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IgG4-related disease presenting as recurrent mastoiditis

Adam I. Schiffenbauer, MD¹, Colleen Wahl, CRNP², Stefania Pittaluga, MD, PhD³, Elaine S. Jaffe, MD³, Ronald Hoffman, MD, MHCM⁴, Arezou Khosroshahi, MD⁵, John H. Stone, MD, MPH⁵, Vikram Deshpande, MD⁶, William A. Gahl, MD, PhD^{2,7}, and Fred Gill, MD, FACP, FIDSA^{2,8}

¹National Institute of Arthritis and Musculoskeletal and Skin Disease, National Institutes of Health, Bethesda, Maryland, USA

²NIH Undiagnosed Diseases Program, National Institutes of Health, Bethesda, Maryland, USA

³Laboratory of Pathology, Clinical Center, National Institutes of Health, Bethesda, Maryland, USA

⁴Ear Institute, New York Eye and Ear Infirmary, New York, New York, USA

⁵Rheumatology Unit, Massachusetts General Hospital, Boston, Harvard Medical School, Boston, Massachusetts, USA

⁶Department of Pathology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

⁷Office of the Clinical Director, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland, USA

⁸Internal Medicine Consult Service, Clinical Center, National Institutes of Health, Bethesda, Maryland, USA

INTRODUCTION

IgG4-related disease (IgG4-RD) is a recently recognized disorder characterized by an overabundance of IgG4-positive plasma cells in affected tissues and, frequently, elevated serum IgG4 levels. First recognized in the context of autoimmune pancreatitisⁱ, IgG4-RD presents as either a localized area of involvement within a single organ or as a multicentric disease, affecting several organs. Those organs include the pancreas, gallbladder, salivary glands, retroperitoneum, kidneys, lungs, prostate, ocular adnexaⁱⁱ, maxillary sinus, ethmoid sinusⁱⁱⁱ, lacrimal glands, breast, liver, large blood vessels, mediastinum, lymph nodes^{iv}, pituitary^v, esophagus^{vi}, and dura mater^{vii}.

The histopathology of IgG4-RD involves a lymphoplasmacytic infiltrate, storiform fibrosis, and obliterative phlebitis. The disease process generally destroys the normal tissue architecture and replaces it with fibrotic tissue, creating a variety of histologic patterns. The appearance can be pseudolymphomatous (characterized by a dense infiltrate of small lymphocytes), sclerosing (characterized by fibrosis with some areas of lymphocyte aggregates), or mixed (characterized by fibrosis, plasma cells, and lymphocytic infiltrates)^{viii}. IgG4-RD lesions can progress by infiltrating the surrounding tissues or by expanding as a space-occupying mass. The lesions are often exquisitely sensitive to glucocorticoids, but long-term, prospective therapeutic trials are lacking.

Corresponding author: Adam Schiffenbauer, NIH Clinical Center, Building 10, Room 6N216A, 10 Center Drive, Bethesda, MD 20892-1616, Telephone: 301-443-5522, Fax: 301-480-9396, adam.schiffenbauer@nih.gov.

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We hereby describe a patient with IgG4-RD manifesting as recurrent inflammatory disease of the middle ear and mastoid, complicated by bone erosion.

METHODS

Study subject

The patient was enrolled in the NIH Undiagnosed Diseases Program and gave written informed consent under a protocol (76-HG-0238) approved by the NHGRI Institutional Review Board.

Histology

IgG4 immunohistochemistry was performed manually, as previously described, using the primary antibody (mouse monoclonal; clone HP6025; Invitrogen, Carlsbad, CA) at a dilution of 1:1000 for a 30 minute incubation at room temperature with a low pH (6.1) antigen retrieval in a proprietary Target Retrieval Solution (TRS; Dako, Carpinteria, CA) ^{ix}. The absolute number of IgG4-positive plasma cells was enumerated as a percentage of the total number of IgG-positive cells in the same area of a 40x field of an Olympus BX50 microscope. Staining for other lymphocyte associated antigens (kappa, lambda, CD20, CD3) was performed on an automated immunostainer.

