Eosinophilic Sialodochitis: A Rare Comorbidity of Severe Asthma

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J Investig Allergol Clin Immunol 2023; Vol. 33(2): 139-140
doi: 10.18176/jiaci.0817

Key words: Sialodochitis. Eosinophils. Asthma. Comorbidity. Benralizumab.

Palabras clave: Sialodoquitis. Eosinófilos. Asma. Comorbilidad. Benralizumab.

Diseases of the parotid gland vary widely, the most frequent being obstructive sialadenitis, which can be caused by mucus plugs, salivary stones, or anatomic anomalies, although in some cases the cause remains unclear [1-2].

The relationship between recurrent swelling of the parotid gland and mucus plugs containing leukocytes and Charcot–Leyden crystals was first described in 1876 by Kussmaul [3]. Since then, similar cases, also involving eosinophilia or high serum IgE levels, have been diagnosed as "allergic parotitis" or "eosinophilic sialodochitis" [4-6,8].

We report the case of an 80-year-old woman with severe persistent eosinophilic asthma, chronic rhinosinusitis with nasal polyps with good tolerance to nonsteroidal anti-inflammatory drugs, bronchiectasis, allergic bronchopulmonary aspergillosis, and eosinophilic esophagitis. She was initially treated with omalizumab for 2 periods (2009-2013 and 2016-2021).

In the last 25 years, she has experienced countless episodes of bilateral parotid gland swelling. These were initially mild and self-limiting but became progressively worse in intensity and frequency over the years, affecting her quality of life. The episodes were not related to a food or drug. She noticed that the oral corticosteroids (OCS) she took for asthma exacerbations not only improved the exacerbations, but also reduced the number of parotiditis episodes. Therefore, she started taking short courses of OCS solely to treat parotiditis, as her asthma control improved significantly while receiving omalizumab.

She has been evaluated by many specialists. Below, we summarize the investigations performed.

Computed tomography of the parotid glands showed no sialolithiasis, lymphadenopathy, or other organ involvement. The cervical lymph nodes were not enlarged.

Given the recurrent and alternating additional symptoms in response to OCS and xerostomia, the patient was referred to the systemic autoimmune diseases department with an initial suspected diagnosis of Sjögren syndrome. Results for ANA, Anti-Ro/La, Ro52, and ANCA were all negative.

Eye tests and parotid scintigraphy ruled out keratoconjunctivitis sicca, and scintigraphy revealed moderate-to-severe dysfunction (grade 3), with a marked decrease in salivary gland uptake and delayed excretion.

Given the clinical and analytical discrepancy, the study was expanded with a parotid magnetic resonance scan, which showed moderate hypertrophy, fatty infiltration on both parotid glands, and diffuse minimal enhancement with dilatation of the parotid ducts, all compatible with "chronic parotitis".

Minor salivary gland biopsy revealed nonspecific chronic sialadenitis. There was no histological evidence of Sjögren syndrome, amyloid deposit, or sarcoid granulomas. Immunohistochemistry for IgG4 was negative. The periductal infiltration was lymphocytic, and eosinophils were not observed, probably owing to the ongoing therapy with OCS.

Throughout the process, periodic analyses showed elevated total IgE levels ranging between 368 and 3017 kU/L, peripheral eosinophilia between 130 and 1320/mm^3, and normal IgG, IgA, IgM, and IgG4. Testing for the fusion gene *FIP1L1-PDGFRA* was negative, as was the ANCA titer. This, together with the absence of other manifestations suggestive of vasculitis, also ruled out the diagnosis of eosinophilic granulomatosis with polyangiitis.

With the suspicion that the inflammation responsible for recurrent parotiditis was due to eosinophilia, a cytological analysis of the parotid secretion was performed. Fine needle aspiration cytology of the salivary glands revealed normal ductal epithelium cells with mild inflammation, macrophages, and eosinophilic granulocytes. As eosinophils were the only inflammatory cell present, an intraductal eosinophilic inflammatory process was suspected. Following these analyses, the patient was diagnosed with eosinophilic sialodochitis.

The patient initially responded to omalizumab. OCS for asthma exacerbations were suspended, thus triggering multiple episodes of parotid gland involvement and forcing her to resort to OCS at least twice per month. Given the good clinical control of asthma and the need to take recurrent OCS cycles for episodes of parotid swelling, it was decided to suspend omalizumab in 2013; the asthma was controlled for 2 years with an inhaled corticosteroid, a long-acting β-agonist, and a long-acting muscarinic antagonist. However, after the progressive loss of asthma control led to the need for continued OCS therapy in 2016, omalizumab was restarted. The patient's

Table. Diagnostic Criteria Proposed by Baer et al [7][a]

Number	Criterion	Fulfilled in the present case
1	Recurrent paroxysmal swelling of the major salivary glands	x
2	Salivary duct mucus plugs containing numerous eosinophils	x
3	Peripheral blood eosinophilia and elevated IgE level	x
4	Associated atopic disease	x
5	Ductal dilatation and occasional focal narrowing of the major salivary gland ducts	x
6	Periductal eosinophil inflammation and fibrosis with associated reactive ductal epithelial cells	
7	Failure to satisfy the diagnostic criteria of IgG4-related disease	x

[a]Mandatory features of eosinophilic sialodochitis include criteria 1 and 2 or criteria 1, 6, and 7.

disease remained under control until 2020, when omalizumab was suspended again due to poor control.

