Late-onset of immunodysregulation, polyendocrinopathy, enteropathy, x-linked syndrome (IPEX) with intractable diarrhea

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Abstract

The syndrome of immune dysregulation, polyendocrinopathy, enteropathy, X linked (IPEX) is a rare disorder caused by mutations in the FOXP3 gene. Diarrhea, diabetes and dermatitis are the hallmark of the disease, with a typical onset within the first months of life. We describe the case of a twelve-year old male affected by a very late-onset IPEX with intractable enteropathy, which markedly improved after starting Sirolimus as second-line treatment. This case suggests that IPEX should always be considered in the differential diagnosis of watery intractable diarrhea, despite its unusual onset.

Keywords: Immunodysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX), Sirolimus, Forkhead box P3 (FOXP3)

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The syndrome of immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) is a rare disorder, characterized by diarrhea, type-1 diabetes mellitus (T1DM) and dermatitis with onset within the first months of life [1,2]. Diarrhea is intractable and persists despite dietary exclusions and bowel rest, resulting in malabsorption and failure to thrive [3]; T1DM can precede or follow enteritis [4-6]; dermatitis is severe with eczematiform, ichthyosiform or psoriasiform aspects [7-10], other autoimmune diseases are often associated [11].

IPEX is caused by germ-line mutations in the FOXP3 gene, a key regulator of immune tolerance, located in the X-chromosome at Xp11.23-Xq13.3 [12-17]. It is critical for the function of CD4+CD25+ regulatory T-cells (TREG) and for the maintenance of peripheral immunologic tolerance [17,18].

Findings

We describe a 12-year-old boy born at term from natural birth after an uncomplicated pregnancy from unrelated parents, referred to our hospital for severe enteritis started one month before with liquid mucus-haematic diarrhoea (height: 50th centile, weight: 10th centile, regularly vaccinated). No potentially triggering events have been reported, such as vaccinations, viral infections or changes in nutrition. In his past history he had recurring episodes of mild atopic dermatitis since the first year of life, a high level of total IgE (400 UI/L), and a constipated bowel (once every two/three days).

