

Cutaneous manifestations of immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome

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Summary

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Background Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is a rare disorder characterized by neonatal autoimmune enteropathy, diabetes and thyroiditis, food allergies and skin rash. IPEX syndrome is caused by mutations in FOXP3, a master control gene of regulatory T cells (Tregs), resulting in absent or dysfunctional Tregs. Data in the literature are scarce and the cutaneous manifestations are rarely depicted.

Objectives To evaluate the frequency and characteristics of cutaneous manifestations found in IPEX.

Methods Retrospective single-centre study of a case series of IPEX. Patients' data were retrieved from medical files and numerous parameters concerning general and cutaneous characteristics of the disease were recorded.

Results Ten children with IPEX were studied. Cutaneous involvement was present in seven of 10 children; age at onset was 0–4 months, median 1.5. All patients presented with atopic dermatitis (AD). Three presented more psoriasiform lesions. Eczema was severe; most affected areas were lower limbs, trunk and face. Pruritus was present in four of seven, and painful fissurary cheilitis in four of seven. Hyper-IgE was found in seven of 10 and hypereosinophilia in five of 10. Skin biopsies showed eczematiform or psoriasiform features. Affected patients were improved by dermatocorticoids; no clear improvement was obtained with immunosuppressive regimens. Other features were urticaria secondary to food allergies and staphylococcal sepsis, mostly *Staphylococcus aureus* and catheter related.

Conclusions AD seems to be a frequent finding in IPEX syndrome, which is characterized by Treg anomalies. This hints to a possible role of Tregs in AD, which is then discussed in this study.

Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX; OMIM 304930) syndrome is a rare, recessive disorder that affects male infants and frequently results in early death. The causative gene has recently been identified as FOXP3 on Xp11.23,^{1–3} which is a key regulator of CD4+ CD25+ regulatory T cell (Treg) development and function. These FOXP3-expressing Tregs are potent suppressors of self-reactive T-cell activation and proliferation. They are also implicated in downregulation of immune response to exogenous antigens, such as dietary food antigens.^{4–7} In IPEX syndrome, mutations of the FOXP3 gene result in absent or dysfunctional Tregs.^{7,8} Affected children usually have an early onset of autoimmune disorders, skin rash and food allergies.^{7,9} They present with neonatal, watery and sometimes bloody diarrhoea that persists despite bowel rest and results in

failure to thrive. They may also develop neonatal insulin-dependent diabetes, thyroiditis and autoimmune cytopenias such as anaemia, thrombocytopenia and neutropenia, as well as numerous circulating autoantibodies. The clinical picture may also include diverse food allergies, hypereosinophilia, hyper-IgE and, more relevantly, skin rash. The latter has been described as eczematiform,^{3,10–12} ichthyosiform^{13,14} or psoriasiform,^{15,16} but data in the literature are scarce and the frequency and characteristics of cutaneous manifestations in IPEX syndrome are rarely depicted. Indeed, published reports of IPEX syndrome are limited; to date, there are some 83 cases published in the general literature while, to our knowledge, only three IPEX cases have been described in the dermatological literature and have addressed the specific dermatological findings seen in this syndrome.

In order to evaluate and better describe the cutaneous manifestations of IPEX syndrome, we studied the characteristics of a series of children followed in our institution for this syndrome.

