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Letter to the Editor

Challenging diagnosis of granulomatosis after switching mepolizumab by dupilumab for severe asthma

The anti-IL4Rα antibody dupilumab could induce blood hypereosinophilia in up to 14% of patients typically without adverse effects [1]. However, some life-threatening events were reported due to vascular involvement [1,2].

We describe the case of Eosinophilic Granulomatosis with Polyangiitis (EGPA) revealed 5 months after dupilumab initiation for oral corticosteroids (OCS)-dependent asthma in a patient previously treated by anti-IL5 antibody.

A 57-old man, former-smoker (20 pack-years until 2006), was admitted in the Emergency Department (March 19th, 2022) for intense headache, cough and fever (38.8 °C) occurred a few days ago, persistent despite antibiotics and analgesics. He had a non-allergic eosinophilic adult-onset asthma became OCS-dependent (30 mg prednisolone/day) from 2008 with iatrogenic diabetes mellitus, dyslipidemia, osteoporosis and hypertension. His asthma was uncontrolled (Asthma Control Test score 10) despite maximal inhaled treatment and OCS with three exacerbations/year and airflow limitation (Forced expiratory volume in the first second-FEV1 61%, Forced Vital Capacity-FVC 82%, FEV1/FVC 0.65). Blood eosinophilia (maximum 830/μL) was repeatedly investigated and bronchopulmonary aspergillosis, EGPA, respectively parasitic infections were excluded. He received omalizumab in 2008 (4 months) and mepolizumab in 2021 (9 months) without asthma outcomes improvement or OCS withdrawal. The last dose of mepolizumab was administered in November 2nd, 2021. Dupilumab, to switch mepolizumab, was started in November 30th, 2021 (the last administration in March 9th, 2022) with monthly monitoring of the blood eosinophils count (BEC) and progressive decrease of prednisolone dose to 10 mg/day.

At admission, the patient had asymptomatic nodular erythematous skin lesions on both forearms, appeared 3 months after starting dupilumab. BEC was increased (1690/μL). CT-scan showed pansinusitis without intracranial thrombosis and diffuse consolidations in both lungs. After increasing the prednisolone at 60 mg/day, the patient was transferred in the Pulmonology Department for investigations with suspicion of tuberculosis, sarcoidosis or cancer. Tests for parasitic infections were negative. Antinuclear, antineutrophil cytoplasmic antibodies (ANCA), anti-proteinase 3 (anti-PR3)-, anti-myeloperoxidase (anti-MPO)-, anti-lactoferrin-, anti-human leucocyte elastase-, anti-bacterial permeability increasing protein-, anti-cathepsin-G-ANCA and anti-alpha-enolase antibodies were negative by ELISA. Rheumatoid factor level was normal. Serum IgE level was 37 UI/mL and IgG for Aspergillus sp negative. Broncho-alveolar lavage showed 3% eosinophils without atypical cells, the absence of acid-fast bacilli, a negative Galactomannan assay and fungal culture. The nasal endoscopy found rhinitis without polyps and lymphoplasmacytic infiltrate. The skin biopsy showed epithelioid and giant cells granulomatous dermohypodermatitis without necrosis, with eosinophilic angiitis, while the bronchial biopsy - a polymorphic infiltrate with multinucleated giant cells and eosinophils in the lamina propria (Fig. 1). Despite increasing dose of prednisolone, BEC increased to 2380/μL. Both myeloid and lymphoid hypereosinophilic syndrome were ruled out. The diagnosis of EGPA was established with a score at 10 points on following criteria: BEC≥1000/ μL (+5), obstructive airway disease (+3), and extravascular eosinophilic predominant inflammation (+2) [3]. Despite three days of IV pulse methylprednisolone therapy (500 mg/day), BEC remained elevated (1040/μL). A treatment by cyclophosphamide was started (15 mg/kg IV every 2 weeks 3 doses, followed by every 3 weeks 3 doses) leading to complete clinical and biological remission. The electromyogram found mixed polyneuropathy rather related to diabetes mellitus than to EGPA.

This is a well-documented case-report of ANCA-negative EGPA with sino-nasal, pulmonary and skin manifestations, revealed after the instauration of dupilumab to switch mepolizumab in a patient with severe eosinophilic OCS-dependent asthma. Five cases with EGPA were reported in a large cohort that studied the long-term safety and efficacy of dupilumab in the moderate-to-severe asthma (not all very well documented), two of them occurred during OCS tapering so the possibility of a pre-existing EGPA was not excluded [4]. Conversely, dupilumab may induce hypereosinophilia due to decreased eosinophils extravasation resulting from reduced chemotaxis by inhibiting eotaxin-3, VCAM-1, and TARC without suppression of eosinophilopoiesis in bone marrow [5]. Other complications (e.g. eosinophilic pneumonia, stroke) after switching from anti-IL5/R to anti-IL4Rα were described, due to hypereosinophilia with tissue damage following previously eosinopenia [1].

