CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 16-2025: A 34-Year-Old Man with a Nasopharyngeal Mass

Regan W. Bergmark, M.D., M.P.H.,[1-3] Yuh-Shin Chang, M.D., Ph.D.,[4-6] Orhan Efe, M.D.,[7,8] and Soma Jobbagy, M.D., Ph.D.[9,10]

PRESENTATION OF CASE

Dr. Rui Han Liu (Otolaryngology): A 34-year-old man was admitted to this hospital because of pain in the left ear with hearing loss, facial droop on the left side, and a nasopharyngeal mass that was identified on computed tomography (CT).

The patient had been well until approximately 8 months before the current presentation, when pain and a sensation of pressure and fullness developed in the left ear. During the subsequent 5 months, he was seen in the primary care clinic of another hospital on five occasions and received three courses of treatment with oral antibiotic agents; however, the patient's symptoms did not abate. He also received one course of prednisone treatment, which provided slight relief of symptoms.

Three months before the current presentation, treatment with neomycin ear drops was started, and the patient was referred to the otolaryngology clinic of the other hospital. Physical examination showed normal external ears and ear canals without edema or drainage. Although the tympanic membranes were intact, serous middle-ear effusions were present in both ears. It was recommended that the patient continue daily use of cetirizine, which he had been taking as needed for allergy symptoms. Treatment with fluticasone nasal spray was started, and a tapering course of oral prednisone was prescribed. The treatment resulted in a slight abatement of his symptoms; however, 2 weeks later, an upper respiratory illness developed, and the ear symptoms increased in severity. The prednisone taper was extended.

Seven weeks before the current presentation, the pain in the left ear became so severe that it awoke the patient from sleep, and he also had pain in the sinuses. He sought evaluation at the emergency department of the other hospital. Treatment with cefdinir was started, oral prednisone was restarted, and a follow-up visit in the otolaryngology clinic was scheduled.

Six weeks before the current presentation, examination in the otolaryngology clinic showed that the tympanic membranes were intact and the right middle ear was well aerated, but the serous middle-ear effusion persisted in the left ear. The patient had edematous turbinates in both nasal passages and clear rhinorrhea. The oropharynx was normal. Nasopharyngoscopy revealed hypertrophied inferior nasal

Author affiliations are listed at the end of the article.

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CME

turbinates and hypertrophied, edematous, and erythematous tori tubarii. An audiogram showed normal hearing in the right ear and mild conductive hearing loss in the left ear. Results of tympanometry were normal in the right ear and "flat" in the left ear, which indicated that the patient had no movement of the tympanic membrane on insufflation, a finding consistent with effusion in the left middle ear. Word-recognition scores were excellent in the right ear and good in the left ear (a score of 90 to 100% is typically considered to be excellent, and 78 to 89% is good). Myringotomy was performed on the left ear. The dosing frequency of fluticasone nasal spray was increased, and treatment with oxymetazoline nasal spray and oral famotidine was started.

During the subsequent 3 days, the patient's sinus pain increased in severity and progressed from the sinuses to the top of the head and down the neck; the pain did not abate with treatment with acetaminophen and ibuprofen. He had new green nasal drainage, sore throat, and hoarseness. He sought evaluation at the emergency department of the other hospital. CT of the head, performed without the administration of intravenous contrast material, showed moderate fluid in the mastoid bones on both sides. Treatment with amoxicillin–clavulanate was started, and a follow-up appointment in the otolaryngology clinic was scheduled.

Four weeks before the current presentation, green nasal drainage and hoarseness persisted, and new swelling and clear discharge developed in the patient's left eye. He sought evaluation at the primary care clinic of the other hospital, and treatment with trimethoprim–sulfamethoxazole was started.