RESULTS

Case Report

A 50 year-old woman presented in January 2000 with left serous otitis media and left facial paresis. She had undergone surgery on the temporomandibular joint (TMJ) at the age of 41, but was otherwise healthy. A myringotomy tube was placed and the facial paresis resolved. However, her left ear continued to drain culture-negative fluid. Computed tomography (CT) revealed mastoid opacification without bony destruction. Since her mastoid was small with a low-lying middle fossa plate, a modified radical mastoidectomy was performed, effectively exteriorizing her disease. Intraoperative cultures for aerobic bacteria, anaerobic bacteria, fungus, and acid-fast organisms were negative, and pathology showed benign inflammatory tissue. The ear healed uneventfully.

The patient was symptom free for 2 years when, following 48 hours of intense left otalgia, she became confused and aphasic. A magnetic resonance imaging (MRI) study of the brain demonstrated a left cerebritis (Fig. 1). Cerebrospinal fluid analysis revealed a pleocytosis, but was culture negative. Intravenous antibiotics and glucocorticoids led to resolution of her symptoms. A repeat CT study revealed extension of her disease into the petrous squamosa, with bony sequestra abutting an emissary vein (Fig. 2); this was attributed to recurrence of pathology in residual air cells. The diseased area was removed by drilling to the inner table of the squamous temporal bone. The patient's symptoms resolved after surgery. Cultures for aerobic, anaerobic, fungal and acid-fast organisms were again negative, and pathology showed benign inflammatory disease. A subsequent rheumatologic evaluation was unrevealing.

Two years later, the patient undertook an airplane trip in the setting of an upper respiratory tract infection. She suffered right barotitis on descent and developed persistent right ear fullness, pain, and hearing loss. She did not respond to oral antibiotics and glucocorticoids. A myringotomy tube was placed and she developed unremitting drainage. Cultures were normal. A CT scan revealed opacification of the mastoid with erosion of the bone of the posterior external auditory canal. A modified radical mastoidectomy was performed. Cultures were negative, and pathology showed benign inflammatory disease. The patient's

symptoms resolved. She underwent a second rheumatologic evaluation which was unrevealing except for an ANA of 1:640.

Eighteen months later, the patient developed recurrent right ear pain. CT confirmed disease expansion in the mastoid bowl, which had developed a convexity. The mastoid was revised, and her symptoms resolved. Cultures were negative, and pathology showed marked chronic mastoiditis with fibrosis and foci of cholesterol clefts.

Twenty months later, the patient again developed recurrent right ear pain. She had a right serous otitis media and an enlarging vascular mass in the mastoid bowl. CT revealed an erosive lesion involving the retrofacial space, and extending infratemporally. On previous imaging this region had been normal, occupied by a few air cells and bone marrow (Figs. 3 A & B). The lesion was debulked surgically. The disease was adherent to the facial nerve, which was not sacrificed. Cultures were negative, and pathology showed marked chronic mastoiditis with focal lymphoid hyperplasia and mild fibrosis.

The patient was accepted into the NIH Undiagnosed Diseases Program. While awaiting admission to the NIH Clinical Center, she was started on prednisone 60 mg/day which was tapered down to 10 mg/day over 5 weeks. The prednisone halted the disease progression, with improvement of symptoms and radiographical stability.

Upon arriving at the NIH the patient's physical examination was remarkable only for bilateral modified radical mastoid cavities. She underwent extensive laboratory evaluation. Her serum IgG4 concentration was 213 mg/dL (normal < 121 mg/dL), with a serum IgE of 185 mg/dL (normal 9-90 mg/dL). Total IgG, IgG1, and IgG2 concentrations were normal. The patient's IgG3 concentration was 18 mg/dL (normal 22-178 mg/dL). Her antinuclear antibody by enzyme-linked immunoassay was 2.9 EU (normal <0.9 EU). Enzyme immunoassays for antineutrophil cytoplasmic antibodies to proteinase-3 and myeloperoxidase were negative. The patient's amylase and lipase levels were normal.

