IgG4-Related Disease Presenting as a Solitary Neck Mass

Tyler McKinnon[1], William T. Randazzo[1*], Brian D. Kim[2], Paul Biddinger[2], Scott Forseen[1]

1. Department of Radiology, Georgia Regents University, Augusta, GA, USA

2. Department of Pathology, Georgia Regents University, Augusta, GA, USA

* **Correspondence:** William Thoburn Randazzo M.D., Department of Radiology, Georgia Regents University, 1120 15th Street, Augusta, GA, 30904, USA
(*wrandazzo@gru.edu*)

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ABSTRACT

IgG4-related disease is a newly recognized entity associated with autoimmune conditions involving almost every organ system. It is characterized by elevated serum IgG4 as well as mass like tissue infiltration by IgG4-positive plasma cells. Imaging findings are nonspecific, vary depending on the site of disease, and include mass like enlargement of the salivary or lacrimal glands and enlarged lymph nodes. Radiographic findings often mimic malignancy, necessitating tissue sampling to confirm the diagnosis. Distinguishing IgG4-related disease from malignancy is important as IgG4 responds well to steroids and conservative management.

CASE REPORT

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A 23 year old female presented with a four-week history of an asymptomatic right sided neck mass. She reported being treated with antibiotics, however, the mass had not changed in size over the course of one month. The patient denied pain, tenderness, fevers, chills, night sweats, weight loss or other associated symptoms. She reported no significant past medical or surgical history, but had a family history significant for a father with acute lymphoblastic leukemia and mother with pancreatic malignancy. She was taking no medications and denied a history of tuberculosis, foreign travel, and tobacco or drug use. On physical exam, a 6 cm x 4 cm firm right level II/III mass was palpated. The patient was then referred for imaging, including an image guided percutaneous biopsy.

Imaging findings

Axial, sagittal, and coronal computed tomography (CT) images of the neck with contrast were obtained and demonstrated a mixed cystic and solid mass measuring 2.9 cm AP x 3.1 cm transverse x 4.0 cm craniocaudal within the right lateral neck, level IIa (Figure 1a-c). The mass did not contact the submandibular or parotid glands and did not involve the internal jugular vein or carotid arteries. The salivary glands were normal on CT. With the use of CT guidance (Figure 1d), an 18-gauge spring-loaded biopsy needle was advanced into the mass and core tissue samples were obtained.

Management and follow-up

The final pathological diagnosis was IgG4 related systemic sclerosing disease (Figures 2 and 3). The patient was subsequently treated with prednisone with a significant decrease in the size of the neck mass subjectively and on physical exam and was followed expectantly.

DISCUSSION

Etiology and demographics

IgG4-related disease is a relatively recently described entity, first proposed by Kamisawa et al [1] in 2003. A consensus statement was issued recently in which the term IgG4-related disease was chosen [2]. However, prior to this point it has also been known as IgG4-related systemic disease, IgG4-related sclerosing disease, multifocal fibrosclerosis, systemic IgG4-related plasmacytic syndrome, and IgG4-related multi-organ lymphoproliferative syndrome [2,3].

This disease was first described when extrapancreatic fibro-inflammatory lesions rich in IgG4+ plasma cells were discovered in association with a form of autoimmune pancreatitis [1]. Since its discovery, this condition has been identified in almost every organ system with many clinical manifestations such as sclerosing cholangitis [4,5], retroperitoneal fibrosis [6,7,8], sialadenitis [9], dacryoadenitis [9], lymphadenopathy [10,11], idiopathic cervical fibrosis [12], infundibulohypophysitis [13,14,15], tubulointerstitial nephritis [16,17], interstitial pneumonia [18], hypothyroidism [19], among many others [20,21]. The finding of diverse organ involvement combined with a specific histologic appearance has drawn comparisons to sarcoidosis [2].

