



BRIEF COMMUNICATION

Severe eczema and Hyper-IgE in Loeys–Dietz-syndrome — Contribution to new findings of immune dysregulation in connective tissue disorders



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Abstract Loeys–Dietz syndrome (LDS) is a connective tissue disorder caused by monoallelic mutations in *TGFBR1* and *TGFBR2*, which encode for subunits of the transforming growth factor beta (TGF β) receptor. Affected patients are identified by vascular aneurysms with tortuosity and distinct morphological presentations similar to Marfan syndrome; however, an additional predisposition towards asthma and allergy has recently been found. We describe two patients with a novel missense mutation in *TGFBR1* presenting with highly elevated levels of IgE and severe eczema similar to autosomal-dominant Hyper-IgE syndrome (HIES). Mild allergic manifestations with normal up to moderately increased IgE were observed in 3 out of 6 additional LDS patients.

Abbreviations: TGF β , transforming growth factor beta; T_{reg}, regulatory T cells; TGFBR, Transforming growth factor beta receptor; LDS, Loeys–Dietz syndrome; MFS, Marfan syndrome; EDS, Ehlers–Danlos syndrome; TAAD, thoracic aortic aneurysm and dissections; HIES, Hyper-IgE syndrome; EBV, Epstein–Barr virus.

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A comparison of this cohort with 4 HIES patients illustrates the significant overlap of both syndromes including eczema and elevated IgE as well as skeletal and connective tissue manifestations.

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1. Introduction

The widely distributed cytokine TGF β plays an essential role in the immune system by regulating T-cell differentiation and promoting immunosuppression through regulatory T-cells (T_{regs}) in vivo [1]. Its impact on immune regulation has mainly been explored in mouse models, where abrogation of TGF β signaling leads to fatal inflammation [2–4].

TGF β signals through a tetrameric complex formed by homodimers of type 1 and type 2 TGF β receptor subunits (encoded by *TGFBR1* and *TGFBR2*) that initiate downstream phosphorylation of Smad and other proteins transferring the signal to the nucleus [5].

Defective TGF- β signalling has only recently been associated with human disease. Loeys–Dietz syndrome (LDS) is an autosomal dominant genetic disease caused by monoallelic mutations in *TGFBR1* or *TGFBR2*. It is related to connective tissue disorders, such as Marfan (MFS) or Ehlers–Danlos syndrome (EDS), which share aberrations in the TGF β pathway [6,7]. Affected patients present with vascular abnormalities, such as arterial aneurysms and tortuosity, a marfanoid *habitus* including skeletal dysmorphisms and lax joints [8]. However, the clinical phenotype of LDS patients can be variable and occur with milder manifestations like isolated thoracic aortic aneurysm and dissections (TAAD) [9].

Apart from connective tissue disorders, genetic defects in TGF β receptors account for many manifestations, and, by way of example, have a long known relevance in tumorigenesis [10–12]. Furthermore, epidemiologic and epigenetic studies identified a strong association of genes related to the TGF β pathway with the development of allergic diseases [13–17]. An allergic phenotype, including asthma, food allergy, allergic rhinitis and atopic eczema, has recently been described with more than 50% prevalence in a cohort of 58 LDS patients carrying either *TGFBR1* or *TGFBR2* mutations [18]. A considerable proportion of LDS patients presented with eosinophilic gastrointestinal diseases (EGIDs), which have also been found in patients with other connective tissue disorders [19].

We describe two related patients with an unreported mutation in *TGFBR1* sharing a more severe phenotype with severe eczema and elevated Immunoglobulin E (IgE). We studied 6 additional LDS patients and compared their clinical and immunological phenotypes to a small cohort of patients with autosomal dominant Hyper-IgE syndrome (HIES) [20,21].

2. Methods and results

2.1. Patients

A five year old girl (P1.1) with highly elevated levels of IgE and severe eczema was referred to our clinic because of suspected autosomal dominant Hyper-IgE syndrome (HIES).

She had a history of recurrent pneumonia during the last three years; methicillin-resistant *Staphylococcus aureus* was isolated from bronchoalveolar lavage during the most recent infection. The eczema had occurred in her first year of life, where IgE levels of 3700–5800 kU/l came to first attention. As her father died due to a sudden rupture of an unknown aortic aneurysm, she and her father's sister (P1.2) were diagnosed with LDS. A missense mutation in *TGFBR1* leading to the amino acid change T274S was found in both patients. P1.1 presented with features characteristic for LDS (Table 1 and Fig. 1), as well as moderate bronchial asthma and allergic rhinitis.

