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Dry crusty nose: Not Just Rhinosinusitis! Hidden IgG4- related disease without IgG4 Level rise

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CASE REPORT

Dry Crusty Nose: Not Just Rhinosinusitis! Hidden IgG4-related Disease Without IgG4 Level Rise

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Abstract

IgG4-related disease (IgG4-RD) is a fibro-inflammatory condition that can affect various organs. Localized sinonasal IgG4-RD is a rare condition characterized by bone and soft-tissue invasion. In this report, we present a case of a patient initially diagnosed with chronic rhinosinusitis, who underwent endoscopic sinus surgery and was later found to have biopsy proven IgG4-related sinonasal disease despite having normal serum levels of IgG4, resulting in erosion of the right lamina papyracea.

Keywords: IgG4-related disease (IgG4-RD), Fibro-inflammatory condition, Localized sinonasal IgG4-RD, Soft-tissue invasion, Chronic rhinosinusitis, Endoscopic sinus surgery, Lamina papyracea

1. Introduction

IgG4-related disease (IgG4-RD) is a relatively unrecognized condition that can impact multiple organ systems, resulting in significant diagnostic delay and high levels of healthcare resource utilization.[1,2] Within the realm of IgG4-RD, localized sinonasal involvement is a rare occurrence, characterized by the invasion of bones and soft tissues.[3]

While measuring serum IgG4 concentrations may be helpful for initial screening, it should not be solely relied upon as a diagnostic marker as elevated levels are nonspecific and may be observed in several other conditions.[4,5] The gold standard for diagnosing IgG4-RD is histopathologic examination,[6] however, even with supporting histopathological evidence, it is crucial to establish a clinicopathological correlation to confirm the diagnosis.[5]

Failure to consider IgGR-RD in the differential diagnosis may lead to diagnostic delay; patients can exhibit clinical symptoms resembling other conditions like plasma cell neoplasms and hypereosinophilic syndromes.[7] Raising awareness about this disease is essential for early detection, which can help prevent significant organ damage, debilitating tissue fibrosis, and potential fatalities.[8]

2. Patient presentation

A 57-year-old man with no significant past medical history visited an ear, nose, and throat clinic due to bilateral nasal congestion accompanied by bilateral excessive nasal dryness and non-exudative, non-bloody, whitish dry crusting for one year. The patient stated that he did not have excessive sneezing, runny nose, itching of the nose/eyes/throat, cough, nasal discharge, postnasal drip, double vision, blurred vision, dry mouth or eye, headache, or facial pain. There were no significant known allergies or family history of significant medical disease. He denied smoking and the use of any recreational drugs or alcohol. Despite using a humidifier at home, he reported minimal improvement in his symptoms.

Upon examination, the patient's vital signs revealed a slightly elevated blood pressure (138/80 mm Hg), while his heart rate, respiratory rate, and oxygen saturation remained within normal

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range in ambient room air. The examination indicated the absence of tenderness in the maxillary or frontal sinuses, and a nasal speculum examination revealed a deviation of the nasal septum to the left side. Sinonasal endoscopy further confirmed the left-sided deviated nasal septum, along with edematous bilateral sphenoethmoid and bilateral hypertrophied inferior turbinates. Firmly adherent bilateral whitish, dry crusting was also noted on the nasal mucosa of the middle meatus, with extension to the inferior part of the middle turbinate and the adjacent nasal septum. Based on these findings, the patient's symptoms were attributed to the deviated nasal septum and inferior turbinate hypertrophy. The patient was advised to use mupirocin rinses in saline, budesonide nasal rinse, azelastine nasal spray, fluticasone nasal spray, and loratidine as part of the treatment plan.

At his follow up appointment three months later, the patient reported worsening of symptoms despite regular use of the previously prescribed medications. In addition to the previously noted symptoms, he reported new discomfort in his right eye and the right lateral side of his nose. He also described a mild, continuous, non-radiating pressure-type pain in the same area, which did not have any specific exacerbating or alleviating factors. The pain in the right eye was noted at rest and was unrelated to ocular movement in any particular direction. The patient also mentioned two episodes of scant bleeding from both nasal cavities while irrigating his nose. During the examination, mild tenderness was noted in the right nasal ala and infraorbital areas. Nasal endoscopy findings were similar to the previous examination, with excessive yellowish crusting in both nasal cavities, thick and friable bilateral middle meatus, and a thick, bulky septum anteriorly. The nasopharynx appeared normal, and there were no remarkable findings in the eustachian tube orifices or Fossae of Rosenmueller, such as polyps or masses.

