Iannuzzi L, et al., J Otolaryng Head Neck Surg 2024, 10: 091
DOI: 10.24966/OHNS-010X/100091

HSOA Journal of Otolaryngology, Head and Neck Surgery

Case Report

Pharyngeal Foreign Body Misdiagnosed as a Manifestation of Dupilumab-Induced Hypereosinophilia in a Patient with Chronic Rhinosinusitis with Nasal Polyps

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Abstract

Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) is a well-defined entity. Dupilumab was the first authorized drug for effective treatment of CRSwNP. Nevertheless, it may lead to side effects including an increase in the absolute eosinophil count.

In this paper we report a case of a pharyngeal eosinophilic finding in a patient in taking Dupilumab for CRSwNP. The patient had already undergone several surgical interventions for CRSwNP, yet had persistent nasal obstruction and discharge, thus he started Dupilumab therapy. In the following months he developed a hypereosinophilic syndrome that was treated and resolved suspending temporarily Dupilumab administration and starting a systemic steroid course.

After multidisciplinary consensus, it was decided to not permanently discontinue biological treatment and the patient restarted the therapy with Dupilumab.

At 2-year follow-up the absolute eosinophil count was normal with a noticeable improvement of nasal and systemic symptoms but a neoplasm was spotted over a rhino-oro-pharyngeal bulging. Biopsy showed no malignancies but infiltration made of lymphoplasmacytic cells and neutrophils with plenty of eosinophils. Initially the lesion was thought to be Dupilumab induced, as the hypereosinophilia.

The progressive growth of the lesion and the presence of a massive neutrophilic infiltrate made us doubt about our first hypothesis. A CT scan and a subsequent surgical exploration finally revealed that a retained fish bone foreign body was responsible for the bulging.

Dupilumab treatment is among the newest and most effective and safe treatments for CRSwNP and, as it may lead to serious side effects, close follow-up of patients is essential to highlight and treat them.

Introduction

Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) is a well-defined clinical entity in which chronic type-2 inflammation of the mucosa plays a major role [1,2]. In recent year's pharmaceutical research focused on targeted biologic therapies, which have demonstrated their efficacy in controlling the disease and improving the quality of life in these patients. Dupilumab is a monoclonal antibody that targets against the IL-4 receptor alpha and was the first authorized biologic for the treatment of CRSwNP, showing good control of polyp and nasal symptoms [3]. Despite its proven efficacy and global safety, Dupilumab has been associated to several side effects, including an increase in the absolute eosinophil count (AEC, normal range <0.5x10^9/L) [4]. It can be defined as blood eosinophilia (BE, 0.5-1.5×10^9/L), hypereosinophilia (HE, ≥1.5×10^9/L without organ involvement) or hypereosinophilic syndrome (HES, ≥1.5×10^9/L associated with eosinophil-mediated organ damage) [3]. In this paper we report the case of a patient in treatment with Dupilumab for CRSwNP, who developed transient HE and a pharyngeal eosinophilic granuloma. CT scan and subsequent surgical exploration revealed an unexpected finding.

Case Report

A 53-year-old male patient first referred to our center in February 2021 with a history of NSAID-ERD (NonSteroidal Anti-Inflammatory Drug Exacerbated Respiratory Disease) and five previous sinus surgeries in the last twenty years for recurrent CRSwNP. He still complained of nasal obstruction, anterior rhinorrhea and anosmia and scored 52 points at SNOT-22 questionnaire. At endoscopic assessment a Nasal Polyp Score (NPS) of 7 (4+3) was estimated. Complete Blood Count (CBC) showed a normal AEC (0.5×10^9/L). Hence, since the patient met both the criteria established by EPOS2020 [1], and Italian Pharmacology Agency (AIFA), injections with Dupilumab were started in February 2021. The patient was addressed to routine follow-up schedule with the instruction to immediately refer to our center in the event of any complication.