We decided to switch to benralizumab in 2021 with the dual objective of controlling asthma and achieving zero eosinophils in blood and tissue. We hoped that this would prevent further episodes of eosinophilic parotiditis. Currently, after 10 months of treatment with benralizumab, sialodochitis is controlled, with only 1 episode during the first month of treatment, since when the patient has remained asymptomatic. In addition, her asthma is well controlled, with a peripheral blood eosinophil count of 0/μL.

Recurrent eosinophilic sialodochitis is considered a rare disease. Only 59 cases have been documented in the literature to date, and the majority are from Japan [7]. The disease is characterized by repeated episodes of inflammation of the salivary glands that improve spontaneously with massage of the glands or systemic corticosteroids. The etiology of eosinophilic sialodochitis is still not fully known, although, the most widely accepted hypothesis is that it results from an allergic process with intraductal eosinophilia [4-6].

Interestingly, the microscopic findings for sialodochitis are very similar to those for bronchial asthma: ductal involvement with preserved parenchyma, mucus plugs, saliva/sputum cytology showing eosinophils and/or Charcot–Leyden crystals, submucosal T-lymphocyte infiltrate and/or periductal eosinophilic inflammation on biopsy, periductal fibrosis, and ductal dilatation.

The clinical history and histopathological and radiological findings we report here are very similar to those described in the literature. In addition, the patient fulfilled the current diagnostic criteria for eosinophilic sialodochitis, as shown in the Table.

As in the present case, the differential diagnosis must be made with IgG4-related disease, Kimura disease, angiolymphoid hyperplasia, eosinophilic granulomatosis with polyangiitis, and hypereosinophilic syndrome.

We present a case of eosinophilic sialodochitis that was successfully treated with benralizumab. Eosinophilic sialodochitis is an infrequent disease that has classically been associated with allergy and/or eosinophilia, which we now refer to as type 2 inflammation. It should be considered in patients with type 2 inflammation who show suggestive symptoms. Benralizumab is a therapeutic option in these cases owing to its absolute antieosinophilic action. It can be prescribed off-label in the absence of severe eosinophilic asthma, its currently approved indication.

Funding

The authors declare that no funding was received for the present study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Lee LI, Pawar RR, Whitley S, Makdissi J. Incidence of different causes of benign obstruction of the salivary glands: retrospective analysis of 493 cases using fluoroscopy and digital subtraction sialography. Br J Oral Maxillofac Surg. 2015;53:54-7.
2. Zhu WX, Chen Y, Liu DG, Yu GY. Eosinophilic Sialodochitis: A Type of Chronic Obstructive Sialadenitis Related to Allergy. Laryngoscope. 2021 Mar;131(3):E800-E806.
3. Kussmaul I. Recurrent salivary gland tumor due to chronic fibrotic inflammation of the Stensen's ducts [Anfallsweise auftertende Speichelgeschwulst in Folge von chronischer eitrig-fibrinöser Entzündung des Stenonschen Ganges]. Berlin Klin Wschr. 1879;15:209-11.
4. Waldbott G, Shea J. Allergic parotitis. J Allergy. 1947;18(1):51-4.
5. Chikamatsu K, Shino M, Fukuda Y, Sakakura K, Furuya N. Recurring bilateral parotid gland swelling: two cases of sialodochitis fibrinosa. J Laryngol Otol. 2006 Apr;120(4):330-3. doi: 10.1017/S0022215106000296. PMID: 16623980.
6. Harkness P. Submandibular salivary disease: a proposed allergic aetiology. J Laryngol Otol. 1995;109:66-7.
7. Baer AN, Okuhama A, Eisele DW, Tversky JR, Gniadek TJ. Eosinophilic sialodochitis: redefinition of 'allergic parotitis' and 'sialodochitis fibrinosa'. Oral Dis. 2017;23(7):840-8.
8. Carey B, O'Neill N, Brown J, Escudier M, Hullah E, Beneng K, et al. Eosinophilic sialodochitis: An emerging atopic condition. Oral Dis. 2022 Apr;28(3):648-56. doi: 10.1111/odi.13821. Epub 2021 Mar 12. PMID: 33660371.

Manuscript received December 20, 2021; accepted for publication April 28, 2022.

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