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IgG4 Related Disease Presenting with Refractory Cough: A Case Report

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Abstract

Immunoglobulin G4-related disease (IgG4-RD) is an immune fibro-inflammatory condition. It is characterized by tumor like organ swelling, storiform fibrosis, infiltrative CD4 T cells, lymphoplasmocytic infiltrate and an elevated serum IgG4. The disease lends itself to a multisystem disorder and isolated organ manifestation can also occur. Common findings of IgG4-RD include autoimmune pancreatitis, sialadenitis, sclerosing cholecystitis, tubulointerstitial nephritis, orbital disease, lymphadenopathy and retroperitonal fibrosis and lymphadenopathy. However, IgG4 related disease of the lung is particularly novel. It manifests as lung nodules, fibrosis and scarring of the lung tissue. In 2015 the international consensus reviewed and re-established a consensus the diagnosing IgG 4. A criterion for the diagnosis of IgG4-RD encompasses a set of clinical, pathological and serological features in conjunction with specific criteria for organ specific involvement. Recognizing and differentiating IgG4-RD to other similar pathologies is essential for managing the underlying condition, preventing long-term complications and necessary for appropriate treatment.

Keywords: Immunoglobulin; Lymphoplasmocytic infiltrate; Storiform fibrosis

Introduction

Immunoglobulin G4-related disease is an immune mediated condition resulting in disease in various organs of the body such as the pancreas, kidneys, salivary glands, lung, liver, lymph nodes, biliary tract and orbits of the eyes. The disease is recognized by a characteristic pattern of pathological, serological or clinical features shared amongst the organs system that are involved. In some cases, IgG4-RD can mimic malignant, infectious or inflammatory disorders and therefore distinguishing the disease is crucial [1].

The international consensus statement on IgG4-RD established bases for the diagnosis IgG4-RD from findings in multiple organs. The definitive algorithm for diagnosing IgG4-RD includes: (1) organ swelling (enlargement, mass or nodular lesions) or organ dysfunction in one or more organs on physical examination; hematological studies showing a serum IgG4+ concentration of ≥ 135 mg/dL; histopathology indicating marked lymphocyte and plasmacyte infiltration with fibrosis and IgG4 + plasma cell infiltration (IgG4+/total IgG+ cells > 40% AND > 10 IgG4+ cells on high power field) [2].

As discussed in literature, the etiology of if IgG4-RD remains to be completely understood. However, increasing evidence suggests an autoimmune picture with involvement of CD4+ T cells and T follicular helper cells (Tfh). IgG4 antibodies are currently thought to be non-pathogenic and arise due to a down regulatory response to an underlying process [3].

Cases of IgG4-RD are rare with contributing factors being poor recognition, understanding and under-reporting. Majority cases are found in middle aged. Variation in organ manifestation appears to vary with gender. In males, there is increased tendency to affect the pancreas, causing autoimmune pancreatitis type 1 as well as retroperitoneal fibrosis and tubulointerstitial nephritis. Higher prevalence for head and neck involvement is seen in females causing sialadenitis, dacryoadenitis and thyroiditis according to a study [4].

Multisystem disease accounts for the majority of IgG4-RD cases and isolated single organ disease is less common. The

involvement of the lung in patients with IgG4-RD is becoming increasingly recognized [5]. In three large case series conducted by Chen at al, Fernandez Codina et al and Inner et al, lung involvement was accounted for in 32%, 9% and 13% of cases respectively [6]. Another study reported 13% of AIP with IgG4 lung involvement. Isolated cases of IgG4 lung disease were reported in 20% of cases, while the remaining 80% had multi-organ involvement. It also stated IgG4-RD of the lung was the seventh most common manifestation [7].