The first semester of treatment was marked by the progressive appearance of systemic symptoms with recurring night fever,

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Citation: Iannuzzi L, Curatoli L, Pontillo V, De Candia N, Marzullo A, et al. (2024) Pharyngeal Foreign Body Misdiagnosed as a Manifestation of Dupilumab-Induced Hypereosinophilia in a Patient with Chronic Rhinosinusitis with Nasal Polyps. J Otolaryng Head Neck Surg 10: 091.

Received: January 29, 2024; **Accepted:** February 08, 2024; **Published:** February 15, 2024

arthralgias and myalgias. CBC showed a severe and progressive HE (AEC 5.18×10^9/L in June 2021, 7.1×10^9/L in November 2021).

The Dupilumab administration was temporarily suspended and a long-term systemic steroid course was started with progressive resolution of the symptoms and normalization of the AEC at serial close laboratory tests. A complete work-up was performed in order to exclude hematological malignancies, immunologic disease or eosinophil-mediated systemic organ involvement. Thus, after multidisciplinary consensus, it was decided not to permanently discontinue treatment with Dupilumab.

The patient attended a follow-up examination every 3 months. At 2-year follow-up AEC was normal (0.5x10^9/L), with no complaint of systemic symptoms, NPS was 0+0, and SNOT-22 scored 15 points. However, flexible endoscopic nasopharyngoscopy showed a bulging on the posterior wall of the naso-oro-pharyngeal transition zone, covered by a multi-lobulated and hyperaemic mucosal lesion (Figure 1). Prompt biopsy for histological examination was performed, finding a normal-appearing pharyngeal mucosa with diffuse lymphoplasmacytic and neutrophilic infiltration and extensive presence of intra-capillary eosinophils (Figure 2). The first hypothesis related the origin of the lesion with the recent history of HE. Thus, Dupilumab was initially suspended and replaced with a Short-Term Scheme of Oral (OCS) and Intranasal Corticosteroids (INCS). Despite this, after 2 months of close observation, the lesion was slightly increased in size. Hence, a CT scan was performed. Surprisingly, it showed a reactive granuloma-like reaction surrounding a retained Foreign Body (FB) of around 27x1x1mm, presumably a fish bone (Figure 3). Surgical exploration under general anesthesia confirmed the suspicion: A 25mm long fish bone was removed from the submucosal tissues (Figure 4).

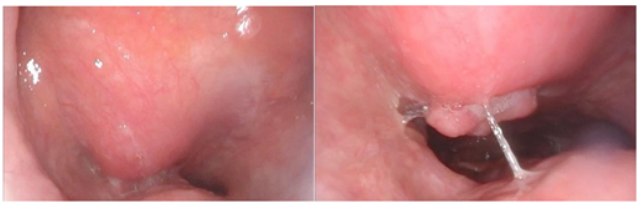

Figure 1: Flexible fiberoptic image of the rhino-pharyngeal bulging frontal view.

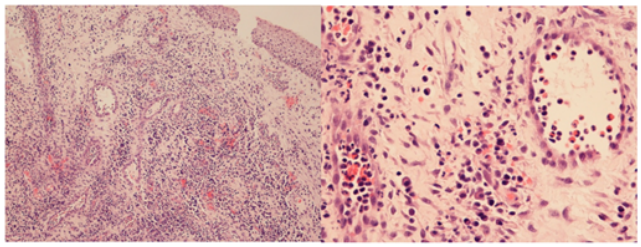

Figure 2: Histological detail at 10x and 40x enlargement of the naso-oro-pharyngeal biopsy.

After one month, as the pharyngeal bulging disappeared and the AEC was normal (0.56x10^9/L), the patient resumed Dupilumab treatment.

At last follow-up (6 months from the surgery) no signs of pharyngeal disease were detected, AEC was normal while NPS (0+0) and SNOT-22 (15 points) confirmed the efficacy of the treatment on CRSwNP.