On admission, he was dehydrated (7% of weight loss). Blood tests revealed hypoproteinaemia and hypogammaglobulinemia (Table 1), so albumin was replaced. Abdominal ultrasound highlighted wall thickening of the bowel loops. Esophagastroduodenoscopy (EGDS) and colonoscopy revealed ulcerative lesions at the stomach, duodenum, terminal ileum and colon, giving rise to a suspect of inflammatory bowel disease. Biopsies revealed villous blunting and inflammatory infiltration of the mucosa. After starting intravenous methylprednisolone, metronidazole and parenteral nutrition a partial remission was observed.
| Patient | Age at onset | Mutation | AA change | Clinical features | Histology | Management | Outcome | Ref. |
|---------|--------------|----------|-----------|------------------|-----------|------------|---------|------|
|         | Age at dg    | Nucleotide change | FOXP3 | Molecular defect |          | Previous therapy | SIR | HSCT |
| 1       | 7y 10y       | c.968-20A>C | NA | NA | Dermatitis, enteropathy | Lymphoplasmocellular eosinophilic infiltrate. Villous atrophy. | Steroids, AZA, CsA, FK, MTX, TPN, Total colectomy at 10 y | Y | N | Stable at 16 yr on SIR+MTX. [19] |
| 2*      | 2m NA        | NA        |       | Enteropathy, erythematous eczema-like dermatitis | Lymphoplasmocellular infiltrate with marked eosinophilia. High rate of enterocyte apoptosis. Subtotal villous atrophy. | Steroids, FK, AZA | Y | N | Stable for 1.5 yr on SIR+AZA [19] |
| 3*      | 2m NA        | NA        |       | Enteropathy, erythematous eczema-like dermatitis | Similar findings with that of his brother (pt.4) | Steroids, FK; AZA | Y | N | Stable for 6 m on SIR+AZA [19] |
| 4       | 2y 4y        | 1061delC | Frameshift P354Q | Premature stop codon. Truncated FKH domain | Entero pathy, non specific dermatitis | Mild villous blunting | Metronidazole, steroids, mesalamine, IFX, AZA, 6-MP | Y | N | Stable at 7 yr [20] |
| 5       | 1w 7y        | 200G>T | Q70H | Predicted abnormal reading frame | Eczema, enteropathy, AHA, ITP, arthritis | Inflammation with villous atrophy | IVIG, steroids, TPN, antibiotics | Y | N | Stable at 8 yr [20,21] |
| 6*      | 3w NA        | g.-6247-4859del | NA | ↓ Accumulation of unspliced mRNA | Skin/food allergies, Enteropathy, erythematous-eczematous skin rash | Lymphoplasmocellular infiltrate with marked eosinophilia. High rate of enterocytes apoptosis. Severe to total villous atrophy | Steroids, FK, AZA TPN | Y | N | Stable for 6 yr on SIR+AZA [22] |
| 7*      | 2m NA        | g.-6247-4859del | NA | ↓ Accumulation of unspliced mRNA | Skin/food allergies, Eczema, Enteropathy | NA | Steroids, FK, AZA TPN | Y | N | Stable for 4 yr on SIR+AZA [22] |
| 8       | 5w NA        | g.-6247-4859del | NA | ↓ Accumulation of unspliced mRNA | Enteropathy, Eczema, Allergy | NA | Steroids, FK, AZA | Y | N | Stable at 9 yr on SIR+AZA [23] |
| 9       | 3w NA        | g.-6247-4859del | NA | ↓ Accumulation of unspliced mRNA | Enteropathy, Eczema, HP gastritis, Allergy | NA | Steroids, FK AZA | Y | N | Stable at 6 yr on SIR+AZA [23] |
| 10      | Birth NA     | g.-1121T>G | F374C | Full length FOXP3 with abnormal FKH domain | T1DM, HTH, Enteropathy, Eczema, AHA, ITP, Allergy. | NA | Steroids, FK506 | Y | N | Died at 14 m during HSCT induction [23] |
| 11      | 6w NA        | 751-753del GAG | E251del | Disrupts FOXP3 oligomerisation | Enteropathy, Eczema, HTH, Interstitial Nephritis, AHA, Allergy. | NA | FK506 | Y | Y | Died at 10 yr after HSCT [23] |
| 12      | 1m 6y        | 1150G>A | A384T | Full length FOXP3 with abnormal FKH domain | Entero pathy, Eczema, FTT, T1DM, AHA, Interstitial Pneumonia, Alopecia, Thyroiditis. | Eosinophil infiltration without villous atrophy | MG, CsA, steroids, TPN, fludarabine-autologous lymphocytes, FK, MTX, Rituximab, cyclophosphamide. | Y | N | Stable at 16 yr on others drugs [4,24,25] |
|   |      |     |     |     |      |     |     |     |     |
|---|------|-----|-----|-----|------|-----|-----|-----|-----|
| 13| Birth| 7 w | 1150G>A | A384T | ↓ | Full length FOXP3 with abnormal FKH domain | Enteropathy, T1DM, Exfoliative Dermatitis, HTH, Pancytopenia | NA | TPN | Y | N | Died at 7 w [26] |
| 14| Birth| 4½ y | AAUAAA/AAUAAG | NA | ↓ | Polyadenylation defect resulting in unstable FOXP3 mRNA | Enteropathy, Dermatitis, T1D | NA | MTX, steroids, TPN. | Y | Y | Stable at 1 yr [27] |
| 15|      | 1 w | 1015C>G | P339A | ↓ | Missense mutation. Predicted to yield full length FOXP3 | Enteropathy, Eczema, T1DM, FTT, Euthyroid Thyroiditis, AIH, AHA | Villous atrophy | Steroids, FK; AZA | Y | N | Died at 5.5 m before HSCT [28] |
| 16|      | 3 m | Exon 10 | NA | NA | NA | NA | FTT, Enteropathy, Eczematous Dermatitis, ITP stomatitis | NA | Cyclophosphamide, VCR, TPN | N | Stable 2½ yr on other drugs [29] |

*Brothers; 6-MP 6-Mercaptopurina; AHA autoimmune haemolytic anaemia; AIH Autoimmune hepatitis; AZA Azathioprine; CsA Cyclosporine; FTT: failure to thrive; FK: tacrolimus; HSCT hematopoietic stem cell transplantation; HTH Hypothyroidism; IFX Infliximab; ITP immune thrombocytopenic purpura; IVIG Intravenous Immunoglobulin; Y: Yes; yr: years; m: months; MTX Methotrexate; NA Not Available; N: No; Ref. References; SIR Sirolimus; T1DM Type 1 Diabetes mellitus; TPN Total Parenteral Nutrition; VCR Vincristine; w: weeks; ↓: reduction of expression.*
Ten days later, for a worsening of symptoms, EGDS and colonoscopy were repeated, with a superimposable picture. Particularly, the biopsies of the colon showed lympho-granulocytic acute inflammation with Graft-versus-Host Disease-like aspect, a lesion typically reported in IPEX (Figure 1) [30]. Due to the inability to control the symptoms the patient underwent ileostomy.

