Eosinophilic sialodochitis: a rare comorbidity of severe asthma

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The pathology of the parotid gland (PG) can be very varied; the most frequent disease is obstructive sialadenitis which can be caused by mucus plugs, salivary stones, or anatomic anomalies, although in some cases the cause remains unclear [1-2].

In 1876 Kussmaul described, for the first time, the relationship between recurrent swelling of PG and mucus plugs that contained leukocytes and Charcot–Leyden crystals [3]. Since then, similar cases with the addition of eosinophilia or high serum IgE have been diagnosed as "allergic parotitis" or "eosinophilic sialodochitis (ES)" [4-6,8].

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

In this context, she has presented in the last 25 years countless episodes of bilateral PG swelling, which were initially mild and self-limited but got progressively worse in intensity and frequency over the years, affecting her quality of life. Those episodes were not related to any food or drug. She noticed that when using oral corticosteroids (OCS) to treat her asthma exacerbations, they also improved and the number of parotiditis

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episodes reduced. Therefore, she started taking short courses of OCS solely to treat these episodes, as her asthma control improved significantly while receiving Omalizumab.

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

Computerized tomography (CT) of the parotid glands showed no sialolithiasis, lymphadenopathy or other organicity. No cervical adenopathies.

Given the recurrent and alternating additional symptoms in response to OCS, as well as dry mouth sensation, she was referred to the Systemic Autoimmune Diseases service, with an initial suspected diagnosis of probable Sjögren's syndrome. ANA, Anti-Ro/La, Ro52, ANCA were all negative.

Eye tests and parotid scintigraphy: eye dryness was ruled out, and the scintigraphy showed moderate to severe dysfunction, grade III, with marked decrease in salivary gland uptake and delayed excretion.

Given the clinical and analytical discrepancy, the study was expanded with a parotid MRI that showed moderate hypertrophy, fatty infiltration on both PGs, diffuse minimal enhancement with dilatation of the parotid ducts, all compatible with “chronic parotitis”. Also, a minor salivary gland biopsy was performed, where nonspecific chronic sialadenitis was observed. There was no histological evidence of Sjögren's syndrome, deposits of amyloid substance or sarcoid granulomas. Immunohistochemistry for IgG4 was negative. The periductal infiltration was lymphocytic, and eosinophils were not observed, probably due to the recurrent intake of OCS.

Throughout the whole process, periodic control analyzes showed elevated total IgE levels, ranging between 368-3017 KU/L, peripheral eosinophilia between 130-1320 cells/ mm3, and normal IgG, IgA, IgM and IgG4. The fusion gene FIP1L1-PDGFRA was

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negative, as were ANCA. This, together with the absence of other manifestations suggestive of vasculitis, also ruled out the diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA).

With the suspicion that the inflammation responsible for the recurrent parotiditis was due to eosinophils, a cytological analysis of the parotid secretion was performed. Saliva cytology showed normal ductal epithelium cells with mild inflammation, macrophages and eosinophilic granulocytes. As eosinophils were the only inflammatory cell present, a pathological diagnostic value of an intraductal eosinophilic inflammatory process was offered. Following these analyzes, a diagnosis of eosinophilic sialodochitis was finally reached.

The patient initially responded to Omalizumab. OCS for asthma exacerbations were suspended, which triggered multiple episodes of PG, forcing her to resort to OCS at least twice/month. Due to good clinical control of her asthma and the need to take recurrent OCS cycles for episodes of parotid swelling, it was decided to suspend Omalizumab in 2013, and the asthma was controlled for 2 years with inhaled corticosteroid (ICS), long-acting β-agonist (LABA) and long-acting muscarinic antagonist (LAMA). However, after the progressive loss of asthma control led to the need for continued OCS in 2016, Omalizumab was restarted and control was achieved until 2020, when it was suspended again due to poor control.

We decided to switch to benralizumab in 2021 for a dual purpose: asthma control and 0 blood and tissue eosinophils, which hopefully would lead to 0 episodes of eosinophilic parotiditis. Currently, after 10 months of treatment with benralizumab, sialodochitis is controlled, with only one episode during the first month of treatment, after which she has

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remained asymptomatic to date. Also, her asthma is well controlled and 0 eosinophils in peripheral blood have been achieved.

Recurrent eosinophilic sialodochitis is considered a rare disease: there are 59 cases documented in the literature to date, the majority of which are in Japan [7]. It 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 this pathology is still not fully known; however, the most accepted hypothesis is that it derives from an allergic process with intraductal eosinophilia [4-6].

The findings of sialodochitis at a microscopic level are curiously very similar to those found in bronchial asthma: both affect the ducts and preserve the parenchyma; there are mucus plugs, or saliva/sputum cytology, containing eosinophils and/or Charcot-Leyden crystals; biopsies show submucosal T lymphocytic infiltrate and/or periductal eosinophilic inflammation, periductal fibrosis and ductal dilatation.

The clinical history as well as histopathological and radiological findings in our patient are very similar to those described in the literature, and she fulfills the current diagnostic criteria for ES, as shown in Table 1.

As with our patient, the differential diagnosis must be made with the following [7]:

• IgG4-related disease

• Kimura disease

• angiolymphoid hyperplasia

• eosinophilic granulomatosis with polyangiitis

• hypereosinophilic syndrome.

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Thus, we present a case of eosinophilic sialodochitis, an infrequent pathology classically related to allergy and/or eosinophilia, with what we now call Type 2 (T2) inflammation, successfully treated with benralizumab. It should be considered in patients with T2 inflammation who show suggestive symptomatology. Benralizumab is a therapeutic option in these cases (off-label if there is no severe eosinophilic asthma, its currently approved indication) due to its absolute anti-eosinophilic action.

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Conflicts of Interest

All authors declare that they have no conflicts of interest.

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Table 1. Diagnostic criteria proposed by Baer et al [6].		
Number	Criteria	Fullfilled by our pacient
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 epitelial cells	
7	Failure to satisfy the diagnostic criteria of IgG4-related disease.	x
Mandatory features of eosinophilic sialodochitis include criteria 1 and 2 or criteria 1,6 and 7.		

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