Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/igg4-rd-case-conversations-systemic-disease-infiltrating-the-skull-base/24301/

Time needed to complete: 30 minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

IgG4-RD Case Conversations: Systemic Disease Infiltrating the Skull Base

Dr. Chwalisz:
Well, good morning. My name is Bart Chwalisz. I'm a Neurologist, Neuroimmunologist, and Neuro-Ophthalmologist at Massachusetts General Hospital and Massachusetts Eye and Ear.

Dr. Marsiglia:
Hello, everyone. I am Marcela Marsiglia. I am a Neuroradiologist at Massachusetts General Hospital and Brigham and Women's Hospital.

Dr. Stone:
Hello. I'm Dr. John Stone. I'm Professor of Medicine at Harvard Medical School and a Rheumatologist at the Massachusetts General Hospital.

Dr. Chwalisz:
So these are our disclosures.

So today, we'll be having a conversation about IgG4-related disease, and this will be in a case-based format. And we'll be specifically focusing on IgG4-related disease as a systemic disease, but one that can have important head and neck manifestation, and in this case, is infiltrating the skull base.

So let me start by describing the case. So this is a 58-year-old man who presented to us in April 2019, initially with a complaint of anosmia, difficulty smelling. He was being worked up by our ENT colleagues, and during this workup developed acutely left eye pain, blurry vision, and was noted to have a left afferent pupillary defect suggestive of an optic neuropathy. He was treated with steroids and had some improvement. He had sparse but important prior medical history that he had had endoscopic sinus surgery, previously for chronic sinusitis, and also had had surgery for left lacrimal duct occlusion after developing a lacrimation, meaning excessive tearing. So here are some images from the CT at presentation.

Dr. Marsiglia:
So here we see the CT scan from this patient. These are images from a neck CT with contrast. And we are seeing on our left, pointed by red arrows, an area of hyperdensity around the left cavernous sinus region and the anterior clinoid. On the right-hand side, we see a sagittal projection with that hyperdensity, also being pointed by the red arrow.

So here we have a coronal T1 post contrast of the same patient presentation. And pointed by the red arrow, we see an ill-defined area of abnormal enhancement.

Where we look with the green arrow, we see the optic nerve. And we can compare with the opposite side, we see that there is some abnormal enhancement.

So here we are seeing, on the right, an axial slice of the MRI on T1 post-contrast image of our patient, and we see soft tissue enhancement in the ethmoid air cells, where the red arrow is pointing. And we see involvement of the left orbit with abnormal enhancing tissue extending into the extraconal fat. Here we have a coronal view also T1 post-contrast image in which we see sinus abnormal enhancing tissue extending into the left orbit, involving the extraconal fat, going in proximity to the medial rectus muscle, but not

involving the muscle.

This is an additional coronal view of T1 post-contrast imaging in which we see evidence of prior paranasal sinus surgery, where there's absence of a portion of the medial wall of the maxillary antrum bilaterally. And we see abnormal enhancing tissue in the paranasal sinus superiorly. Adjacent to that, intracranially, we see dural thickening and enhancement, predominantly at the skull base. Pointed by the red arrow, we see that enhancement extending interiorly in more fine lines that represents leptomeningeal enhancement.

So on additional images and the different slides, we see that the paranasal sinus disease, with enhancing tissue, was centered at the cribriform plate and extended intracranially. And here we're seeing in addition to dural thickening enhancement, that enhancement also extends further into the intracranial compartment, affecting the brain tissue as well.

On STIR imaging, we can see hyperintensity into the parenchyma, pointed here by the red arrow.

In summary of the radiological findings in this patient, we see paranasal sinus surgical changes, enhancement in abnormal tissue that is extending intracranially, generating pachymeningeal and leptomeningeal disease, and even involving a small portion of the brain parenchyma.

So that leads us to a broad differential diagnosis. And there were multiple considerations, including new malignancy and non-malignant possible etiologies. When seeing these images, we considered possible diseases such as lymphoma, which would be an infiltrative mass that can present in the same shape and with the same radiological characteristics that we see in this case. We considered esthesioneuroblastoma because of the location. It's many times a larger bulky mass. But our case is the perfect location for these kind of tumors. And we also have to consider sinonasal carcinoma malignancies in the paranasal sinuses because of the location and pattern of spread. But it's not specific. There are other possible considerations, including inflammatory or infectious diseases.

