CLINICAL VIGNETTE

IgG4-related Disease with Cutaneous Manifestations Treated with Dupilumab

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Case

A 62-year-old male with chronic sinusitis, asthma and diabetes presented with pruritic right ear rash and diffuse myalgias for several months. He was on stain treatment for six years which was discontinued due to concern for statin induced myopathy. Past medical history also includes eczema, hypertension, and osteoarthritis. On exam, the right ear lobule appeared erythematous and waxy (Figure 1). Strength exam was unremarkable. Serum IgG4 returned elevated at 1090 mg/dL (nl 1-123 mg/dL). Punch biopsy of the ear lobule showed cutaneous IgG4-releated disease. Histology showed a prominent lymphoplasmacytic infiltrate with IgG and IgG4 immunohistochemical stains showing a IgG4+/IgG+ plasma cell ratio of approximately 80-90% and IgG4+ plasma cell count of 150 per high-power field. Computed Tomography (CT) angiogram of the neck, thorax, abdomen, and pelvis was without aortitis and retroperitoneal fibrosis. However, aneurysmal dilatations of 2.6 cm and 1.6 cm was seen at the infrarenal abdominal aorta and left common iliac artery. CT also showed multiple enlarged cervical lymph nodes. Subsequent fine-needle aspiration of a right neck lymph node was negative for carcinoma. Magnetic Resonance Cholangiopancreatography showed intrahepatic biliary ductal dilatation with presumed IgG4-RD cholangiopathy. Evaluation for other systemic autoimmune diseases such as connective tissue diseases including dermatomyositis, sarcoidosis, and ANCA-associated vasculitis was unrevealing (Table 1). Treatment for IgG4-related disease was started with Prednisone 40 mg per day and tapered off after six months. With decreasing doses of prednisone, serum IgG4 levels increased (Figure 2). The patient initially refused treatment with conventional disease modifying antirheumatic drugs, expressing concern over the infectious side effects. He eventually agreed to treatment with dupilumab, 300 mg every two weeks. It was started about two months prior to the completion of the steroid taper. His IgG4 levels improved but remained elevated (Figure 2). The patient's right ear lobule rash also improved. Additional DMARD treatment with mycophenolic acid and azathioprine resulted in gastrointestinal intolerance and the discontinuation.

Discussion

IgG4-related disease is a fibroinflammatory disorder that can result in multiorgan disease, including cutaneous manifestations. Common anatomic locations for cutaneous involvement include the head and neck with the most common morphologic features of lesions being papules, plaques, and nodules.[1] The other commonly involved organs the major salivary glands, orbits, lacrimal glands, pancreas, kidneys, the aorta, and the retroperitoneum.[2]

When treatment is indicated, glucocorticoids are typically first line for IgG4-RD, with the steroids tapered over three to six months.[3] Steroid-sparing agents that have been used include azathioprine, mycophenolate mofetil, methotrexate, and rituximab.[3] Dupilumab has been described as a potential steroid-sparing treatment for IgG4-RD. It is a monoclonal antibody acting on the interleukin 4 (IL-4) receptor alpha subunit, which interferes with IL-4 and interleukin-13 cytokines.[4] IL-4 has been described as contributing to class-switching of B cells, as part of IgG4 production.[5] Several case reports describe patients with elevated IgG4 serum levels with concomitant other indications for dupilumab use, including asthma or rhinosinusitis, and reported improved IgG4 levels following treatment.[6] The adverse effects of treatment with dupilumab are still being characterized, including potential for enthesitis, arthritis, and tenosynovitis.[7]

Conclusion

The most common treatment for IgG4-RD includes systemic glucocorticoids, but there is potential for use of dupilumab as a steroid-sparing agent. The limited case reports using dupilumab in IgG4-RD highlights the need for controlled clinical trials.

Figures and Tables

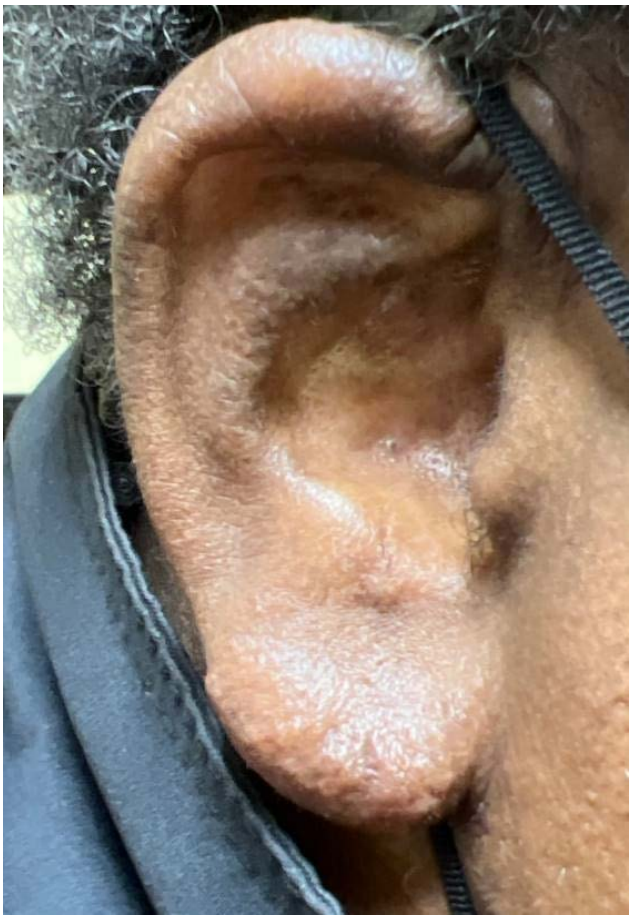

Figure 1. Photograph of right ear showing erythematous waxy appearance.