This condition is characterized by elevated serum IgG4 along with mass like tissue infiltration by IgG4-positive plasma cells in association with sclerosis and fibrosis of exocrine glands and extranodal tissues [10]. The most characteristic factor of this disease is an increased amount of IgG4+ plasma cells in the involved tissues or a high serum IgG4 level [11]. Recently, a consensus statement has been issued defining the histopathologic characteristics seen in IgG4-related disease, taking into account IgG4 counts, IgG4-to-IgG ratio, and histologic findings of dense lymphoplasmacytic infiltrate, storiform fibrosis, and obliterative phlebitis [2].

While this disease is of uncertain etiology, it is thought to be an autoimmune entity based on the presence of antibodies such as antinuclear antigen and rheumatoid factor as well as its responsiveness to steroid administration [22].

Currently, the disease epidemiology remains largely undefined. Generally, it is thought to be a disease of middle-aged and older men, however it has been found more recently that the age and gender predilection may be different depending on the initial disease manifestation. In groups with manifestations other than those involving the head and neck, men are the primary group affected, making up 75-86% of the described cases in one study. On the other hand, in cases involving the head and neck, both genders appear to be equally affected with a male predilection of 48% [23]. However, these studies are not declared as definitive and further studies are needed to provide more data.

Clinical and imaging findings

To date, IgG4-related disease of the head and neck has primarily been described as it relates to the salivary glands and orbits [2,24,25], including in a recent study by Fujita et al [26]. It has also been postulated as the underlying cause of idiopathic cervical fibrosis [12] and various forms of thyroiditis [19], particularly Riedel's thyroiditis. There have also been several case reports documenting pathologically proven infundibulohypophysitis.

Salivary gland swelling has been reported in up to 24% of patients with autoimmune pancreatitis. Chronic sclerosing sialadenitis, also known as a Kuttner tumor, has been discovered to be a manifestation of the IgG4-related disease process and presents as painless, firm, bilateral swelling of the salivary glands, however unilateral involvement has been identified as well [24]. Cervical and mediastinal lymphadenopathy have also been associated with salivary gland involvement, generally bilaterally [20]. Contrast-enhanced CT studies have demonstrated diffuse enlargement of the submandibular glands frequently accompanied by bilateral cervical lymphadenopathy [24]. Ga-67 scintigraphy has been shown to demonstrate increased uptake in a homogenous pattern. In that same study, MRI detected homogenous salivary gland swelling with no discernable mass and no evidence of ductal dilation [27].

The orbital involvement seen in IgG4-related disease appears to primarily involve the lacrimal glands in the form of IgG4-related dacryoadenitis. This involvement has been found to be unilateral or bilateral and may extend to adjacent structures, but typically spares the extraocular muscles [24]. Contrast-enhanced CT studies are fairly nonspecific, with the lacrimal gland generally found to be both enlarged and homogeneously enhancing [27]. One study of MR imaging of head and neck lesions in IgG4-related disease has demonstrated bilaterally enlarged lacrimal glands, which exhibit homogeneous low signal intensity on both T1- and T2-weighted images. On gadolinium contrast-enhanced studies, homogeneous enhancement was exhibited as well [25].

Idiopathic cervical fibrosis, first described by Rice et al in 1975 [29], has been attributed to many causes such as infection, Hodgkin lymphoma, autoimmune disease, sarcoidosis, prior surgery, trauma, and many other causes. Despite this, most cases have been considered idiopathic. More recently, many cases have been determined to fall under the umbrella of IgG4-related disease [12]. Generally, these patients are found to present with neck masses resembling enlarged lymph nodes. A study by Cheuk et al analyzed biopsy specimens of these masses and discovered that while exhibiting morphological characteristics of idiopathic cervical fibrosis, they also fulfilled the morphologic and immunohistologic criteria for a diagnosis of IgG4-related disease [12]. Several of these patients were also noted to have other manifestations of fibrosclerosing disease, further supporting a relationship with IgG4-related disease.

There have been many reports documenting various radiologic findings associated with IgG4-related disease [24,25,28]. However, there have been very few imaging studies describing IgG4-related disease of the head and neck, and those that have been described generally focus on orbital and salivary gland involvement [25].

