

developed a reddish oval patch on her back (*figure 1F*). Skin biopsy showed thickened and hyalinized collagen, suggestive of localized scleroderma (morphea) (*figure 1G, H*). At this point, we searched for scleroderma-related autoantibodies. Interestingly, both anti-topoisomerase I Ab (ATA; x16) and anti-RNA polymerase III Ab (RNAPIII; 52), which are associated with diffuse cutaneous systemic sclerosis (dcSSc), were detected. Anti-centromere antibody (ACA), which is associated with limited cutaneous systemic sclerosis (lcSSc), was not detected. No sclerosis was apparent at this time, except for morphea on the back. One year later, while under PSL at 9 mg/day, the patient developed sclerosis in her fingers and forearms (*figure 1I*). Skin biopsy showed thickened and hyalinized collagen, suggestive of sclerosis (*figure 1J, K*). Collectively, the patient developed SLE, SS, RA, localized scleroderma, and dcSSc, therefore, she was diagnosed with overlap syndrome. Neither renal dysfunction (nephritis or renal crisis) nor interstitial lung disease has so far developed.

In principle, autoantibodies in SSc are mutually exclusive except for anti-U1-RNP Ab in one case [1]. However, the coexistence of ACA and ATA is not very rare.

Two studies have addressed the coexistence of ACA and ATA in SSc based on published reports and found coexistence in 0.52% (28/5,423) [2] and 0.6% (29/4,687) [3] of SSc patients, respectively. By contrast, the coexistence of two dcSSc-associated autoantibodies (ATA and RNAPIII) is very rare [4]. To the best of our knowledge, the coexistence of ATA and RNAPIII has been only reported in one patient [5]. In this regard, our case is the second to demonstrate the coexistence of two dcSSc-associated autoantibodies.

In addition to the presence of ATA and RNAPIII, several other autoantibodies (such as anti-ssDNA Ab, anti-Sm Ab, anti-SS-A Ab, anti-SS-B Ab, and anti-CCP Ab) were also detected in our patient. This suggests that the production of autoantibodies is abnormally enhanced, possibly reflecting the aberrant B and plasma cell activities. In this regard, we speculate that our case demonstrated overlap between ATA-positive dcSSc and RNAPIII-positive dcSSc, along with other systemic autoimmune rheumatic diseases. ■

Disclosure. *Conflicts of interest: none.*

¹ Department of Dermatology,
Faculty of Medicine, University of
Yamanashi, Yamanashi,

² Department of Dermatology,
University of Tokyo Graduate
School of Medicine, Tokyo, Japan
<yogawa@yamanashi.ac.jp>

Takae SHIMIZU¹
Youichi OGAWA¹
Ozumi TOMITA¹
Yoshihide ASANO²
Shinji SHIMADA¹
Tatsuyoshi
KAWAMURA¹

1. Iaccarino L, Gatto M, Bettio S, *et al.* Overlap connective tissue disease syndromes. *Autoimmun Rev* 2013; 12: 363-73.

2. Dick T, Mierau R, Bartz-Bazzanella P, *et al.* Coexistence of antitopoisomerase I and anticentromere antibodies in patients with systemic sclerosis. *Ann Rheum Dis* 2002; 6: 121-7.

3. Heijnen IA, Foocharoen C, Bannert B, *et al.* Clinical significance of coexisting antitopoisomerase I and anticentromere antibodies in patients with systemic sclerosis: a EUSTAR group-based study. *Clin Exp Rheumatol* 2013; 31: 96-102.

4. Mierau R, Moinszadeh P, Riemekasten G, *et al.* Frequency of disease-associated and other nuclear autoantibodies in patients of the

German Network for Systemic Scleroderma: correlation with characteristic clinical features. *Arthritis Res Ther* 2011; 13: R172.

