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Letter to the Editor

Successful treatment with dupilumab of adult-onset asthma and periocular xanthogranuloma syndrome overlapping IgG4-related disease

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Adult onset asthma and periocular xanthogranuloma syndrome (AAPOXs) is a rare non-Langerhans cell histiocytosis (NLCH) characterized by a periocular infiltration of foamy histiocytes and Touton giant cells [1]. AAPOXs can coexist IgG4-related disease (IgG4-RD) [2]. Corticosteroids are first-line therapy for patients with AAPOXs or IgG4-RD but long-term use has side effects and disease flares can occur when tapering [3,4]. Dupilumab is a monoclonal antibody that binds to the interleukin 4 (IL-4) receptor alpha, inhibiting the IL-4 and IL-13 receptors (rIL-4/13). It is an FDA-approved treatment of severe asthma and of inadequately controlled sinonasal polyposis, two conditions present in AAPOXs syndrome. Moreover, dupilumab could have a beneficial effect on IgG4-RD [5]. We report here two consecutive patients with AAPOXs fulfilling IgG4-RD criteria who were successfully treated with dupilumab.

Case 1: a 42-year-old woman presented with a relapsing periocular xanthogranuloma, disabling asthma and sinonasal obstruction despite a corticosteroid therapy.

Nine years earlier, she had been reported as having AAPOXs and definite IgG4-RD (patient number 3) [3]. Corticosteroid sparing agents such as methotrexate (20 mg weekly), rituximab (1 g twice) and azathioprine (2 mg/kg/d) successively failed to control asthma and chronic sinusitis. A long-term treatment with a minimal prednisone dose of 7 mg daily had been preferred resulting in gestational diabetes, osteoporosis and bilateral cataract.

At presentation, orbital magnetic resonance imaging (MRI) and Positron emission tomography – computed tomography (PET/CT) scan were performed (Table 1). After 6 months dupilumab treatment (300 mg fortnightly), asthma control was fully achieved, nasal obstruction disappeared and eyelid swelling decreased. Prednisone was gradually tapered and finally withdrawn at 6 months. At 18 months, no relapse occurred, and MRI abnormalities and IgG4-RD Responder Index (RI) decreased [6].

Case 2: a 72-year-old man was referred for relapsing AAPOXs. Eight years previously, a palpebral biopsy revealed fibrous septa infiltrated by characteristic Touton giant cells as well as significant IgG4+ plasma cell infiltrate (i.e., IgG4+/IgG+ ratio > 0.9 and IgG4+ cells > 40/HPF) [1,7]. High dose prednisone was administered but due to hyperglycemia, 20 mg weekly methotrexate was introduced enabling prednisone weaning. Two years before presentation, methotrexate was stopped and the patient was subsequently only treated for asthma with inhaled therapy. He presented with bilateral swelling of the eyelids and recurrent polyposis. MRI showed orbital abnormalities, without infraorbital nerve involvement, and PET/CT revealed multiple FDG uptakes (Fig. 1). Six months after dupilumab initiation (300 mg fortnightly), nasal obstruction and palpebral swelling decreased. At 18 months, all the FDG-uptakes disappeared. IgG4-RD RI and biological markers dramatically decreased (Table 1). No relapse occurred and corticosteroids were avoided.

Herein, we have shown that dupilumab is effective in controlling polyposis and severe asthma even when they are part of a particular syndrome associated with NLCH. Although not histologically proven, the palpebral involvement, a major feature of AAPOXs, also appear to have responded to dupilumab. This treatment may therefore target Touton's cells that are possibly M2 differentiated macrophages expressing rIL-4/13 [8]. As recently described, dupilumab also had an effect on serum IgG4 levels and lacrimal or salivary glands swelling as well as lymph nodes [5]. However, it is difficult to distinguish dupilumab's effect on AAPOXs from its effect on IgG4-RD, since AAPOXs and IgG4-RD share common features [2]. We suggest that dupilumab may induce a durable response and could be an alternative for long-term corticosteroids use in AAPOX's patients.

