

## Immune Thrombocytopenic Purpura in a Patient with Atopic Dermatitis Treated with Dupilumab

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Atopic dermatitis (AD) is a highly pruritic, chronic inflammatory skin disease with major socioeconomic impact. Severe cases of AD often require systemic treatment (1). Currently available options include classic immunosuppressants and the new biologic agent dupilumab (2). Dupilumab is a monoclonal antibody that directly blocks the shared alpha chain subunit of interleukin (IL)-4 and IL-13 receptors, thereby inhibiting the IL-4/IL-13 pathway. Both represent key cytokines in type 2 T helper cells (Th2)-mediated AD pathophysiology (3). To date, dupilumab has presented a low profile of side-effects, most commonly, conjunctivitis (3, 4).

### CASE REPORT

We report here a case of a 70-year-old woman with AD, who developed immune thrombocytopenic purpura (ITP) during treatment with dupilumab. The patient had a history of AD with insufficient response to topical treatment. Systemic therapy, with dupilumab 300 mg, administered every 2 weeks subcutaneously, was therefore commenced in December 2018. Skin lesions and pruritus improved, severity SCORing Atopic Dermatitis (SCORAD) values decreased from 61 to 15 within 6 months. The patient's skin condition was examined regularly and laboratory testing was performed, including full blood count and differential parameters for renal function, liver function, inflammation, and electrolytes. After 3 months of dupilumab treatment, the patient presented elevated platelet counts of 528 G/L, as had been documented previously by her general practitioner. After an additional 6 months, platelet counts were within the normal

range again. In January 2020, approximately one year after the onset of dupilumab, she had platelet counts of 54 G/L whilst being clinically asymptomatic. After a further 3 months, she presented with haematoma on the trunk and extremities and petechiae on her lower legs (Fig. 1). Dupilumab administration was paused immediately, as her platelet levels had fallen below 5 G/L in April.

The patient was referred to our Department of Hemato-oncology on the same day. Histopathological skin examination revealed a superficial perivascular, lymphocytic infiltrate lacking granulocytes, as well as extravasal erythrocytes. Malignancy, infectious diseases, bone marrow damage, myelodysplastic syndromes, splenomegaly, autoimmune disorders, autoimmune thyroid diseases, and severe vitamin deficiency were excluded by laboratory tests, testing for platelet autoantibodies, abdominal sonography and bone marrow examination with cytology and histology, which indicated increased peripheral consumption of platelets in accordance with ITP. The interdisciplinary board considered ITP, probably medication-induced, as a causal diagnosis. During hospitalization, she received dexamethasone pulse therapy (40 mg/day) for 4 days. Her platelet levels increased to 68 G/L before discharge.

The patient's longstanding medications included candesartan, l-thyroxine, budesonide/formoterol spray and gabapentin. Dupilumab and intermittent use of cefuroxime for nasopharyngitis, most recently in February 2020, were new medications. A detailed medical history did not reveal any other potential triggers for ITP. This incidence was reported to the Drug Commission of the German Medical Association.

As of May 2020, the patient's AD is well controlled without systemic treatment (SCORAD 16). Her platelet levels are closely monitored in a hemato-oncological outpatient clinic. Her therapy initially consisted of systemic steroid therapy. At time of writing, the patient receives oral thrombopoietin-receptor agonist eltrombopag due to lack of remission.



Fig. 1. Haematoma and petechiae on both lower legs, which had developed after dupilumab therapy.

## DISCUSSION

We report here a patient with AD who developed an ITP during treatment with dupilumab. This human monoclonal antibody has shown a good efficacy for treatment of moderate-to-severe AD. AD inflammation is driven by a dysbalance of Th2 and type 1 T helper cells (Th1). Dupilumab blocks the signalling of pro-inflammatory Th2 cytokines IL-13 and IL-4, thus reverting the Th1/Th2 balance (5). It presents a low side-effect profile compared with immunosuppressants such as cyclosporine. Common side-effects include conjunctivitis, oral herpes simplex reactivation, eosinophilia and injection-site reactions (3). As shown in clinical trials, dupilumab may lead to a mild decrease in platelet levels compared with placebo, but these changes were not clinically significant (4). These included grade 2 and 3 thrombocytopenia, but the magnitudes of change in platelet levels were similar in the dupilumab and placebo groups, while grade 4 thrombocytopenia occurred only in the placebo group (4). As of 2020, approximately 50,000 patients worldwide receive dupilumab, and, to date, this is the first published report of dupilumab-associated ITP.

ITP is classified into a primary *de novo* form, comprising 80% of cases, and a secondary form. Known trigger factors for secondary ITP include infections or interacting drugs (6). Therefore, the nasopharyngitis or the use of cefuroxime might have contributed to our patient's ITP. Gabapentin is a known trigger for thrombocytopenia, but since it had been taken at a stable dose since 2014, a causative relation was considered unlikely. The pathophysiology of ITP involves Th1-dominated inflammation, as a Th1/Th2 imbalance with an increased Th1 cell count is present in patients with ITP (7, 8). In AD, Th1/Th2 imbalance is shifted towards Th2 inflammation. Blocking of Th2 cytokine production by dupilumab may revert this imbalance towards Th1 responses, as evidenced by the occurrence of psoriasis upon dupilumab treatment (9). Hence, dupilumab-mediated changes towards Th1 responses may trigger ITP. The observation of clinical symptoms, such as purpura or haemorrhages, in dupilumab-treated patients should lead to closer monitoring of platelet counts, so as to not miss a possible case of ITP. In conclusion, a combination of nasopharyngitis, cefuroxime intake and reversion of a Th1/Th2 imbalance

by dupilumab may have contributed to the ITP in this patient.

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## REFERENCES

1. Wollenberg A, Oranje A, Deleuran M, Simon D, Szalai Z, Kunz B, et al. ETFAD/EADV Eczema task force 2015 position paper on diagnosis and treatment of atopic dermatitis in adult and paediatric patients. *J Eur Acad Dermatol Venereol* 2016; 30: 729–747.
2. Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, Fink-Wagner A, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part II. *J Eur Acad Dermatol Venereol* 2018; 32: 850–878.
3. Seegraber M, Srour J, Walter A, Knop M, Wollenberg A. Dupilumab for treatment of atopic dermatitis. *Expert Rev Clin Pharmacol* 2018; 11: 467–474.
4. Wollenberg A, Beck LA, Blauvelt A, Simpson EL, Chen Z, Chen Q, et al. Laboratory safety of dupilumab in moderate-to-severe atopic dermatitis: results from three phase III trials (LIBERTY AD SOLO 1, LIBERTY AD SOLO 2, LIBERTY AD CHRONOS). *Br J Dermatol* 2020; 182: 1120–1135.
5. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med* 2016; 375: 2335–2348.
6. Arnold DM, Nazi I, Warkentin TE, Smith JW, Tótl L, George JN, et al. Approach to the diagnosis and management of drug-induced immune thrombocytopenia. *Transfus Med Rev* 2013; 27: 137–145.
7. Perera M, Garrido T. Advances in the pathophysiology of primary immune thrombocytopenia. *Hematology* 2017; 22: 41–53.
8. Ogawara H, Handa H, Morita K, Hayakawa M, Kojima J, Amagai H, et al. High Th1/Th2 ratio in patients with chronic idiopathic thrombocytopenic purpura. *Eur J Haematol* 2003; 71: 283–288.
9. Senner S, Eicher L, Aszodi N, Prinz JC, French LE, Wollenberg A. Psoriasis bei Dupilumab-behandeltem atopischem Ekzem. *Hautarzt* 2020; 71: 383–386.