CASE REPORT

IgG4-related disease with atypical laryngeal presentation and Behçet/granulomatous polyangiitis mimicking features

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SUMMARY

The following report describes two male patients with an ongoing medical history with a predominant laryngeal focus, who were finally diagnosed with IgG4-related disease (IgG4-RD). Their primary symptoms included hoarseness and pain of the throat, and they had undergone multiple laryngeal surgeries and laser treatments due to tumorous growth with limited success. Due to the onset of additional symptoms, they initially received the diagnoses granulomatous polyangiitis (GPA) and Behçet's disease. However, further analysis showed elevated IgG4 levels in serum and infiltration of IgG4-positive plasma cells upon biopsy of laryngeal and pulmonary tissue. Treatment was started with moderate doses of prednisone, leading to a rapid resolution of symptoms.

BACKGROUND

IgG4-related disease (RD) is a relatively new disease entity, mostly known to manifest pseudotumours in pancreas, kidneys, salivary glands and hepatobiliary system with corresponding symptoms.

The cases we describe regard uncommon presentations of IgG4-RD starting in the laryngeal area in two previously healthy individuals. They were exposed to multiple—in retrospect probably unnecessary—surgeries; one patient even required a tracheostomy due to immobility of the vocal chords as a result of fibrosis. Had the right diagnosis been made at the onset of symptom presentation, the adequate treatment—high to moderate doses prednisone—would have limited the life-long complications as well as eliminated the exposure to repeated surgery. Our aim is to increase awareness concerning this lesser known initial presentation of IgG4-RD, the way it can mimic other autoimmune diseases, as well as review the pathogenesis.

CASE PRESENTATION

Case 1

A 56-year-old man was presented to our rheumatologists, having a 12-year ongoing medical history concerning the laryngeal tract, with more recent involvement of lungs and prostate. His initial symptom had been hoarseness in the follow-up of rhinitis, which was shortly followed by a stenosis of the right anterior subglottic area, as well as progressive vocal chord rigidity due to unexplained fibrosis over the course of the following 3 years. This lead to the initial immobility of the right vocal chord followed by the subsequent immobility of the left. There was neither any involvement of the thyroid, salivary glands or mediastinal lymph nodes, nor was there any sign of damage to the laryngeal recurrent nerve. For the tumorous mass causing the stenosis, he received laser therapy up to five times, and received a tracheotomy when there was an increased inspiratory stridor and dyspnoea, alongside the vocal chord immobility. Upon follow-up 4 years later, dyspnoea and coughing were still present. Upon radiological imaging of the lungs, eight spherical-shaped lesions were observed, and investigation of interstitial fluid showed a positive Aspergillus precipitin test. Under suspicion of Aspergillosis, he received voriconazol, followed by iteroconazol 20 mg for several weeks each, in combination with 5 mg of prednisone, which lessened the symptoms significantly, but did not deplete them. He experienced no B symptoms.

There was no history of arthritis or skin lesions, although he did suffer from unexplained urine retention and prostate problems. Family history was negative for rheumatological and other immunological diseases.

Physical examination showed no indicative abnormalities. Owing to long-standing symptoms of the laryngeal and pulmonary area in combination with the spherical lesions of the lungs, diagnostic investigation was performed for GPA, which was thereafter the assumed diagnosis despite a negative antineutrophil cytoplasmic antibody (ANCA).

Case 2

A 57-year-old man was presented to our rheumatologists after being conferred by the Ear-Nose-Throat department. He had an ongoing medical history concerning recurrent hyperplasia of both pharynx and larynx, and had been under treatment for almost 16 years. His primary symptoms included hoarseness and ulceration of the mouth and throat. So far, biopsy following microlaryngeoscopy had been dubbed consistent with a chronic infection with aspecific markers, and additional immunostaining had rendered no further results or diagnoses. Prior to referral, he had undergone multiple surgeries for the removal of hyperplastic tissue, labelled as pseudotumour and had received the diagnosis chronic laryngitis/stomatitis aphtosa. In addition, he had a 3-year history of ulcerations on his glans penis, which could not be linked to sexually transmitted diseases. Further medical history mentioned a resolve of symptoms upon an intake of 60 mg of prednisone which had

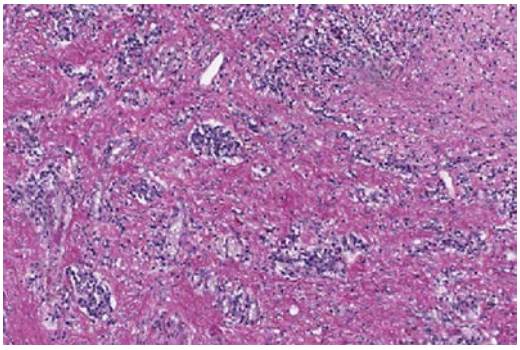

Figure 1 Histopathlogy of obtained lung tissue (case 1) stained with PAS-D, showing significant storiform fibrosis in IgG4-related disease. PAS-D, Periodic Acid Shift–Diastase staining.