Three weeks before the current presentation, the patient was evaluated again in the otolaryngology clinic because of persistent pain in the left ear that radiated to the throat and ear pressure and muffled hearing that gave him the sensation of being underwater. Flexible fiberoptic transnasal laryngoscopy performed through the left nostril revealed edematous left nasal turbinates with green purulent drainage and edematous, erythematous tori tubarii with a cobblestone appearance and white drainage. The epiglottis and the base of the tongue were normal. The vocal cords were mobile but difficult to visualize because of copious amounts of thick white drainage. Interarytenoid and postcricoid edema was present. No polyps or masses were seen. Treatment with trimethoprim–sulfamethoxazole and prednisone was continued, treatment with nystatin mouthwash was started, and surgical myringotomy with tympanostomy was planned.

Nine days before the current presentation, an examination performed while the patient was under anesthesia revealed prominent bulges in the anterior and inferior walls of both external ear canals and intact tympanic membranes. The right middle-ear space was clear, but a serous effusion was present in the left middle ear. Surgical myringotomy was performed and tympanostomy tubes were placed in both ears. Treatment with ciprofloxacin–dexamethasone ear drops was started. The patient's symptoms abated briefly, but the ear pain and pressure recurred the following day. The symptoms persisted, and he presented to the emergency department of this hospital for further evaluation.

In the emergency department, the patient reported ongoing ear pain and hoarseness, along with new odynophagia and dysphagia. He had had an unintentional weight loss of approximately 13.6 kg in the previous month. His medical history included mild seasonal allergies, gastroesophageal reflux disease, and chronic neck pain that had been treated. Additional medications included famotidine, and acetaminophen and ibuprofen were used as needed for pain. The patient was born in the United States, lived with his wife and two children in a rural area of New England, and worked as an accountant. He drank alcohol rarely and did not smoke cigarettes or use illicit drugs. He had no known family history of cancer or autoimmune disease.

On physical examination, the patient appeared well. The blood pressure was 161/99 mm Hg, the heart rate 106 beats per minute, the respiratory rate 18 breaths per minute, and the oxygen saturation 97% while the patient was breathing ambient air. The external ears and ear canals were normal. The tympanic membranes had tympanostomy tubes in place, but the lumens were not visible. The pupils were equal, round, and reactive to light. The extraocular muscles and facial sensation appeared to be normal; however, the face was asymmetric, with drooping of the left cheek and flattening of the left nasolabial fold, and there was weakness on puffing the cheeks

and smiling. Delayed blinking of the left eye, along with weak eye closure on the left side, was observed. On raising the eyebrows, weakness was observed in the left eyebrow. His hearing appeared to be normal, and palate elevation, shoulder shrug, tongue protrusion, and speech were also normal. Muscle tone and strength and sensation to light touch were normal in the arms and legs. The remainder of the examination was normal.

The blood level of C-reactive protein was 101.9 mg per liter (reference value, <8), and the erythrocyte sedimentation rate was 71 mm per hour (reference range, 0 to 14). The blood level of alanine aminotransferase was 137 U per liter (reference range, 10 to 55), the aspartate aminotransferase level 55 U per liter (reference range, 10 to 40), the alkaline phosphatase level 226 U per liter (reference range, 45 to 115), and the γ-glutamyltransferase level 300 U per liter (reference range, 8 to 61). The complete blood count with differential count was normal, as were the results of tests of renal function and coagulation. Imaging studies were obtained.

Dr. Yuh-Shin Chang: CT angiography of the head revealed prominence of the soft tissue in the posterior nasopharynx that was more pronounced on the left side than on the right side and extended into the left poststyloid parapharyngeal space, where the soft tissue encased and mildly narrowed the left internal carotid artery at the skull base (Fig. 1A). There was opacification in the mastoid air cells on both sides (Fig. 1B). Contrast-enhanced magnetic resonance imaging (MRI) of the skull base revealed enhancing soft tissue with a masslike appearance and reduced diffusivity in the nasopharynx that was more pronounced on the left side than on the right side. There was involvement of the prevertebral longus colli muscles and left poststyloid parapharyngeal space with encasement of the left internal carotid artery (Fig. 1C and 1D). In addition, dural thickening and enhancement was present in the left middle cranial fossa, which extended along the left tentorial leaflet. Multiple cranial nerves, including both trigeminal nerves, the left facial nerve, and the left hypoglossal nerve, showed enhancement (Fig. 1E, 1F, and 1G). No osseous erosion or abnormality of the bone marrow signal were seen in the adjacent skull base.

