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REVIEW

Severe hypereosinophilia in a patient treated with dupilumab and shift to mepolizumab: the importance of multidisciplinary management. A case report and literature review

Sara Munari[1,2], Giulia Ciotti[3], Walter Cestaro[1,2], Lorenzo Corsi[2,4], Silvia Tonin[2,4], Andrea Ballarin[4], Ariel Floriani[4], Cristina Dartora[4], Annamaria Bosi[4], Matteo Tacconi[4], Francesco Gialdini[1], Michele Gottardi[3], Francesco Menzella[2,4]

[1]Otolaryngology Unit, S. Valentino Hospital, Montebelluna (TV), AULSS2 Marca Trevigiana, Italy; [2]Pulmonology and Otolaryngology Multidisciplinary Unit, S. Valentino Hospital, Montebelluna (TV), AULSS2 Marca Trevigiana, Italy; [3]Onco Hematology, Department of Oncology, Veneto Institute of Oncology IOV – IRCCS, Padua, Italy; [4]Pulmonology Unit, S. Valentino Hospital, Montebelluna (TV), AULSS2 Marca Trevigiana, Italy

Abstract

Type 2 inflammation is a heterogeneous condition due to the complex activation of different immunological pathways. Rapid progress in research to evaluate the efficacy of biologics for chronic rhinosinusitis with nasal polyps and asthma has led to the availability of effective therapeutic options. These drugs are safe, but temporary iatrogenic hypereosinophilia may sometimes be associated with clinical symptoms or organ damage. Here, we describe a case of severe hypereosinophilia in a patient with chronic rhinosinusitis with nasal polyps and asthma treated with dupilumab and a subsequent therapeutic shift to mepolizumab that led to maintenance of symptom control and concomitant normalization of blood eosinophil count.

Keywords: asthma, chronic rhinosinusitis with nasal polyps, clonal haematopoiesis, dupilumab, hypereosinophilia, mepolizumab.

Citation

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Introduction

Type 2 (T2) inflammation is a heterogeneous condition maintained and amplified by synergistic interactions between the innate and adaptive branches of the immune system, resulting in tissue infiltration of eosinophils, mast cells, and basophils and production of numerous pro-inflammatory cytokines, including IL-4, IL-13 and IL-5.[1] It can lead to the development, persistence and amplification of a predominant eosinophilic endotype that may be associated with an immunoglobulin E (IgE)-mediated allergic phenotype. However, the mechanisms underlying T2 inflammation-mediated diseases are often multiple pathways with multi-signal activation and sometimes the coexistence of endotypes. This leads to diverse and varied phenotypic presentations and poses additional complexities in the management and outcomes of these patients.

Chronic rhinosinusitis with nasal polyps (CRSwNP) affects 1–2.6% of the general population,[2] and T2 inflammation represents the dominant driver in approximately 80% of cases in Western countries. Up to 65% of patients with CRSwNP have comorbid asthma, which tends to be associated with more severe sinus and lung disease, high nasal polyp scores, recurrence of polyps after surgery, frequent need for systemic corticosteroids, and poor asthma control.[3] Allergic rhinitis also represents a common comorbidity, with the prevalence of allergic sensitization ranging from 50% to 70% amongst these patients.[4]

Rapid progress in research evaluating the efficacy of biologics for refractory CRSwNP has led to the availability of effective therapeutic options. Monoclonal antibodies (mAbs) against IL-4/IL-13 receptor-α (dupilumab), anti-immunoglobulin E (omalizumab) and anti-IL-5

(mepolizumab) are available as treatment biologics for CRSwNP.[5] These agents now have extensive efficacy and safety data, with sporadic adverse events (AEs) that require care and adequate patient assessment before starting therapy. This approach is important not only for achieving better outcomes in the context of precision medicine but also for diagnosing and preventing possible eosinophil disorders, including various pathologies in which eosinophils play a crucial pathophysiological role. Such pathologies can affect any organ and compartment of the body not only the respiratory system. After recruitment in inflamed tissues, eosinophils cause tissue damage by generating oxidative stress through eosinophil peroxidase, altering the architectural organization of the extracellular matrix and stimulating cellular cytotoxicity through granule proteins such as eosinophil cationic protein or antibody-dependent cellular cytotoxicity.[6,7] Many questions remain unanswered. In addition, a better method for identifying the tissue endotype and the development of additional biomarkers predictive of response to biologics, which allow for the selection of suitable patients, are needed for both asthma and CRSwNP, where even less certainty of outcome exists and the choice of the appropriate treatment option is not always easy. The safety profiles of all mAbs have now been more clearly demonstrated, but questions remain on their efficacies in the presence of AEs or biomarker alterations, especially in the case of asymptomatic or symptomatic increased blood eosinophil count (BEC).[8]