Also P1.2 manifested LDS and allergic diseases (Table 1). Strikingly, years before her diagnosis of LDS, she was seen by an immunologist with suspected HIES, which could not be confirmed. Although she had no history of severe infections, her IgE level was 60,400 kU/l at that time and she was suffering from severe eczema persisting until adulthood. Other than an elevated IgG of 19.3 g/l, no additional abnormalities were found. Of interest, she reported retention of deciduous teeth in her childhood. No other family member had presentations related to LDS or HIES.

After identifying these two patients with LDS and immune dysregulation, we analyzed 6 additional LDS patients for similar phenotypes. P1.3 had a history of recurrent sinusitis, mild bronchial asthma and allergies with moderately elevated IgE (Table 1). Of note, also he reported retention of two deciduous teeth. Two out of five patients with heterozygous *TGFBR2* missense mutations had mild allergies, none had elevated IgE. Infection susceptibility was not pathological.

Since we observed similarities to clinical presentations of HIES in P1.1 and P1.2, we included 4 HIES patients with monoallelic STAT3 mutations as controls in our immunological studies (Table 1).

Written informed consent was obtained from all patients and parents for blood sampling and collection of clinical data. The study was approved by the ethical board of the University Hospital Freiburg, Germany.

2.2. Immunological analysis

In order to define the immunologic phenotype and a possible overlap of LDS and HIES patients, we evaluated occurrence of infections, allergy, and connective tissue abnormalities associated with either LDS or HIES (Table 1). Considering the role of TGF β in T-cell differentiation [22], we studied the distribution of IFN γ , IL-4 and IL-17 producing CD4⁺ T-cells and CD4⁺CD25⁺FOXP3⁺ regulatory T cells (T_{regs}) by flowcytometry, as well as the fraction of class-switched memory B-cells, immunoglobulin levels and vaccine titers (Table 1, Fig. 1). Healthy donors served as controls.

Except the elevated levels of IgE, and slightly, but not significantly, reduced IL-17 production in T helper cells of P1.1

and P1.2, our studies did not reveal any pathological findings in LDS patients. Levels of IgG, IgM and IgA were in normal ranges, and vaccine responses were unaffected. In contrast to HIES patients, the fraction of Th17 and switched memory B-cells was not altered in LDS patients compared to healthy controls. Of note, all patients of this cohort had no significantly abnormal T_{reg} numbers.

2.3. TGF β signaling

To determine TGF β signaling efficiency, we assessed Smad2 phosphorylation in patient-derived EBV-transformed B-cells after dose-dependent TGF β challenges (Fig. 1). Cells were starved for 4 h under serum-free conditions before being challenged with 0, 0.1, 0.5, and 10 ng/ml TGF β (Miltenyi) for 30 min. Protein was extracted from lysed cells and phosphorylated Smad2 (CellSignal) was detected by immunoblotting of adjusted protein amounts of all samples. Subsequently, all blots were stripped twice followed by Smad2 (CellSignal) and beta-actin (Sigma) detection as loading controls.

Compared to healthy controls, phosphorylated Smad2 appeared to be normal to slightly reduced in the majority of patients (Fig. 1). However, Smad2 phosphorylation was repeatedly non-inducible in P6.1 carrying a missense mutation in *TGFBR2*, which was an unexpected incidental finding.

3. Discussion

Whereas most of the knowledge about TGF β function has been derived from mouse models, the translation into clinical studies is limited. Heritable connective tissue disorders such as MFS, vascular EDS (type IV) and LDS overlap with clinical presentations such as thoracic aortic aneurysm and dissection (TAAD), heart valve regurgitation, facial and skeletal malformations, skin changes and dural ectasia. MFS is caused by loss-of-function mutations in fibrillin-1 encoded by *FBN1*, and manifestations of this disorder are related to increased TGF β liberation from its binding proteins in the extracellular matrix involving interaction with fibrillin-1 [6,7]. Vascular EDS exhibits abnormal type III collagen biosynthesis and is caused by mutations in *COL3A*, where TGF β associates with collagen synthesis and extracellular matrix degradation [23]. Patients with LDS carry mutations in either *TGFBR1* or *TGFBR2*, which relate to various phenotypes comprising LDS type 1 with cleft palate, craniosynostosis, or hypertelorism, LDS type 2 with vascular EDS-like phenotype or TAAD phenotype [23,9]. Although altered TGF β signaling is well described in genetic connective tissue disorders; the consequences for immune dysregulation in humans has only recently been discovered and not explored in full detail.