5. Fritsch S, Pizzol VI, Paiva Edos S, Muller Cde S. Autoantibodies coexistence in systemic sclerosis: how to interpret it? *Rev Bras Reumatol* 2012; 52: 952-5.

doi:10.1684/ejd.2018.3475

Rituximab revisited: successful management of severe childhood atopic dermatitis

Atopic dermatitis (AD) is a chronic inflammatory disease affecting up to 25% of the paediatric population. A subset of patients follows a recalcitrant course for which there is an unmet need for effective therapy. In rarer instances, an underlying primary immunodeficiency, such as hyper-IgE syndrome (HIES), should be suspected.

A seven-year-old Caucasian boy from non-consanguineous parents presented with widespread, intensely pruritic ill-defined erythematous plaques (*figure 1A-C*). Severe atopic eczema was diagnosed in the third month of life, while food allergies and asthma were diagnosed at two and five years old, respectively. His medical course was characterized by multiple exacerbations and hospitalizations, some due to mucocutaneous infections of viral aetiology (disseminated varicella and herpetic gingivostomatitis). Immunoglobulin E (IgE) (51,120 KUI/L; range ≤ 403.0) and both relative

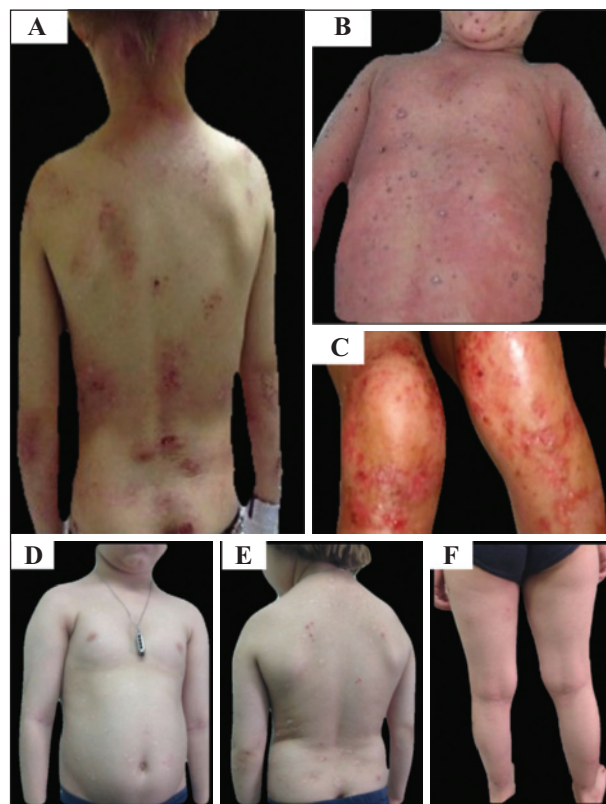


Figure 1. Severe widespread atopic eczema: A-C) pre-treatment with rituximab; D-F) near-complete remission two months after the last rituximab infusion.

(11.4%) and absolute ($1,630 \times 10^9/L$) eosinophil blood values were increased. Blood immunophenotyping was unremarkable, namely for maturation and activation markers (T cells: CD3+ CD4+ CD45RA+ CD45RO+ CD62L+; B cells: CD27- IgD+ IgM+ CD27+IgD/MZL CD38++), the Toll-like receptor pathway, lymphocyte proliferative responses to mitogens and antigens, as well as Th17 populations. Due to the clinical and laboratory findings, a diagnosis of autosomal recessive (AR) HIES, *DOCK8* deficiency syndrome, was suspected. *DOCK8* sequencing revealed a heterozygous mutation in exon 37: c.4636A>G (p.Arg1546Gly).