In this article, we describe a case of dupilumab-induced severe hypereosinophilia associated with clonal haematopoiesis (CH) that led to the patient's hospitalization, treatment discontinuation and subsequent shift of dupilumab to mepolizumab. The patient's signed consent was not necessary as the data were de-identified so that her identity could not be ascertained in any way.

Case study

A 64-year-old woman who was a retired office worker and former smoker (20 pack/years) with familiarity with eosinophilic CRSwNP visited our clinic for observation. She had been diagnosed with allergic eosinophilic T2 high asthma in 2013 and CRSwNP in 2015 and undergone multiple endoscopic sinus surgeries (most recently in 2019) and polypectomy. In addition, she had been receiving frequent bursts of oral corticosteroid (OCS) therapy (four bursts on average, with prednisone 25 mg for 7–10 days every 12 months). At the time of the first evaluation, biomarker tests revealed a BEC of 1.28×10^9/L and normal levels of antinuclear, antimyositis and antiextractable nuclear antigen antibodies. The serum precipitin assay results for hypersensitivity pneumonitis, *Aspergillus* antigen, serum immunoglobulins (IgA, IgM and IgG) and IgG sub-classes were normal. The radioallergosorbent test result was slightly positive for grass pollen (*Phleum pratense*). Diffuse fine granular cytoplasmic fluorescence (c-ANCA) and perinuclear fluorescence (p-ANCA) tests for the detection of antineutrophil cytoplasmic antibodies (ANCA) were also performed to exclude ANCA-associated vasculitis, with negative results. High-resolution chest computed tomography (CT) revealed no centrilobular nodules, ground-glass opacities or other parenchymal changes. Pulmonary function tests revealed moderate obstruction (forced expiratory volume in 1 sec (FEV_1), 1.91 L, 64% of the predicted value; FEV_1/forced vital capacity, 66%). However, complete bronchial reversibility was achieved after administration of 400 µg of inhaled salbutamol (FEV_1 + 16%).

On nasal endoscopy, we found bilateral massive polyposis, thick eosinophilic mucus and a nasal polyp score (NPS) of 8. The Sino-Nasal Outcome Test-22 (SNOT-22) score was 72. A CT scan demonstrated an almost complete opacification of the paranasal sinuses with a Lund–Mackay CT (LMCT) scan score of 23, and a high-resolution chest CT scan showed normal findings. The patient experienced recurrent asthma exacerbations despite a high dose of inhaled corticosteroid combined with long-acting β2 agonists extra-fine beclomethasone-formoterol at 800/24 µg/day and long-acting muscarinic antagonist tiotropium bromide at 5 µg/day. The previously administered montelukast proved ineffective and was therefore not reintroduced. The patient was also receiving a mometasone furoate nasal spray (100 µg daily). In the previous year, she had two instances of moderate exacerbations of asthma, with an asthma control test (ACT) score of 14, which confirmed poorly controlled asthma. Therefore, given the frequent use of OCS and multi-recurrent CRSwNP, treatment with dupilumab was started on 20 February 2023 at a dose of 600 mg (two 300-mg subcutaneous (SC) injections), followed by 300 mg SC every 2 weeks. Subsequently, asthma control, sense of smell and nasal airflow improved. One month after the first administration, the ACT score increased to 21, the NPS score decreased to 5 and the SNOT-22 score decreased to 45. The LMCT score was 16. Spirometry revealed a FEV_1 of 2.01 L, 84% of the predicted value, which confirmed the rapid improvement of respiratory function. Despite these positive outcomes, 30 days after the first administration of dupilumab, a BEC of 52.7×10^9/L was found. Considering the presence of hypereosinophilia, as a precautionary measure, administration of the anti-IL-4/IL-13 agent was discontinued. One week later, the patient was hospitalized with complaints of diffuse arthralgia, conjunctivitis and dyspnoea. Her troponin level was increased but returned to normal by applying the appropriate control measure. High-dose corticosteroid therapy was performed (high-dose intravenous steroids with 1-g methylprednisolone