To date, there have been no reports of imaging studies of the neck in a patient with an asymptomatic unilateral solitary cervical soft tissue mass in the absence of salivary gland involvement. In this case, we have described a case of IgG4-related disease manifesting as a neck mass with immunohistologic evidence of IgG4-related disease.

Differential Diagnosis

The differential diagnosis of a soft tissue neck mass is broad and includes both benign and malignant processes, including congenital branchial cleft cysts, infectious/reactive lymphadenopathy, lymphoma, and metastatic involvement of the cervical lymph nodes. In many cases, age, medical history, associated symptoms, and clinical course are helpful in narrowing the differential diagnosis. For instance in our patient, age of presentation, absence of symptoms and unremarkable past medical history made metastatic disease less likely.

Regarding the imaging findings, a congenital branchial cleft cyst is a simple cyst [30,31] rather than the mixed solid and cystic mass seen in Figure 1. However, variable sonographic appearance has been reported with complex or pseudosolid findings described [31]. In addition, a branchial cleft cyst would not be expected to present as a newly discovered and growing soft tissue mass in an adult, however, they are classically off midline. Benign lymphadenopathy due to an infectious process is typically diagnosed clinically with resolution after conservative management and non-specific lymphadenopathy demonstrated on imaging. A neck mass that does not resolve requires further workup and the other entities on the differential may be considered more likely.

Lymphoma is of most concern in a young adult with a newly discovered cervical soft tissue mass and must be strongly considered, particularly in the presence of constitutional symptoms. Imaging findings in both IgG4-related disease and lymphoma overlap with solid or low attenuating lymphadenopathy being the most common findings [32-34] but with indistinct nodal margins described in lymphoma [32]. Metastatic spread to the cervical lymph nodes, typically due to squamous cell carcinoma of the head and neck, results in lymphadenopathy also with potential necrotic changes seen as solid and cystic components on CT [34-38]. Apparent diffusion coefficients (ADC) have been described as useful in differentiating metastatic lesions from lymphoma and benign lymphadenopathy [35] on magnetic resonance imaging (MRI); metastatic lymph nodes demonstrated the highest ADC values (0.410 +/- 0.105 x 10-3 mm2/s) with lower ADC values for inflammatory lymph nodes (0.320 +/- 0.062 x 10-3 mm2/s) and even lower values for nodal lymphoma (0.223 +/- 0.056 x 10-3 mm2/s). However, metastatic disease was considered much less likely in this case due to both age and lack of risk factors.

Treatment and prognosis

The importance in distinguishing between these different entities and considering IgG4-related disease in the differential diagnosis of an asymptomatic neck mass with solid and cystic components on CT scan is that IgG4-related disease responds well to corticosteroids and with other immunomodulators used as second line treatment [39]. Thus, the correct diagnosis may prevent the patient from undergoing more radical forms of treatment or procedures. Nonetheless, tissue sampling is often required in a non-resolving neck mass to confirm the diagnosis, as there is a lack of specificity on imaging.

TEACHING POINT

IgG4-related disease is characterized by elevated serum IgG4 and mass like tissue infiltration by IgG4-positive plasma cells and is associated with a myriad of autoimmune conditions. Imaging findings are nonspecific and in many cases may mimic malignancy, necessitating tissue sampling to confirm the diagnosis as patients with IgG4-related disease respond well to corticosteroids and can be managed expectantly.