Dr. Chwalisz:
Additional workup was performed that included normal CBC and serum chemistries, and in inflammatory workup, including a negative ANCA, ANA, and rheumatoid factor, as well as other inflammatory serologies that was unrevealing. A polyclonal hypergammaglobulinemia was found with a serum IgG4 level of 280 mg/dL, normal being less than 86. A lumbar puncture was performed, and CSF was notable for a mild pleocytosis and mildly elevated protein.

So at this point, we were faced with this extensive skull-based lesion that had infiltrated multiple compartments, including the sinuses, the orbit, intracranially, it was threatening to multiple sensory systems, as the patient had anosmia and was starting to have vision loss, and it was starting to affect the brain itself. The differential diagnosis, as noted, included multiple neoplastic inflammatory and infectious disorders. And the decision was made to proceed to biopsy.

On pathology, the biopsy showed a dense lymphoplasmacytic infiltrate with occasional eosinophils, a prominent deep-seated storiform type fibrosis, and findings suggestive of obliterative phlebitis. We do have some sample pictures in a moment. The slides were stained for IgG and IgG4, and the IgG4 to IgG plasma cell ratio was found to be greater than 40%. So at this point, a clinical pathologic diagnosis of IgG4-related disease was made.

So what did we learn from this case? Well, we learned that it's very important to systematically evaluate all the compartments, anatomic compartments at the skull base, to delineate the extent of a disease. That helps formulate a mature diagnosis of potential systemic illnesses that could affect this area. And so this is best done clinically and radiologically with oftentimes both MRI and CT imaging, which is complementary, as MRI is better for soft tissues and CT for bones. So the skull base is a hotbed for systemic disease, IgG4-related disease is an important player in that regard. Dr. Stone?

Dr. Stone:
So what is IgG4-related disease? IgG4-related disease is a great mimicker of our time, because it can imitate so many different other types of conditions: inflammatory, infectious, and malignant. And remarkably, although it is not a vanishingly rare condition, it wasn't recognized as being a unique disease entity until 2003. It is a multiorgan disease, and a classic other organ that can be involved in this condition is the pancreas, a condition known as autoimmune pancreatitis type 1.

As Dr. Chwalisz has emphasized, IgG4-related disease is a clinical pathologic diagnosis, by which I mean the pathologist cannot make the diagnosis by himself or herself; the diagnosis really ultimately has to be made by the clinician, integrating clinical, serological, radiological, and pathology information.

This patient's biopsy had classic histopathological features, a lymphoplasmacytic infiltrate with a lot of IgG4-positive plasma cells. Storiform fibrosis, the pathologists use this term storiform, which is derived from the Latin word storea, which means woven mat. And IgG4-related disease is ultimately a form of vasculitis. One of its pathology hallmarks is obliterative phlebitis, but it can involve vessels of

any size, up to and including the aorta.

So we should think about IgG4-related disease when there is multiorgan involvement. The pancreas, as I have mentioned, the retroperitoneum can be involved with retroperitoneal fibrosis, the thyroid gland with a condition known as Riedel thyroiditis. The disease has a tendency to involve the head and neck; not only the base of the skull, but also the major salivary glands, including the submandibular gland, the parotid gland, and the lacrimal glands as well. So we need to think about this diagnosis when we have an inflammatory disease involving multiple organ systems.

It is important to think through the differential diagnosis, as was done in this case. ANCA-associated vasculitis, particularly granulomatosis with polyangiitis, is a terrific mimicker of IgG4-related disease and vice versa. Other granulomatous conditions, including sarcoidosis and infections such as tuberculosis have to be excluded. And because of the polyclonal hypergammaglobulinemia, hematopoietic disorders are often invoked during the workup: lymphoma, multiple myeloma, and histiocytoses.

It's critical to make the diagnosis because IgG4-related disease is such a treatable condition, in contrast to some of the other things on the differential diagnosis.

Dr. Chwalisz:
So as has been alluded to, IgG4-related disease will often present in a head and neck area, including some of the areas that are, you know, amenable to external inspection in the face and around the eyes. So there may be orbital signs that the clinician should be alert to, including involvement of a lacrimal glands, so dacryoadenitis, which sometimes can be appreciated because it's causing some swelling externally, but is best really seen when the upper eyelid is elevated. There may be proptosis, there may be swelling, you know, super or infra orbitally as well.

