Drug-induced granulomatosis is dupilumab the new kid on the block?

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LETTER TO THE EDITOR

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Drug-induced granulomatosis: is dupilumab the new kid on the block?

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Dupilumab is an IgG4 antibody directed toward IL-4 and IL-13, two major effectors of the Th2 immunity response. It was originally developed for severe and/or refractory atopic dermatitis, nevertheless its use has secondarily been broadened to severe asthma [1].

We report herein the case a 28-year-old, non-smoker male who presented to the emergency department with confusion, headaches, emesis and photophobia. His medical history included only a severe atopic dermatitis leading to dupilumab initation 4 months earlier. Physical examination revealed a meningoencephalitis syndrome, and a bilateral parotidomegaly. Biology exhibited a T4 cells lymphopenia (262/mm3, N=530-1300), with a polyclonal hypergammaglobulinemia up to 14.3g/L (N=8-13.5) and an elevated plasmatic Angiotensin Converting Enzyme (ACE) (93UI/L, N<70). Cranial MRI revealed a diffuse micronodular meningitis with brain infiltration. Cerebrospinal fluid analysis showed an hyperproteinorachia (3,49g/L), an hypercellularity up to 80 cells/mm3 with 89 % of lymphocytes, and an ACE elevation up to 1.09 UI/l (N=0.06-0.25). Chest CT-scan revealed a perilymphatic micronodular lung infiltration, without mediastinal lymphadenopathy. Broncho-alveolar lavage (BAL) fluid analysis showed an elevated T4/T8 ratio (12.29). Bronchial and accessory salivary glands samples examination revealed non-necrotising epithelioid granulomas. Dupilumab was stopped, and a corticosteroid treatment was implemented, associated with methotrexate. Under this regimen, the evolution was favourable and, to date the patient remains in complete clinical remission, 6 months after systemic sarcoid-like granulomatosis diagnosis and dupilumab cessation.

This is the first case of systemic sarcoid-like granulomatosis occurring under dupilumab reported so far [2,3]. The chronology of disease onset (4 months after treatment initiation), the rarity of the disease, and its particularly aggressive form in the present case, raise the question of the role of dupilumab in the disease development.

The development of non-caseating gigantic granulomas is a hallmark of sarcoidosis. These granulomas are the result of macrophage cell fusion, surrounded by $CD4^+$ T-cells and Th17 [4]. An imbalance of the Th1/Th2

response towards the Th1 pathway has been incriminated in granuloma formation at the early stage of the disease [5]. Hence, we could easily hypothesise that dupilumab may directly trigger granulomatosis reactions through its anti-IL4 and IL13 effects. Regarding Th17 lymphocytes, IL-4 and 13 have been reported to decrease IL-23 production, with reduced Th17 function [6], and thus their inhibition under dupilumab may enhance Th17 recruitment and activation.

Nevertheless, such hypothesis would not consider the pivotal role of macrophages in granuloma formation. Indeed, a M2 macrophages polarisation state has paradoxically been found as a central mechanism in the pathogenesis of sarcoidosis:

- Helming *et al.* found IL-4 to be a major effector of the macrophage's fusions and thus of granuloma genesis [7]
- Locke *et al.* highlighted recently the key role of IL-13 in macrophage polarisation, in an *in vitro* model of sarcoidosis [8]
- A recent study has also brought to light that some M2 macrophages cell surface markers, such as CD204, were overexpressed on macrophages from bronchoalveolar fluids of sarcoidosis patients in comparison with controls suffering from lung carcinoma [9]

Nonetheless, despite these evidences for the role of M2 macrophages polarisation in sarcoidosis [8], redirecting macrophage towards a M1 activation could also paradoxically favour granulomatosis formation. Indeed, a predominant M1 macrophages activation has also been described in the early stages of granuloma formation in *in vitro* models [10]. Thus, exploring the natural history of macrophage polarisation in sarcoidosis and the connection between a possible uncontrolled early M1 phase and a secondary ineffective or unadapted M2 phase may help to decipher the possible involvement of dupilumab in the onset of systemic sarcoid-like granulomatosis.

A thorough pharmacovigilance monitoring will henceforth be important for registering future cases, thus fostering further investigations of these hypotheses.

References:

1 Barranco P, Phillips-Angles E, Dominguez-Ortega J, Quirce S. Dupilumab in the management of moderate-to-severe asthma: the data so far. Ther Clin Risk Manag. 2017; 13: 1139-1149.

2 Chopra A, Nautiyal A, Kalkanis A, Judson MA. Drug-Induced Sarcoidosis-Like Reactions. Chest 2018; 154: 664-677.

3 Cohen Aubart F, Lhote R, Amoura A, et al. Drug-induced sarcoidosis: an overview of the WHO pharmacovigilance database. J Intern Med 2019. doi: 10.1111/joim.12991.

4 Ten Berge B, Paats MS, Bergen IM et al. Increased IL-17A expression in granulomas and in circulating memory T cells in sarcoidosis. *Rheumatology (Oxford)* 2012 51: 37–46.

5 Broos CE, van Nimwegen M, Hoogsteden HC, Hendriks RW, Kool M, van den Blink B. Granuloma formation in pulmonary sarcoidosis. Front Immunol. 2013; 4: 437.

6 Guenova E, Skabytska Y, Hoetzenecker W et al. IL-4 abrogates Th17 cell-mediated inflammation by selective silencing of IL-23 in antigen-presenting cells. Proc Natl Acad Sci USA 2015; 112: 2163–8.

7 Helming L, Gordon S. Macrophage fusion induced by IL-4 alternative activation is a multistage process involving multiple target molecules. Eur J Immunol 2007; 37: 33–42.

8 Locke LW, Crouser ED, White P et al. IL-13 regulated Macrophage Polarization during Granuloma Formation in an In Vitro Human Sarcoidosis Model. Am J Respir Cell Mol Biol 2019 ; 60 : 84-95.

9 Lescoat A, Ballerie A, Augagneur Y et al. Distinct Properties of Human M-CSF and GM-CSF Monocyte-Derived Macrophages to Stimulate Pathological Lung Conditions In Vitro: Application to Systemic and Inflammatory Disorders with Pulmonary Involvement. Int J Mol Sci 2018 ; 19. Pii; E894. doi: 10.3390/ijms19030894.

10 Huang Z, Luo Q, Guo Y et al. Mycobacterium tuberculosis-induced polarization of human macrophage orchestrates the formation and development of tuberculous granulomas in vitro. PLoS One 2015; 10: e0129744.