administered daily, usually for 3 days and then continuing orally with prednisone 50 mg), which resulted in progressive decalage during hospitalization and resolution of arthralgia and conjunctivitis, and reduced the eosinophil count to 0.91×10^9/L. The serum p-ANCA and c-ANCA titres remained negative, without other diagnostic and classification criteria applied for vasculitis. The high-resolution chest CT scan and echocardiogram showed no abnormalities. Because echocardiography did not show left ventricular systolic dysfunction with wall motion abnormalities, thrombus deposits on the surface of the endocardium or other abnormalities that might raise suspicion of cardiac involvement, the consultant cardiologist had not deemed it necessary to also perform a magnetic resonance imaging (MRI) scan. This was also because the patient had started high-dose intravenous corticosteroid therapy early.

In addition, no faecal parasites were found. Given the presence of hypereosinophilia, tests were performed to exclude primary/clonal forms of eosinophilia. Multi-flow cytometry and T cell receptor (TCR) rearrangement analysis excluded the presence of B and T cell clones. In the peripheral blood assessments for *PDGFRA*, *PDGFRB*, *FGFR1*, *PCM1–JAK2* and *FLT3* gene fusions, no alterations were identified. A myeloid/lymphoid neoplasm with associated eosinophilia and tyrosine kinase gene fusions was excluded. A mutational analysis through next-generation sequencing (NGS) revealed a likely pathogenetic variant on the *DNMT3A* gene (chromosomal position chr2:25467496, exon 14, nucleotide variant c.1579del, amino acid change p(Gln527SerfsTer124) with a variant allele frequency (VAF) of 7.14%). Given the absence of symptoms but increased BEC after tapering of the OCS dose (11.3×10^9/L), administration of mepolizumab 100 mg SC every 4 weeks was started, which elicited progressive responses for both asthma and CRSwNP. We did not choose in the first instance a dose of mepolizumab 300 mg, commonly used in eosinophilic granulomatosis with polyangiitis (EGPA) and hypereosinophilic syndrome (HES), because a diagnosis was not completely clarified in our patient. By Italian National Health Service rules, it is mandatory to have diagnostic certainty in order to obtain authorization to prescribe the 300 mg dosage instead of the 100 mg. Clearly, in case the patient did not achieve a complete response to the lower dosage, we would have requested the option to proceed with mepolizumab 300 mg.

No bone marrow biopsy was performed because it was not considered useful by haematology specialists as the patient was already in a treatment context and her BEC was completely normal. Any histological outcome would have been poorly interpretable and probably distorted but immediate start of mepolizumab therapy was collegially preferred to secure the patient's safety. As per multidisciplinary agreements and with the patient herself, osteomedullary biopsy will be performed if there is a recurrence of hypereosinophilia despite biologic therapy or if there is clinical worsening with evidence of organ damage.

On a multidisciplinary follow-up visit with a pulmonologist and ear, nose and throat specialist after 3 months, the patient showed an NPS score of 0, SNOT-22 score of 13, ACT score of 23 and improvement of hyposmia (Table 1). The BEC was 0.17×10^9/L, and the spirometric values further improved (FEV_1 2.18 L, 98% of the predicted value; FEV_1/forced vital capacity, 78%). Hence, OCS therapy was discontinued and a step-down inhalation therapy was decided by reducing the extra-fine beclomethasone-formoterol dosage to 400/12 µg/day and continuing with tiotropium bromide 5 µg/day. After 6 months of treatment, the CRSwNP parameters were stable without evidence of polyps. The LMCT score further improved to 12 compared with the baseline score of 23. The patient had no asthma exacerbations, with

Table 1. Comparison between dupilumab and mepolizumab outcomes.

