Successful treatment of eosinophilic fasciitis with the anti-IL5 receptor monoclonal antibody benralizumab

Sirs,

Here we report a case of eosinophilic fasciitis (EF) successfully treated with benralizumab.

A 37-year-old man was admitted to our outpatient clinic in June 2019 because of progressive swelling and induration of upper and lower limbs together with progressive weakness and mild arthralgias.

In January 2019 the patient experienced intestinal infestation from Enterobius vermicularis, eradicated with mebendazole. No other disease or drug use was recorded.

Physical examination evidenced stiff, hard skin of upper limbs in presence of *peau d'orange* and groove sign, lower limbs oedema and tenderness at metacarpophalangeal and wrist joints.

Laboratory parameters showed increased C-reactive protein (CRP) (16.8 mg/l; normal <10 mg/l), leucocitosis (WBC 12100/mm^3) with significant eosinophilia of 3510/mm^3 (normal 300–500/mm^3) and elevated immunoglobulin G of 2030mg/dl (normal 900–1500mg/dl). ANA, ENA, RF, ACPA and ANCA were negative. Vascular disease and oncohaematological or infectious causes of eosinophilia were excluded.

Deep skin and fascial biopsy from the left upper limb showed immune cell infiltrate characterised by CD3 and CD20 lymphocytes and abundant eosinophils. The inflammatory infiltrate was mainly located at interstitial and perivascular level. The fascia showed initial signs of fibro-sclerosis; no involvement of the striated muscle was highlighted. Histological and clinical findings allowed the diagnosis of EF.

Intravenous metilprednisolone was administered, followed by per os prednisone with a relapse at drug tapering accompanied by an increase in eosinophil count. Methotrexate was added but failed to control skin lesions. In May 2020 benralizumab 30 mg/8 weeks was added with immediate improvement in skin hardness, eosinophil count normalisation (130/mm^3) and CRP reduction (0.4 mg/dl). The patient is actually continuing therapy with benralizumab and methotrexate, while steroids have been discontinued. After two years the patient did not experience any relapse of disease and eosinophils remained within the normal range. No adverse events to benralizumab were recorded.

Our patient's clinical picture was a classic EF presentation characterized by pain, swelling and stiffness of the extremities, typically accompanied by eosinophilia, hypergammaglobulinaemia and elevated inflammatory markers (1). The hallmarks of EF are the *peau d'orang*e appearance of the affected skin and the linear depression along the course of veins known as *groove sign*, mainly on forearms and lower legs (2).

The diagnosis requires a full-thickness biopsy, typically characterised by a thickened fascia with an inflammatory infiltration, mostly composed of lymphocytes and eosinophils.

EF in our patient may be associated with the previous helminth infection, as it is a recognized potential trigger of disease (3).

To date, about 300 patients with EF have been reported worldwide. Treatment of EF is still challenging and is mainly based on case series and reports.

Systemic glucocorticoids are the first-line therapy. However, relapses are frequent and require the addition of immunosuppressive agents (4). Limited data are available regarding the use of anti-TNF, anti-IL-6 agents and Janus kinase inhibitors (5-7).

The rationale to use benralizumab, a monoclonal antibody, targeting the subunit α of the IL-5 receptor (IL-5R), expressed on mature eosinophils and their precursors, resides in the ability of this molecule to induce antibody dependent cytotoxicity with consequent profound cell depletion. In cases of relapsing EF refractory to standard treatment, benralizumab may represent a promising alternative therapeutic option. In literature there are only two cases of EF treated with benralizumab: one developing as a complication of checkpoint inhibitor treatment and another one who experienced other anti-IL5 treatment failure (8, 9).

In conclusion, benralizumab can be considered a viable treatment option in patients with refractory EF. To our knowledge this is the third patient affected from EF to be successfully treated with the anti-IL5R benralizumab and has the longest follow-up, with a 28 months period of observation.