Dr. Liu: The patient was admitted to this hospital, and a diagnostic test was performed.

DIFFERENTIAL DIAGNOSIS

Dr. Regan W. Bergmark: I am aware of the final diagnosis in this patient's case. This 34-year-old man presented with 8 months of symptoms consistent with eustachian tube dysfunction, including ear fullness, ear pain, hearing loss, middle-ear effusions, and recurrent otitis media despite treatment with multiple courses of antibiotics. Symptoms did not abate with treatment for conditions known to commonly cause eustachian tube dysfunction, such as allergic rhinitis or chronic rhinosinusitis,[1] and progressed despite myringotomy and placement of middle-ear ventilation tubes.

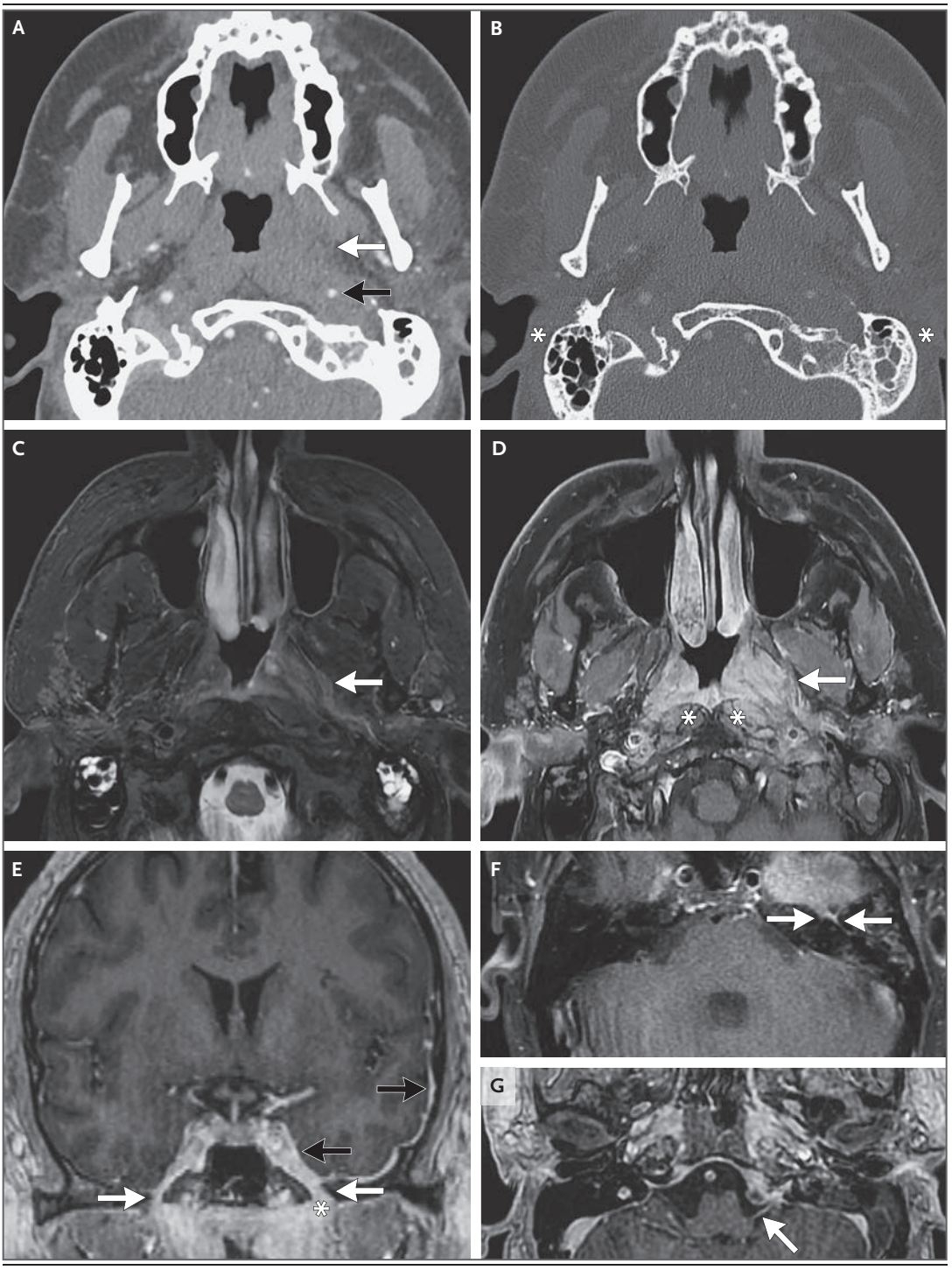
Seven weeks before the current presentation, sinus pain and headache developed. Facial droop consistent with cranial neuropathy subsequently developed, and the patient was found to have elevated levels of inflammatory markers and a nasopharyngeal mass with intracranial extension on imaging studies. In constructing a differential diagnosis, I will consider cancer, infection, and autoimmune disease that could explain months of progressive eustachian tube dysfunction and the imaging findings found on presentation to this hospital.