Outcomes	Baseline	Dupilumab (first 4 weeks)	Mepolizumab (after 6 months)
NPS	8	5	0
SNOT-22	72	45	13
LMCT	23	16	12
OCS	Four bursts every 12 months	0	0
FEV_1	1.91 L, 64%	2.01 L, 84%	2.30 L, 112%
Asthma exacerbations	2	0	0
ACT	14	21	24

ACT, asthma control test; FEV_1, forced expiratory volume in 1 second; LMCT, Lund–Mackay computed tomography scan score; NPS, Nasal polyp score; OCS, oral corticosteroids; SNOT-22, Sino-Nasal Outcome Test.

an ACT score of 24, and the spirometric values were improved, with a FEV_1 of 2.30 L (112% of the predicted value; Table 1). The BEC was 0.13×10^9/L; thus, OCS therapy was no longer necessary, and tiotropium bromide was discontinued whilst maintaining the remaining therapies at the same doses.

Discussion

The current treatment approaches for CRSwNP include intranasal corticosteroids, a therapeutic course of OCS, and endoscopic sinus surgeries. However, approximately 25–40% of patients will relapse after OCS therapy or adequate sinus surgery, and often need several surgeries in their lifetimes.[9] The introduction and widespread use of biologics have represented a new frontier in the treatment of these conditions. The first to be approved (in 2019) for CRSwNP was dupilumab, a fully human IgG4 mAb directed against the IL-4 and IL-13Rα sub-unit.[10,11] It is currently used in the treatment of various T2 inflammation-related conditions, including severe asthma (SA), atopic dermatitis, and eosinophilic esophagitis and, more recently, eosinophilic inflammation in chronic obstructive pulmonary diseases.[12] It has also been approved for paediatric use, primarily for atopic dermatitis and asthma.[13] In a real-life setting, dupilumab has been shown to be effective in most patients with CRSwNP, with significant decreases in NPS, nasal congestion score and the need for revised surgery or OCS therapy, and increases in quality of life and olfaction.[14] Its effectiveness has also been demonstrated in patients with severe asthma as an add-on maintenance therapy, improving lung function and reducing the exacerbation rate.[15] The anti-IL-5 agent mepolizumab can bind free soluble IL-5, which leads to a complex inhibition of eosinophilic inflammation. Thus, it is approved for the treatment of severe eosinophilic asthma and, more recently, EGPA and HES, for which it has been demonstrated to reduce the frequency of disease flares, disease severity, OCS use and BEC compared with placebo.[16,17]

Although not as common as with these drugs, AEs still exist and might constitute a significant burden. The most common AEs reported in patients receiving dupilumab therapy are local injection site reaction, erythema (6%), nasopharyngitis (13%), headache (7%), epistaxis (6%), worsening of asthma (2%) and nasal polyps (3%).[18] Serum sickness, anaphylactic reactions and ulcerative keratitis are rare AEs. Conjunctivitis and keratitis occur more frequently in patients with atopic dermatitis than in patients with asthma and CRSwNP.[19]

Reports of other AEs, such as anaphylactic reactions to humanized biologics, are rare but may occur due to immunogenicity resulting from the use of cell lines from transgenic mice that do not generate human carbohydrate side chains.[20] Several clinical studies have demonstrated reassuring safety profiles of omalizumab and mepolizumab, showing an anaphylaxis frequency of <0.1%.[21] Thus far, dupilumab is the only mAb with no evidence of anaphylaxis use, and this is related to the high degree of humanization, as it is currently the only therapeutic agent with 99% human components.[22]

Analysing other potential types of adverse reactions during therapy with biologics, authors have performed a retrospective analysis based on AE reports sent to the FDA Adverse Event Reporting System database to identify infections, intestinal infestations and cases of pneumonia.[23,24] The prevalence of pneumonia cases was higher for mepolizumab (36.8%), followed by omalizumab (32.6%), benralizumab (19.2%) and dupilumab (5.7%). A moderate-to-strong indication of increased relative risk of pneumonia was found with administration of mepolizumab, omalizumab and benralizumab but not with dupilumab.

A transient increase in eosinophil count has been reported in randomized clinical trials (RCTs) of dupilumab; it generally occurs in the first few weeks of treatment and returns to baseline or lower by the end of the treatment period.[25] However, in rare cases, it can result in possible organ damage.[26] Overall, the evaluation of data from all dupilumab studies revealed that the incidence rates of treatment-emergent eosinophilic AEs ranged from 0% to 13.6%.[25] An increase was detected in patients with asthma, CRSwNP and atopic dermatitis but not in those with eosinophilic esophagitis.