Materials and methods

This was a retrospective study of the case series of children with IPEX syndrome followed at Necker-Enfants Malades Hospital, Paris. The clinical diagnosis of IPEX syndrome was based on the following criteria: (i) the clinical association of a severe neonatal diarrhoea requiring parenteral nutrition, with early autoimmune disorders, consisting of circulating auto-antibodies along with various features of autoimmune diabetes mellitus and/or thyroiditis, and at the same time severe allergy manifestations (food allergy, cutaneous allergy); and (ii) occurring in a boy. When possible, the clinical diagnosis of IPEX syndrome was confirmed after genotyping of the FOXP3 gene. Patients' clinical and biological data were analysed retrospectively. Within the general characteristics of the disease, the parameters that were recorded were: family history of similar disease (more particularly chronic diarrhoea in male infants with failure to thrive and death or neonatal diabetes); the patient's origin; age at beginning of symptoms; features of the autoimmune enteropathy including protracted diarrhoea, failure to thrive, necessity of parenteral nutrition and result of intestinal biopsy; the presence of insulin-dependent diabetes, thyroiditis, haematological abnormalities including autoimmune anaemia, thrombocytopenia and neutropenia; the presence of diffuse lymphadenopathy and/or hepatosplenomegaly, renal involvement or recurrent infections; and, more relevantly, presence of cutaneous involvement and its characteristics. Concerning the latter, we noted the age at onset of cutaneous symptoms, their localization as well as the presence of hair and nail involvement and the presence of pruritus and xerosis. A family history of relevant skin disorders was also recorded. When present, skin biopsies were studied. Laboratory analyses were assessed for hypereosinophilia, hyper-IgE and circulating autoantibodies. Finally, we investigated the effect of local treatments given for the cutaneous involvement in IPEX, as well as the effect on skin of the various systemic treatments (given to control the severe enteropathy or other features of autoimmunity).

Results

Patients

Ten boys with IPEX syndrome were gathered. Seven had died before 2 years of age and only two of our patients have survived to date. Genotyping of the FOXP3 gene, performed in nine patients, showed a mutation in all nine patients. A family history of a similar disorder was found in half the cases, mostly among brothers, maternal cousins or uncles of the affected children. Eight patients were of European and two were of Arabic origin. Age at beginning of symptoms ranged

from 0 to 6 months (median 1 month); presenting symptoms were diarrhoea in four of 10 cases, diabetes in three of 10 and dermatitis in three of 10. Chronic, watery, sometimes bloody diarrhoea was present in 100% of the patients. All boys had a severe protein-losing enteropathy with subsequent failure to thrive and a need for total parenteral nutrition for initial stabilization. Histopathological studies of intestinal biopsies showed characteristic villous atrophy with intense T-cell, plasmacytic and eosinophilic infiltration in the lamina propria, with no or only a moderate increase of intraepithelial lymphocytes. The remaining characteristics and clinical features of the patients with IPEX syndrome are reported in Table 1, along with the corresponding FOXP3 mutations and protein changes.

Cutaneous involvement

Cutaneous involvement was present in seven of 10 children. Characteristics and features of skin involvement are reported in Table 2. Age at onset of cutaneous manifestations ranged from 0 to 4 months (median 1.5 months). All seven boys presented with features of atopic dermatitis (AD). Cutaneous involvement was diffuse and severe and consisted of erythematous exudative plaques at some times and more lichenified plaques at other times (Fig. 1a). Most affected areas were the lower limbs, trunk and face. The cutaneous lesions evolved into exfoliative erythroderma in two boys. The eczema had features of follicular eczema in one patient, of eczema/prurigo (Fig. 1b) in another and, in a third boy, it was initially confused with acrodermatitis enteropathica because of predominant periorificial localization. Three patients presented at some time a more psoriasiform aspect of their lesions (Fig. 1c,d), with well-defined erythematous plaques involving limbs and trunk, and hyperkeratotic psoriasiform plaques of the scalp. Painful, severe, fissurary and bleeding cheilitis was found in four of seven patients without mucous involvement (Fig. 1e). Cheilitis was not explained by zinc or other nutritional deficiencies. Onychodystrophy was found in two of seven patients. In one of the patients it was most probably secondary to numerous episodes of mycotic and bacterial perionyxis (and onyxia) and in another boy it was associated with palmar keratoderma (fungal cultures were negative). Pruritus was a frequent finding. It was present in four of seven patients and often interfered with sleep. A family history of atopy was present in three of seven patients and no familial history of psoriasis was found.

Other cutaneous features were episodes of inflammatory oedema of the lips and perioral area or Quincke oedema secondary to food allergies in three of 10 patients; all three patients equally had atopic eczema. Also, staphylococcal sepsis was an extremely frequent feature. It was present in seven of 10 patients and was sometimes recurrent (sepsis was found in six of seven of children with eczema and in one of three of those without AD). The *Staphylococcus* incriminated was mainly *S. aureus* followed by *S. epidermidis* and the sepsis was most frequently catheter related, and could be lethal.