Clinical features suggestive of pulmonary involvement include cough, shortness of breath, hemoptysis, pleurisy, chest pain and fevers [8]. Patients may be asymptomatic until significant organ involvement. Lymphadenopathy appears to be a common occurrence across IgG4-RD cases. Asthma or allergy presents in up-to 40% of all cases [9]. With reference to imaging findings, literature describes four particular patterns of respiratory involvement including solid nodular, bronchovascular, alveolar interstitial and round shaped ground glass opacities [10]. Other presentations of lung related IgG4-RD include interstitial pneumonia, primary lung cancer, sarcoidosis, lymphoproliferative disease and obliterative phlebitis and storiform fibrosis [10]. Confirmation of IgG4-RD with respiratory involvement requires diagnostic criteria established through a collection of serological, imaging and histopathology studies. A set of criteria for recognizing individual organ involvement was proposed by the Study Group of Intractable Disease from the Ministry of Health, Labour and Welfare (MHLW) in Japan and is increasing in acceptance [11]. Referred to as diagnostic criteria for IgG4 related respiratory disease (RRD) [Image A], the diagnostic criteria includes chest imaging findings showing intrathoracic lesions; serology of elevated series IgG4 concentration of ≥135 mg/dl; and significant histopathology obtained from biopsy of the sample from intrathoracic tissue. It is also important to exclude conditions with similar presentation features such Castleman disease, Wegeners granuloma, Churg-Strauss Syndrome, Sarcoidosis, Rosai-Dorfman disease, respiratory infections and tumors [11]. In this study, we report a case of persistant cough later diagnosed with IgG4-RD upon serological, histological and imaging findings.

Case Report

A 51 year Caucasian female was referred to the respiratory out-patient clinic for evaluation of chronic cough. Asthma was diagnosed as an adolescent and reported to be well controlled under control. She has since then presented to hospital on one occasion with exacerbation of the asthma and reports exacerbation 3 to 4 times a year with suboptimal asthma control and notable increase following cyclone in 2017. She has had 6 exacerbations of asthma in the last 12 months but no admissions to ICU.

She reports a long history of a chronic dry cough which is triggered by cold air, respiratory infections and becomes productive with tenacious green sputum. There is no history of sputum plugs. The cough is associated with a wheeze, SOB, chest tightness, throat clearing, globus sensation and gradually progressive decline in exercise tolerance (18-month history with MRC grade 1). The ongoing cough is also worse at night and when supine, often waking her up from sleep. There no symptoms suggestive of cardiac failure. Nocturnal cough resolves with PRN salbutamol. No history of anorexia, fever of night sweats. A patient wakes up numerously at night due to nocturia or coughing. She is a shift worker and sleeps at 9 am with a latency of 20 minutes. No reported apnea or choking episodes due to no collateral history. She experiences occasional morning headache and feeling unrefreshed at 5am but no xerostomia. There often daytime somnolence and naps, scoring an Epworth sleep scale of 10, though no reported falling asleep while at the wheel.

Patient has background history of gastroesophageal reflux disease (GORD), seasonal allergic rhinitis, sinusitis with postnasal drip, hay fever with childhood eczema and Bronchiectasis. Medications included Esomeprazole, Symbicort 200/6, Spiriva Respimat 2.5, Ventolin, Rhinocort, Citalopram and uses Ventolin when required 3-4 times weekly when well. Vaccinations are reported to be up to date.

The patient has no significant family history. The patient is an ex-smoker with a 5.5-year pack history for which she ceased smoking 20 years ago and consumes alcohol once weekly. Patient also reported THC use, last reported in 2018. She lives in a split-level home and is independent with ADLs. Work history includes hostel manager and tourism work on boats. There may be possible exposure to asbestos and mould during work at in produce but details are unknown. No reported exposure to coal, dust, birds or tuberculosis.

On review the patient reported an improving cough with less phlegm, nil worsening of wheeze and Epworth sleep score of 10. No decrease in exercise tolerance while she is able to walk long distance and upstairs without dyspnea. She reports 2 pillow orthopnea and paroxysmal nocturnal dyspnea. Her appetite has been normal although reported weight gain of 12kg in 18 months. She also states low energy and tiredness. Sleep was described to be disturbed and reports snoring loudly.