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FIGURES

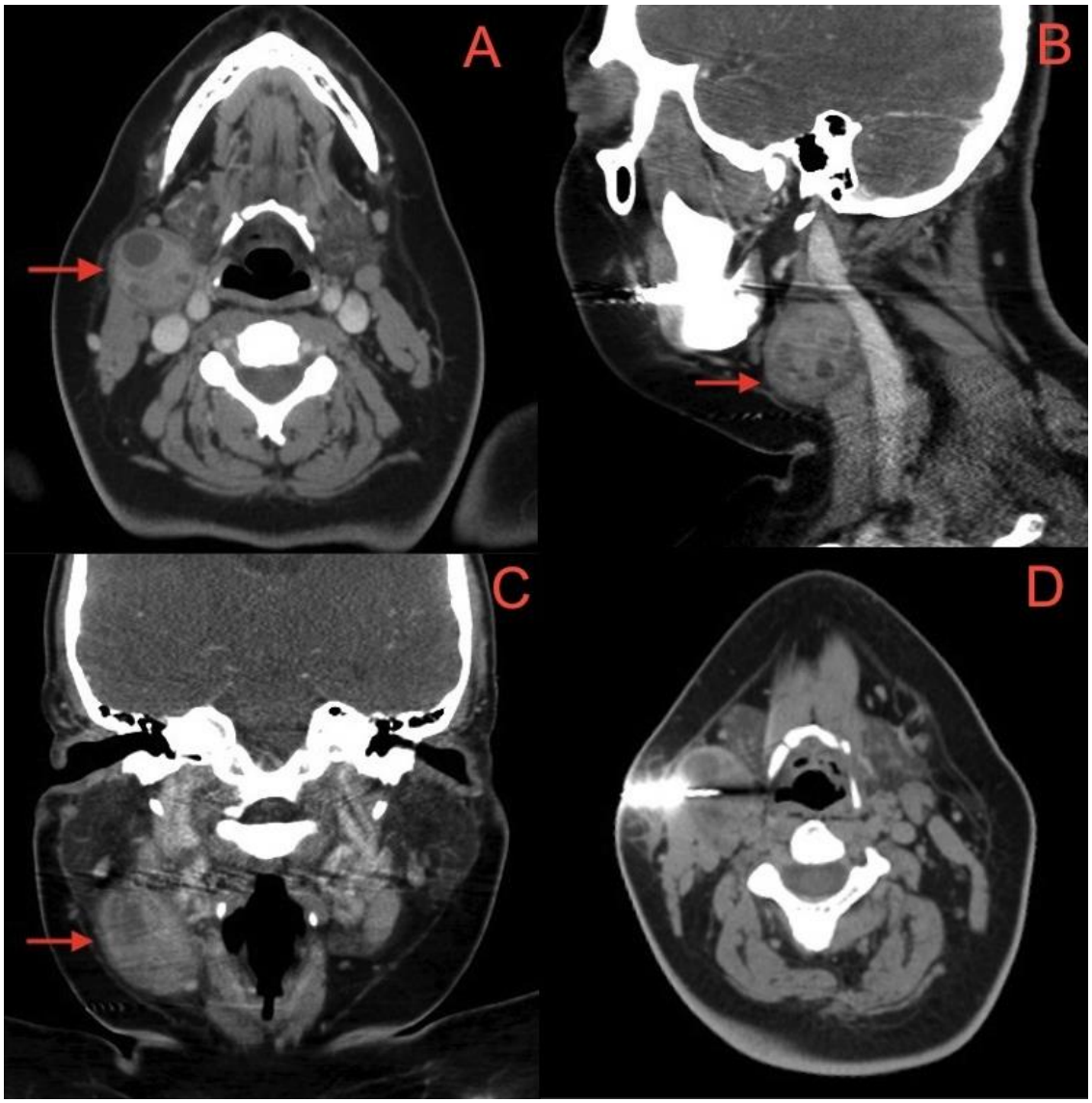

Figure 1: 23 year old female presented with a painless palpable right neck mass, which was subsequently diagnosed as IgG4-related disease. FINDINGS: Axial (A), sagittal (B), and coronal (C) contrast enhanced CT of the neck in the venous phase demonstrates a mixed cystic and solid enhancing mass measuring 2.9 cm AP x 3.1 cm transverse x 4.0 cm craniocaudal within the right lateral neck, level IIa (arrows) anterolateral to the common carotid artery and jugular vein with the mass bordering the anterior margin of the sternocleidomastoid muscle. Axial noncontrast CT (D) demonstrates image-guided placement of an 18-gauge spring-loaded biopsy needle into the right neck cystic and solid mass with the needle tip in the center of the lesion; core tissue samples were obtained. TECHNIQUE: A-C: Axial contrast enhanced CT, General Electric LightSpeed VCT, 37 mAs, 120 kVp, 2.5 mm slice thickness, 100 mL Omnipaque 350. D: Axial noncontrast enhanced CT, General Electric LightSpeed VCT, 100 mAs, 120 kVp, 2.5 mm slice thickness.

