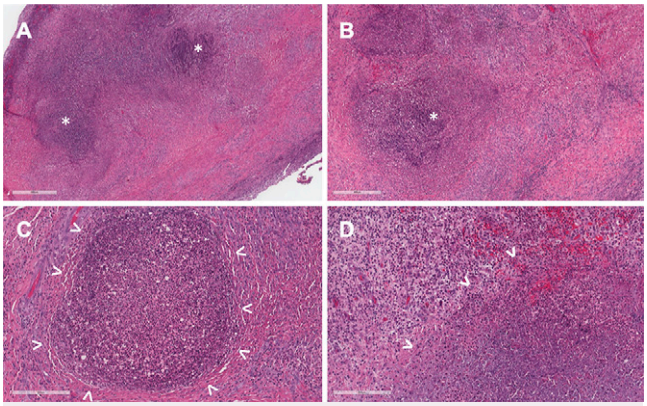

FIG. 2. Hematoxylin and eosin–stained sections through the abnormal dural tissue. **A:** Original magnification ×1 (low magnification). **B:** Original magnification ×5. Microabscesses are noted with *asterisks*. **C and D:** Original magnification ×10. Stains demonstrate changes associated with chronic inflammation and microabscesses (outlined with *arrowheads*).

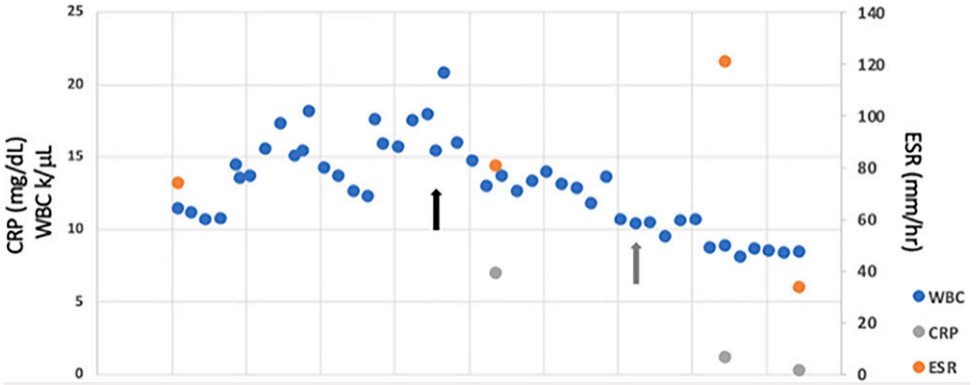

FIG. 3. Patient leukocytosis and inflammatory markers throughout his hospitalization. *Blue circles* indicate white blood cell (WBC) count in thousands per microliter (k/μL) on the left axis. *Orange circles* indicate erythrocyte sedimentation rate (ESR) in millimeters per hour (mm/hr) on the right axis (normal laboratory values 0–20). *Gray circles* indicate CRP in milligrams per deciliter (mg/dL) on the left axis (normal laboratory value < 0.3). The *black arrow* indicates time of surgery; the *gray arrow* indicates initiation of antibiotics.

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).

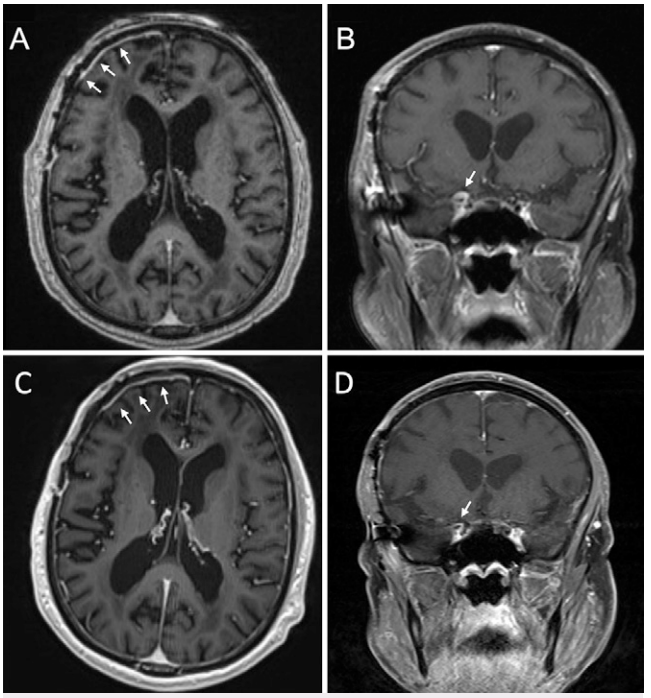

FIG. 4. Postoperative and post-antibiotic T1-weighted post-gadolinium MRI scans demonstrate significant radiographic improvement of dural enhancement. Postoperative and post-antibiotic T1-weighted post-gadolinium MRI scans at 6 weeks in axial (**A**) and coronal (**B**) sections demonstrate significant improvement of dural enhancement (*arrows*). Repeat MRI at 6 months after surgery (**C and D**) demonstrates continued improvement of dural enhancement (*arrows*).

Discussion

HCP is characterized by inflammation and hypertrophy of the dura mater, with the three meningeal layers becoming fused by dense fibrotic membranes.[11] 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.[12] 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.[13] Several cases resulting from infectious causes have been reported, including syphilis, tuberculosis, *Aspergillus*, *Candida*, and *Petriellidium boydii*.[13–16] Infectious HCP is commonly related to sinusitis and chronic otitis media, leading to skull base osteomyelitis.[17,18] Other causes include traumatic, neoplastic, and inflammatory conditions such as rheumatoid arthritis and sarcoidosis.[19,20] 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 ptosis 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.[21] 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.

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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, Simon, Borys. Drafting the article: Zielke, Kim, Simon, Borys, Prabhu. Critically revising the article: Pappu, Zielke, Kim, Prabhu. 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.