In the Liberty Asthma QUEST RCT, 4.1% (52) of patients had eosinophilia.[27] Of these patients, 22 had hypereosinophilia (>3000/μL). In 8 patients, dupilumab treatment was discontinued and, in 4 patients, eosinophilia was symptomatic. In the VENTURE study, which included 210 patients, 13% of patients had hypereosinophilia (>3000/μL) but none were symptomatic.[28] In the pivotal randomized clinical trials of dupilumab in CRSwNP SINUS-24 and SINUS-52, 50% of the patients enrolled had concomitant asthma, of whom three with uncontrolled asthma had been diagnosed with EGPA.[19] In this study, one patient in the placebo group also showed EGPA. Most patients treated with dupilumab, even those treated with an anti-IL-5 mAb, experienced intense flare-ups of nasal symptoms after discontinuation of the treatment. These data support the large body of evidence that shows that EGPA can appear during tapering and discontinuation of OCS therapy, often masking the presence of this vasculitis similarly to previous cases treated with other drugs such as montelukast.[29–31] In the TRAVERSE open-label extension study, 2282 adults and adolescents treated with dupilumab were enrolled, excluding those with a BEC of ≥1500 cells/μL

at the time of administration.[32] A transient increase in the incidence of blood eosinophilia was observed in 3.6% of the patients between weeks 4 and 12, with a progressive decrease over the remainder of the observation period, which, at the end of 148 weeks, reached a value lower than those obtained from the pivotal QUEST and VENTURE studies.[25] In the TRAVERSE study, most patients did not experience clinical symptoms associated with hypereosinophilia and did not require treatment discontinuation. In 0.2% (5/2282) of the cases, eosinophilia was then associated with the onset of EGPA. Cases of EGPA have also been reported during treatment with other mAbs. Data from EudraVigilance, the European Medicines Agency's pharmacovigilance database, confirmed the occurrence of rare cases of EGPA during treatment with biologics for SA. The total number of cases reported until March 2022 indicated the highest rate for benralizumab (1.32%), followed by mepolizumab (0.80%), and the lowest rate for dupilumab (0.46%).[33]

Eosinophilic pneumonia (EP) is another possible but rare AE related to dupilumab administration. The mechanisms that lead to this condition and the potential predisposing factors are not yet fully known. An analysis of data from the FDA Adverse Event Reporting System database revealed that 110 cases of EP associated with dupilumab use were reported between 2017 and 2023.[23] A higher incidence rate was found amongst patients aged 45–60 years and especially amongst those >60 years of age.

Our patient had severe hypereosinophilia after starting dupilumab therapy, with a BEC of >50×10^9/L and pronounced symptoms; therefore, a haematological substrate was suspected.

The presence of clonal mutations in cases of hypereosinophilia has been a fairly well-established finding because of the advent of NGS, during which typical CH mutations have been found in many cases of idiopathic HES, mainly those that affected a single gene and at a rather low VAF.[34,35]

NGS is an extremely useful method for identifying somatic mutations and fusion genes even in contexts where classical methods have not shown any alterations. In recent years, it has played a crucial role in the differential diagnosis of haematological malignancies such as chronic eosinophilic leukaemia-not otherwise specified (CEL-NOS).[36] As already mentioned, a bone marrow study was not performed in our patient; therefore, data on the histological structure are not available. However, a molecular study to identify classic rearrangements associated with haematological malignancies with hypereosinophilia and an NGS study were still performed. CEL-NOS is defined by persistent eosinophilia that does not meet the criteria for other genetically defined entities and can be distinguished from idiopathic HE/HES on the basis of the presence of increased blasts in bone marrow and peripheral blood, specific histological bone marrow features and/or the presence of clonal karyotypic/molecular abnormalities.[34,35]

Our patient displayed a likely pathogenetic variant on the *DNMT3A* gene, with a VAF of 7.14%; therefore, a diagnosis of CEL-NOS was considered. However, whether this specific mutation was pathogenetically related to an overt haematological neoplasm was not completely clarified in our patient.