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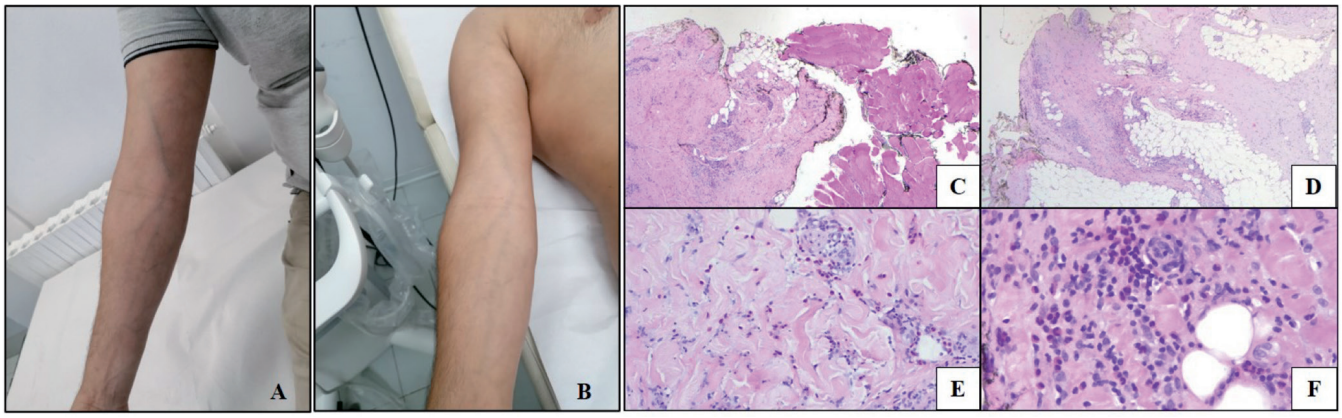

Fig. 1. Clinical and histological findings of our patient.
A: Evidence of skin changes, including dyschromia, skin thickening, groove sign and *peau d'orange* appearance of the upper limbs at diagnosis. **B**: Almost complete resolution of skin lesions after treatment with benralizumab. **C-F**: Histological findings demonstrating immune cells infiltrate involving the fascia and the deep layers of the skin and fascial fibro-sclerosis. The fascial connective tissue appears thickened, sclerotic, and infiltrated by inflammatory elements. H&E stain, original magnification 40x (**C**). The inflammatory process extends to the hypodermis and deep dermis. H&E stain, original magnification 40x (**D**). A particular of the inflammatory infiltrate mainly composed by eosinophilic granulocytes and, to a lesser extent, by lymphocytes, plasma cells and histiocytes. The surrounding stroma appears sclerotic. H&E stain, original magnification 200x (**E**) and 400x (**F**).

References

1. PINAL-FERNANDEZ I, SELVA-O' CALLAGHAN A, GRAU JM: Diagnosis and classification of eosinophilic fasciitis. *Autoimmun Rev* 2014; 13: 379-82. https://doi.org/10.1016/j.autrev.2014.01.019
2. LEBEAUX D, SÈNE D: Eosinophilic fasciitis (Shulman disease). *Best Prac Res Clin Rheumatol* 2012; 26: 449-58. https://doi.org/10.1016/j.berh.2012.08.001
3. IHN H: Eosinophilic fasciitis: From pathophysiology to treatment. *Allergol Int* 2019; 68: 437-9. https://doi.org/10.1016/j.alit.2019.03.001
4. SHINOZAKI A, HAYASHI S, HONGO T, MAKI O, SATOKO I, KEN I: Efficacy of methotrexate for steroid-resistant eosinophilic fasciitis with delayed start of treatment: a case report. *Int J Dermatology* 2022 May 15. https://doi.org/10.1111/ijd.16299
5. KHANNA D, AGRAWAL H, CLEMENTS PJ: Infliximab may be effective in the treatment of steroid-resistant eosinophilic fasciitis: report of three cases. *Rheumatology* 2010; 49: 1184-8. https://doi.org/10.1093/rheumatology/keq062
6. VÍLCHEZ-OYA F, SÁNCHEZ-SCHMIDT JM, AGUSTÌ A *et al*.: The use of tocilizumab in the treatment of refractory eosinophilic fasciitis: a case-based review. *Clin Rheumatol* 2020; 39: 1693-8. https://doi.org/10.1007/s10067-020-04952-5
7. KIM SR, CHAROS A, DAMSKY W, HELD P, GIRARDI M, KING BA: Treatment of generalized deep morphea and eosinophilic fasciitis with the Janus kinase inhibitor tofacitinib. *JAAD Case Rep* 2018; 4: 443-5. https://doi.org/10.1016/j.jdcr.2017.12.003
8. SHAMRIZ O, HERSHKO AY, TALMON A *et al:* The efficacy of off-label IL-5-modulating treatment in rare eosinophil-mediated diseases. *Allergol Int* 2021; 70: 266-8. https://doi.org/10.1016/j.alit.2020.10.001
9. LISY F, HILTBRUNNER S, GKIKOPULOS N *et al:* Treatment of checkpoint inhibitor induced eosinophilic fasciitis with benralizumab and intravenous immunoglobulin. *Ann Case Report* 2022; 7. https://doi.org/10.29011/2574-7754.100765