Staining of previously obtained tissue from her mastoid revealed a lymphoplasmacytic infiltrate with large areas of storiform fibrosis (Fig. 4). Immunohistochemical stains for kappa and lambda light chains confirmed the polyclonal nature of the plasma cell infiltrate. The IgG4: total IgG ratio was >50%. Admixed CD20+ B-cells and CD3+ T-cells were present, but plasma cells predominated (Fig. 5). There were also cholesterol clefts noted on the biopsy.

DISCUSSION

IgG4-RD is a recently recognized clinical entity that has become an important consideration in many cases in which a diagnosis is not forthcoming. IgG4-RD has been shown to extensively involve the head and neck with cases reported of disease in the orbital adnexa, sinus and nasal cavities, salivary and submandibular glands, and thyroid^x. The pathologically confirmed mastoiditis and destructive bony lesions that occurred in our patient have not been reported to our knowledge. IgG4-RD can be difficult to diagnose because one critical part of the evaluation, immunostaining of tissue for IgG4, is not performed routinely on biopsies. Moreover, clinicians seldom order IgG subclasses. The diagnosis is also complicated by the many different types of lesions produced by the disease. These range from destructive, enlarging masses to locally invasive lesions that can be aggressive enough to mimic malignancy.

In our case, the histological findings of a polyclonal lymphoplasmacytic infiltrate, storiform fibrosis, and increased numbers of IgG4-positive plasma cells were diagnostic of IgG4-RD. The diagnosis was supplemented by the finding of elevated concentrations of IgG4 and IgE

in the serum. Our patient also exhibited mastoid disease accompanied by extensive bony destruction. Involvement of the inner ear has been reported in one patient^{xi}, so the present case suggests that IgG4-RD should be suspected in patients with possible immune mediated otologic lesions. Bone destruction due to IgG4-RD is an uncommon finding^{xii}. The presence of characteristic IgG4-RD histology in this patient's bone lesion proves that the disease can mimic malignancy with erosion of adjacent organs.

The diagnosis of IgG4-RD is critical because the disorder has specific, efficacious treatment options that can lead to improved care and help avoid unnecessary surgeries. Such treatments involve the administration of high-dose glucocorticoids, and this remains the first line therapeutic option. Although most patients respond swiftly to glucocorticoids, some require a second. Other treatments used to treat this condition include azathioprine, cyclophosphamide, methotrexate, mizoribine, bortezomib, and rituximab. Among these agents, B cell depletion with rituximab appears to offer the quickest therapeutic response, with a targeted effect on the IgG4 subclass of immunoglobulins^{xiii}.

CONCLUSIONS

IgG4-RD is an under-recognized disease process that can affect numerous organ systems with high morbidity. The middle ear and mastoid should be added to the growing list of organs affected by IgG4-RD, and destructive bone lesions in the sinuses and middle ear spaces, mimicking malignancy or Wegener's granulomatosis, should prompt clinicians to order the appropriate diagnostic tests. More awareness of this diagnosis and its expanding treatment options will significantly improve patient care for a wide variety of problems.

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Fig. 1.
Magnetic resonance imaging of the brain from 2003 revealing left-sided cerebritis.

Fig. 2.
Extension of disease in temporal squamosal; sequestrum is adjacent to emissary vein.

Fig. 3.
Evolution of new disease in retrofacial air cell tract.

Fig. 4. Biopsy of the mastoid shows marked fibrosis with an infiltrate comprising plasma cells and other inflammatory cells (hematoxylin and eosin stain).

Fig. 5.
The majority of the plasma cells stained for IgG4 (immunohistochemical stain, hematoxylin counterstain).