As is now well known, somatic mutations involving *DNMT3A* are quite frequent in cases of CH, and the frequency increases with age. CH of indeterminate potential (CHIP) is characterized by the age-related acquisition and expansion of haematopoietic cell clones in the absence of evidence of haematological malignancies.[37] These somatic mutations are typically found in haematological neoplasms and classically involve epigenetic regulator genes. The presence of CHIP is associated with a moderate risk of developing an overt haematological malignancy (approximately 0.5–1% per year) and is strongly linked with an increased incidence of coronary heart disease. CHIP correlates with increased risk of congestive heart failure, chronic obstructive pulmonary disease, osteoporosis and all-cause mortality.[38,39]

Recently, several studies have demonstrated that almost 30% of patients with persistent hypereosinophilia and no other features of haematological malignancies carried somatic mutations associated with myeloid neoplasms.[40,41] The most frequently affected genes are those involved in DNA methylation and chromatin modification such as *DNMT3A*, *ASXL1*, *TET2*, *SRSF2* and *EZH2*. All analysed cases were initially categorized as idiopathic hypereosinophilic syndrome and idiopathic hypereosinophilia and, in most cases, patients had mutations that affected a single gene and had a generally low VAF.[42] Despite the presence of clonal alterations, in all analysed cases of idiopathic hypereosinophilic syndrome/hypereosinophilia, no significant changes were found in the bone marrow, except for increased eosinophil count. On the other hand, CEL-NOS was characterized by hypercellular bone marrow with megakaryocyte MDS-like abnormalities, presence of fibrosis and marked eosinophils, and granulocyte proliferation.[43,44]

In the present case, the combination of chronic inflammation related to CRSwNP, recurrent infection and ageing might have contributed to the favourable conditions for a selective expansion of adapted mutant haematopoietic stem cells and the development of the CH that might have contributed to the eosinophilic proliferative

drive after dupilumab exposure.[45,46] Despite the lack of bone marrow morphological data, the absence of cytopenia, peripheral blasts and organomegaly (e.g. splenomegaly and hepatomegaly) made CEL-NOS an unlikely diagnosis, even in the presence of a clonal mutation.

Our patient also showed good response to IL-5 therapy directed to mAb and achieved a persistently normal BEC and satisfactory symptom control. From the currently available data, HES associated with myeloproliferative neoplasia appears to show only a poor or transient response to anti-IL-5 mAbs.[47,48]

According to the classic definition, the normal range for absolute eosinophil count (AEC) is within $<0.5\times10^9$/L, and a BEC of $>1.5\times10^9$/L on two blood examinations with an interval of at least 1 month is considered hypereosinophilia (moderate, $1.5–5\times10^9$/L; severe, $>5\times10^9$/L).[49] The mechanisms underlying dupilumab-induced hypereosinophilia are not yet fully understood, but a possible explanation is that it inhibits eosinophil trafficking to the tissues, leading to a transient increase in BEC. In individuals with asthma and related diseases such as CRSwNP, haematopoietic signals generated at the inflammatory trigger site are directed to the bone marrow, where increased turnover and trafficking of CD34þ haematopoietic progenitor cells are stimulated.[36] From there, haematopoietic progenitor cells exit and travel to the lungs via peripheral blood, where *in situ* differentiation occurs, determined by locally produced cytokines. IL-5 drives local haematopoietic processes, whilst IL-13 can trigger further homing of haematopoietic progenitor cells to the airways.[50] Chemokines and adhesion molecules regulate the adhesion of circulating eosinophils to blood vessels with receptors on the endothelium such as vascular cell adhesion molecule 1 (VCAM1), which is regulated by IL-4. Upon binding, eosinophils enter the tissue, and their migration is guided by chemokines, including IL-5 and IL-13. By blocking both IL-4 and IL-13 signalling, dupilumab may inhibit vascular cell adhesion molecule 1 expression and eosinophil migration. As IL-4 and IL-13 do not mediate eosinophil maturation and release into the blood, eosinophil migration into the tissue is reduced, resulting in a transient increase in BEC.[25]

