

PROF. MAREK LOMMATZSCH (Orcid ID : 0000-0002-9305-9348)

PROF. CHRISTIAN VIRCHOW (Orcid ID : 0000-0003-4291-1956)

Article type : Letter to the Editor

**Manuscript Acceptance Date: 24-May-2021**

## **Eosinophilic pleural effusion and stroke with cutaneous vasculitis:**

### **two cases of Dupilumab-induced hypereosinophilia**

Marek Lommatzsch<sup>1§</sup>, Paul Stoll<sup>1</sup>, Jörg Winkler<sup>2</sup>, Daniel Zeise-Wehry<sup>3</sup>,  
Michael Tronnier<sup>4</sup>, Marc-André Weber<sup>5</sup> and J. Christian Virchow<sup>1</sup>

<sup>1</sup>Department of Pneumology and Critical Care Medicine, University of Rostock, Germany

<sup>2</sup>Outpatient Clinic for Pneumology and Allergology, Leipzig, Germany

<sup>3</sup>Department of Neurology, Stroke Unit, Helios-Klinikum Berlin-Buch, Germany

<sup>4</sup>Department of Dermatology, Helios-Klinikum Hildesheim, Germany

<sup>5</sup>Institute of Diagnostic and Interventional Radiology, Pediatric Radiology and  
Neuroradiology, University of Rostock, Germany

#### **§Corresponding author:**

Prof. Dr. Marek Lommatzsch

Abteilung für Pneumologie und Internistische Intensivmedizin

Zentrum für Innere Medizin, Universität Rostock

Ernst-Heydemann-Str. 6, 18057 Rostock, Germany

Tel: +49 (0) 381 / 494 – 7461; Fax: +49 (0) 381 / 494 - 7392

E-mail: marek.lommatzsch@med.uni-rostock.de

**Total word count:841.Figures: 2.**

**Funding:** None.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/ALL.14964](https://doi.org/10.1111/ALL.14964)

This article is protected by copyright. All rights reserved

**Contributorship Statement:** All authors were involved in the assessment and treatment of the patient, and in the writing and correction of the manuscript.

**Conflicts of interest:** The authors report no conflicts of interest regarding this report.

**Institutional Review Board approval:** Not applicable.

**Patient consent statement:** Patients gave their consent to publish the cases anonymously.

**Conclusion:** Treatment with the anti-IL-4 receptor alpha antibody Dupilumab can increase blood eosinophils in patients with severe asthma, typically without adverse clinical effects. We report 2 patients with severe asthma who developed excessive blood eosinophilia ( $>10,000$  eosinophils /  $\mu\text{l}$ ) with severe adverse effects within the first 6 weeks after initiation of Dupilumab treatment. A 49-year old man developed left-sided eosinophilic pleural effusion, a 66-year old woman atrial fibrillation, a stroke (with diffuse bilateral infarctions) and vasculitis of the skin. We conclude that Dupilumab treatment can lead to severe hypereosinophilia with organ complications in the first 6 weeks of treatment. We, therefore, recommend to monitor blood eosinophil counts in the first weeks after Dupilumab treatment initiation.

#### **To the Editor:**

Treatment with the anti-IL-4 receptor alpha antibody Dupilumab can cause increases in blood eosinophils, typically without adverse effects<sup>1,2</sup>. This blood eosinophil increase is probably caused by an inhibition of the endothelial expression of VCAM-1 and ICAM-1 which is essential for eosinophil extravasation and dependent on IL-4 receptor alpha<sup>3</sup>. We report cases of Dupilumab-induced hypereosinophilia with severe adverse effects occurring within the first 6 weeks after treatment initiation:

#### **Case 1**

A 49-year-old man (15 pack years until 2017) with severe intrinsic, adult-onset asthma and CRSwNP (not previously treated with biologics) suffered from recurrent asthma exacerbations requiring prednisolone bursts despite high-dose ICS/LABA/LAMA treatment. There were no other chronic diseases. In January 2020, poor asthma control (ACT: 8 points), a reduced FEV<sub>1</sub> (67% predicted), elevated blood eosinophils (800/ $\mu\text{l}$ , 12 %) and high FeNO (66 ppb) were documented. Due to the high FeNO value and the well-established beneficial effects of Dupilumab on CRSwNP<sup>4</sup>, treatment with Dupilumab (200