Table 1 General characteristics, features and FOXP3 mutations of patients with IPEX syndrome

Patient	Skin lesions	Enteropathy ^a	Endocrinopathy ^b	Haematological anomalies ^c	Membranous glomerulonephritis	Recurrent infections ^d	FOXP3 mutation and corresponding protein change
1	Yes	Yes	Yes	Yes	No	Yes	c.1113 T>G p.F371C (ref. 13)
2	Yes	Yes	Yes	Yes	Yes	Yes	c.736-1 G>A p.L246-V272 del
3	Yes	Yes	Yes	No	No	Yes	c.1101 C>G p.F367L
4	Yes	Yes	Yes	Yes	No	Yes	c.560 C>T p.F187L
5	Yes	Yes	Yes	Yes	Yes	Yes	c.1121 T>G p.F374C
6 ^e	Yes	Yes	No	No	No	Yes	g.-6247_-4859 del (ref. 7)
7 ^e	Yes	Yes	No	No	No	Yes	g.-6247_-4859 del (ref. 7)
8	No	Yes	Yes	Yes	No	Yes	c.751-753 del GAG p.E251 del
9	No	Yes	Yes	Yes	No	Yes	c.751-753 del GAG p.E251 del
10	No	Yes	No	Yes	No	Yes	Not done

^aDiarrhoea, failure to thrive, food allergies; ^bdiabetes, thyroiditis/thyroid antibodies; ^ccytopenias, hepatosplenomegaly/lymphadenopathy; ^dpneumonias, sepsis, other; ^eindicates siblings.

Table 2 Characteristics and features of skin involvement in patients with IPEX syndrome

Patient	AD	Psoriasiform rash	Erythroderma	Histology	Sepsis ^a	Other
1	Yes	No	Yes	Spongiotic dermatitis or psoriasiform	Yes, <i>S. epidermidis</i>	Congenital ichthyosis
2	Yes	No	Yes	Eczema, chronic/lichenified	Yes, <i>S. epidermidis</i> , <i>S. aureus</i>	Initial suspicion of acrodermatitis enteropathica, cheilitis
3	Yes	No	No	No	Yes, <i>S. aureus</i>	
4	Yes	Yes	No	Eczematiform, excoriated prurigo, psoriasiform	No	Cheilitis, scalp involvement, onychodystrophy, eczema/prurigo, perioral oedema
5	Yes	Yes	No	Eczematiform, psoriasiform	Yes, <i>S. hominis</i> , <i>S. epidermidis</i>	Follicular eczema
6 ^b	Yes	No	No	No	Yes, <i>S. aureus</i>	Cheilitis, oedema/Quincke, onychodystrophy
7 ^b	Yes	No	No	No	Yes, <i>S. aureus</i> , <i>E. cloacae</i>	Cheilitis, oedema/Quincke
8	No	No	No	No	No	
9	No	No	No	No	Yes, <i>S. aureus</i>	
10	No	No	No	No	Yes	

^a*Staphylococcus* and *Enterobacter* spp. ^bIndicates siblings. AD, atopic dermatitis.

Skin biopsies

Four of seven patients had one or more skin biopsies because the lesions were particularly diffuse or erythrodermic, resistant to topical corticosteroids or varied in their presentation over time. They showed either subacute/chronic spongiotic dermatitis (Fig. 2a, b) or psoriasiform changes (Fig. 2b,c) also

consistent with a chronic lichenified eczema. In one biopsy only a slight perivascular lymphocytic infiltrate was seen in the upper dermis (Fig. 2d). The other samples showed a moderate to intense superficial dermal infiltrate associating eosinophils and lymphocytes with epidermal lymphocyte exocytosis (Fig. 2a,b). No neutrophil corneal abscesses or spongiotic pustules were seen. In one biopsy a few scattered apoptotic



Fig 1. Clinical aspects of cutaneous involvement in children with IPEX syndrome. Eczematiform involvement of extremities with lichenified pruriginous plaques (a), eczema-prurigo (b), extensive cutaneous involvement in a boy with diffuse psoriasiform plaques (c,d) and atopic dermatitis with involvement of convexities of the face and severe bleeding cheilitis (e).

keratinocytes were observed in the epidermis beside focal epidermal ulceration consistent with an excoriated prurigo.