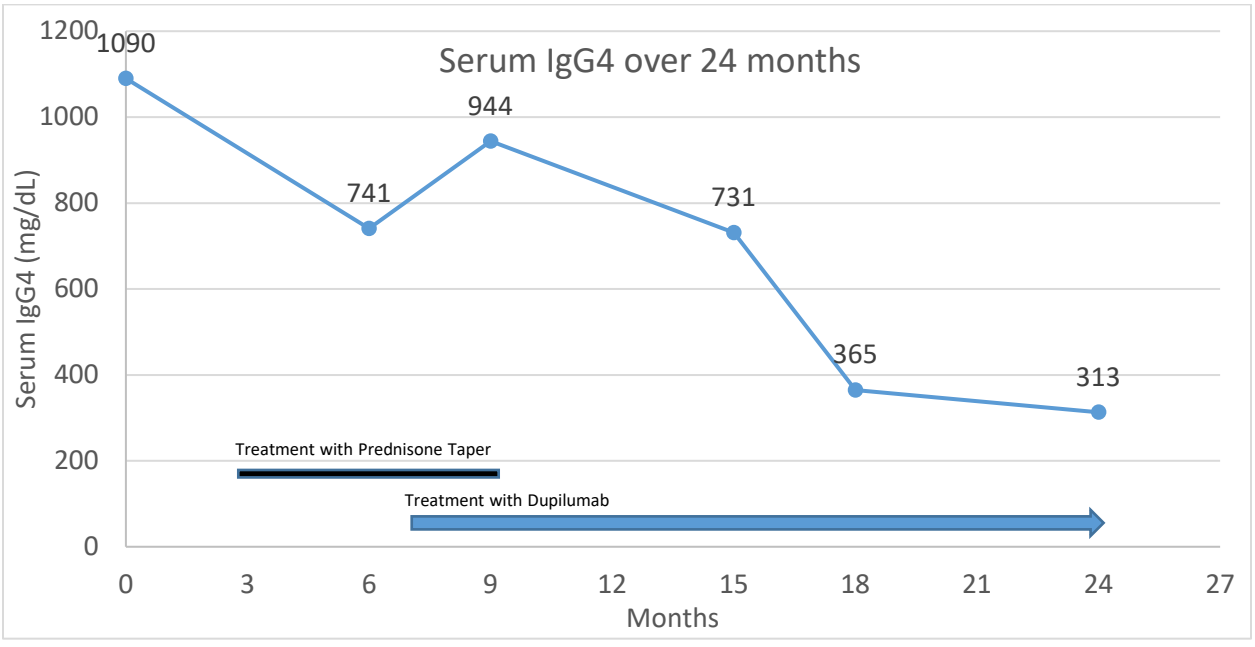

Figure 2. Serum IgG4 over 24 months.

Table 1 Laboratory findings at initial diagnosis of IgG4-related disease.	
Laboratory (reference range)	**Value**
WBC (4.16 - 9.95 x10E3/uL)	9.0
Absolute Eosinophil Count (0.00 – 0.50 x10E3/uL)	0.17
Hemoglobin (13.5 - 17.1 g/dL)	9.6
Platelet Count (143 – 398 x10E3/uL)	323
Sedimentation Rate By Modified Westergren (< OR = 12 mm/hr)	109
C-Reactive Protein (<0.8 mg/dL)	3.9
Urea Nitrogen (7 - 22 mg/dL)	15
Creatinine (0.60 - 1.30 mg/dL)	1.1
Albumin (3.9 - 5.0 g/dL)	3.6
Alkaline Phosphatase (37 - 113 U/L)	68
Aspartate Aminotransferase (13 - 62 U/L)	27
Alanine Aminotransferase (8 - 70 U/L)	37
Creatinine Kinase (63 - 472 U/L)	731
Aldolase (1.5 – 8.1 U/L)	10.2
Lipase (13 – 69 U/L)	30
Immunoglobulin G serum (nl 726-1521 mg/dL)	2470
Immunoglobulin A serum (nl 87 - 426 mg/dL)	142
Immunoglobulin M serum (nl 44 - 277 mg/dL)	66
Immunoglobulin E serum (nl < 113 kIU/L)	877
Immunoglobulin G Subclass 1 (nl 240 - 1118 mg/dL)	974
Immunoglobulin G Subclass 2 (nl 124 - 549 mg/dL)	590
Immunoglobulin G Subclass 3 (nl 21 - 134 mg/dL)	123
Immunoglobulin G Subclass 4 (nl 1 – 123 mg/dL)	1090
Antinuclear Antibody (negative <1:40 titer)	<1:40
Rheumatoid Factor (<25 IU/mL)	<10
SSA Antibody (<20 U)	<20
SSB Antibody (<20 U)	<20
C-ANCA (<1:20 titer)	<1:20
P-ANCA (<1:20 titer)	<1:20
Proteinase-3 Ab (<20 CU)	<20
Myeloperoxidase Ab (<20 CU)	<20
Angiotensin Converting Enzyme (9 – 64 U/L)	27
C3 (76 - 165 mg/dL)	141
C4 (14 - 46 mg/dL)	33
Urinalysis	
Protein/Creatinine Ratio, Ur (0.0 - 0.4)	0.2
RBC per HPF (0 - 2 cells/HPF)	0
WBC per HPF (0 - 4 cells/HPF)	0

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