Topical and systemic steroids provided transient, albeit, insufficient relief. Systemic immunomodulation with cyclosporine and methotrexate was ineffective. The corticosteroid-induced side effects led to unacceptable morbidity and steroid-sparing alternatives were sought. Due to the ineffectiveness of conventional systemic treatments to address the skin disease and paucity of therapeutic options at the time, rituximab (RTX) (375 mg/m² once weekly for four weeks) was attempted when the patient was eight years of age. The patient's baseline SCORAD (SCORing Atopic Dermatitis) was 75.2. A marked improvement was already observed by the third infusion. Two months after the fourth treatment (figure 1D-F), he was almost clear (SCORAD 12.4). Systemic steroids were slowly withdrawn over two weeks, from the second infusion to the fourth infusion, with no relapse. IgE levels were reduced by 77.1% with treatment (51120-11693 KUI/L), but no relief from food allergies was reported. Remission persisted for 10 months. A significant relapse was then observed, but retreatment with RTX led again to a near-complete clearance. Currently, three years later, at 11 years of age, the patient's quality of life is far improved as AD is now manageable, with occasional minor relapses treated with topical steroids. No further infectious, autoimmune or neoplastic processes were observed to date on longitudinal follow-up.

Current approaches for severe AD are often insufficient. Topical agents are inappropriate for widespread disease, while conventional systemic agents provide variable success at the expense of long-term toxicity. Dupilumab is an emerging, encouraging therapy, although not yet available in many countries and without proven usefulness for paediatric AD.

To our knowledge, this is the first case of a severe childhood AD treated with RTX, an anti-CD20 biological drug that depletes B cells through several cell death mechanisms. Formerly approved in 1997 for B-cell lymphomas, RTX is nowadays used for a wide spectrum of malignant and immune disorders. Its success in adult AD was firstly demonstrated in 2008 [1]. Further evidence followed with isolated reports [2] and case series [3]. Nevertheless, there is still a paucity of robust evidence regarding its use for AD [4], especially in the paediatric population where the disease is exceedingly common. This is reflected, to a certain degree, by two conflicting reports in which RTX failed to improve AD in adults [5, 6]. Moreover, AD immunological mapping is focused on T-cell driven inflammation, whereas the B-cell role is unclear. Notwithstanding, lesional CD20+ cell density correlates with disease severity and was suggested as a biomarker for severe AD [7]. In addition, CD19- AD murine models have less dermo-epidermal thickening and lower CD4+ and eosinophilic counts [8].

More recently, a distinct B-cell signature was identified in AD [7]. By differentially polarizing naïve T cells into T_H1/T_H2 effector responses [9], dysregulated B cells may act as positive regulators within the AD framework by amplifying characteristic pathological T-cell chronic activation. Both experimental and clinical evidence available provide significant rationale to explore B-cell therapies for the management of moderate-to-severe AD.

In addition to early-onset severe eczema, this patient had asthma, food allergies, recurrent mucocutaneous infections, increased IgE, and eosinophilia [10], which led us to suspect AR-HIES/*DOCK8* syndrome. Through genetic testing, we identified an interesting heterozygous *DOCK8* mutation. To date, the literature has focused on *DOCK8* syndrome associated with bi-allelic mutation or deletion [11], thus the significance of our finding is unclear. It is possible that this mutation represents merely a fortuitous event or a contributing factor with regards to the impressive severity of the disease. Moreover, to date, our patient has not yet developed further infectious, autoimmune or neoplastic manifestations, suggestive of primary immunodeficiency. Further clarification should be sought by studying the health repercussions in heterozygous *DOCK8* carriers.

In summary, our case highlights the efficacy, tolerability, and durable remission of recalcitrant paediatric eczema with B-cell targeted therapy. It is possible that only a subset of AD patients with distinct immunological derangements will be able to benefit from this approach. Studies to identify predictive markers of AD responsiveness to RTX are warranted. In addition, we highlight that primary immunodeficiency should be suspected in early-onset severe eczema. The health consequences of *DOCK8* heterozygous mutation should be further studied in longitudinal trials. ■

Disclosure. Funding sources: none. Conflicts of interest: none.