Blood tests

Blood tests revealed hypereosinophilia in five of 10 patients: four of seven patients with skin involvement and one of three patients with no cutaneous involvement. Eosinophil counts

ranged from 0.79×10^9 to 6.0×10^9 cells L^{-1} . Hyper-IgE was found in seven of 10 patients: six of seven with skin involvement and one of three without. Two cases showed positive IgE against cow's milk proteins, ranging from 1000 to 11 000 kU L^{-1} . Circulating autoantibodies were present in nine of 10 cases and were most frequently anti-enterocyte and anti-AIE75kDa (an autoantibody directed against a gut and kidney-specific antigen with a molecular weight of 75 kDa¹⁷),

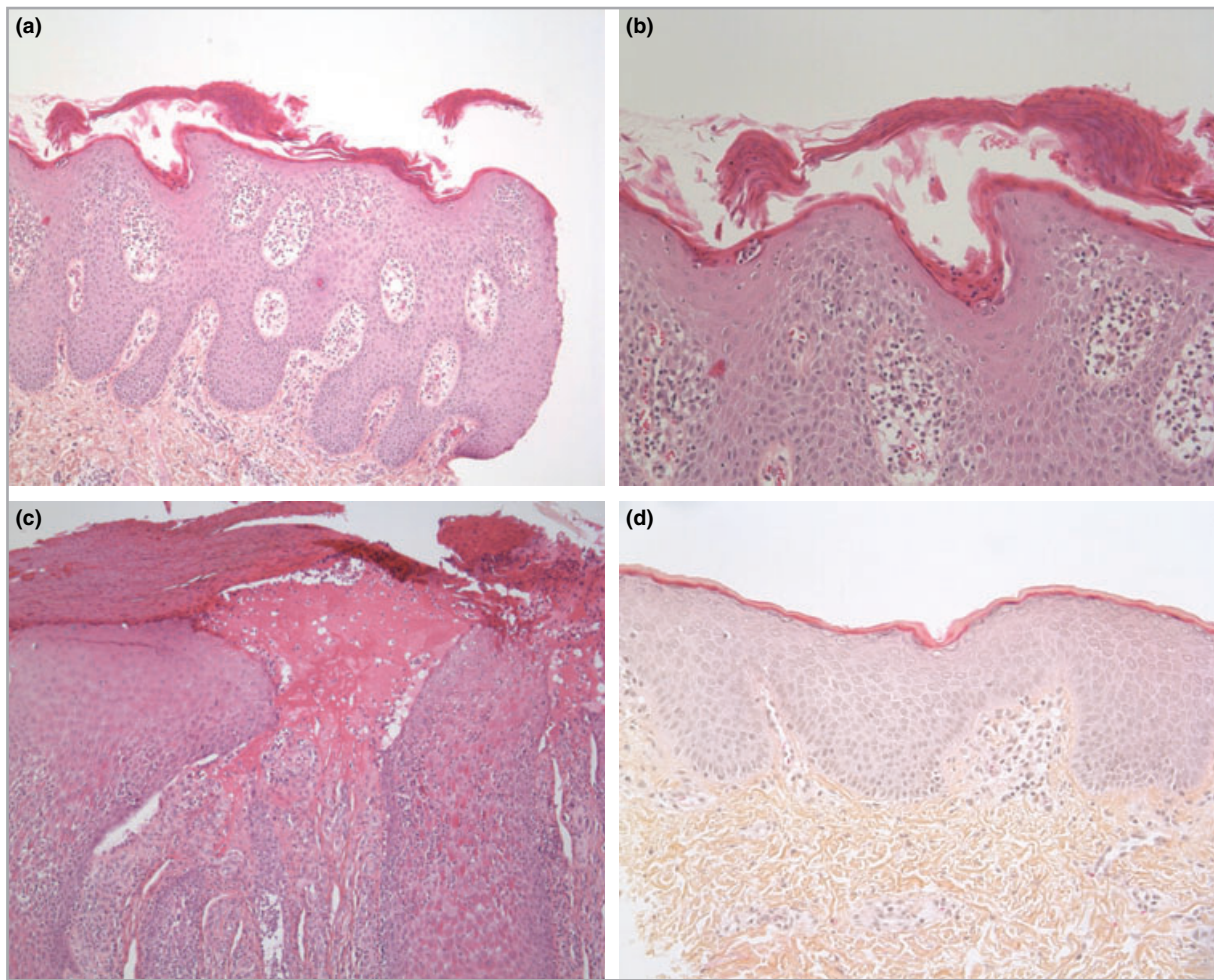


Fig 2. Histopathological aspects of cutaneous involvement in IPEX syndrome. Spongiotic dermatitis associated with epidermal psoriasiform changes showing psoriasiform epidermal hyperplasia (a,b), spongiosis (a,b), lymphocytic exocytosis (a,b) and parakeratotic hyperkeratosis (b,c). Few scattered apoptotic keratinocytes in the epidermis beside focal epidermal ulceration (c). In another patient, chronic epidermal hyperplasia consistent with chronic lichen simplex was associated with a slight perivascular infiltrate in the upper dermis (d).

followed by antinuclear, antired blood cells, antiplatelets and antismooth muscle antibodies, as well as antithyroid antibodies.

Treatment

Dermocorticoids improved the lesions but high doses were necessary and there was an immediate relapse at tapering or cessation of topical corticotherapy. Topical tacrolimus was used in two patients but did not give satisfactory results. Also, there was no clear improvement of atopic eczema with any of the various immunosuppressive treatments given to control the severe enteropathy characteristic of IPEX syndrome. Indeed, a given immunosuppressive regimen could give notable improvement in one patient but be ineffective in another. It was then impossible to draw a conclusion regarding the efficacy of systemic treatments on the cutaneous involvement in IPEX. Systemic treatments included high-dose systemic corticosteroids in all 10 patients (steroid pulses at 20 mg kg⁻¹

followed by oral prednisone at 2 mg kg⁻¹ daily), given alone or in combination with azathioprine (in seven of 10 cases), ciclosporin (six of 10), cyclophosphamide (three of 10), tacrolimus (six of 10), sirolimus (four of 10) and rituximab (three of 10) as well as antithymocyte globulin (three of 10). Three IPEX patients followed at Necker-Enfants Malades Hospital underwent a bone marrow transplantation (BMT), but ultimately all three died. In one case, BMT allowed induction of remission for over 2 years. Of note, in one of the patients, BMT notably improved AD. Seven of 10 patients died prematurely, most frequently of sepsis. Other causes of death included pneumonia, respiratory failure, cardiac arrhythmia and multiple organ failure following stem cell transplantation.