Despite the age of the patient was atypical for the onset of IPEX, we evaluated the presence of autoantibodies to harmonin, which resulted positive (>100 U.A.). Then, diagnosis was confirmed by the genetic examination of FOXP3 gene, revealing a mutation in the exon 9 (1040G > A), with substitution of Arginine to Histidine (R347H). The mother resulted negative. The total number of lymphocyte and lymphocyte subpopulations was normal, particularly T_{REG} were 5% of the total number.

Intravenous cyclosporine (range: 200-350 mg/dl) and methylprednisolone (2 mg/kg) were started, which reduced diarrhea and abdominal pain. After sixty days of parenteral nutrition the patient returned to oral feeding with the normalization of albumin levels (Table 1). Because of the onset of post-prandial hyperglycaemias, we excluded T1DM (Table 1) and glycaemia normalized after tapering steroid therapy. After thirty-four days since the beginning of sirolimus, cyclosporine was suspended. After twelve months the patient is well, without recurrence of the disease.

**Conclusions**

This case indicates that IPEX can have an atypical age of presentation. Thus, it should always be considered in the differential diagnosis of intractable diarrhea.

Four patients have been previously reported with IPEX with the same amino-acid substitution (R347H) found in our patient. The age of onset for all these subjects was within the first year of life and the first symptoms were recurrent ear infection, high IgE levels, T1DM, and gastritis. All had gastrointestinal symptoms with failure to thrive: two intractable diarrhea, two severe gastritis with mucosal atrophy or eosinophilic infiltration. Other symptoms were: coombs-negative haemolytic anaemia, food allergy, pancreatic endocrine failure, intractable hypertension, intestinal metaplasia, steatorrhea, and hypogammaglobulinemia. Patients received corticosteroid and calcineurin inhibitors. One patient died after allogeneic hematopoietic stem cell transplantation (HSCT) due to an infection.

Recently, evidence that patients with a severe form of IPEX may have circulating FOXP3+ T cells, as it is the case of our patient, which suggests that the cellular basis for the disease may be a result of a functional defect of Treg cells [1,26]. Mainly, R347H mutated-FOXP3 has been demonstrated as effective as wild-type-FOXP3 in converting normal T cell into Treg in vitro [31] and in maintaining the ability to suppress the production of cytokines, hallmark of Treg cells, conferring suppressive capacity on CD4+ T cells.

In 2005, three patients were successfully treated with sirolimus [19]. Since then, 16 patients received sirolimus and nine are in complete or partial remission (Table 2).
Table 2 Variables of our patient at the time of admission to our hospital, when he started the second line therapy with Sirolimus and after three months since the beginning of this therapy