¹ Department of Dermatology,
Hospital de Santo António dos
Capuchos,
² Department of Paediatrics,
Hospital de Dona Estefânia, Centro
Hospitalar de Lisboa Central,
Lisbon, Portugal
<brunoduarte@campus.ul.pt>

Bruno DUARTE¹
Ana CORDEIRO²
Maria João
PAIVA-LOPES¹

1. Simon D, Hösli S, Kostylina G, Yawalkar N, Simon HU. Anti-CD20 (rituximab) treatment improves atopic eczema. *J Allergy Clin Immunol* 2008; 121: 122-8.
2. Ponte P, Lopes MJP. Apparent safe use of single dose rituximab for recalcitrant atopic dermatitis in the first trimester of a twin pregnancy. *J Am Acad Dermatol* 2010; 63: 355-6.
3. Sánchez-Ramón S, Eguíluz-Gracia I, Rodríguez-Mazariego ME, et al. Sequential combined therapy with omalizumab and rituximab: a new approach to severe atopic dermatitis. *J Investig Allergol Clin Immunol* 2013; 23: 190-6.
4. Snast I, Reiter O, Hodak E, Friedland R. Are biologics efficacious in atopic dermatitis? A systematic review and meta-analysis. *Am J Clin Dermatol* 2018; 19: 145-65.
5. McDonald BS, Jones J, Rustin M. Rituximab as a treatment for severe atopic eczema: failure to improve in three consecutive patients. *Clin Exp Dermatol* 2016; 41: 45-7.
6. Sedivá A, Kayserová J, Vernerová E, et al. Reply to: Anti-CD20 (rituximab) treatment for atopic eczema. *J Allergy Clin Immunol* 2008; 121: 1514-5.

7. Czarnowicki T, Gonzalez J, Bonifacio KM, *et al.* Diverse activation and differentiation of multiple B-cell subsets in patients with atopic dermatitis but not in patients with psoriasis. *J Allergy Clin Immunol* 2016; 137: 118-29.e5.
8. Yanaba K, Kamata M, Asano Y, *et al.* CD19 expression in B cells regulates atopic dermatitis in a mouse model. *Am J Pathol* 2013; 182: 2214-22.
9. Harris DP, Haynes L, Sayles PC, *et al.* Reciprocal regulation of polarized cytokine production by effector B and T cells. *Nat Immunol* 2000; 1: 475-82.
10. Aydin SE, Kilic SS, Aytekin C, *et al.* DOCK8 deficiency: clinical and immunological phenotype and treatment options - a review of 136 patients. *J Clin Immunol* 2015; 35: 189-98.
11. Biggs CM, Keles S, Chatila TA. DOCK8 deficiency: insights into pathophysiology, clinical features and management. *Clin Immunol* 2017; 181: 75-82.

doi:10.1684/ejd.2018.3476

Primary cutaneous Ewing sarcoma in a young girl

A seven-year-old girl presented with a non-progressive erythematous nodule of 5 mm in diameter that had appeared on the back of her right hand one year earlier (*figure 1A*). Excision of the tumour by shave-coagulation was conducted. Histopathological analysis revealed a circumscribed lesion in the reticular dermis composed of densely packed sheets of small and uniform cells with a pseudovascular pattern (*figure 1B, C*). Immunohistochemical analysis demonstrated a strong positive CD99 cell membrane signal, suggestive, but not specific to, cutaneous Ewing sarcoma (ES) (*figure 1E, F*). Tumour cells also stained positive for cytoplasmic granular PAS (periodic acid-Schiff) (*figure 1D*).

Molecular analysis using fluorescence *in situ* hybridisation (FISH) confirmed the diagnosis of ES by revealing a specific chromosomal translocation involving the *EWSR1* (ES breakpoint region 1) gene on chromosome 22 and *FLII* (Friend leukaemia virus integration 1) gene on chromosome 11, leading to an oncogenic fusion.

The extended workup, including radiography and echography of the right hand, as well as magnetic resonance imaging and positron emission computed tomography, proved negative.

The final diagnosis was primary cutaneous ES (pCES).