mg every 2 weeks) was started on February 6<sup>th</sup>: subsequently, asthma control, sense of smell and nasal airflow improved. However, the patient presented on March 18<sup>th</sup> with severe, left-sided chest pain: chest X ray revealed pleural effusion (**Fig. 1**). Dupilumab was stopped and the patient admitted to hospital where massive blood eosinophilia (10.530 eosinophils/ $\mu$ l; 50,2%) was recorded. Serum p-ANCA and c-ANCA titres were negative (< 1:10). Thoracocentesis drained 2500 ml of an eosinophilic exudate (56 g protein/dl; 14.4 million leukocytes/ml: 58% eosinophils). Prednisolone treatment (0.5 mg Prednisolone per kg body weight per day, for 2 weeks) led to clinical improvement. On April 2<sup>nd</sup>, Benralizumab treatment was started and Prednisolone stopped. In November 2020, asthma control was good (ACT: 25 points), FEV<sub>1</sub> improved (105% predicted), eosinophils were undetectable (0/ $\mu$ l). The pleural effusion was completely resolved (**Fig. 1**).

## Case 2

A 66-year-old woman (never-smoker) with severe intrinsic, adult-onset asthma (not previously treated with biologics) suffered from recurrent asthma exacerbations (one led to resuscitation/mechanical ventilation) requiring prednisolone bursts, despite high-dose ICS/LABA and Montelukast treatment. In addition to asthma, she suffered from chronic lower back pain (due to herniated discs) and diffuse arthritis (with no established specific diagnosis): both conditions were treated with Paracetamol on an as-needed basis. In October 2020, asthma control was poor (ACT: 6 points), FEV<sub>1</sub> reduced (53% predicted), FeNO high (89 ppb) and eosinophils low (10 eosinophils/ $\mu$ l; 0.1%). There was no pharmacological explanation for these surprisingly low eosinophil counts: she denied taking Prednisolone or being treated with Prednisolone since August 2020, and there was no documented treatment with other immunosuppressants or with biologics. However, a non-informed use or treatment with systemic immunosuppressants since August 2020 cannot be excluded. Due to the high FeNO value, and the absence of blood eosinophilia (precluding treatment with biologics targeting the IL-5 pathway) or allergies (precluding treatment with Omalizumab), treatment with Dupilumab was initiated on October 27<sup>th</sup> (300 mg every 2 weeks). Asthma control improved in the following weeks, with no further exacerbations (this was communicated in a phone call). On December 2<sup>nd</sup>, 2020, she was hospitalised with atrial fibrillation. Despite anticoagulation, acute right-sided

hemiparesis and aphasia occurred on December 9<sup>th</sup>. In the stroke unit, right-side predominant tetraparesis, dysphasia, hemianopia to the right, neglect to the left, reduced consciousness and massive blood eosinophilia (10.961 eosinophils/ $\mu$ l; 41,9%) were detected. MRI showed diffuse cerebral infarctions (**Fig. 2A**), biopsies of new livid cutaneous maculae revealed vasculitis and vascular occlusions (**Fig. 2B**). Serum p-ANCA and c-ANCA titres were negative (< 1:10). High-dose methylprednisolone treatment (1000 mg/day) was immediately started and then tapered, Dupilumab was stopped. Neurologic symptoms strongly improved in the following weeks and asthma control was good (the latter was communicated in a phone call): further prednisolone tapering is planned.

### *Discussion*

In previous case series, none of the patients developed > 8000 eosinophils/ $\mu$ l blood within the first 12 months of Dupilumab treatment, and there were no cardiac, pulmonary or neurologic complications <sup>2,5</sup>. Bilateral stroke after 6 months of Dupilumab treatment was reported in a 20-year old man with atopic dermatitis, however, eosinophils were not measured <sup>6</sup>. A 56-year-old man with severe asthma suffered an eosinophilic pneumonia after 5 months of Dupilumab treatment, with eosinophils increasing from 660 to 2714/ $\mu$ l <sup>7</sup>. In our cases, organ complications occurred already within the first 6 weeks of treatment, and were accompanied by excessive increases in blood eosinophils. Indeed, all complications were related to eosinophilia: (1) the pleural effusion was eosinophilic and resolved completely after prednisolone and Benralizumab treatment, (2) there was no other explanation for a newly emerged cutaneous vasculitis, (3) the stroke was either due to vasculitis or thromboembolic events: even in the latter case, eosinophilia-associated hypercoagulability <sup>8</sup> probably plays a role. We conclude that Dupilumab treatment can, in rare cases, lead to (1) excessive blood eosinophilia (> 10.000 eosinophils/ $\mu$ l) with (2) organ complications (3) within the first 6 weeks of therapy. We, therefore, recommend to monitor blood eosinophils in the first weeks after treatment initiation and/or after discontinuation of oral corticosteroid treatment, even if a lower Dupilumab dose (200 mg) is chosen (case 1) or eosinophils are low at baseline (case 2).

