CLINICAL VIGNETTE

54-Year-Old Male with Chronic Headache and Worsening Dysphagia and Odynophagia

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A 54-year-old male with hypertension and chronic headache presented to the Emergency Room with worsening dysphagia and odynophagia. He also had daily headaches for the past year, described as dull, throbbing, and diffuse, starting frontally & radiating to the posterior/occipital region. He denied photophobia, phonophobia, or nausea. He also reported worsening hearing particularly on the left as well as dizziness described as vertigo without ataxia. He had tried ibuprofen and acetaminophen for the headaches without any relief. About two months before he developed difficulty swallowing solids which progressed to difficulty swallowing liquids prompting his ED evaluation.

He reported 20-pound weight loss but otherwise negative review of systems. He denied any fever or chills, cardiopulmonary symptoms, abdominal pain, diarrhea or constipation. He had hypertension and was taking celecoxib, amlodipine, tramadol, acetaminophen with iodine #3, eszopicione, and pantoprazole.

He had recently traveled to China and social history included 45 pack year smoking and two glasses of wine at night, and denied any illicit drug use. He worked in the restaurant industry.

His father died of liver cancer and had no any family history of connective tissue disease.

On physical exam his vital signs were normal. He was thin and uncomfortable due to pain. Mental status was intact and attention within normal limits. His speech was fluent and his comprehension, production, and speech repetition were normal. Cranial nerves were normal except for mild tongue deviation to the right, without lingual weakness. Motor exam was normal and sensation intact to light touch. Reflexes were 2+ throughout and gait was normal. He did not have any rashes, joint tenderness or swelling. His cardiovascular, pulmonary and abdominal examinations were unremarkable.

Laboratory evaluation included normal complete blood counts and comprehensive metabolic panel. Rheumatologic testing included neg Anti-Nuclear Antibody (ANA) and further rheumatologic work up was also unrevealing including negative dsDNA, RF, ANCA, SSA/SSB, Sm/RNP, TPO, C3/C4. Antiphospholipid antibodies (anti-cardiolipin, Beta 2 Glycoprotein and DRVVT) were normal. His hepatitis B/C, HIV, RPR, QuantiFERON gold and Cocci IgM and IgG were all negative or normal. Immunoglobulins (Ig) G was normal as was IgG4 subtype. Sedimentation rate was elevated greater than 100. Lumbar puncture revealed a WBC of 30, with 79% lymphocytes and 21% monocytes. CSF protein was high at 180. CSF serologies included negative Cocci Complement fixation, VDRL, fungal, bacterial and AFB culture and stain were all negative.

MRI brain revealed nodular thickening and enhancement of the dura of the posterior falx, tentorium with extension along the walls of the internal auditory canals which raised concern for metastatic cancer. He was admitted and underwent dural biopsy. GMS, PAS, AFB and Gram Stains were negative for fungal, mycobacterial and bacterial organisms. Biopsy revealed markedly inflamed dura with lymphoplasmacytic inflammation, acute inflammatory tissue necrosis, histiocytic and meningothelial proliferation, and rare multinucleated giant cells consistent with idiopathic pachymeningitis.

He was treated with pulse dose steroids for 3 days and transitioned to prednisone 60mg daily which were tapered over 8 months. He also received 6 monthly doses of intravenous cyclophosphamide. MRI and labs improved with treatment and CSF pleocytosis resolved. Despite these improvements, the patient continued to have chronic headaches which were treated with Tricyclic antidepressants and Serotonin and Norepinephrine Reuptake Inhibitors.

Definition and Epidemiology

This case illustrates the wide differential associated with hypertrophic pachymeningitis (HP) and the need for a broad evaluation to determine the correct etiology and treatment. Hypertrophic pachymeningitis is associated with marked inflammatory hypertrophy of the dura mater which subsequently causes neurological deficits due to compression of adjacent structures. Depending on the site of inflammation, cases are divided into spinal, intracranial or craniospinal pachymeningitis.[1] Hypertrophic pachymeningitis is a rare diagnosis and prevalence is not well established. However, Hahn et al. attempted to determine the relative incidence of different etiologies of HP, compare their associated imaging findings and compare clinical features of the underlying syndromes.[2] They had to rely on a retrospective review of twenty-two cases of HP seen in a single neurology practice over a ten-year period and compared their findings to earlier case series.

Differential Diagnosis

The differential diagnosis of HP includes infectious causes: bacterial, fungal, viral; inflammatory causes: sarcoidosis, granulomatosis with polyangiitis, rheumatoid arthritis, polyarteritis nodosa, IgG4-related disease, malignancy: lymphoma, meningioma, craniopharyngioma, metastatic disease and idiopathic.[2] The prior review found the most common diagnosis was idiopathic HP, constituting eleven (50%) of the twenty-two cases. There were six cases (27%) of neurosarcoidosis, and two cases (9%) of Wegener's granulomatosis.[2]

Regarding infectious causes, bacterial infections related to sphenoid and ethmoid sinusitis and chronic otitis media have been reported.[1] Similarly, bacterial infections of the dural and subdural layers can also cause pachymeningitis in the setting of neurosurgical procedures. Tuberculosis and syphilis should be considered. Aspergillus and Candida can cause pachymeningitis via hematogenous spread or direct extension from craniofacial infections.[1] Immunosuppression is a risk factor for bacterial and fungal causes of pachymeningitis. The virus HTLV-I has also been identified as a cause of pachymeningitis.[1]

Testing should include serum assays for autoimmune disorders with ANA, dsDNA, rheumatoid factor, ANCA, SSA/SSB, anti-TPO antibodies, C3, C4, and antiphospholipid antibodies. Infectious testing should include HIV, syphilis (RPR), tuberculosis and coccidioidomycosis IgM and IgG serologies. IgG levels and subtypes should be checked for Ig-G4-related disease. A lumbar puncture is necessary to test for protein, cell count, AFB, bacterial and fungal stains and cultures, cocci complement fixation and VDRL. The serum and CSF ACE levels can also be checked for sarcoidosis.