Disclosure of interest

L. Sesé reports Consulting fees from Boehringer-Ingelheim, Roche/Genentech, Astra Zeneca Support for attending meetings and/or travel from Sanofi, Boehringer Ingelheim, Oxyvie, outside the submitted work. Y. Uzunhan reports personal fees and non-financial support from Boehringer-Ingelheim, personal fees from Sanofi, personal fees from CSL Vifor, grants and non-financial support from Oxyvie, personal fees from Pfizer, personal fees and non-financial support from GSK, outside the submitted work. O. Freynet, R. Dothe, S. Abad, F. Finet and M. Soussan declare that they have no competing interest.

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Table 1
Characteristics, treatment and follow-up of patients with relapsing AAPOX syndrome/IgG4-RD.

		Case 1[a]		Case 2	
Age at diagnosis/age at start of dupilumab (years)		30/41		62/72	
Gender		Female		Male	
		M0	M18	M0	M18
Clinical presentation		– Bilateral swelling of the upper and lower eyelids – Uncontrolled asthma (ACT score: 18/25, 4 severe exacerbations/year) – Stage 3 nasosinusal polyposis (SNOT22 score: 50)	– Regression of bilateral swelling of the entire eyelids – ACT score: 24/25 – No exacerbation – Stage 1 polyposis (SNOT22 score: 14)	– Bilateral swelling of the upper and lower eyelids – Controlled asthma (ACT score: 23/25) – Stage 2 bilateral nasal polyposis (SNOT22 score: 67)	– Reduction of the eyelid swelling – Controlled asthma (ACT score: 25/25) – Stage 1 bilateral nasal polyposis (SNOT22 score: 32)
MRI presentation		– Bilateral process thickening centered on the lacrimal glands (R:12 × 29 × 28 mm, L: 10 × 25 × 26 mm) – Enhancing after Gadolinium injection on the T1-weighted sequences	– Regression of bilateral expansive process on the lacrimal glands (R:11 × 21 × 25 mm, L: 10 × 15 × 23 mm) – Slightly Gadolinium contrast enhancement of the lacrimal glands	– Extraconal upper medial left intraorbital lesion (6 × 11 × 15 mm) responsible for mass effect on the superior rectus muscle. – Contrast enhancement of the mass and left superior rectus	– Total regression of the extraconal process. Normal exam
PET/CT presentation		– Bilateral tumefaction of the eyelids – Right maxillary sinus	– Full reduction in hypermetabolic foci	– Upper intraorbital left mass – Ethmoidal sinuses – Sub-mandibular salivary glands – Cervical and mediastinal lymphadenopathies – Prostate	– Total morphometabolic regression of all involved foci
PFT	FEV1 pre/post bronchodilatators	1.40(57%) /2.08(84%)	1.27(52%) /1.99(82%)	2.74(95%) /2.72(94%)	2.86(102%) /3.00(107%)
	FEV1/FCV	57%	57%	55%	65%
	RV	3.08 (211%)	2.06(138%)	55%	65%
	RV/TPC post-bronchodilatators	143%	112%		
Biomarkers					
Eosinophilia ($n < 500/mm^3$)		640	193	701	450
Total IgE ($n < 100$ UI/mL)		846	360	697	54
IgG4 (n: 0.002–1.6 g/L)		1.45	0.30	10.87	1.6
IgG3 (n: 0.17–0.8 g/L)		0.15	0.36	0.21	0.38
IgG2 (n: 0.6–5.9 g/L)		3.1	2.2	1.05	2.05
IgG1 (n: 4–10 g/L)		5.1	6.85	10.9	10.9
IgG4/IgG ratio (n: M < 0.12/F < 0.11)		0.15	0.03	0.47	0.11
Index Responder IgG4-RD[b,c]		6	1	14	0
Treatments co administered with dupilumab		– Prednisone 7 mg/d – Cumulative daily dose of 1280 μg of inhaled budesonide, 36 μg of inhaled formoterol and tiotropium	– No prednisone since M12 – Cumulative daily dose of 1280 μg of inhaled budesonide, 36 μg of inhaled formoterol and tiotropium	– Cumulative daily dose of 1280 μg of budesonide, 36 μg of formoterol)	– Cumulative daily dose of 1280 μg of budesonide, 36 μg of formoterol)

ACT: asthma control test, SNOT22: Sino-Nasal Outcome Test-22, PFT: pulmonary function test, FEV1: forced expiratory volume in 1 second, FVC: forced vital capacity, RV: residual volume, TPC: total pulmonary capacity, PET/CT: positron emission tomography/computed tomography, MRI: magnetic resonance imaging, SUVmax: maximal standard uptake value.