A recent research using patient samples and mouse modeling suggested an interesting mechanism for the transition from hypereosinophilia to vasculitis in EGPA. Following environmental insults, the release of IL-33 could stimulate ILC2s to produce IL-13, which increases vascular permeability and migration of eosinophils into extravascular space with more severe tissue damage. In this model, the loss of IL4Rα signaling was associated with less important histopathologic findings [6]

The diagnosis in this case was challenging. If no case of tuberculosis has been previously described during treatment by dupilumab, skin sarcoid-like reactions and cancers (e.g. lung, gastric) were reported [4,7]. There were no arguments for tuberculosis, sarcoidosis or cancer in our patient. Despite several differences, histological findings were decisive for the diagnosis of EGPA, supporting the importance of multiple site biopsies in difficult cases. ANCA were negative but it is known that only 40% of patients with EGPA produce detectable antibodies [8]. Even the anti-lactoferrin-, anti-human leucocyte elastase-, anti-bacterial permeability increasing protein-, anti-cathepsin-G-ANCA and anti-alpha-enolase antibodies, sometimes positive in EGPA, were negative. Skin involvement is a common complication occurring in 40–70% of EGPA patients and anti-alpha-

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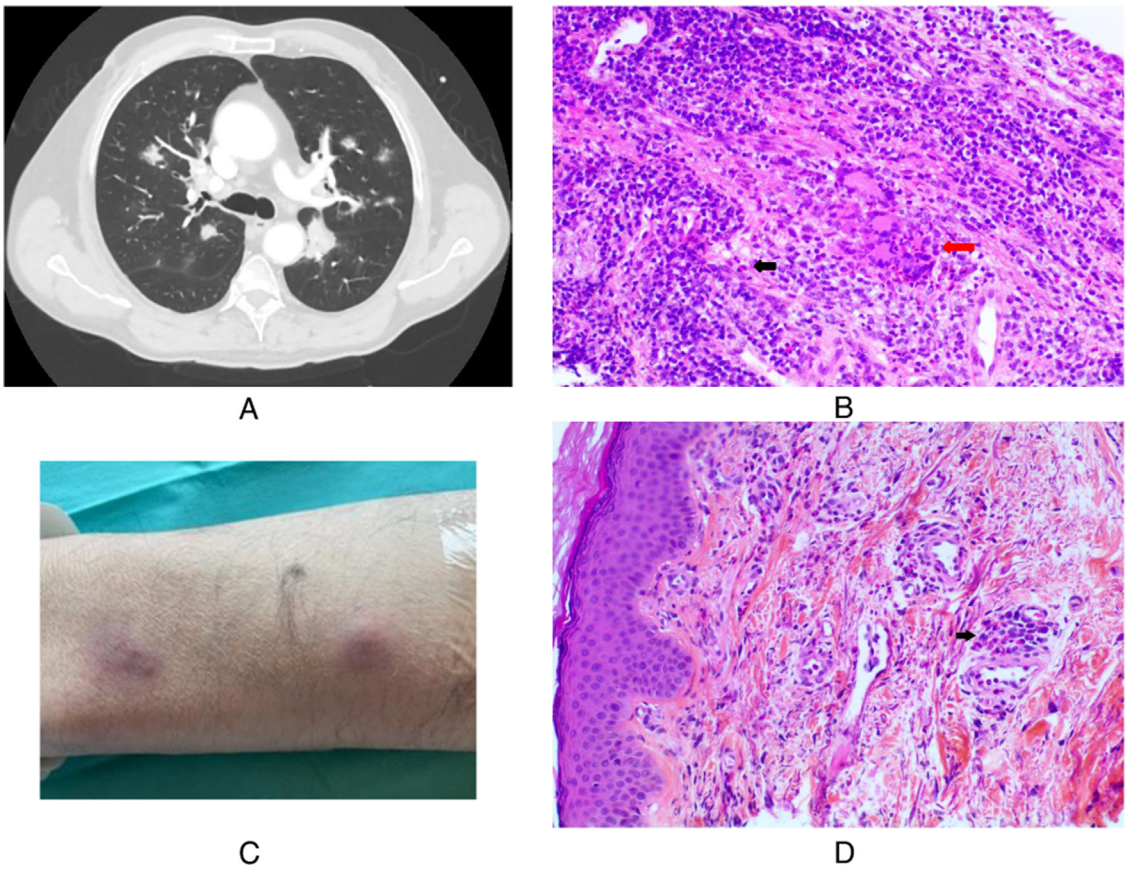

Fig. 1. A. Chest CT-scan (axial section): diffuse lung consolidations and ground glass images, **B. Bronchial biopsy:** granulomatous inflammation with giant and epithelioid cells (red arrow), eosinophils (black arrow), lymphocytes, plasma cells (HES, x400), **C. Photograph of the skin lesions (right forearm**), **D. Skin biopsy**: eosinophilic angiitis in the superficial dermis**.** Black arrow: eosinophils. (HES, x200).

enolase antibodies are positive in this population with a sensitivity of 82% [9] but it was not the case of our patient. Although the sinus and pulmonary imaging were more suggestive for granulomatosis with polyangiitis, the diagnosis of EGPA was established after discussion by multidisciplinary team given the medical history and histological findings. Despite a non-severe disease at admission, the immunosuppressive treatment was administered in reason of refractory symptomatic hypereosinophilia and suspicion of neurological involvement.

This patient had probably latent EGPA incompletely controlled by the anti-IL5 therapy administered at low dose (100 mg/4 weeks) for his OCS-dependent asthma. Dupilumab-induced hypereosinophilia was maybe just the revealing factor. The multiple site biopsies were really helpful for the diagnosis. Furthermore, after switching from anti-IL5/R to anti-IL4Rα agent, clinical evolution and BEC should be carefully monitored in patients with OCS-dependent asthma.

Consent to publish

Written informed consent for publication of his clinical history and images was obtained from the patient.

Declaration of Competing Interest

Lea Covarel, Heloise Pina, Elodie Lellig, Jean Staentzel, Luc Groshaeny, Thomas Moulinet, Philippe Campoli, Fabien Pointille, Pierre Vaillant have no conflicts of interest.

Pascale Martin reports speaker and consulting fees from AstraZeneca, GSK, Sanofi outside the submitted work.

Cecile Rumeau reports speaker and consulting fees from ALK, Sanofi outside the submitted work.

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