NASOPHARYNGEAL CANCER

Although serous otitis media with effusion is most often caused by eustachian tube dysfunction, it is important to rule out cancer. In one systematic review of data from patients with isolated serous otitis media of unknown cause, 5.5% of the patients ultimately received a diagnosis of nasopharyngeal cancer.[2] Nasopharyngeal cancers are often diagnosed at a late stage owing to their mundane presenting symptoms of eustachian tube dysfunction, headache, and postnasal drip. A diagnosis requires a high index of suspicion since it is necessary to perform nasopharyngoscopy to identify most nasopharyngeal cancers.

Epithelial cancers are the most common sinonasal and nasopharyngeal cancers, and nasopharyngeal carcinoma is the most common epithelial cancer of the nasopharynx.[3] Nasopharyngeal carcinoma is often associated with Epstein–Barr virus (EBV) infection, with a higher prevalence among persons from Southeast Asia and northern Africa.[4]

Salivary gland cancers such as adenocarcinoma and adenoid cystic carcinoma may arise from



the nasopharyngeal minor salivary glands. Sinonasal lymphoma can manifest as a mass or a diffuse prominence of lymphoid tissue. Diffuse large B-cell lymphoma is the most common lymphoma of the sinuses and nasopharynx. Natural killer T-cell lymphomas are also associated with EBV infection and are most prevalent among persons from Southeast Asia and South America.[3-5]

Rare primary cancers of the nasopharynx include olfactory neuroblastoma, clival chordoma, and primary melanoma, and it is possible for other cancers to metastasize to the soft tissue or

Figure 1 (facing page). CT and MRI Images.
An axial CT angiogram of the neck (Panel A) reveals diffuse soft-tissue prominence in the nasopharynx (white arrow) that is more pronounced on the left side than on the right side and encases the distal cervical internal carotid artery on the left side, resulting in mild asymmetric stenosis (black arrow). The posterolateral pharyngeal recesses and the eustachian tubes are effaced on both sides. A reformatted CT image to emphasize bone (Panel B) shows associated mastoid effusion (asterisks). No osseous erosion is present in the adjacent central skull base. MRI was performed. An axial T2-weighted fat-saturated image (Panel C) and an axial T1-weighted fat-saturated image, obtained after the administration of intravenous contrast material (Panel D), show an intermediate T2-hyperintense, enhancing mass in the posterior nasopharynx that is more pronounced on the left side than on the right side (arrows) and that extends into the left poststyloid parapharyngeal space. There is diffuse enhancement in the adjacent prevertebral longus colli muscles (Panel D, asterisks). No bone marrow signal abnormality is present in the base of the skull. A coronal volumetric T1-weighted image, obtained after the administration of intravenous contrast material (Panel E), shows enhancement of the V3 segments of both trigeminal nerves (white arrows), asymmetric thickening of the V3 segment of the left trigeminal nerve (asterisk), and pachymeningeal thickening and enhancement along the left middle cranial fossa, left cavernous sinus (black arrows), and left tentorial leaflet (not shown). Axial T1-weighted images (Panels F and G), performed with the administration of intravenous contrast material, show additional cranial-nerve enhancement involving the geniculate ganglion and proximal tympanic segment of the left facial nerve (Panel F, arrows) and cisternal segment of the left hypoglossal nerve (Panel G, arrow).