Clinical examination were within the normal limts

Cardiovascular, neurological and abdominal examinations were un-remarkable. Full blood count, renal function and liver function were unremarkable. Immunoglobulin subclass screen revealed:

- IgG of 17g/l,
- IgG4 of 2.97g/L
- ESR of 232

- RAST A. fumigatus was positive

Vasculitis screen was unremarkable.

Chest X-ray revealed large volume lungs. A persisting nodule measuring up to 13mm was again noted in the right upper lobe and resolving focal patchy ground glass changes in the left upper lobe. Spirometry results were as follows: FEV1 2.45 (81%), FVC 3.49 (91%), FEV1/ FVC 88%, DLCO 96.1%, KCO 86.9 and these parameter were within the normal limits. BAL was unremarkable and histology demonstrated degree of lymphoplasmacytic infiltrates with some degree of fibrosis.

A. Diagnostic factors
I. Chest imaging
Imaging findings include any of the following intrathoracic lesions, **Hilar/mediastinal lymphadenopathy** **Bronchial wall/Broncho vascular bundle thickening, interlobular septal wall thickening,** **Nodular shadow** **infiltrative shadow, pleural thickening and/or effusion.**
II. Serology
Elevated serum IgG4 concentration of ≥135 mg/dl
III. Histology
Two or more of the following items are required from intrathoracic organ tissues.
a: ≥3 Items; b: 2 items
(1) Marked lymphoplasmacytic cell infiltration into interstitium of peribronchovascular sheath, interlobular septal wall, and/or pleura. **(2) IgG4/IgG-positive cell ratio >40% and/or >10 IgG4-positive cells/high power field.** **(3) Obliterative phlebitis or obliterative arteritis.** **(4) Storiform fibrosis or fibrosis consisting of proliferating spindle-shaped cells around infiltrating lymphocytes.**
B. Diagnosis
1. Definite diagnosis (definite): I+II+IIIa, or I+II+IIIb+IV Histological definite diagnosis [definite (histological)]: I+all four items of III **2. Probable diagnosis (probable): I+II+IV, or I+II +IIIb+V** **3. Possible diagnosis (possible): I+II+IIIb**

Discussion

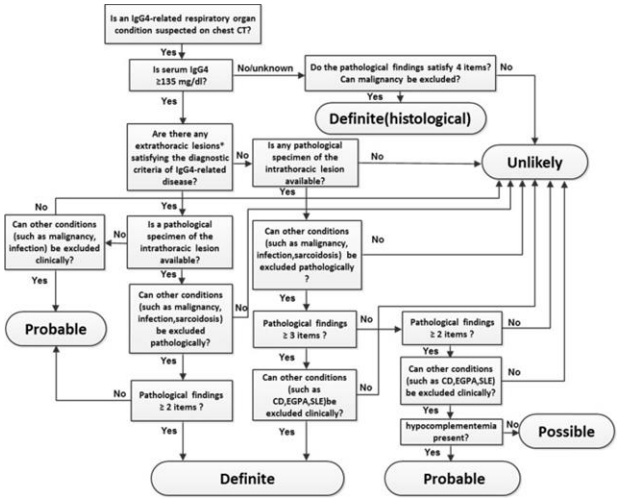
Overall, a diagnosis of IgG4 related disease of the lung was considered. It became evident following findings from the clinical features, spirometry, blood results, radiographic reports and histopathology of lung tissue. The presentation is consistent with a rare case of isolated IgG4 related lung disease, presenting as chronic cough. Based on history and clinical presentation, our patient had allergic hypersensitivity with features of poorly controlled recurrent asthma. IgG4-RD with ear, nose, throat manifestation could also be suggested [12-19].