Marek Lommatzsch, MD  
Paul Stoll, MD  
Jörg Winkler, MD  
Daniel Zeise-Wehry, MD  
Michael Tronnier, MD  
Marc-André Weber, MD, MSc  
Johann Christian Virchow, MD

## FIGURE LEGENDS

**Figure 1.** Chest X ray of patient 1 before initiation of Dupilumab treatment (February 2020: **A**), at hospital admission (March 2020: **B**) and after drainage, Prednisolone treatment and 7 months of Benralizumab treatment (November 2020: **C**).

**Figure 2.A:** MRI scans of the brain (fluid attenuated inversion recovery sequence) of patient 2 (on the day of admission to the stroke unit: December 9<sup>th</sup>, 2020) showing multiple infarctions in all cerebral vascular territories, but no central occlusion of a larger artery. Computed tomography of the head using a specialised software (DynaCT, Siemens, Germany: performed on December 16<sup>th</sup>, 7 days after initiation of methylprednisolone treatment) did not proof cerebral vasculitis (data not shown), a cerebral biopsy was not performed. Therefore, it could not be definitely resolved whether the infarctions were due to a vasculitis and/or due to diffuse (thrombo)embolic events. Courtesy of Prof. Marius Hartmann, Institut für Neuroradiologie, HELIOS-Klinikum Berlin-Buch, Germany. **B:** Histologic analysis of a skin biopsy of patient 2 (H&E stainings). *Left picture:* Skin biopsy, magnification x 40, small- to medium-sized vessels in the deeper dermis are occluded (arrow). *Right picture:* Skin biopsy, magnification x 400. The infiltrate around the occluded vessel (arrow) with increased number of eosinophils (arrowhead).

## Abbreviations:

|                  |                                           |
|------------------|-------------------------------------------|
| ACT              | Asthma Control Test                       |
| ANCA             | Anti-Neutrophil Cytoplasmatic Antibody    |
| CRSwNP           | Chronic Rhinosinusitis with Nasal Polyps  |
| FeNO             | Fractional exhaled nitric oxide           |
| FEV <sub>1</sub> | Forced Exhaled Volume in the first second |
| H & E            | Hematoxylin and eosin                     |
| ICAM-1           | Intercellular Adhesion Molecule 1         |
| ICS              | Inhaled Corticosteroid                    |
| LABA             | Long-acting Beta agonist                  |
| LAMA             | Long-acting Muscarinic antagonist         |
| MRI              | Magnetic Resonance Imaging                |
| VCAM-1           | Vascular Cell Adhesion Molecule 1         |