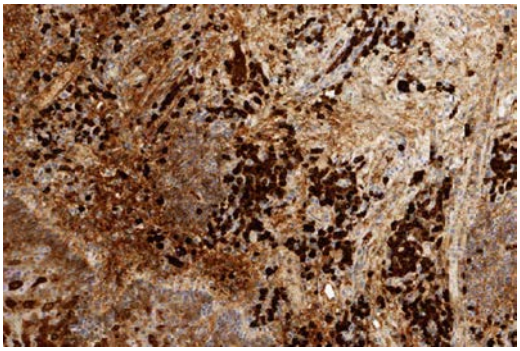

Figure 2 IgG4 immunohistological staining of laryngeous tissue (case 2) showing mass infiltration of IgG4+ plasma cells. This was also seen in our first patient.

been administrated due to lethargy for a period of 10 months. However, when prednisone use was tapered and then aborted, the symptoms returned. Further symptoms mentioned were morning stiffness and arthritis, which was objectified upon physical examination. These symptoms, in addition to the oral and genital ulcera, rendered diagnosis highly suspected for Behçet's.

INVESTIGATIONS

Case 1

Radiological imaging showed the persistence of the previously observed spherical lesions in the hiliary area (despite proper treatment of alleged Aspergillus infection). An open lung biopsy was performed to strengthen the then assumed diagnosis of GPA. The patient was tested for ANCA, anti-CCP and ANA, which were absent in serum. Biopsy showed pulmonary hyalinising granulomas, which upon additional immunohistological staining were a result of increased influx of IgG4 plasma cells and storiform fibrosis (figure 1). Subsequent measurement of IgG4 levels in serum showed a clear elevation of 1.8 g/L (normal range: 0.01–1.4 g/L). Biopsy of the larynx showed a similar histological presentation, confirming the diagnosis for IgG4-RD.

Case 2

A pathergy test was performed, which was negative; yet, due to low sensitivity of this test (especially in the Caucasian population) and the undeniable presence of orogenital ulceration with persisting acute phase response, Behçet's disease was assumed to be the correct diagnosis. During previous prednisone use, the patient had been tested for IgG4-related disease by means of blood serum and biopsy, both of which rendered inconclusive results.

When samples were obtained while the patient was prednisone free, biopsy and serum did show elevated IgG4 levels of 1.96 g/L, infiltration of tissue with high counts of plasma cells with IgG4-specific markers (figure 2), as well as fibrotic tissue.

The combination of IgG4 levels in serum and histological findings postbiopsy of the hyperplastic tissue of the larynx confirmed the diagnosis of IgG4-RD.

DIFFERENTIAL DIAGNOSIS

- GPA (case 1)
- Behcet's (case 2)
- Anklylosis of the laryngeal joints
- Malignant neoplasm
- Sjogren
- Sarcoidosis

TREATMENT

When the diagnosis of IgG4-related disease was confirmed, our first patient was started on monotherapy of prednisone 20 mg, administered for 2 months to be eventually tapered to 10 mg/daily.

The second patient was started on 60 mg prednisone daily, to be continued for 4 weeks, after which the dosage was tapered by 5 mg/2 weeks, to reach a target dose of 10 mg daily.

OUTCOME AND FOLLOW-UP

Shortly after the initiation of treatment, there was a complete resolution of laryngeal symptoms, as well as pulmonary and urogenital in case 1 and urogenital in case 2. Both patients were seen for 3-monthly checkups. The bilateral vocal chord immobility in our first case due to rigidity as a result of fibrosis was thought to be consistent with IgG4-RD, but was rendered irreversible. Thus, the hereby resulting tracheostoma was a life-long complication. In addition, he showed an exacerbation of pulmonary symptoms 2 years post-treatment initiation with prednisone, upon which the dosage was raised from 10 to 20 mg daily, with good response. Azathioprine 150 mg once daily was added to the treatment, in the hope of discontinuation of prednisone therapy in the future. A rapid symptom resolution was objectified soon after. The patient in case 2 reported no new developments and maintained a dosage of 10 mg prednisone.

DISCUSSION

IgG4-related disease, previously called hyper-IgG4, multifocal idiopathic fibro sclerosis and IgG4-related sclerosing disease, among others, is a relatively new diagnosis, officially recognised as a multisystemic condition as recent as 2003.[1] It remains a disease of unknown exact pathogenesis, where it is unclear whether IgG4 elevation is primary or secondary, that is, the cause or the effect of disease expression.