Recent studies have shown that, going beyond the classical division of eosinophils defined by morphological changes into normodense and hypodense eosinophils, murine eosinophils from lung tissue can be phenotypically divided into two distinct sub-types: resident eosinophils and inducible eosinophils.[7] The former with expression of Siglec-$F^{int}CD62L^{+}CD101^{low}$ and the latter Siglec-$F^{high}CD62L^{-}CD101^{high}$.[51] Other recent studies by Matucci et al. observed that, in severe eosinophilic asthma, a significantly higher percentage of circulating $CD62L^{low}$ cells was observed compared with controls, expressing higher levels of CCR3, CD69 and lower levels of CD125 (IL-5R), CRTH2, CD86 and CD28 compared with $CD62L^{bright}$ cells.[52] In CRSwNP, eosinophils showed a high percentage of $CD62L^{low}$ phenotype, significantly higher than that observed in peripheral blood. The surface expression of IL-3R, IL-5R, CD69 and CD86 was significantly higher in the $CD62L^{low}$ eosinophils of nasal polyps compared with those of blood. In addition, eotaxin 3 mRNA expression correlated positively with the percentage of $CD62L^{low}$ cells in the nasal polyp. This evidence allows us to conclude how two different sub-phenotypes of eosinophils can be identified in the blood and nasal polyps of patients with severe eosinophilic asthma, with a preferential accumulation of inflammatory $CD62L^{low}$ cells in CRSwNP. Further studies will be needed in the future to more thoroughly investigate the heterogeneity of eosinophils and their functional plasticity in human and murine tissues, but this emerging field could provide further insights into the different roles of these cells in the context of individual organs and better explain the reasons for spontaneous or drug-induced hypereosinophilia.

Although temporary hypereosinophilia is only rarely associated with clinical symptoms or sequelae[52,53] and is almost always transient, it remains important for clinicians to base judgment on individual patient histories and baseline eosinophil counts. Further monitoring and evaluation may be appropriate in cases in which elevated eosinophil counts persist or are associated with signs or symptoms that raise clinical suspicion of an eosinophilic condition such as EGPA, EP or HES, which is characterized by hypereosinophilia and abnormal accumulation of eosinophils in organs and tissues, including the skin, lungs and gastrointestinal tract.[54] The clinical manifestations of HES are highly variable and not always easy to detect, ranging from asymptomatic eosinophilia to severe tissue damage and organ failure. HES should often be considered in the differential diagnosis of EGPA. Few conflicting reports on this eosinophilic condition are found in the literature related to dupilumab. Some case reports have indicated that treatment with anti-IL-4/IL-14 was markedly effective and well tolerated in treatment-recalcitrant patients with HES, and only one case of HES detected after dupilumab administration because of its OCS-sparing effect has been reported.[55–57]

For patients with insufficient control of upper and/or lower airway disease or significant side-effects/hypereosinophilia, a careful multidisciplinary approach is mandatory to determine the most suitable therapy. This underlines the importance of having a range of available drugs so that the best treatment can be provided according to patient characteristics. Our patient had an excellent and rapid response to dupilumab therapy, with important and simultaneous improvements in the clinical outcomes of CRSwNP and asthma. After withdrawal

of dupilumab and its replacement with mepolizumab, the patient maintained control of CRSwNP and asthma, and achieved normal blood eosinophilia, even after discontinuation of OCS therapy. A network meta-analysis was performed to compare the efficacies of different biologics as therapies for CRSwNP.[58] On the basis of its NPS and safety profile, dupilumab was theoretically the best choice, and mepolizumab was the second-best option for CRSwNP on the basis of a smaller body of literature due to a more recent introduction into clinical practice and less evidence of efficacy. An analysis based on a systematic review confirmed the moderate supremacy of dupilumab but could not clearly identify the biologic agent that is most effective for the treatment of CRSwNP.[59] In another network meta-analysis, the same conclusions were reached in terms of the superiority of dupilumab in the treatment of CRSwNP.[60] However, in the literature, the evidence on asthma confirms the substantially similar efficacy of dupilumab and mepolizumab when various outcomes were compared.[61]

Consequently, the confirmation of the positive outcomes of CRSwNP after the shift from dupilumab to mepolizumab is another interesting aspect of our case report, in addition to the discussion of the haematological condition that emerged after dupilumab administration.