| Variables                        | Reference range, age and sex-adjusted | Admission | Start SIROLIMUS | 3 months after SIROLIMUS |
|----------------------------------|---------------------------------------|-----------|-----------------|-------------------------|
| White-cell count — per mm³       | 4.5 - 13.5                            | 15.01     | 4.04            | 5.01                    |
| Hemoglobin — g/dl                | 11.5 - 14.5                           | 16.3      | 11.7            | 11.5                    |
| Hematocrit — %                   | 35 - 42                               | 46.0      | 34.4            | 35.7                    |
| Differential count — %           |                                       |           |                 |                         |
| Neutrophils                      | 40.0 - 74.0                           | 89.6      | 51.2            | 48.0                    |
| Lymphocytes                      | 19.0 - 48.0                           | 6.6       | 30.3            | 38.0                    |
| Monocytes                        | 30 - 90                               | 2.4       | 13.5            | 7.6                     |
| Eosinophils                      | 0.0 - 60                              | 0.4       | 1.7             | 4.4                     |
| Basophils                        | 0.0 - 1.5                             | 0.3       | 1.1             | 0.7                     |
| Platelet count — per mm³         | 250 - 550                             | 522       | 247             | 273                     |
| Glucose                          | 60 - 100                              | 125       | 107             | 77                      |
| Insulinemia — microU/mL          | 7 - 24                                |           |                 | 6.8                     |
| C-peptide — ng/mL                | 1.1 - 4.4                             |           |                 | 2.7                     |
| Islet cell autoantibodies        | Neg                                   |           |                 | Neg                     |
| Glutamic acid decarboxylase— UI/ml| <10 Neg                               |           |                 | Neg                     |
| UREA — mg/dl                     | 15 - 50                               | 72        | 40              | 18                      |
| Creatinine — mg/dl               | 0.5 - 1                               | 0.91      | 0.54            | 0.35                    |
| Uric Ac. — mg/dl                 | 2.2 - 6.6                             | 8.6       | 5.2             | 3.4                     |
| Total Colesterol — mg/dl         | 130 - 204                             | 121       |                 |                         |
| TG — mg/dl                       | 31 - 108                              | 40        |                 |                         |
| HDL — mg/dl                      | > 35                                  | 62        |                 |                         |
| LDL — mg/dl                      | < 170                                 | 50        |                 |                         |
| Electrolytes — mmol/L            |                                       |           |                 |                         |
| Sodium                           | 136 - 146                             | 128       | 139             | 142                     |
| Potassium                        | 3.5 - 5.3                             | 5.5       | 4.3             | 4.3                     |
| Chlorine                         | 98 - 106                              | 85        | 103             | 105                     |
| Calcium                          | 8.8 - 108                             | 9.6       | 9.3             | 9.2                     |
| Phosphorus — mg/dl               | 2.9 - 5.4                             | 7.6       | 5               | 4.4                     |
| Magnesium — mg/dl                | 1.6 - 2.6                             | 2.2       | 1.6             | 2.1                     |
| Plasma Osmolarity — mOsm/L       | 278 - 305                             | 266       |                 |                         |
| Protein — g/dl                   |                                       |           |                 |                         |
| Total                            | 6.4 - 8.1                             | 4.1       | 6.2             | 6.7                     |
| Albumin                          | 3.5 - 5                               | 2.4       | 4.2             | 4.3                     |
| γ –Globulin — %                  | 11.1 - 18.8                           | 10.5      | 11.4            | 13.4                    |
| Bilirubin — mg/dl                |                                       |           |                 |                         |
| Total                            | 0.20 - 1.10                           | 1.54      | 0.44            | 0.3                     |
| Direct/Indirect                  | 0.00-0.30/< 0.80                      | 0.48/1.06 | 0.21/0.23      | 0.1/0.2                 |
| AST/ALT — U/L                    | < 38/< 41                             | 16/10     | 16/10           | 22/17                   |
| Total Amylase — U/L              | 30 - 100                              | 50        | 60              |                         |
| Iron — μg/dl                     | 53 - 119                              | 47        | 52              |                         |
| U.I.B.C./T.I.B.C. — μg/dl        | 110-330/250-400                       | 300/347   | 273/325         |                         |
Table 2 Variables of our patient at the time of admission to our hospital, when he started the second line therapy with Sirolimus and after three months since the beginning of this therapy (Continued)

| Variable                        | Admit | After 3 months |
|---------------------------------|-------|----------------|
| Ferritin (ng/mL)                | 7 - 140 | 22 - 160 |
| TSH (microU/mL)                 | 0.6 - 6.3 | 1.93 - 1.02 |
| FT3 (pg/mL)                     | 2.5 - 5.5 | 3.6 - 4.1 |
| FT4 (pg/mL)                     | 9.0 - 17.0 | 20.7 - 12.9 |
| ATA (UI/mL)                     | < 115 | 23 - 16 |
| Anti TPO Ab (UI/mL)             | < 34 | 12 - 13 |
| ESR (mm)                        | < 15 | 6 - 15 |
| CRP (mg/dL)                     | < 0.5 | 0.05 - 2.05 |
| Ab anti harmonine IgG(U.A.)     | < 3.0 Absent | >100 |
| > 0.3 Present |
| ANA                             | < 1.80 | < 1.80 |
| AMA                             | < 1.40 | < 1.40 |
| ENA                             | < 0.7 Neg | Neg |
| 0.7 - 1.0 Bl |
| > 1.0 Pos |

Considering that sirolimus seems to be as effective as the calcineurin inhibitors, with less toxic effects, it can be considered as a valid therapeutic option for bringing these patients to HSCT in their best clinical condition.

Consent
Written informed consent was obtained from the parents of the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Ethical approval
Internal ethical committee of Sant-Orsola approved the study.

Abbreviations
IPEX: Syndrome of immune dysregulation, polyendocrinopathy, enteropathy, X linked; TIDM: Type-1 diabetes mellitus; EGDS: Esophagogastroduodenoscopy; FKHL: Forkhead/winged helix domain; mTOR: Mammalian target of rapamycin; HSCT: Hematopoietic stem cell transplantation.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
ZD and IC reviewed relevant articles on the literature, collected all the patient’s data and drew the manuscript. FS and PA contributed to the diagnosis and provided clinical assistance. RM, ML and AP contributed to the conception and design, and revisited critically the manuscript. EG carried out the molecular genetic studies and drafted the manuscript. All authors read and approved the final manuscript.

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