IgG4-RD has a precedence to affect the middle aged male population according to literature but in this case the patient was female, making the case unique. Physical examination was largely unremarkable. Findings on CT imaging revelased bronchiectatic changes, peribronchial centrilobular ground-glass opacities. Manifestations of IgG4-RD were not evident in other systems of the body including liver, bile duct or pancreas.

Laboratory data showed an IgG4 level of 297 mg/dL (17g/L, reference range: 2.4 - 121.0 mg/dL) which fulfills the serological criteria, Section A Part II of the diagnostic criteria required IgG4-RD. Blood test revealed an elevated ESR of 232 (reference range) as well positive RAST A. fumigatus. Spirometry indicated normal lung function and results were unremarkable for this patient, although reversibility was not recorded.

Tissue biopsy remains gold standard for the diagnosis of organ specific involvement of IgG4-RD, thus bronchoscopy was conducted in the light of a definitive diagnosis. Despite, optimal samples were difficult to obtain through brushings to assess cytology, microscopy and sputum. From brushings of the right lower lobe, microscopy showed bronchial epithelial cells, alveolar macrophages and leukocytes. However, no significant eosinophilia or plasmacytosis was observed.

Histology demonstrating the degree of lymphoplasmacytic infiltrates and there was no comment on the CD4 T cells + plasma B cells levels or eosinophil infiltration. Some degrees of fibrotic changes were noted as well.



Systemic manifestations

IgG4-RD can virtually effect any organ system of the body. It has a variety of clinical presentations and manifestations that may not be mutually exclusive. In the absence of significant clinical

suspicion, tests for IgG4-RD are not recommended as diagnostic [20,21]. Multiple organs are affected in 60 to 90% of incidences of IgG4-RD [17,19]. Due to the extent of organ involvement, one study looked at 2 cross-sectional studies in the attempt to categories types of IgG4-RD. It comprised of 765 cases and identified four groups with distinct patterns of organ involvement and manifestations using latent class analysis (LCA). IgG4-RD was classified into 4 groups: Group 1, Pancreato-Hepato-Biliary disease (31%); Group 2, Retroperitoneal Fibrosis and/or Aortitis (24%); Group 3, Head and Neck-Limited disease (24%) and Group 4 (22%), classic Mikulicz syndrome with systemic involvement [22]. Conditions previously considered as single entities are now regarded as manifestations of IgG4-RD [2].

Lymphadenopathy

IgG4 disease effects the lymph nodes causing lymphadenopathy in 41% of patients with multiple organ involvement [12]. Presenting symptoms relate to the mass effect of the lymph nodes and the lymphadenopathy itself tends to be non-tender. It can occur in isolation or along with other manifestations. Multiple groups of lymph nodes may be involved including hilar, intraabdominal, mediastinal and axillary. Biopsies have poor specificity for diagnosis and may not reflect the extent of disease in other organs [13]. Histopathology shows features of storiform fibrosis, IgG4+ plasma cells, eosinophilic infiltration consistent with classical IgG4-RD [14,15].

Autoimmune pancreatitis

Of the two subtypes of autoimmune pancreatitis only one has been associated with IgG4-RD. The most common and typical form is Type 1 (IgG4-related) autoimmune pancreatitis (AIP), also referred to as lymphoplasmacytic sclerosing pancreatitis [17]. Presentation includes painless obstructive jaundice making distinguishing AIP from pancreatic cancer difficult but essential so that surgery can be avoided in unnecessary. Patients may also experience secondary diabetes mellitus as seen in 50% of cases [13,16]. Though likely to be an underestimation, AIP from IgG4-RD has a prevalence of 0.82 in 100,00 in Japan in early studies [18]. Characteristically on CT imaging, an enlarged “sausage shaped” pancreas with surrounding edema is highly suggestive of AIP. Diagnostic criteria for AIP resulting from IgG4-RD requires combined ductal and parenchymal imaging, serum IgG4 concentration, pancreatic histology, presence of extra-pancreatic disease and response to glucocorticoids. Endoscopic ultrasounds, MRCP and PET scans may aid diagnosis [13].