bone in the nasopharynx. Given this patient's progressive symptoms and notable weight loss, there is a high suspicion for cancer. In addition, the nasopharyngeal mass extended intracranially, which led to dural thickening and enhancement. The absence of bony invasion does not rule out cancer, and performing a biopsy of the mass is critical.

INFECTION

Sinusitis can be complicated by the spread of infection into surrounding structures, such as the skull base, intracranial space, or orbits. Infections at the base of the skull usually occur in persons with clinically significant immunocompromise, such as that associated with poorly controlled diabetes, hematologic cancer, or the use of immunosuppressive medications (e.g., drugs administered for the treatment of autoimmune diseases or after organ transplantation). Acute invasive fungal sinusitis is immediately life-threatening, with an associated mortality of approximately 50%, and is considered a surgical emergency; it is usually seen in patients with profound immunodeficiency.[6] Bacterial osteomyelitis of the skull base may occur after an infection of the sinuses that extends posteriorly into the clivus. It also can occur in the context of an ear infection.

This patient's elevated levels of inflammatory markers could be a sign of infection; however, he had no known immunocompromising conditions, the paranasal sinuses had only mild inflammatory changes, and the middle-ear effusion did not appear to be infected. The patient had also received multiple courses of empirical antibacterial therapy without improvement. These findings make a diagnosis of infection unlikely. In addition, MRI did not show marrow edema or other changes that would be suggestive of osteomyelitis. Although infection remains a possible diagnosis in this patient, and could co-occur with cancer, an autoimmune disease is the most likely diagnosis.

AUTOIMMUNE DISEASE

Granulomatosis with polyangiitis (GPA) may lead to or manifest as sinonasal inflammatory changes.[7] GPA involving the head and neck can be challenging to diagnose, since biopsies of abnormal sinonasal tissue are usually nondiagnostic, without clear evidence of vasculitis. Testing for antineutrophil cytoplasmic antibodies (ANCA) can help make the diagnosis but may be negative in patients with GPA, especially in patients with disease isolated to the head and neck. Intranasal cocaine use can cause an ANCA-associated vasculitis that mimics GPA, and treatment may not be effective without cessation of the drug.[8]

Eosinophilic GPA is another vasculitis that may lead to or manifest as sinus disease.[9] Patients with sarcoidosis, autoimmune overlap syndromes, systemic lupus erythematosus, and relapsing polychondritis can all present with sinonasal manifestations. This patient's young age and markedly elevated levels of inflammatory markers are features that are highly suspicious for autoimmune or inflammatory disease. Intracranial extension of a nasopharyngeal mass is atypical in most patients with inflammatory diseases, but it can occur.

Furthermore, patients with IgG4-related disease and fibrosing inflammatory pseudotumor of the nasopharynx can present with extensive intracranial involvement, as was seen in this patient.[10,11] In addition to performing a biopsy, laboratory testing for blood levels of ANCA, antinuclear antibodies, angiotensin-converting enzyme, and immunoglobulin subclasses may be helpful in supporting a specific diagnosis.