Although the lesion was restricted to the skin and well-defined, the patient's young age and the tumour's metastatic potential prompted us to initiate neoadjuvant chemotherapy, followed by surgery and maintenance chemotherapy according to the Euro-Ewing 88 protocol (less intensive than the standard protocol).

The treatment consisted of five bimonthly courses of induction chemotherapy, consisting of cyclophosphamide at 150 mg/m² for seven days, followed by doxorubicin at 35 mg/m² on day 8. After this induction, surgery was performed with margins of at least 5 mm, which were negative. Radiological evaluation revealed no suspicious mass, and no additional radiotherapy was conducted. Maintenance chemotherapy was initiated consisting of two phases. The

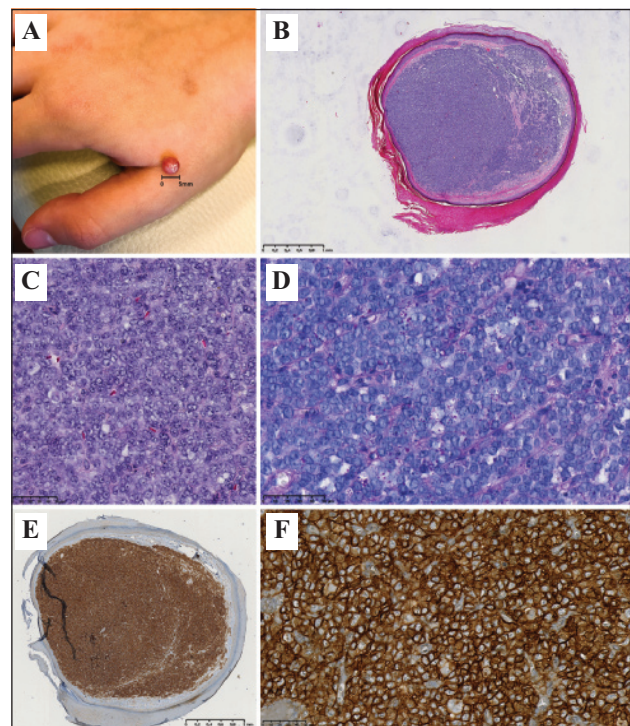


Figure 1. Clinical and histopathological features. **A)** Nodular erythematous lesion on the back of the right hand, between the first and second metacarpal. **B)** Nodular lesion in the dermis (haematoxylin-eosin stain; $\times 2.5$ magnification). **C)** Densely packed sheets of small uniform cells (haematoxylin-eosin stain; $\times 40$ magnification). **D)** Cytoplasmic granular PAS positivity of tumour cells (Periodic acid-Schiff stain; $\times 48$ magnification). **E)** CD99 expression in tumour cells. **F)** Strong positive CD99 cell membrane signal.

first period included vincristine at 1.5 mg/m² weekly for 11 weeks and actinomycin every two weeks for up to six doses. The second period comprised six courses of cyclophosphamide and doxorubicin, similar to the induction scheme [1]. There was no evidence of disease progression one year after the diagnosis.

ES, or primitive neuroectodermal tumour (PNET), is mostly a primary tumour arising from bone or soft tissues. pCES is a very rare condition, with approximately 150 cases reported to date [1-3]. Most cases are observed in young adult female patients [3]. The lesion presents as a dermal or hypodermic circumscribed mobile nodule with a size < 5 cm (1-12 cm), but clinical presentations may be heterogeneous. The most common locations are the extremities and trunk [3, 4].

Histopathological diagnosis of ES is tricky, requiring immunohistochemistry and molecular biological investigations to exclude other conditions associated with undifferentiated mesenchymal cells. CD99 antibody is not specific to ES and can be expressed in haematological malignancies, carcinomas, and sarcomas. However, the combination of cytoplasmic granular PAS positivity of tumour cells (ES cells are rich in glycogen) and a cell membrane CD99 positive stain is highly suggestive of ES [5].