A culture of the nasal crusting revealed the presence of gram-positive rods, specifically Diptheroids. To further investigate potential sinonasal disease, a computed tomography (CT) scan of the nose and paranasal sinuses (Fig. 1) was performed that showed mild to moderate mucosal thickening in the frontal, ethmoid, sphenoid, and maxillary sinuses, indicative of pansinusitis with erosion of right lamina papyracea. The globes, extraocular muscles, and optic nerves appeared symmetric and within normal limits. Considering these findings, the patient was prescribed a two-week course of Amoxicillin/clavulanic acid and initiated on a tapering dose of oral steroids, starting at 60 mg, to address the presumed

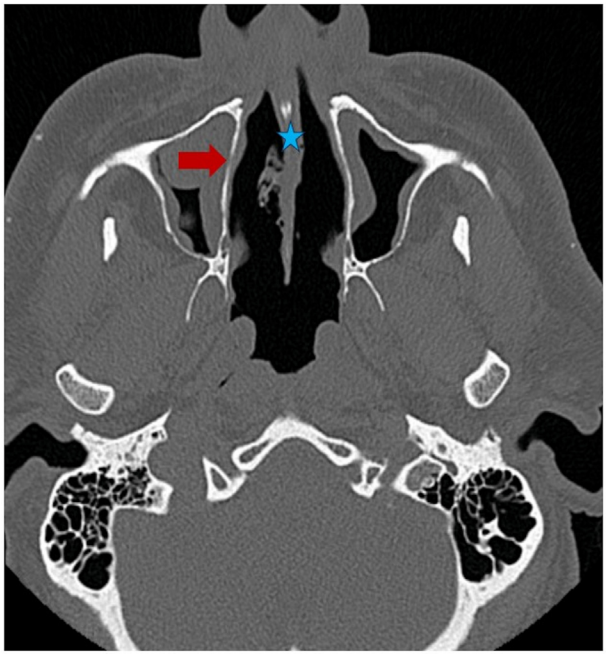

Fig. 1. Computed tomography of nose and paranasal sinuses without contrast demonstrated: mild to moderate mucosal thickening of frontal/ethmoid air cells/sphenoid/maxillary sinus consistent with pansinusitis with erosion of right lamina papyracea (arrowhead). Mucosal thickening obscures the ostiomeatal units bilaterally. Leftward deviation of the nasal septum (star) with a left-sided spur contacting the left inferior turbinate.

chronic rhinosinusitis. Additionally, an autoimmune workup was ordered to rule out ANCA-associated vasculitis, given his history of nasal bleeding. However, the suspicion for vasculitis remained low due to the absence of lower respiratory tract symptoms and preserved renal function without hematuria.

Despite treatment with antibiotics and steroids, the patient's symptoms remained unresponsive. An immunological workup (Table 1) revealed slightly elevated levels of IgG3 (121 mg/dL) and IgE (131 kU/L). However, Complement levels and IgG1/IgG2/IgG4 were within normal range. Tests for anti-myeloperoxidase antibodies (MPO), anti-proteinase 3 antibody (PR3), P-ANCA, and C-ANCA were negative making a diagnosis of small vessel vasculitis less likely. To further investigate the underlying cause of the patient's symptoms, he underwent functional endoscopic sinus surgery. The procedure involved nasal septal biopsy and submucosal resection of bilateral inferior turbinates. Additionally, bilateral maxillary antrostomy, ethmoidectomy, frontal sinusotomy, and sphenoid sinusotomy were performed. The sinus contents were removed, and steroid impregnated stents were placed in the bilateral nasal cavities. Intraoperative findings revealed friable and inflamed mucosa throughout

Table 1. Laboratory diagnostics.