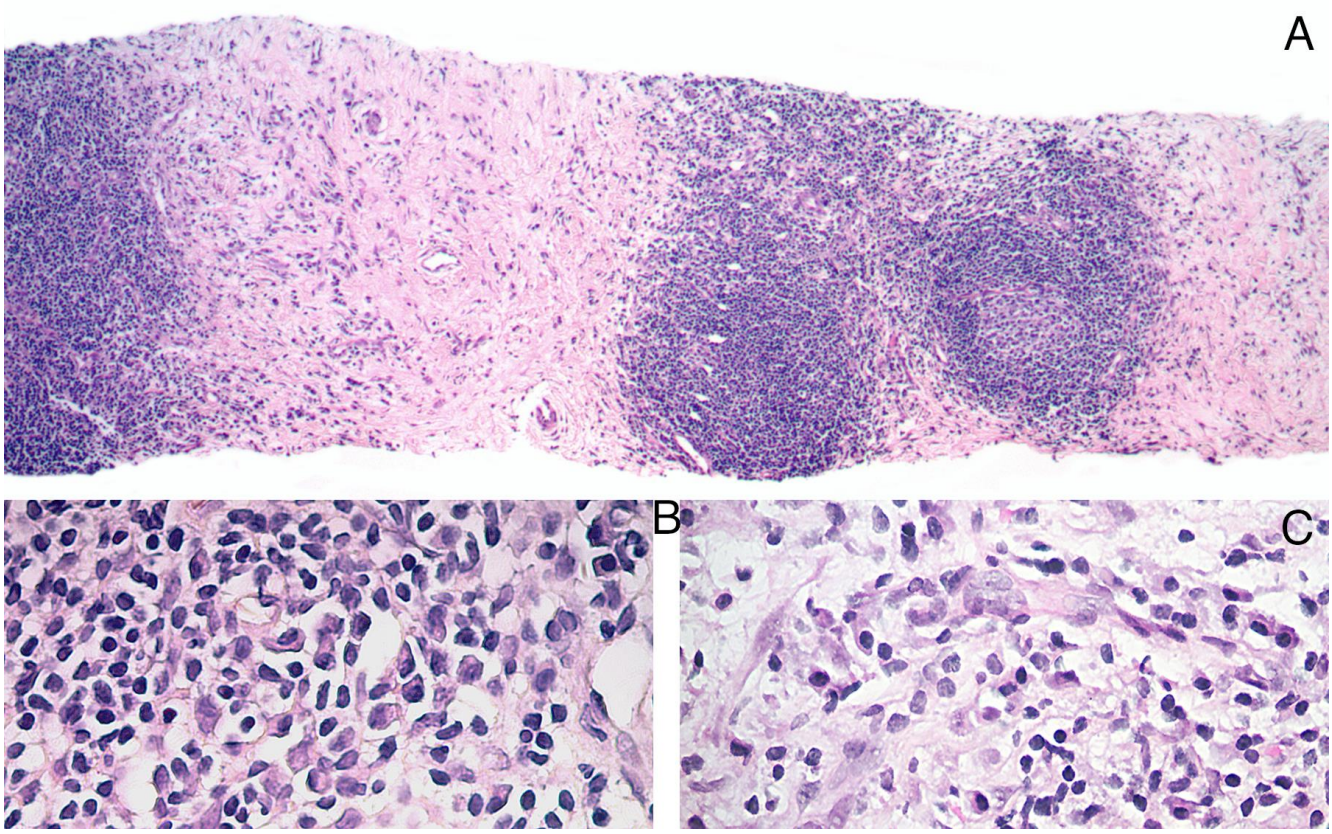

Figure 2: 23 year old female presented with a painless palpable right neck mass, which was subsequently diagnosed as IgG4-related disease. FINDINGS (H&E stained sections): A. Needle core biopsy showing areas of sclerosis admixed with lymphoid aggregates (40x). B. Focus of abundant plasma cells (100x). C. Venule showing phlebitis with infiltrate of plasma cells (100x).