Pathogenesis

The pathogenesis is related to inflammation secondary to the underlying etiology. If no underlying cause is found it is considered idiopathic.

Clinical Manifestations

The patient described indolent, chronic headaches as a well as progressive focal neurologic deficits that correlated with the imaging findings of the dural thickening. These included worsening dysphagia, odynophagia and left sided hearing loss. On cranial nerve exam, the patient's tongue was noted to protrude slightly to the right. Additional findings can include seizures, paralysis and ataxia.

Imaging

In hypertrophic pachymeningitis, MRI imaging typically shows well-circumscribed hyperintense laminar thickening of the dura, with low T2 signal intensity and enhancement after intravenous infusion of gadolinium.[3] In this case, the MRI showed nodular thickening enhancement of the dura of the posterior falx, and tentorium with extension along the walls of the internal auditory canals accounting for the auditory deficits. Location and pattern of dural enhancement on imaging has been postulated as a diagnostic tool to help discern the underlying etiology but is not as specific as biopsy. In their limited series review, Hahn et al noted that idiopathic HP generally exhibited diffuse, regular enhancement that most commonly involved the posterior fossa. They also commonly noted thickening of the falx and tentorium in these cases.[2] This is in contrast with most of their neurosarcoidosis cases, which showed a focal, nodular enhancement pattern.[2] Dumont et al. also notes that involvement of the leptomeninges and substance of the central nervous system are more typical in cases of neurosarcoidosis.[1]

Pathology

A dural biopsy is generally recommended in all cases of hypertrophic pachymeningitis to solidify the diagnosis. Most cases of idiopathic pachymeningitis are characterized by a non-necrotizing chronic inflammatory infiltrate of lymphocytes, plasma cells, and occasional histiocytes, giant cells, polymorphonuclear cells, or eosinophils.[1] This in contrast to other specific causes of pachymeningitis including IgG4-related disease, in which biopsy specimens show abundant infiltration of IgG4+ lymphoplasmacytic cells, storiform fibrosis, high-grade sclerosis and obliterative phlebitis.[4,5] Samples must be appropriately prepared and stained for the presence of IgG4+ cells, which can lead to overrepresentation of idiopathic HP diagnoses in the literature. This is especially important as circulating serum IgG levels do not reliably predict biopsy findings.[5]

Diagnosis

Taking together the history, physical exam findings, laboratory evidence, imaging findings and ultimately the pathology results is often necessary to make a specific diagnosis of pachymeningitis and is required to make a diagnosis of idiopathic HP. The diagnostic criteria for other causes of pachymeningitis rely on extracranial manifestations of disease as well. For example, the Zajicek criteria is used to make the diagnosis of neurosarcoidosis. In the absence of histologic evidence of noncaseating granulomas, a probable diagnosis of neurosarcoidosis is made if the clinical manifestations are consistent with neurosarcoidosis with CSF or MRI findings consistent with neurosarcoidosis.[6] Of the vasculitides, GPA has been most associated with HP. Diagnosis of GPA in these patients can be made based on histopathological findings of necrotizing granulomatosis as well as histologic evidence of necrotizing glomerulonephritis, presence of stable pulmonary nodules and paranasal sinus involvement.[7] These clinical manifestations are especially important in making the diagnosis of the underlying cause of HP as patients may have positive rheumatologic markers without systemic manifestations of other diseases.[2]

Treatment

In general, corticosteroids remain a mainstay of treatment for HP from all causes. In some patients, treatment can result in

resolution of symptoms as well as remission although some may relapse as steroids are tapered.[1] In these cases, the use of azathioprine or methotrexate can be helpful in the effort to taper off steroids. Thus far, radiotherapy has not been shown to be of significant benefit.[1] In cases of isolated spinal HP, laminoplasty and dural decompression may need to be considered depending on symptoms and urgency, however the previously mentioned medications have been shown to reduce dural thickening in the spine as well.[1]

Prognosis

This case demonstrated more difficulty controlling the patient's symptoms of headache and dizziness while the imaging findings remained stable through the treatment course. Methotrexate was used to help taper the dose of prednisone. Additional agents used included cyclophosphamide and rituximab.

Summary

This case demonstrates the need to consider a broad differential diagnosis for hypertrophic pachymeningitis including idiopathic, which is highly represented in case studies of this disease. To date, diagnosis largely relies on histopathological data in addition to extracranial manifestations that may correlate with other disease processes such as sarcoidosis, GPA, or RA in addition to non-autoimmune diseases such as malignancy and infectious diseases. Currently, imaging findings can be associated with certain diagnoses but definitive diagnosis relies heavily on biopsy results.

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