NEXT STEPS

Cancer, infection, and autoimmune disease can manifest similarly, and establishing a diagnosis can be challenging. More than one diagnosis is possible, given that cancer or autoimmune disease may lead to sinus obstruction with resulting infection. Treatment for autoimmune disease typically involves the use of high-dose glucocorticoid therapy and other immunosuppressive medications, which can be catastrophic in patients with severe infection and can obscure the diagnosis of cancers such as lymphoma.

Performing a biopsy is critical in trying to reach a diagnosis before initiation of empirical treatment. Preoperative review of imaging can help identify biopsy targets, such as viable soft tissue and bone. Intraoperative examination of a frozen section can expedite certain cancer diagnoses but is typically not diagnostic for lymphoma. To evaluate for lymphoma, biopsy specimens need to be sent for permanent-section analysis and for evaluation by flow cytometry, which may require specific protocols for tissue handling. Intraoperative examination of a frozen section to evaluate for fungal forms or necrosis indicative of invasive fungal sinusitis can guide intraoperative surgical resection and antifungal management. Cultures of swabs and biopsy specimens of soft tissue and bone can guide management of infectious causes associated with the presence of a nasopharyngeal mass. The next step in the diagnostic evaluation of this patient is to perform a biopsy, with the understanding that an inflammatory disease may be a diagnosis of exclusion for which concurrent laboratory testing for levels of ANCA, antinuclear antibodies, angiotensin-converting enzyme, and immunoglobulin subclasses can be helpful. Testing of blood for the presence of EBV DNA may also be considered.[12]

HOSPITAL COURSE

Dr. Daniel Restifo (Medicine): After admission to this hospital, treatment with broad-spectrum antimicrobial agents (including antifungal medication) was started and a diagnostic biopsy was planned. A biopsy of the nasopharynx on the left side was performed at the patient's bedside on hospital day 1, which showed marked inflammation. On hospital day 3, an endonasal endoscopic biopsy of the nasopharyngeal mass was performed in the operating room, which also showed inflammation. On hospital day 6, a third biopsy was performed in the operating room, and the results of ANCA testing that had been performed on hospital day 3 became available.

DIAGNOSTIC TESTING

Dr. Soma Jobbagy: The diagnostic test in this case was an endonasal endoscopic biopsy of the patient's nasopharyngeal lesion with histopathological evaluation. The initial biopsy specimens obtained on hospital days 1 and 3 showed markedly inflamed respiratory-type mucosa with ulceration and abscess formation with fibrinous and neutrophilic exudate. Although no definitive vasculitis was seen on either biopsy, the sampling was superficial, which, in conjunction with the extent of necrosis, limited evaluation of vascular structures.

A third biopsy, performed on hospital day 6, showed granulomatous inflammation with evidence of active vasculitis with florid fibrinoid necrosis of vascular walls (Fig. 2A). Verhoeff–van Gieson elastic staining showed focal disruption of the elastic lamina in the vascular wall (Fig. 2B). Of note, the vasculitis was detected on only one of three biopsy specimens submitted for histopathological evaluation, a finding that highlights the challenges posed by both spatial and temporal sampling variability in the evaluation of vasculitis. Deep or extensive biopsies of viable tissue may be critical for diagnosis; however, in patients with inflammatory conditions, even extensive sampling on biopsy may not yield a diagnosis.

No evidence of a lymphoproliferative disorder was present on histopathological analysis with the use of ancillary immunohistochemical staining, or on a separately performed flow cytometric

evaluation of biopsy specimens. Chromogenic in situ hybridization for EBV-encoded RNA, which was performed to rule out EBV-associated sinonasal neoplasms such as nasopharyngeal carcinoma and extranodal natural killer T-cell lymphoma, was negative.[13] No fungal forms were identified on Grocott's methenamine silver staining, a finding that helps to rule out a destructive fungal process.