Some algorithms have been proposed in the literature that suggest how to manage cases of hypereosinophilia that occur during treatment with dupilumab. In cases with BECs between 1.5 and 3×10^9/L in asymptomatic patients, follow-up with routine blood count every month until the hypereosinophilia is resolved or in case of worsening has been suggested. In cases with BECs $>3\times10^9$/L, evaluation for possible organ damage has been proposed. When a diagnosis of HES is reached, dupilumab therapy must be suspended and a specific therapy should be initiated. If a diagnosis of HES or other hypereosinophilic condition with organ damage is not made and the BEC is $\geq3\times10^9$/L, a short-term course of systemic corticosteroid therapy is suggested, without interruption of dupilumab treatment given its benefits. For persistent hypereosinophilia, a multidisciplinary evaluation should always be conducted.[62]

Caminati et al.[63] reported a similar approach underlining the importance of a through differential diagnosis before prescribing dupilumab to minimize the risk of unravelling an underlying pathology that would then be attributed to dupilumab or its steroid-sparing effect. In cases with BECs $\geq1.5\times10^9$/L without other alterations, follow-up with a complete blood count every 30 days is suggested. Only when organ damage is suspected and the BEC is $\geq1.5\times10^9$/L or hypereosinophilia persists should a complete evaluation be performed. If no consequent pathology emerges, patients should continue dupilumab treatment with follow-up by a multidisciplinary team who can decide whether a short course of systemic steroids is necessary. Only when organ damage is confirmed should dupilumab administration be withdrawn. Clearly, hypereosinophilia induced or unmasked by dupilumab could not be predicted with certainty. Thus, dupilumab remains a safe drug, with ever-increasing evidence in this sense. In practical terms, appropriate follow-up should include evaluations of all blood parameters for organ damage, especially when clinical manifestations are suspected and/or BECs are >5000 cells/mm^3. In this case, instrumental tests such as pulmonary function tests and imaging tests such as chest radiography and/or CT, echocardiography and neurological evaluation should also be performed.[63]

Baseline blood eosinophil levels alone are not sufficient to predict hypereosinophilia. However, a review of pivotal studies for all indications of dupilumab found that a baseline AEC of >0.5 is a potential risk factor of hypereosinophilia during dupilumab treatment.[25] Even in a retrospective study that involved patients with CRSwNP and asthma, AEC at 2 months after the start of dupilumab treatment was a predictor of long-lasting hypereosinophilia of >12 months.[64] An AEC of ≥3.0 was identified as a potential risk factor, whilst an AEC of <1.5 was found to have a potential protective effect. The mean baseline pre-therapy AECs were higher in patients who subsequently had AECs ≥1.5 but showed no statistically significant association with long-lasting hypereosinophilia. Another potential risk factor is having a baseline age of >45 years, and the risk further increases in patients aged >60 years (Box 1).[23]

Conclusion

The available data confirms the safety profile of dupilumab.[65] Moreover, in terms of cost-to-benefit ratio, the benefits linked to the prescription of dupilumab must not

Box 1. Risk factors of dupilumab-induced hypereosinophilia.

Risk factors
Baseline blood eosinophil count (>1500 cell/μL)
Age >45 years
Underlying haematological conditions
Chronic OCS use
Persistent AEC ≥1500 cell/μL after dupilumab starting

AEC, absolute eosinophil count; BEC, blood eosinophil count; OCS, oral corticosteroids.

be underestimated because patients eligible for biologic treatment are affected by difficult-to-treat pathologies that require high amounts of systemic steroids. Clinically significant hypereosinophilia related to dupilumab administration is rare, whilst systemic steroid damage is frequent and has a great impact on economic costs and patient health.[66,67] Further investigations would be useful to better understand and identify clinical characteristics and biomarkers to support the risk stratification of patients according to clinically relevant or asymptomatic hypereosinophilia. However, the availability of different therapeutic options allows for effective and differentiable weapons based on various conditions, blood eosinophil values, symptomatic or non-symptomatic hypereosinophilia and other risk factors. As increasingly evident and confirmed in our case, multidisciplinary management is crucial for a correct and in-depth assessment of these patients with complex cases and for the appropriate use of biologics, even when rare and sometimes unexpected conditions such as CH emerge.

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Correspondence: Francesco Menzella, Pulmonology Unit, S. Valentino Hospital Montebelluna, AULSS2 Marca Trevigiana, Via Sant' Ambrogio di Fiera, n. 37, 31100 Treviso, Italy. Email: francesco.menzella@aulss2.veneto.it

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