Discussion

IPEX syndrome is an X-linked recessive disorder of early childhood. It affects male infants and is most often lethal. Major symptoms are severe secretory enteropathy causing

failure to thrive, early-onset diabetes mellitus, and dermatitis. Our study highlights the frequency of severe cutaneous involvement in IPEX syndrome, consisting mainly of AD manifestations sometimes with clinical psoriasiform features. Published reports of IPEX syndrome are limited: to date, there are some 83 cases published in the general literature, and the most frequent signs seemed to be diarrhoea with subsequent failure to thrive, type 1 diabetes, and dermatitis.^{3,18} In a review of literature concerning IPEX syndrome in 2002, Wildin *et al.* noted that 23 of 58 patients had cutaneous involvement, described as dermatitis or eczema.³ Since then, another 17 patients with IPEX syndrome have been reported, eight of whom showed cutaneous involvement. Skin lesions were described mainly as eczematiform,^{3,10–12} but also as ichthyosiform^{13,14} or psoriasiform.^{15,16} The few skin biopsies mentioned were nonspecific and sometimes had psoriasiform features.^{15,16} To our knowledge only three IPEX cases were described in the dermatological literature and addressed the specific dermatological findings seen in this syndrome. The first report in 2004 by Nieves *et al.* described a boy with IPEX syndrome and AD who presented a few years later a psoriasiform dermatitis as well as idiopathic urticaria and an autoimmune skin disorder, alopecia areata.¹⁵ The second report, by McGinness *et al.* in 2006, described a child with IPEX syndrome who presented with an autoimmune skin disorder, pemphigoid nodularis,¹⁹ and in 2007, McLucas *et al.* reported a nonspecific case of Norwegian scabies in a child with IPEX syndrome.²⁰ Of note, there was another case of biopsy-proven bullous pemphigoid described in the general literature.²¹ In our series of 10 patients followed at Necker-Enfants Malades Hospital, seven patients presented eczematous dermatitis with AD characteristics. Skin involvement had an early onset in life (namely in the first months) and was severe and diffuse. Lesions evolved into erythroderma in two cases. Cutaneous lesions often showed resistance to classical treatments such as dermocorticoids or topical tacrolimus and could be complicated by staphylococcal sepsis. Also, three patients showed the coexistence of features of AD on certain body areas with features of psoriasis on other areas. Severe painful cheilitis was also a frequent finding. Moreover, cutaneous manifestations of allergy were noted in three patients who presented one or more episodes of oedema of the lips and/or Quincke oedema. Hence, the early onset in life of severe allergies associated with clinical or biological manifestations of autoimmunity in a male patient should bring to mind the possibility of IPEX syndrome.