Dr. Marsiglia, some of these things can be seen radiologically too, right?

Dr. Marsiglia:
Yes, correct. So here we're seeing three images of patients who suffer from IgG4-related ___opathy. In the first one, we have a T1 post contrast, showing that the patient has proptosis, the eyes are extending far beyond anteriorly, and we use a line usually going from bone to bone to be able to measure that.

In the second image, we see a coronal CT, and we see that the left orbit is abnormal size of the extraocular muscles. We like to look at symmetry to be able to determine that. And here we have the medial rectus and the inferior rectus muscles, which are enlarged and ill-defined with some evidence of inflammation around it. We see some fat stranding in the orbital fat around those muscles.

And in the last image, we have a coronal T1 post contrast in which we see orbital congestion. It's a post-contrast image, and we see there's a lot of contrast pooling in the muscles and orbital fat. And we also can see that by comparison with the other side.

Dr. Chwalisz:
So there can be a lot of inflammation in the different compartments of a skull base. That does overlap, as has been mentioned, with other inflammatory infections and neoplastic disorders, but there are some features that might make one particularly suspicious of IgG4-related disease, including if there's enlargement of the glands, so the lacrimal or salivary glands, the pituitary gland can be involved as well. There may be concomitant lymphadenopathy. There could be mass formation in the orbit and other areas. And one thing that is particularly characteristic is there can be significant enlargement of the trigeminal branches, especially the infraorbital nerve, or, you know, the pterygopalatine fossa going further back.

These may or may not be associated with symptoms such as paresthesias, so it can be asymptomatic. And then there could be effects on the adjacent tissues. So there can be an orbital myositis. There may be bone destruction or remodeling, although destruction would be rare and be more suggestive of a neoplastic disorder. As we saw in our case, intracranial extension is possible. And the optic nerve, especially the optic nerve sheath, may become involved.

So Dr. Marsiglia, maybe can comment on some of this here.

Dr. Marsiglia:
Yeah. So in this slide, we see very interesting and very representative images of the disease. We have T1 post-contrast images where there's structures showing abnormal enhancement. On the top image, we see enhancing bulky extensive soft tissue in an abnormal shape. This is the area of the sella turcica. We see the flow voids of the internal carotid arteries bilaterally, which serve as a landmark. And there is just this ill-defined soft tissue without a normal shape to any of the structures that are normally identified in that area. And also it extends towards the cavernous sinus in this region. So it's both here and enhancing abnormally.

In the bottom images we see on the left also bulky abnormal enhancing tissue that represents branches of nerves that are just enlarged and abnormal in intensity and shape. And on the right, we see the infraorbital nerve, pointed by the yellow arrow, that is also enhancing and abnormally enlarged. We can see that by comparison with the other side. And there's also abnormal enhancing tissue within the orbital contents in the inferior portion on this left side.

Dr. Chwalisz:
And I think you'd agree that, generally speaking, an MRI would have greater sensitivity and allow us to delineate these tissues better than CT. But CT does have a role, doesn't it?

Dr. Marsiglia:
Yes, absolutely. So CT, we usually, in a vast majority of cases, will be like an initial fast imaging in which we can already suspect some abnormalities, as we saw in the first slide of our case, or the first imaging slide. We see hyperdensity or abnormal enhancement. We can see a subtle shift of structures from their expected location. But MRI is really a modality that will give more detail and soft tissue definition. We're able to really distinguish better the extent of disease, what anatomical structures are being involved or shifted by disease. So, many times, patients have a CT as a screening tool, but we do as a next step, an MRI to really get all the details.

Dr. Chwalisz:
Right. When approaching disease in a skull base, you know, that can be a difficult area. It's a difficult area anatomically, it's also an area that many clinicians are not terribly familiar with. It's important to realize that in each one of these compartments that constitute the skull base, such as the orbit, the cavernous sinus, the sella, the pachymeninges, they are focal inflammatory disorders that are considered idiopathic and unique to that area, in each one of these areas, such as orbital pseudo tumor, Tolosa Hunt syndrome, hypophysitis, they can generally always be mimicked by a variety of inflammatory disorders, malignancy, and infections. So when considering disease in this area, you have to formulate a differential diagnosis of your systemic associations and rule them out with the appropriate serologies, CSF examination, and radiological examination, and oftentimes a biopsy is necessary. And so IgG4-related disease enters the differential diagnosis of inflammation in each one of these areas. And of course, as we saw, can overlap multiple.