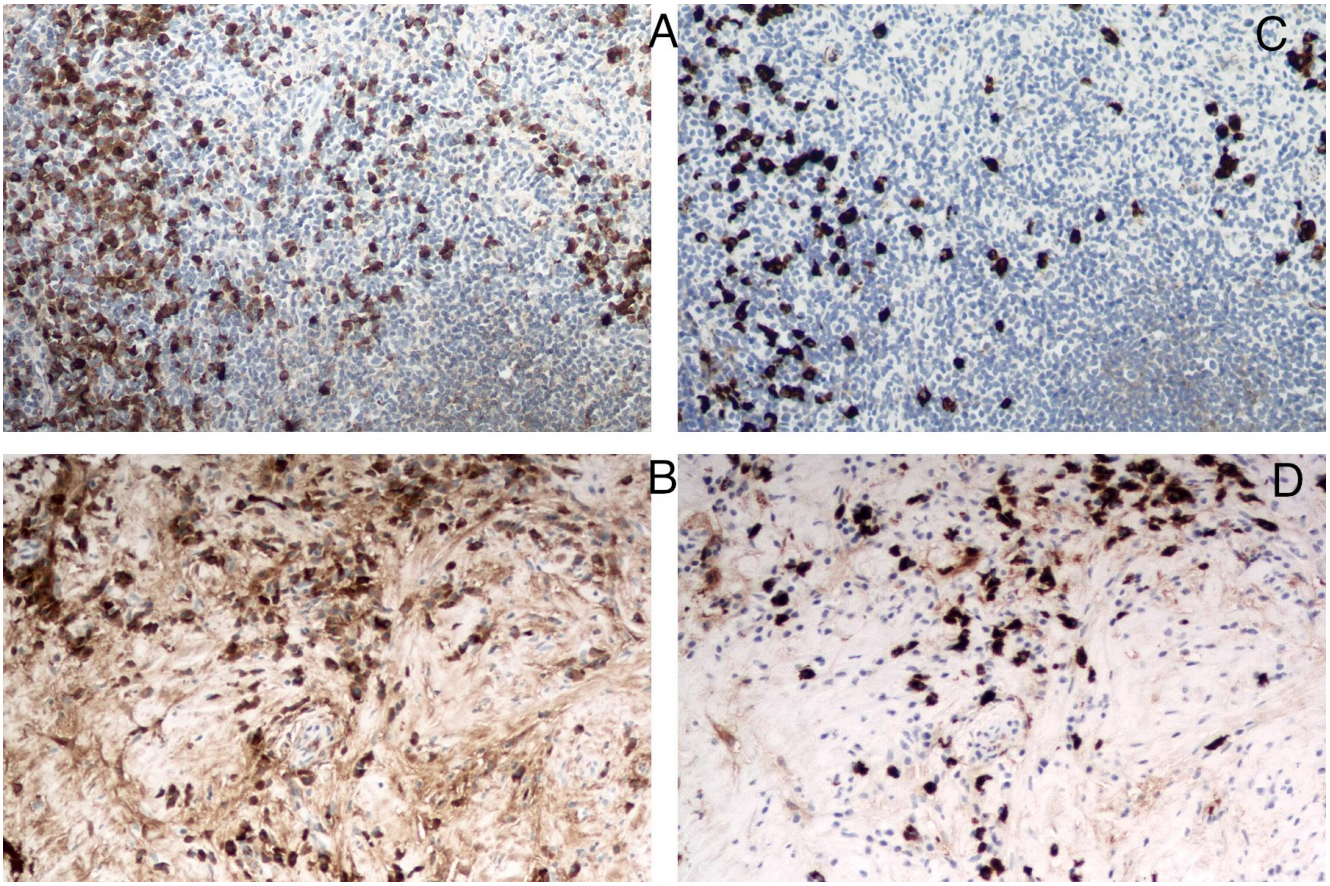

Figure 3: 23 year old female presented with a painless palpable right neck mass, which was subsequently diagnosed as IgG4-related disease. FINDINGS: Biopsy tissue immunostained for IgG (A and B) and IgG4 (C and D). Plasma cells are highlighted in a cellular area (A and C) and a sclerotic area (B and D) (100x).

Etiology	Unclear. Theorized to be autoimmune in nature due to serum markers such as anti-nuclear antibodies.
Incidence	Poorly defined but estimated to be 2.6 -10.2 cases per 1 million people per year.
Gender ratio	More common in males, 75-86% male predominance in cases not involving head and neck; 48% males in cases involving head and neck.
Age predilection	Generally > age 65.
Risk factors	Unclear.
Treatment	Corticosteroids first line; azathioprine, mycophenolate mofetil, methotrexate, rituximab are alternative treatments [38].
Prognosis	Good. Patients show good response to steroid treatment with dramatic decrease in size of lesions.
Findings on imaging	Nonspecific and variable depending on particular organ involved. Masses involving soft tissue of neck as in this case demonstrate mixed solid and cystic components with peripheral enhancement and no local invasion on contrast enhanced CT.

Table 1: Summary table for IgG4-related disease

	CT	**US**	**MRI**
IgG4-Related Disease	• Homogeneously enhancing, mass like enlargement of salivary/lacrimal glands [38] • Homo/heterogeneous lymphadenopathy • Overlapping imaging findings with lymphoma and metastasis	• Lymphadenopathy +/- necrotic changes • No specific features • Overlapping imaging findings with lymphoma and metastasis	• No specific features • Enlarged, homogeneously enhancing lacrimal glands • Overlapping imaging findings with lymphoma and metastasis