With this study, we enlarge the spectrum of clinical presentations of immune dysregulation in LDS patients. The T274S mutation is located in the kinase domain of TGF β receptor 1 close to other mutations reported in Marfan-related disorders [12], but has not been reported before. The fact that the two affected individuals have similar LDS and immune manifestations suggests a strong genetic association. Overall, 5 out of 8 LDS patients of our cohort presented with allergic diseases and moderate IgE elevation, along with recent findings in larger cohorts [19,18]. Given the small size of our cohort, skewing of these findings towards patients with

TGFBR1 versus *TGFBR2* mutations might not be relevant. An equal distribution of allergic manifestations and elevated IgE has been reported previously in LDS patients with defects in either *TGFBR1* or *TGFBR2* [18]. We therefore argue that the more severe IgE elevation and eczema manifestation in our patients is either due to the specific mutation or to additional mutations in the family favoring these manifestations.

Whereas complete knockout of *Tgfr2* is embryonically lethal in mice [24], conditional knockout of *Tgfr2* in T-cells and dendritic cells results in depletion of Foxp3⁺ T_{regs} and an autoinflammatory phenotype [4,25]. This does not correspond to the observed clinical manifestations in LDS patients, in agreement with the widely accepted concept that LDS is caused by monoallelic missense mutations in genes encoding TGF β receptor subunits leading to gain of function and enhanced rather than reduced TGF β signaling. However, findings in conditional *Tgfr2*^{-/-} mice suggest alterations of T-cell differentiation and homeostasis that affect peripheral tolerance and T_{reg} function in particular. We did not find significant abnormalities in T-cell differentiation by analyzing total numbers of Th1, Th2, Th17 cells and T_{regs} . In contrast to our observations, an increased number of total T_{regs} (defined as CD4⁺CD45⁺CD127^{lo}), with elevated CD45RA⁻CD25^{inter}Foxp3^{inter}, but unaffected CD45RA⁻CD25^{high}Foxp3^{high} populations has been found in LDS patients, although without functional impairment [18]. Furthermore, a slight skewing towards IL-13 producing T-lymphocytes in response to TGF β stimulation was noticed, but also no difference in IL-17 or IFN γ cytokine expression. Of note, our study is limited by a small number of patients.

Studying TGF β signaling, we did not find a clear alteration of Smad2 phosphorylation in patient EBV cells, except for one *TGFBR2*-mutated patient (R537C) with consistently non-inducible TGF β response. These findings contrast previous studies, in which enhanced TGF β signaling has been demonstrated on tissue sections and lymphocytes of LDS patients [8,18]. However, the detailed study of reported *TGFBR2* mutations in defined cellular systems revealed a dominant-negative effect for this mutation [26]. These controversial findings could indicate a more complex regulation of TGF β signaling in vivo, which could also differ among cell types. Furthermore, the lacking correlation of inducible Smad2 phosphorylation with clinical presentations suggests the involvement of other downstream targets.

Although from a molecular standpoint there is no direct connection between pathways involving TGF β and the transcription factor STAT3 [27], the phenotypic resemblance to HIES of P1.1 and P1.2 prompted us to study similarities among the two diseases. Noteworthy, HIES is associated with connective tissue disorders [28], which can also include vascular abnormalities [29]. Besides eczema and Hyper-IgE we observed significant clinical overlaps with HIES patients, particularly lax joints, predisposition to scoliosis, and retention of deciduous teeth. However, we did not find abnormalities in numbers of Th17 or class-switched memory B-cells, which are characteristic for HIES. Because of the attributed role of TGF β in Th17 differentiation [30], abnormalities in patients with TGF β receptor mutations had been considered and ruled out before [31]. After all, the pathogenic mechanisms leading to the altered immune phenotype in LDS patients are still elusive.

Table 1 Clinical and immunological phenotype of investigated patient cohort.