Dr. Stone, would you tell us about treatment?

Dr. Stone:
Certainly. So as scary as this patient's presentation was, and as worrisome as the differential diagnosis was, ultimately making the diagnosis led to effective treatment. And this is extremely rewarding for clinicians and radiologists and pathologists and everyone involved in the patient's care.

First, steroids are universally effective at inducing good treatment responses, but this is a disease in which the continued use of steroids at high to moderate doses is really problematic. First of all, the responses are not sustained. When the steroids are tapered to a low enough dose, the disease inevitably comes back. And there are multiple adverse effects. This patient, being a middle-aged male with other potential comorbidities, puts patients at risk for a number of adverse effects related to steroids. Remember, this disease tends to target the pancreas, so the patients often have glucose intolerance as a result of their disease, and having to treat them with steroids simply exacerbates that problem.

Unfortunately, there's really not any good evidence that conventional non-biologic disease-modifying drugs such as azathioprine or mycophenolate mofetil or methotrexate are effective at controlling the disease. But there is substantial experience with B cell depletion strategies such as rituximab, which suggests that B cell depletion therapies, now under clinical trials, really are a highly effective way of approaching the disease.

So our patient received intravenous steroids, followed by high-dose oral glucocorticoids, and had an excellent response, which was very rewarding. But shortly, the steroid-induced side effects began to appear, and the glucocorticoids ultimately were discontinued in favor of B cell depletion. The patient is continued on nasal steroids. Rituximab very quickly consolidated the remission that the patient was heading toward following the start of glucocorticoids. And as the glucocorticoids were tapered, the side effects went away. There were some continued radiologic sequelae, but clinically, the patient has had a return to certainly very normal physiologic function.

Treatment with B cell depletion in the era of COVID has been problematic. And with this patient, we really had to struggle with concerns about COVID and immunity to COVID. He was not able to respond to vaccines. This led to a great deal of anxiety. And we had multiple discussions about whether we should continue to treat with rituximab on an ongoing basis. Fortunately, his disease was controlled, and we felt that he was really in a deep remission. So after several rituximab infusions, we elected to stop and simply to follow his disease.

Fortunately, IgG4-related disease has a very good biomarker, namely the serum IgG4 concentration. His serum IgG4 concentration normalized with therapy, and we follow that closely now as an indication for when he might need to be retreated. We're seeing him now

on a 6-month basis. He's getting labs done every 4 or 5 months and planning annual radiology follow-up.

Dr. Chwalisz:
And from a neuro-ophthalmic perspective, he has done exceptionally well. His visual acuity is now 20/20 in both eyes. He has normalized his visual fields that were previously abnormal. There isn't even an afferent pupillary defect anymore. There's measurable, minimal residual left relative proptosis. So that's a reminder, just like there can be residual radiological disease, that maybe some of the fibrotic element may not completely respond to treatment, and that may be okay if a function is good. Eye movements are normal. Trigeminal function is normal. And the MRI has shown stable residual disease. IgG4 levels have normalized.

Dr. Stone:
I think it's important to emphasize that in virtually any other era of medicine, certainly when I was in medical school and in training, the approach to this patient would have been very difficult. He may have been subjected to fairly radical surgery. If medical therapy was opted for, ultimately, it would have been characterized by very high doses of steroids and probably cytotoxic therapies, cyclophosphamide in particular. But in this case, the astute and timely recognition of the correct diagnosis and the availability of biologic therapy that is felt to be effective, led to an excellent treatment outcome and the ability to discontinue the toxic conventional medications. We believe that this patient's long-term prognosis is very good. The use of B cell depletion strategies in this era requires a lot of consideration about prophylaxis and the timing of vaccinations, but it is proving to be an excellent way to treat IgG4-related disease.

Dr. Chwalisz:
Well, thank you very much for listening to our case presentation and this discussion about IgG4-related disease. And I hope this was informative and enjoyable.

Dr. Stone:
Thank you, Bart. It's been a pleasure for me to discuss the case with you.

Dr. Marsiglia:
Thank you very much, Bart, for the invitation to discuss this very interesting case.

Dr. Chwalisz:
Well, thank you very much.