Brachial Cleft Cyst	• Simple, low attenuating cystic lesion [29] • +/- thin peripheral enhancement with infection	• Variable ranging from anechoic, internal debris, complex, to pseudosolid [30] • Increased through transmission • No internal color Doppler flow	• T1 hypo /hyperintense depending on protein content • T2 hyperintense • +/- thin peripheral enhancement with infection [29]
Lymphoma	• Homogeneous bilateral lymphadenopathy [32] • Lymph node size > 10 mm* short axis [33] • Calcified lymph nodes [32] if treated • Low density lymph nodes [32] • Salivary gland, parotid gland, or thyroid mass [32]	• Lymph node size > 10 mm* short axis • Loss of fatty nodal hilum • Homogeneous mass +/- focal hypoechogenicity	• Necrosis (focal T1 hypointensity +/- T2 hyperintensity) with peripheral enhancement [31] • Indistinct nodal margins [31] • Lymph node size > 10 mm* short axis
Metastasis	• Dependent on primary lesion • Irregular, necrotic masses • Irregular [33] or homogeneous [36] nodal enhancement • Lymph node size > 10 mm* short axis	• Irregular morphology, round • Loss of normal hilar echogenicity [36] • Lymph node size > 10 mm* short axis • Heterogeneous, echogenic parenchyma [37] • Increased peripheral/ parenchymal nodal color Doppler flow [36,37]	• Architectural abnormality with hypo T1 and hyperintense/ heterogeneous T2 [35] • Elevated ADC [34]

Table 2: Differential table for head and neck IgG4-related disease. * > 11 mm in subdigastric region [32]

ABBREVIATIONS

ADC: Apparent diffusion coefficient
CT: Computed tomography
MRI: Magnetic resonance imaging
US: Ultrasound

KEYWORDS

IgG4 related disease; neck mass; sclerosing disease; autoimmune