[a] Previously published.

[b] See Fig. 1

[c] Wallace ZS, et al. *Arthritis Care Res* 2018 [5].

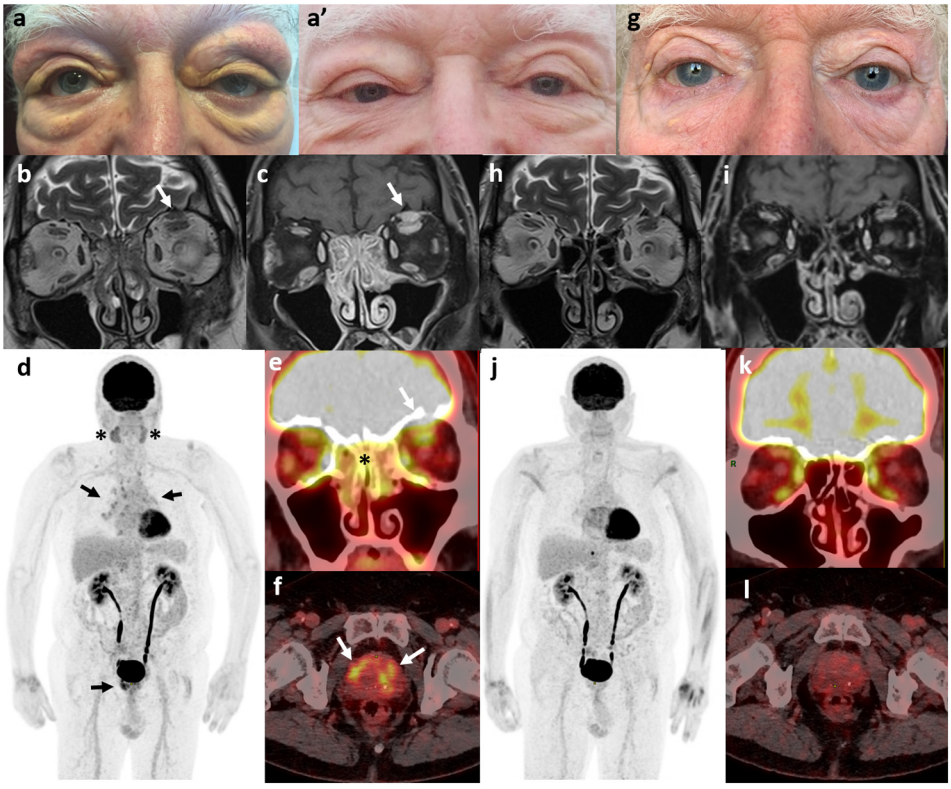

Fig. 1. Clinical and morphological evaluation in-patient 2 before and after dupilumab administration. a: bilateral yellow swelling of the upper and lower eyelids in patient 2 prior to any treatment; a': Relapsing swelling of the eyelids in patient 2 before dupilumab; b and c, arrow: orbital MRI T2-weighted and Gadolinium-enhanced T1-weighted images with fat suppression prior to biotherapy revealed a gadolinium contrast enhancement of an extraconal mass surrounding the left superior rectus; d, e,f: FDG PET/CT evaluation shows intense FDG uptake foci at the top of the left orbit (Maximum Standard Uptake Value, SUVmax = not evaluable) (e, arrow) and an ethmoidal uptake (e, star) related to an extensive nasal polyposis (SUVmax 5.7), bilateral hypermetabolic sub-maxillary glands (SUVmax = 5.3); d, stars: bilateral hilar and mediastinal hypermetabolic lymphadenopathies (SUVmax = 4.7) (d, arrows), and a FDG uptake of the prostate (d and f, arrows) related to a biopsy-proven lymphoplasmacytic infiltrate (SUVmax = 9); h, i: after an 18 months dupilumab treatment; g: the periocular oedema fully regressed; h,i: orbital MRI showed the disappearance of all abnormalities; j, k, l: FDG PET/CT highlighted complete regression of all hypermetabolic lesions.

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