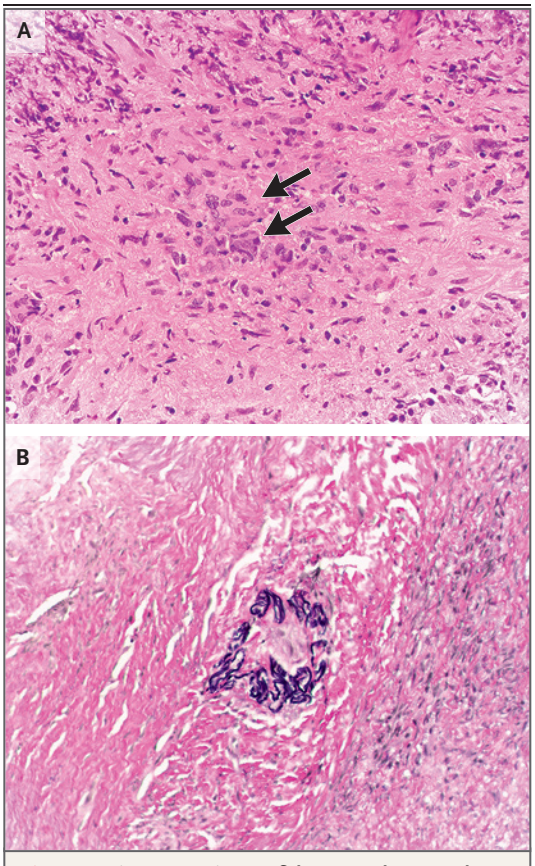


Figure 2. Biopsy Specimen of the Nasopharyngeal Mass.

Hematoxylin and eosin staining of the biopsy specimen (Panel A) shows granulomatous inflammation and florid fibrinoid necrosis of vascular walls, along with multinucleated giant cells (arrows), neutrophilic infiltrates, and areas of karyorrhectic nuclear debris. Verhoeff–van Gieson elastic staining (Panel B) highlights loss of linearity of elastic fibers (black staining), a finding that reveals disruption and fragmentation of vascular wall elastic lamina in a medium-sized vessel. To qualify as a true necrotizing vasculitis, the affected vessels should fall outside zones of generalized tissue necrosis.

Positive indirect immunofluorescence staining revealed ANCA with a cytoplasmic pattern. An enzyme-linked immunosorbent assay (ELISA) confirmed the presence of anti–proteinase 3 antibodies (PR3-ANCA), with antibody activity measured at 77 units (reference value, <20). An ELISA for antibodies to myeloperoxidase was negative.

The findings of the biopsy performed on hospital day 6, interpreted in the context of the clinical presentation of this patient and the positive test for PR3-ANCA, were diagnostic of GPA.[14,15]

PATHOLOGICAL DIAGNOSIS

Granulomatosis with polyangiitis.

DISCUSSION OF MANAGEMENT

Dr. Orhan Efe: When determining treatment for patients with ANCA-associated vasculitis, it is essential to evaluate the extent of the disease with the Birmingham Vasculitis Activity Score (BVAS), which helps to determine whether the condition is organ-threatening or life-threatening.[16-18] This patient's BVAS was 19 (scores range from 0 to 63, with higher scores reflecting more severe disease). He had organ-threatening disease with cranial-nerve involvement and narrowing of the internal carotid artery due to severe nasopharyngeal disease. Therefore, an immediate and aggressive treatment was required.

Many randomized clinical trials have investigated the best induction treatment for ANCA-associated vasculitis. Treatment with intravenous or oral cyclophosphamide in combination with a tapering course of glucocorticoids has shown high efficacy. The RAVE and RITUXVAS trials showed that rituximab had a similar efficacy to that of cyclophosphamide.[19,20] Some centers, including ours, use a combination of both treatments, especially in patients with more severe disease, as was the case in this patient.[21] Treatment with avacopan, which blocks C5 receptors on neutrophils, was shown to be effective as a steroid-minimizing strategy in the ADVOCATE trial and has become standard care.[22] These treatments should be started immediately to avoid further organ-threatening or life-threatening disease. Thus, this patient received treatment with

pulsed doses of intravenous methylprednisolone administered daily for 3 days, followed by tapering doses of prednisone, two intravenous rituximab infusions given 2 weeks apart, a short course of low-dose bridging therapy with oral cyclophosphamide for 8 weeks, and avacopan for 9 months. The patient received prophylaxis with trimethoprim–sulfamethoxazole, omeprazole, calcium, and vitamin D for the duration of glucocorticoid use.