The causative gene in IPEX syndrome, FOXP3, is predominantly expressed in CD4⁺ CD25⁺ Tregs and is a master control gene of their development and function. FOXP3 also plays a central role in the generation of Tregs. These are actively involved in maintenance of peripheral self-tolerance by actively suppressing activation and expansion of self-reactive T cells.^{5,22} Tregs are also responsible for downregulating the immune response to foreign antigens.²³ FOXP3 encodes a transcriptional (co)repressor that inhibits activation-induced cytokines gene transcription, namely interleukin (IL)-2, IL-4 and

interferon- γ .^{24–27} When FOXP3 is mutated, Treg generation is impaired,^{9,28} leading to loss of self-tolerance and uncontrolled T-cell activation with overproduction of cytokines,^{11,15,29} lymphoproliferation^{2,5} and lymphocytic infiltration of tissues responsible for the early features of autoimmunity and allergy characteristic of IPEX syndrome. Approximately one-third of patients with IPEX syndrome lack identifiable mutations of FOXP3;³⁰ the IPEX phenotype is then believed to result from mutations within promoter or enhancer elements of the FOXP3 gene, or genes related to activation/expression of FOXP3,^{9,27} or in the CD25 gene (IL-2R α).³⁰ Also, recently, dysfunctional Tregs were identified and incriminated in a subset of patients with IPEX syndrome.^{7,31,32}

From our study and from the overall literature data, atopic eczema appears to be a very frequent feature of IPEX syndrome, which is characterized by a defect of Tregs. The frequency of AD in IPEX syndrome thus hints to a possible role of Treg anomalies in atopy. A recent study demonstrated the absence of FOXP3⁺ CD4⁺ CD25⁺ Tregs in AD skin, despite high levels in peripheral blood of patients with AD. This suggests a dysregulated control of inflammation by natural Tregs, with no suppression of antigen-specific activation of T cells in atopic skin. The result is an uncontrolled activation of T cells by allergens or superantigens and their prolonged survival within the inflamed skin where they can be reactivated.³³ A study by Ou *et al.* has shown that, despite increased numbers of peripheral blood Tregs with normal immunosuppressive activity in patients with AD, these Tregs lost their immunosuppressive properties after stimulation with staphylococcal superantigen, leading to T-cell hyperactivation in patients with AD.³⁴ Moreover, there is recent evidence that Treg defects may contribute to the pathogenesis of psoriasis. The fact that some of the children in our series displayed psoriasiform features may not be a simple coincidence. Indeed, a recent study by Sugiyama *et al.* revealed a profound functional deficit of Tregs in psoriasis, with a subsequent inability to restrain the ongoing chronic inflammation,³⁵ while Verhagen *et al.* also demonstrated in their study that psoriatic skin, like AD skin, lacked FOXP3⁺ CD4⁺ CD25⁺ Tregs.³³ Although psoriasis has not been directly proven to be an autoimmune disease, these recent findings suggesting a dysregulated control of inflammation by CD4⁺ CD25⁺ Tregs provide an important basis to support this hypothesis.

With such new evidence for a preponderant role of Treg depletion or dysfunction in the pathogenesis of AD, as well as psoriasis, it is tempting to think that new therapies aiming at increasing the number and/or function of Tregs could dramatically improve manifestations of AD and psoriasis, as well as manifestations of allergy, autoimmunity and graft-versus-host disease.

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