Patients/ families	Heterozygous mutations	Age at evaluation (y)	Clinical phenotype		
			Vasculature/skeleton/ connective tissue/teeth	Atopy/ immunodysregulation	Infections
<i>Patients with TGFBR1 mutations</i>					
P1.1	T274S	6	- Elongation and dilatation of the aortic root - Joint hypermobility - Bifid uvula	- Severe eczema - Bronchial asthma - Pollen rhinitis - Food allergies	- Recurrent pneumonia - Recurrent otitis media - Recurrent panaritria
P1.2	T274S	41	- Aortic aneurysm - Joint hypermobility - Scoliosis (<10°) - History of retinal detachment - Retention of deciduous teeth	- Severe eczema - Bronchial asthma - Pollen rhinitis - Food allergies	
P2.1	M253I	37	- Aortic aneurysms - Scoliosis (<10°) - Retention of deciduous teeth (2)	- Mild atopic eczema - Mild bronchial asthma - Pollen rhinitis	- Recurrent sinusitis - 2 episodes of pneumonia
<i>Patients with TGFBR2 mutations</i>					
P4.1	R460C	53	- Aortic aneurysms - Scoliosis (<10°) - Joint hypermobility	- Mild pollen rhinitis	
P4.2	R460C	33	- Aortic aneurysms - Joint hypermobility	- Mild atopic eczema - Mild pollen rhinitis - Mild food allergies	- 3 episodes of otitis media - 2 episodes of sinusitis
P4.3	R460C	30	- Aortic aneurysms - Scoliosis (<10°) - Joint hypermobility		
P5.1	R528S	15	- Aortic aneurysms - Scoliosis (>20°) - Bifid uvula		
P6.1	R537C	54	- Aortic aneurysms - Scoliosis		- 3 episodes of sinusitis
<i>Patients with STAT3 mutations</i>					
P7.1	K340E	16	- Joint hypermobility - Scoliosis - High palate - Retention of deciduous teeth (14)	- Severe eczema	- Up to 30 episodes of pneumonia - History of septic arthritis (knee) - Recurrent cutaneous abscesses
P8.1	ND	10	- Retention of deciduous teeth (4)	- Moderate eczema - Bronchial asthma - Pollen rhinitis	- 10 episodes of otitis media - Recurrent pneumonia - Recurrent cutaneous abscesses
P9.1	R382L	11	- Joint hypermobility	- Severe eczema	- 5 episodes of sinusitis - 3 episodes of otitis media - 5 episodes of pneumonia - Recurrent cutaneous abscesses
P10.1	T622I	14	- Scoliosis - High palate - Retention of deciduous teeth (6)	- Moderate eczema	- Recurrent pneumonia - History of a lung abscess
ND, not determined.					

ND, not determined.

4. Conclusion

Connective tissue disorders such as LDS can be associated with immune dysregulation and allergic diseases varying in prevalence and severity. Increased infection susceptibility should be actively looked for in LDS. It would be of interest,

whether pharmacological treatment with angiotensin II receptor antagonists, which has proven good efficiency in treating vascular manifestations in mouse models of MFS [32–34] would also have an impact on immunological phenotypes. The pathogenesis of immunologic presentations in patients with connective tissue disorders including

Laboratory results					
Switched memory B-cells	IgG (g/l)	IgA (g/l)	IgM (g/l)	IgE (kU/l)	Vaccine titers (tetanus/measles/varicella)
14.51 (↑)	1510 (↑)	178	75	3615 (↑)	–/+/+
ND	1595	219	82	24,600(↑)	+ /+ /ND.
4.68	901	372	32 (↓)	454 (↑)	+ /+ /+
11.25	941	225	129	61	+ /+ /+
9.15	922	127	133	14	ND /+ /+
6.04	1500	114	63	1	+ /+ /+
20.29 (↑)	1112	164	73	29	+ /ND /ND
14.59	1467	291	125	89	+ /+ /+
0.96 (↓)	1147	109	53 (↓)	7753 (↑)	– /+ /+
2.92 (↓)	1460	184	135	ND	+ /+ /+
5.47	1230	102	90	ND	– /+ /+
1.94 (↓)	1400	28 (↓)	108	6846 (↑)	+ /+ /+

the impact of additional genetic and environmental factors needs further investigation.

Conflict of interest statement

The authors have no financial conflict of interest.