After induction treatment, patients with ANCA-associated vasculitis should receive maintenance therapy since the risk of relapse is approximately 40% at 4 years.[23] Rituximab is the current standard maintenance therapy for ANCA-associated vasculitis.[24] This patient continued to receive rituximab infusions every 4 months, which allowed for persistent peripheral B-cell depletion. We plan to extend the infusion intervals at the 2-year mark to allow for B-cell repopulation between the infusions to reduce the risk of complications of B-cell depletion such as infection and inflammation.[25]

Dr. Restifo: Two weeks after the patient started immunosuppressive therapy, his facial numbness resolved and facial nerve paresis abated; repeat transnasal nasopharyngoscopy showed a decrease in the inflammation of the nasopharynx on the left side. After 1 month of treatment, he had an increase in headache and fatigue that corresponded to tapering of the dose of prednisone, and the prednisone taper was extended from 3 months to 5 months. After 2 months of treatment, headache and fatigue had completely resolved and repeat laboratory testing showed normal blood levels of aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase. The patient had residual autophony of breath and voice, a symptom suggestive of patulous eustachian tube dysfunction in the left ear. A hearing test revealed moderately severe, symmetric sensorineural hearing loss. Three months after receiving a diagnosis of GPA, the patient was evaluated by the facial plastic surgery consultant because of residual subtle depression of the left eyebrow and left oral commissure; no intervention was planned. Five months after initiation of immunosuppressive therapy, the ANCA level was less than 20 units. Fifteen months after the initial diagnosis, the patient continues to receive rituximab infusions every 4 months.

PATIENT PERSPECTIVE

The Patient: Over the course of the 8 months before I was admitted to this hospital and ultimately diagnosed with GPA, I had countless emergency room visits, primary care appointments, and otolaryngology appointments at various health care facilities. I received prescriptions for a variety of antibiotics and steroids and even had tympanostomy tubes placed in my ears. Each procedure and prescription led to a partial relief of symptoms that came back shortly after. I was very discouraged that I was continuing to suffer from symptoms, and I felt like my health concerns were not being taken seriously. It was a very frustrating time. The tipping point for me was when the pain returned the day after I received tympanostomy tubes. I came to the emergency department of this hospital and was diagnosed with GPA.

Being admitted was one of the most stressful times in my life, but it was a relief to finally receive a diagnosis. Since being discharged, I have had several ups and downs, but I am feeling more like myself than I have in a long time. As a result, I am able to be a present father and husband. I'm very thankful and I hope teaching about the unusual presentation of my case can help others receive a diagnosis sooner.

FINAL DIAGNOSIS

Granulomatosis with polyangiitis.

This case was presented at Otolaryngology Grand Rounds at Massachusetts Eye and Ear.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

AUTHOR INFORMATION

[1] Department of Surgery, Brigham and Women's Hospital, Boston; [2] Department of Surgical Oncology, Dana–Farber Cancer Institute, Boston; [3] Department of Otolaryngology–Head and Neck Surgery, Harvard Medical School, Boston; [4] Department of Radiology, Massachusetts General Hospital, Boston; [5] Department of Radiology, Massachusetts Eye and Ear, Boston; [6] Department of Radiology, Harvard Medical School, Boston; [7] Department of Medicine, Massachusetts General Hospital, Boston; [8] Department of Medicine, Harvard Medical School, Boston; [9] Department of Pathology, Massachusetts General Hospital, Boston; [10] Department of Pathology, Harvard Medical School, Boston.

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