Parameters	Normal range	Result
ESR	0–30 mm/h	12 mm/h
CRP	0–10 mg/dL	6 mg/dL
WBC	3.8–10.8 Thousand/uL	12.6 Thousand/uL
Absolute eosinophil count	15–500 cells/uL	164 cells/uL
CRP	0–10 mg/L	6 mg/L
ANA	Negative	Negative
IgG	603–1613 mg/dL	1532 mg/dL
IgG1	248–810 mg/dL	746 mg/dL
IgG2	130–555 mg/dL	521 mg/dL
IgG3	15–102 mg/dL	121 mg/dL
IgG4	2–96 mg/dL	45 mg/dL
IgE	≤ 114 kU/L	131kU/L
Myeloperoxidase ab	0.0–0.9 units	<0.2 units
Proteinase 3 antibodies	0.0–0.9 units	<0.2 units
P-ANCA titer	<1:20	<1:20
C-ANCA titer	<1:20	<1:20
C3 complement	82–185 mg/dL	180 mg/dL
C4 complement	15–53 mg/dL	51 mg/dL

the nasal cavities bilaterally with a granulation tissue along the right caudal septum. Frozen section analysis ruled out malignancy or vasculitis in this tissue. Biopsies were obtained at the site and sent for further analysis.

Following the procedure, the patient experienced ongoing symptoms including pain in his forehead, bilateral nasal cavities, as well as in both eyes. The pain was partially relieved by Ibuprofen 800 mg twice daily and Tylenol 1000 mg twice daily. He also reported excessive tearing from both eyes and intermittent blurring of vision, although he denied any redness in his eyes. Ophthalmologic exam was reported as unremarkable. Subsequently, the pathological examination of the right nasal septal biopsy revealed fibrous tissue with chronic inflammation and thick-walled vessels. The specimens from the right and left maxillary sinus antrostomy showed glandular tissue with chronic inflammation (Fig. 2A). Immunostaining for IgG4 demonstrated a significant presence of IgG4 plasma cells, with up to 60 IgG4 plasma cells per high-powered field (Fig. 2B). In-situ hybridization for Kappa and Lamda indicated a polyclonal population of plasma cells, suggesting IgG4-associated sclerosing disease involving both the bilateral nasal cavities and the eye orbit. Grocott methenamine silver (GMS) stain was negative for fungal forms. The patient denied any shortness of breath or abdominal/urinary symptoms, making the involvement of other organs less likely.

The patient was referred to the rheumatology clinic for further management of his IgG4-RD. Considering that the first-line treatment for IgG4

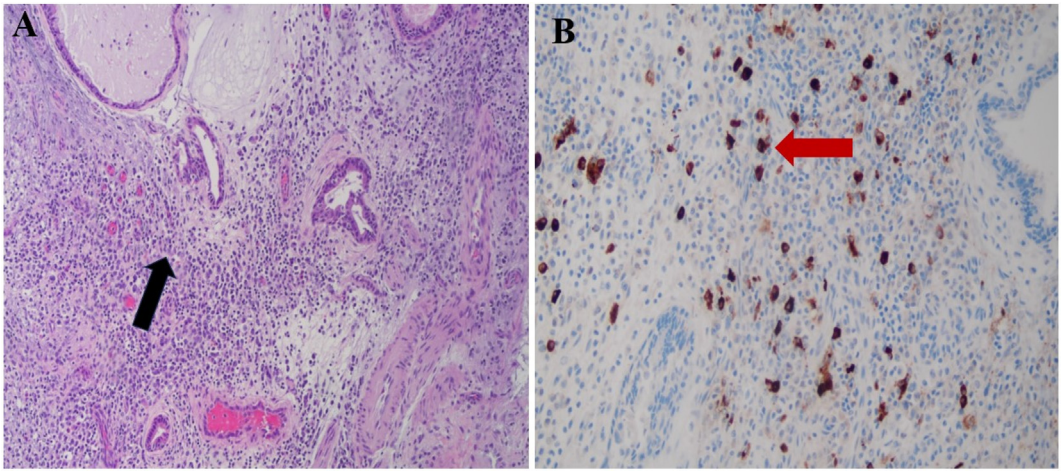

Fig. 2. Histopathology A. Respiratory mucosa with marked inflammatory infiltrate, with prominent plasma cells throughout. (H&E, 100x). B: IgG4-positive plasma cells highlighted on immunostain (IgG4, 200x).