Book review

Passion for Excellence, My long life Journey into Medicine and Public life
Haralampos. M. Moutsopoulos MD
(Springer Biographies , October 2022)

An old friend reads, remembers and analyses. Glancing through the pages of Professor Haralampos (Harry) M. Moutsopoulos' book in which he describes his long-life journey motivated by his dreams and his hot-blooded character, I must confess that I still find him youthful, rebellious and reverently devoted to the moral values taught to him by his parents, his teachers and his social background, which formed his whole personality. Since a very early age, he learned to struggle for excellence without taking into consideration risks and cost. A passionate teacher must raise questions and doubts to his students, awaken their curiosity and sharpen their critical mind to be able to participate in fertile debates. Besides, the art of teaching is the ability to persuade, adopt and even reinforce the interlocutor's opinion. Several times, during the exciting adventure of knowledge, Professor Moutsopoulos had to cope with these principles, even though sometimes his experiences were bitter and traumatising. In those cases, his ethos and rebellious nature prevailed. Thus, with his hard work, motivated by the dreams of youth, his passion for helping the sufferer, and his investigative nature, Professor Moutsopoulos became a symbol of excellence. Always gazing upwards, overcoming obstacles, or even changing course, in order to achieve his goals and his moral standards. A multidisciplinary education, the production of new knowledge and the insistence on assimilating novelty were among his prime goals. Thanks to his education, talent and his incessant hard work, he achieved them all. His recognition worldwide as a clinician-scientist of the highest rank constituted an irrefutable fact. During his entire life, Professor Moutsopoulos never stopped pursuing scientific production and introducing young students into the dreamy world of knowledge. He never stopped teaching his students and young colleagues the sense of human and medical duty. After his education and work in renown medical centres in the USA, he repatriated to his homeland. Moutsopoulos desire to offer his help back in his homeland where he had spent his childhood. After all, our childhood is our true homeland. Neither his indisputable scientific prestige nor his young age could prevent the pettiness of some people. But Harry got rid of all the thorny obstacles, opened new roads, and created the background to pave new paths. There were many people who clashed with him because of his fight against the decline but he always followed his father's exhortation: "Good would always triumph". After completing the necessary reforms at the university of his hometown, he decided to undertake the arduous task of reforming the Department of Pathophysiology in the Medical School, at the University of Athens, where many years ago, he first became acquainted with medical and scientific knowledge. These new pursuits were filled with thorny obstacles, but Moutsopoulos had already become a hurdle race champion. The obstacles were overcome and his dream of reforming the national health system has been fulfilled. During his life journey, Moutsopoulos fought against corruption, favouritism, ingratitude, nepotism, and all kinds of power games. He resisted and struggled against all circumstances and, in most cases, was vindicated. In a country torn by a troubled political system, there are some few bright personalities that can really make the difference. Along his long-life journey, Harry met some charismatic people and forged collaborations with them in order to ameliorate and modernise the basic infrastructures. Professor H. Moutsopoulos reached the top of his academic and scientific career. He became a life member of the Academy of Athens holding the Chair of Medical Sciences-Immunology in Science Section. What is his legacy? Professor Moutsopoulos has set the example of a man who has defended the values of meritocracy, responsibility, and respect for the sufferer, but above all, he was the one who set the standards for the pursuit of new medical knowledge.

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