Sclerosing cholangitis

Sclerosing cholangitis from IgG4-RD is often associated with type 1 AIP as the commonest extra-pancreatic manifestation in more than 70% of cases. To note, it is distinct from primary sclerosing cholangitis and cholangiocarcinoma and definitively excluding these conditions may require endoscopic transpapillary biops [13,19]. Tissue biopsy of IgG4-RD sclerosing cholangitis reveals dense IgG4+ plasma infiltrates, transmural fibrosis, obliterative phlebitis and elevated IgG4 serum levels [13].

Salivary and lacrimal glands

Mikulicz’s disease and Küttner tumor are now considered subcategories of IgG4-related sialadenitis and are often seen in conjunction with AIP [23,24]. IgG4-RD can affect both major and minor salivary glands. Mikulicz’s presents with dacryoadenitis (lacrimal) along with enlargement of the submandibular and parotid gland. Enlargement of the submandibular gland is a form of sclerosing sialadenitis, which is known as a Küttner tumor. This varies in contrast to Sjögren’s syndrome where parotid gland involvement s predominates [13]. IgG4-related sialadenitis and dacryoadenitis demonstrates typical IgG4-RD characteristics obtained from tissue samples as seen in other organ sites.

Orbital

Common ophthalmic manifestations of IgG4-RD include frank proptosis and orbital swelling often involving the lacrimal gland (dacryoadenitis). Orbital myositis and orbital pseudotumours due to IgG4-RD may also present as proptosis. Less commonly scleritis, nasolacrimal duct obstruction and nerves surrounding the orbits can be compressed. Of patient with IgG4-RD, ophthalmic disease is accounted for in estimated 17-23% of cases [13,25,26].

Chronic periaortitis and retroperitoneal fibrosis

Up to two thirds of cases of idiopathic retroperitoneal fibrosis are as result of IgG4-RD. It is one of the most common manifestations of IgG4-RD. Previously known an Ormond’s disease, the classification of chronic periortitis currently incorporates 3 manifestations; IgG4-RD related retroperitoneal fibrosis, IgG4-related abdominal aortitis, and IgG4-related perianeurysmal fibrosis. Three broad regions are known to effect in chronic periaortitis, which include the periaortic/arterial, periureteral and retroperitoneum. Chronic periaortitis can present with non-specific back, flank, lower abdominal, lower limb pain or oedema and obstructive uropathy which may cause delay in diagnosis [27,28].

IgG4 related retroperitoneal fibrosis tends to present with fibrotic and chronic inflammatory changes affecting the infra-renal aorta, iliac arteries and regional tissue. In the laboratory, the IgG4+ plasma cell to total plasma cells ratio that is obtained from tissue sample, provides a useful tool for diagnosis. Often storiform fibrosis and obliterative phlebitis are also present and consistent with classic IgG4-RD characteristics [13,29,30].

Thoracic aorta, branches of aorta and coronary lesions

Non-infectious aortitis is known to be caused by IgG4-RD [31]. Aneurysms and dissections of the thoracic aorta are common findings in IgG4 related aortitis, though primary aortic branches are spared unlike in Giant Cell and Takayasu's arteritis. Medium size vessels and coronary arteries can also be effected by IgG4-RD [13]. Radiographic findings of primary vessel disease showing inflammation of vessel walls was found in 8.1 percent of patients with IgG4-RD [32].

Thyroid disease

IgG4-RD of the thyroid gland manifests as rare form of thyroiditis, called Riedel's thyroiditis. A hard goiter is noted along with symptoms such as dyspnea, dysphagia and hoarseness as a result of correlating compression of surrounding structures. Features of IgG4-RD that are observed on tissue biopsy include storiform fibrosis, obliterative phlebitis and elevated IgG4: IgG ratio. Cytology may not be conclusive thus diagnosis is often made following resection of the thyroid, for symptomatic treatment and/or ruling out malignancy [33].