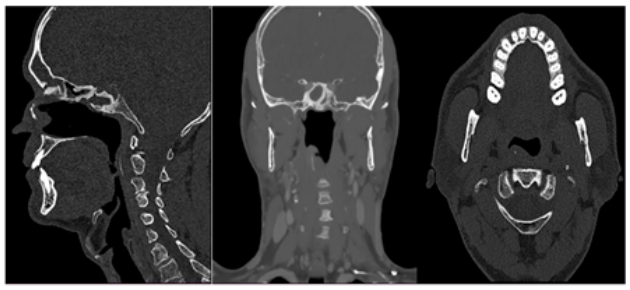

Figure 3: CT scans in sagittal, coronal and axial projection of the fish bone.

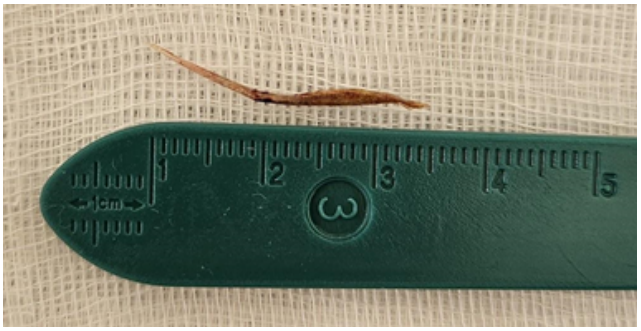

Figure 4: Post-surgical photo of the fish bone extracted.

Discussion

Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) is a well-defined entity resulting from a multifactorial-based inflammation state in which interleukins (IL) 4, 5 and 13 are upregulated leading to polypoid transformation of the mucosa and development of nasal symptoms, such as obstruction, hyposmia or anosmia, rhinorrhea. This is recognized as Type-2 inflammation phenotype [1,2,4]. In recent years new biological therapies have been widely used as they are effectively controlling the disease and improving quality of life in these patients. Dupilumab was the first authorized biologic in treatment of CRSwNP, showing a satisfying control of polyp size and nasal symptoms, via the blockage of the Type-2 inflammation pathway specifically acting on IL-4 and IL-13 [3]. However, some mild to moderate side effects have been recorded in the first years of employment: nasopharyngitis, epistaxis, erythema at injection site, headache [5], and HE [6,7]. This is a potentially life-threatening condition, usually defined as an AEC ≥1.5x10^9, that can be complicated by secondary organ involvement, thus defining a HES [7]. The pathogenesis of HE can recognize several pathways depending on the underlying condition, such as hematological malignancies, parasites infection, allergic disease, vasculitis, or drug-induced mechanisms [8].

In the case of Dupilumab, the increase in AEC is thought to be attributable to the inhibition of specific adhesion molecules leading to the reduction of the eosinophilic migration into tissues [9,10].

Even though the increase is often transient, it requires close monitoring as internal organs may be involved or damaged [11].

In this paper we present a case of incidental finding of a pharyngeal eosinophilic lesion in a patient with a recent history of Dupilumab-induced HE. The first instinct led us to think to a rare presentation in the vast and undefined spectrum of manifestations of HE [12].

However, after a literature review, no similar cases were identified. Moreover, the progressive growth of the lesion and the presence of a massive neutrophilic infiltrate made us doubt about our first hypothesis. A CT scan and a subsequent surgical exploration finally revealed that a retained fish bone foreign body was responsible for the bulging.

Dupilumab treatment is among the newest and most effective and safe treatments for CRSwNP and, as it may lead to serious side effects, close follow-up of patients is essential to highlight and treat them.

Conclusion

Dupilumab and other biologics represent the newest and most fascinating prospectives of pharmacological research in ENT. Their long-term effectiveness and safeness in CRSwNP patients are mainly undiscovered and the possibility to deal with new and undescribed side effects is a possibility. However, old medical principles have not to be forgotten. In the presented case we show how a retained pharyngeal foreign body was initially misdiagnosed as a Dupilumab-induced lesion.

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