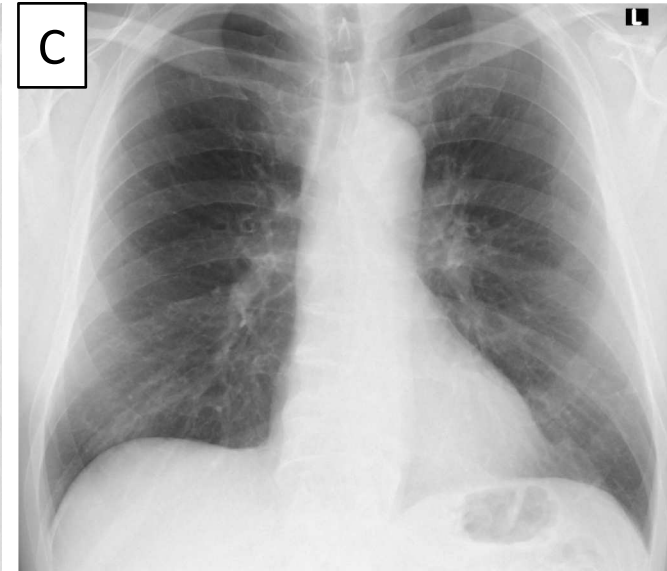
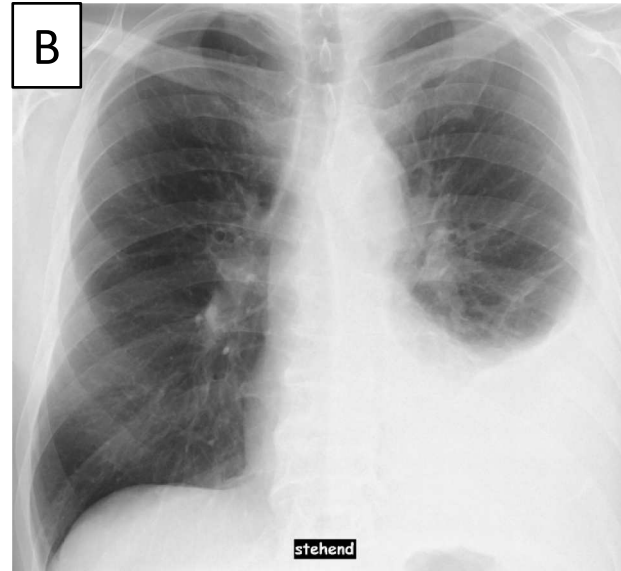
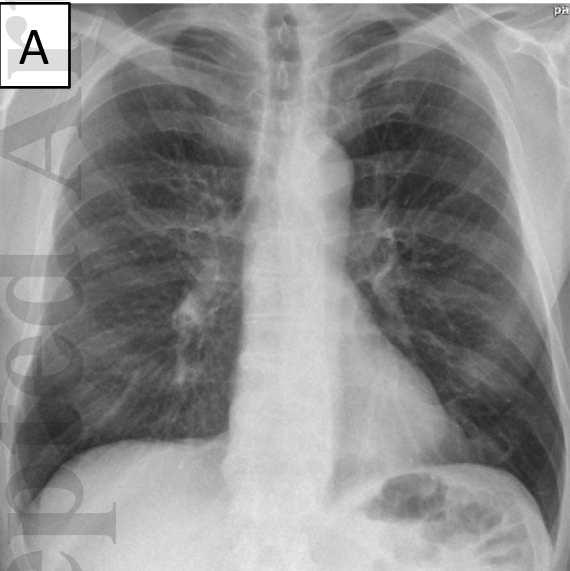
## References:

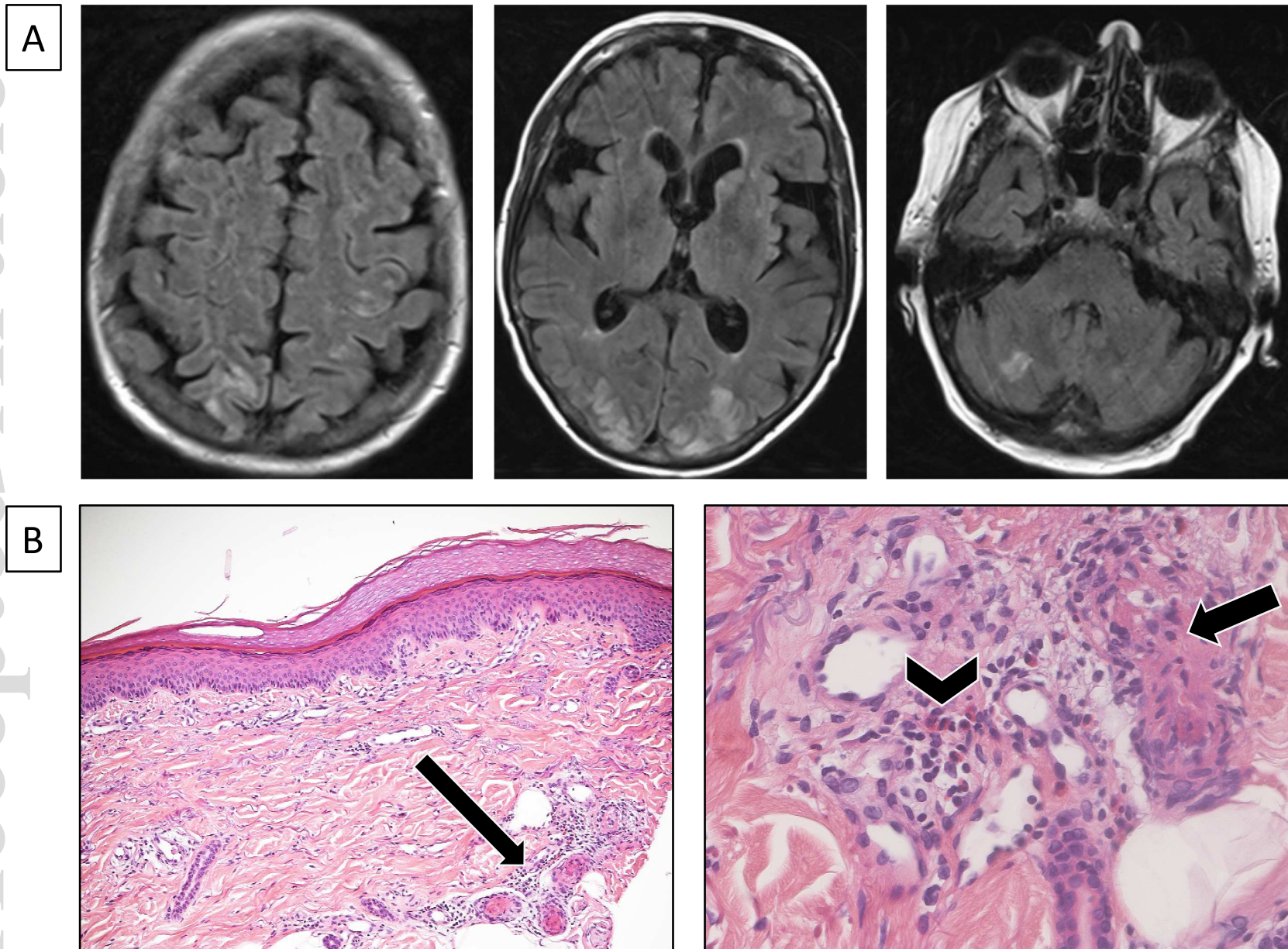
- Accepted Article
1. Bourdin A, Papi AA, Corren J, et al. Dupilumab is effective in type 2-high asthma patients receiving high-dose inhaled corticosteroids at baseline. *Allergy*. 2021;76(1):269-280.
  2. Dupin C, Belhadi D, Guilleminault L, et al. Effectiveness and safety of dupilumab for the treatment of severe asthma in a real-life French multi-centre adult cohort. *Clin Exp Allergy*. 2020;50(7):789-798.
  3. Lommatzsch M. Immune Modulation in Asthma: Current Concepts and Future Strategies. *Respiration*. 2020;99(7):566-576.
  4. Agache I, Song Y, Alonso-Coello P, et al. Efficacy and safety of treatment with biologicals for severe chronic rhinosinusitis with nasal polyps: A systematic review for the EAACI guidelines. *Allergy*. 2021. In press.
  5. Marcant P, Balayé P, Merhi R, et al. Dupilumab-associated hypereosinophilia in patients treated for moderate-to-severe atopic dermatitis. *J Eur Acad Dermatol Venereol*. 2021. In press.
  6. Iwase R, Ishiguro T, Fujita K, Ishibashi S, Yokota T. Dupilumab for Atopic Dermatitis, a Possible Risk Factor of Juvenile Ischemic Stroke: A Case Report. *J Stroke Cerebrovasc Dis*. 2020;29(6):104763.
  7. Menzella F, Montanari G, Patricelli G, et al. A case of chronic eosinophilic pneumonia in a patient treated with dupilumab. *Ther Clin Risk Manag*. 2019;15:869-875.
  8. Akuthota P, Weller PF. Spectrum of Eosinophilic End-Organ Manifestations. *Immunol Allergy Clin North Am*. 2015;35(3):403-411.

Before Dupilumab treatment  
(February 4<sup>th</sup>, 2020)

During Dupilumab treatment  
(March 18<sup>th</sup>, 2020)

During Benralizumab treatment  
(November 10<sup>th</sup>, 2020)





This article is protected by copyright. All rights reserved