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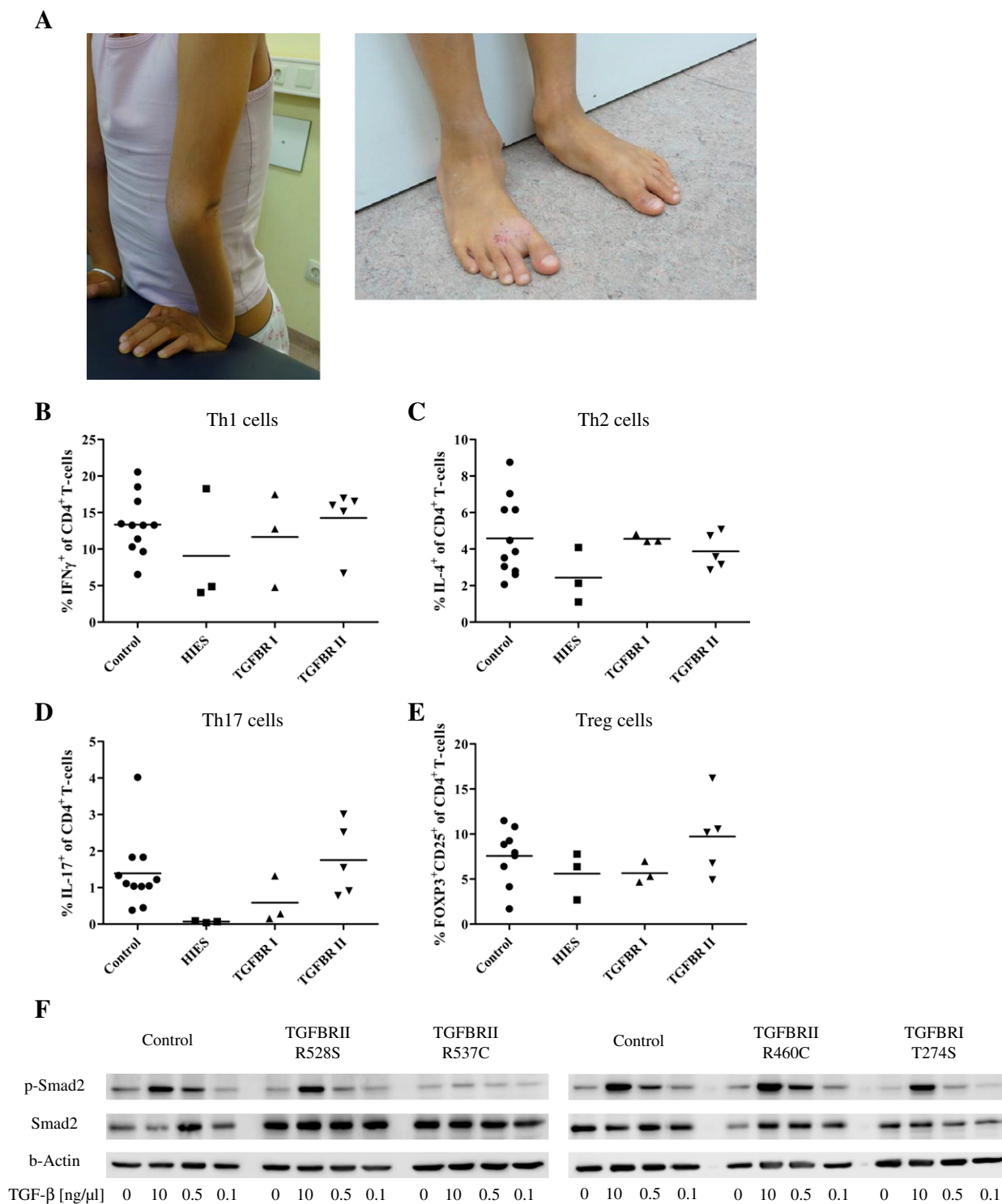


Figure 1 A: Classical morphological features for LDS including lax joints were found in P1.1. B–E: Percentages of $\text{INF}\gamma$ (Th1), IL-4 (Th2), IL-17 (Th17) expressing CD4^+ T-cell subsets and $\text{CD4}^+\text{CD25}^+\text{FOXP3}^+$ regulatory T-cells (T_{reg}) are shown for LDS patients distributed in patient groups with *TGFBR1* and *TGFBR2* deficiencies, HIES and healthy controls (B–E). F: Phosphorylated Smad2 (P-Smad2), Smad2 and beta-actin were detected by immunoblotting of cell lysates from patient-derived EBV-transformed B-cells after dose-dependent challenges with $\text{TGF}\beta$.

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