disease involves the use of steroids for a minimum of 4 weeks, it was hypothesized that the patient's prior poor response to steroids may have been due to an insufficient duration of treatment. Therefore, he was initiated on an oral daily dose of prednisone 60 mg for a duration of 1 month. Since DEXA scan is typically recommended if a patient has been on Prednisone at a dosage of more than 5 mg for one month or longer,[9] we did not pursue a DEXA scan. Additionally, our plan was to order a tuberculosis test during the follow-up visit if the patient requires steroids for more than one month or if there is a consideration to initiate any other immunosuppressant. He was up-to-date with all the recommended vaccinations.

At 1 month follow-up, despite completing a full course of steroids, the patient's sinonasal symptoms did not improve. Therefore, a tuberculosis test was conducted to initiate rituximab therapy. The test revealed that the patient had latent tuberculosis. After treating the latent tuberculosis with once weekly isoniazid and rifapentine for 3 months, the patient underwent induction with two courses of rituximab infusion, 1000 mg spaced 2 weeks apart. At the 1-month follow-up appointment, there was a slight improvement in the patient's eye symptoms and nasal pain. He was then started on maintenance rituximab at a dosage of 500 mg every 3 months. It has been nearly 2 months since he received his first maintenance dose of rituximab. While his orbital and nasal pain, along with nasal dryness, have significantly improved, there is still a presence of minimal nasal crustings. Our plan is to continue with the 3-monthly rituximab regimen until his symptoms are entirely resolved, with the intention of gradually extending the dosing interval to 6 months, ultimately aiming to discontinue it.

3. Discussion

IgG4-RD is a chronic immune-mediated condition characterized by tumefactive lesions, fibrosis, and the presence of a polyclonal infiltrate enriched with IgG4+ plasma cells in various organ systems, excluding synovial tissue.[1,2] It was initially reported in 2001 and officially named in 2010.[10] The estimated incidence of IgG4-RD in the US between 2015 and 2019 was approximately 1.41 per 100,000 person-years, with a period prevalence of 0.003%.[1] However, the actual prevalence is likely higher due to the relatively recent recognition of this disease entity.[1]

Autoimmunity has been proposed as the primary underlying cause of IgG4-related disease, although an allergic etiology is also considered due to observed cytokine expression patterns and the frequent association with allergic predisposition.[11] Previous studies have suggested the involvement of CD4+ T-cell subsets, particularly a Th2-dominant reaction, in the disease's pathogenesis.[10] Recently, CD4+ cytotoxic T lymphocytes (CTLs) have been identified as the predominant CD4+ T-cell subset in both affected tissues and circulation.[6] These CD4+ CTLs secrete fibrosis-promoting cytokines like IL-1β, TGF-β1, and IFN-γ, as well as cytolytic molecules such as perforin and granzymes A and B.[6]

IgG4-RD can manifest as either a localized involvement in a single organ or as a multicentric disease affecting multiple organs (Table 2).[7] Sinonasal involvement in IgG4-RD is uncommon and is more prevalent among older males.[3] Clinical and histopathological features of sinonasal localized IgG4-related disease can resemble other conditions such as ANCA-associated vasculitis, cutaneous plasmacytosis, rhinosinusitis, sarcoidosis, Sjögren's syndrome, and Castleman disease.[4] In our case, the patient initially showed clinical features matching chronic rhinosinusitis, including persistent nasal congestion, nasal pain, and excessive nasal crusts. This was confirmed by the radiological findings of thickened sinus lining. Sjogren's syndrome was also considered due to persistent nasal dryness, although the patient denied dry eyes or mouth. ANCA-associated vasculitis was suspected when the patient began experiencing bloody nasal discharge, but there were no signs of kidney or lung complications.