IgG4 is considered an anti-inflammatory antibody with a damping effect on the effector phase of the immune response, which occurs by means of two exclusive distinguishable functional capacities. First, its inability to activate the classical complement pathway due to decreased affinity for C1q and Fcγ which initiate the cascade. Second, IgG4 antibodies can display Fab arm exchange which leads to the formation of antibodies with two different antigen-binding sites, resulting in the inability to cross-link identical antigens and thus the formation of complexes.[2 3] Owing to these properties, IgG4 antibodies are regarded as part of a regulatory, damage-controlling response.

IgG4 antibody has a low antigen-binding affinity and accounts for less than 5% of total IgG concentration, with IgG4

concentrations ranging from 0.01 to 1.4 mg/dL and a variability of 5–50x between healthy individuals. However, when chronically exposed to antigens, concentration of IgG4 can rise up to 80% of total IgG.[3]

A plausible hypothesis may be that chronic exposure over time to an unknown antigen leads to the triggering of T-helper type 2 response which release IL-4 and IL-13, resulting in a selective increase in B-cell preference for differentiation to IgG4 and class-switch activity of IgM, IgE and IgG, to IgG4.[4 5] Regulatory T cells are activated, functioning as a mediator to dampen the inflammation, leading to the release of cytokines IL-10 and transforming growth factor-beta (TGF-β). This results in a selective increase in B-cell preference for differentiation to IgG4 and class-switch activity of IgM, IgE and IgG, to IgG4, leading to subsequent increase in its concentration.[5] When this cascade loses its self-limiting property, it may lead to the deposition of antibodies and incomplete linked-antigen complexes in various tissues, infiltration of lymphocytic plasma cells and activation of fibroblasts through TGF-β release. These then activate myelofibroblasts, which deposit and contract in the target organ/tissue, leading to the formation of a whirling pattern labelled as storiform fibrosis,[5] which correspond with the various disease presentations. The clinical presentation is in line with this hypothesis, as the onset of IgG4-RD can usually be labelled as subacute, initially restricted to one organ, with eventual progression to manifest fibrosis in multiple sites, which may eventually be irreversible as displayed by the bilateral vocal chord rigidity and immobility in case 1.

No reports were found concerning GPA-like and Behcet-like presentations alongside initial laryngeal pseudotumours, although pulmonary and urogenital manifestations of IgG4-RD have previously been described.[6–8] It is thought that, in analogy to other auto-immune diseases with yet unclear pathways, IgG4-RD can mimic these—and other—more-recognised diseases (eg, Sjogren, sarcoidosis) leading to initial false diagnoses. To our knowledge, only one other case concerning IgG4-RD with initial presentation of a pseudotumour of the laryngeal tract was reported.[9] However, in that case, it concerned a 22-year-old woman with initial shortness of breath, rather than hoarseness, though subglottic stenosis was seen and diagnosis for IgG4 made by means of biopsy after thoracotomy. No additional organs were involved; after prednisone administration, all symptoms were resolved.

Cases of IgG4-RD (not concerning the larynx) have been mentioned where a spontaneous resolution of symptoms occurred in the absence of medical treatment. However, as demonstrated in our case, there is an urgent need for prompt treatment when the larynx is involved, considering the irreversible damage otherwise caused. IgG4-RD can be adequately treated with high doses of prednisone of 0.6 mg/kg for duration of 2–4 weeks to be tapered to 5–10 mg daily in a matter of 3–6 months.[10] Results are usually visible within 3–4 weeks. Relapses are common when medication is discontinued. In case of insufficient response to prednisone, azathioprine (2 mg/kg/day) may be prescribed as a prednisone sparing agent (in analogy with other chronic auto-immune diseases). If resistance persists, rituximab therapy should be effective, due to the presumed short half-life of IgG4-specific plasma cells.[11]

Learning points

- Hoarseness can be a first presentation of IgG4-related disease (IgG4-RD).
- IgG4-RD can be the cause of unexplained non-malignant fibrosis/hyperplasia of laryngeal tissue, with considerable morbidity as a result.
- IgG4-RD presentation can closely mimic other auto immune diseases, in these cases GPA and Behcet's.
- IgG4-RD is easily treated with moderate to high dose prednisone.
- Timely correct diagnosis can prevent unnecessary exposure of patients to potential damaging surgical procedures.

Contributors YS was involved in conception, design, analysis and interpretation of data, drafting of the manuscript. ET was involved in critical revision of the manuscript. RG was involved in acquisition of data, critical revision of manuscript. JT was involved in acquisition, analysis and interpretation of data, critical revision of manuscript. All authors approved the final version of the manuscript.

Competing interests None.

Patient consent Obtained.

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