Kidney

Tubulointerstitial nephritis is the most common finding of IgG4 related renal disease often seen in middle-aged and older males. Histology remains consistent with features observed in other organs and type 1 AIP [34]. Though notably low concentrations of complement (hypocomplementaemia) are demonstrated in IgG4 related tubulointerstitial nephritis compared to other organ manifestations of IgG4-RD. Patient may develop advanced to end stage renal failure, proteinuria and atrophy of kidney despite responsiveness to therapy. CT Imaging may reveal hypodense lesions and an enlarged kidney in relation to the disease. Nodular lesions can mimic renal cell carcinoma in some cases [34,35]. TIN secondary to IgG4 related was observed in 15% of cases from a retrospective study in Japan involving 153 cases of suspected IgG4-RD [34]. Membranous glomerulonephropathy is a less common manifestation of renal IgG4 disease though it is often seen in conjunction with TIN [36].

Ear, nose and throat

Many IgG4-RD patients are not atopic but a considerable proportion present with allergic features relating to the ear, nose and throat. Before the IgG4-RD phenotype is known, patients may suffer from long standing allergic rhinitis, nasal polyps, asthma, sinusitis, obstruction or rhinorrhea. Elevated levels of leukocyte count, mild-moderate peripheral eosinophilia, IgE concentrations above 10-fold are common [37]. In some cases, disease process causes inflammation of the pharynx, hypopharynx, Waldeyer's ring, vocal cords and trachea, with some occurrences of mass lesions [38,39].

Other involved organs and tissues

IgG4-RD can occur in various other forms and organs of the bodies in much rarer instances [13]. Several cases of skin involvement have been reported presenting with erythematous papules typically affecting the head and neck [40]. In the CNS, IgG4-RD affects the brain parenchyma most often resulting in hypertrophic pachymenigiits. Hypophysitis with hypopituitarism is another less common manifestation [41]. Within the mesentery and mediastinum IgG4-RD has been associated with sclerosing lesions causing compression of adjacent vital structures [42]. Liver manifestations if IgG4-RD may resemble autoimmune-hepatitis or hepatic inflammatory pseudotumors [43]. While in the prostate, benign prostatic hypertrophic and prostatitis have been observed [44].

In some cases of asymptomatic IgG4-RD with no presence of organ dysfunction treatment may not be necessary. However, patients should be monitored closely with adequate follow-up by managing teams. IgG4-RD is treated with glucocorticoid as first-line therapy. The dose and regime are based on findings in AIP cases. Typically, prednisolone 0.6mg/kg/day for 2-4 weeks is used an induction and the tapering of corticosteroid is occurs over 3-6 months. A maintenance dose of 2.5-5mg/day may be required for up to 3 years. In refractory or complication IgG4-RD disease, steroid-sparing agents such as azathioprine, mycophenolate mofetil, and methotrexate can be considered. Rituximab may aid B cell depletion refractory disease. Additionally, surgery may be considered on a case to case bases [6,13].

Conclusion

IgG4-RD is a relatively poorly understood condition with unknown definitive aetiology. Cases in the current population are underestimated and undervalued. IgG4-RD may often be overlooked and therefore should be considered by clinicians as an important differential if multiple features are present. The diagnostic criteria outlined in literature should aid definitive diagnosis of IgG4 RD. If suspected, IgG4-RD manifestations in other organs should also be investigated so that appropriate and optimal an treatment can be administered to the patient.

Guarantor of Submission

The corresponding author is the guarantor of submission.

Source of Support

None

Consent Statement

Written informed consent was obtained from the patient for publication of this case report.

Conflict of Interest

Authors declare no conflict of interest.

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