Definite diagnosis is critical as treatments for IgG4-RD and other diseases that mimic it differ.[12] While serum IgG4 levels may be suggestive, a definitive histological diagnosis is necessary to confirm IgG4-RD and rule out similar conditions.[7] The sensitivity of IgG4 levels in diagnosing IgG4-related disease varies depending on the assay used, the number of affected organs, and possibly the patient's geographic origin.[4] About 40% of biopsy-proven IgG4-related disease patients have normal serum IgG4 concentrations.[13] Elevated serum IgG4 levels can also be found in other rheumatological conditions like Churg–Strauss syndrome, multicentric Castleman's disease, and eosinophilic disorders.[3] Radiographic studies are often used for evaluation, but no specific features are highly sensitive or specific for IgG4-RD.[3] Typical radiologic findings include well-defined soft-tissue lesions with homogeneous attenuation on CT and signal intensity on MRI.[4] Histopathologically, IgG4-RD is characterized by a lymphoplasmacytic infiltrate with abundant IgG4-positive plasma cells (>10 IgG4+ plasma cells/high power field or a ratio of IgG4+/

Table 2. Manifestations of IgG4 related disease by organ system.[1]

A. Orbit	**B. Lacrimal and salivary glands**
1. Orbital pseudotumor	1. Mikulicz disease
	2. Kuttner tumor
C. CNS	**D. Upper airways**
1. Hypophysitis	1. Allergy and atopy
2. Hypertrophic pachymeningitis	2. Nasal polyp
	3. Eosinophilic angicentric fibrosis
E. Thorax and mediastinum	**F. Cardiovascular**
1. Asthma	1. Constrictive pericarditis
2. Interstitial pneumonitis	2. Coronary arteritis
3. Inflammatory pseudotumor (Lung, rarely breast)	3. Peri- aortitis
4. Tracheal stenosis	
5. Pleural disease	
6. Mediastinal fibrosis	
G. Renal	**H. Gastrointestinal and hepatobiliary**
1. Membranous glomerulonephropathy	1. Autoimmune pancreatitis
2. Tubulointerstitial nephritis	2. Sclerosing cholangitis/cholecystitis
3. Obstructive uropathy due to retroperitoneal fibrosis	3. Gastritis
	4. Inflammatory mesenteritis
4. Pyelitis	
I. Skin	**J. Thyoid**
Erythematous papules	Reidels thyroiditis
K. Lymphatic and hematopoetic tissue	**L. Others**
1. Lymphadenopathy	Painful neuropathy due to perineural infitrates or retroperitoneal fibrosis
2.Polyclonal hypergammaglobulinemia	

IgG + cells >40%), storiform fibrosis, and obliterative phlebitis,[6,7,14] as seen in our patient.

Awareness of IgG4-related disease is crucial because it is a treatable disorder.[5] Glucocorticoids are the primary treatment for inducing remission in all untreated patients, with a recommended initial dose of oral prednisolone of 0.6 mg/kg/day, administered for 2–4 weeks and then gradually tapered over 2–3 months.[8] The choice of maintenance therapy varies and includes agents such as rituximab, azathioprine, mycophenolate mofetil, methotrexate, 6-mercaptopurine, tacrolimus, and cyclophosphamide, but there is no clear consensus on their efficacy.[4] For relapsed cases, re-administration or an increased steroid dose can be effective, but the addition of immunomodulatory drugs should be considered.[8] Surgical debulking is often necessary, especially for larger or fibrotic lesions.[3] In our case, a two-week course of steroids for presumed chronic rhinosinusitis did not improve symptoms, leading to endoscopic sinus surgery with histopathology confirming IgG4-related disease.

Untreated IgG4-related disease results in destructive lesions, organ failure, and tumor-like growth.[15] In the head and neck region, IgG4-RD lesions typically expand slowly and are associated with bone remodeling with either erosion or sclerosis.[3] Short-term outcomes of steroid therapy for most IgG4-RD patients are favorable in terms of clinical and functional aspects.[8] However, long-term outcomes are uncertain due to factors like relapse, fibrosis development, and potential malignancy.[8] While the association is not fully understood, there is a higher incidence of cancer within three years of IgG4-RD diagnosis compared to the general population, necessitating careful monitoring during follow-up.[16]

4. Conclusion

Differentiating between IgG4-RD and conditions that mimic its features presents a significant challenge. A strong clinical suspicion is necessary to consider IgG4-RD as a potential diagnosis for sinonasal masses, prompting the need for thorough histological and immunohistochemical investigations early in evaluation to ensure accurate diagnosis.

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Conflict of interest

We do not have any conflict of interest.

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