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The plethora, clinical manifestations and treatment options of autoimmunity in patients with primary immunodeficiency

Hatice Ezgi Barış[1], Ayça Kıykım[2], Ercan Nain[2], Ahmet Oğuzhan Özen[2], Elif Karakoç-Aydıner[2], Safa Barış[2]

[1]Department of Peditarics, Marmara University Pendik Training and Research Hospital, İstanbul, Turkey
[2]Department of Peditarics, Division of Allergy and Immunology, Marmara University Pendik Training and Research Hospital, İstanbul, Turkey

Abstract

Aim: Although the association between primary immunodeficiency and autoimmunity is already well-known, it has once again become a topic of debate with the discovery of newly-defined immunodeficiencies. Thus, investigation of the mechanisms of development of autoimmunity in primary immunodefficiency and new target-specific therapeutic options has come to the fore. In this study, we aimed to examine the clinical findings of autoimmunity, autoimmunity varieties, and treatment responses in patients who were genetically diagnosed as having primary immunodeficiency.

Material and Methods: The files of patients with primary immunodeficiency who had clinical findings of autoimmunity, who were diagnosed genetically, and followed up in our clinic were investigated. The demographic and clinical features of the patients and their medical treatments were evaluated.

Results: Findings of autoimmunity were found in 30 patients whose genetic mutations were identified. The mean age at the time of the first symptoms was 8.96±14.64 months, and the mean age of receiving a genetic diagnosis was 82.55±84.71 months. The most common diseases showing findings of autoimmunity included immune dysregulation, polyendocrinopathy, enteropathy X-linked syndrome (16.7%); autoimmune lymphoproliferative syndrome (10%); lipopolysaccharide-responsive beige-like anchor protein deficiency (10%); and DiGeorge syndrome (10%). Twelve (40%) patients showed findings of autoimmunity at the time of first presentation. The most common findings of autoimmunity included inflammatory bowel disease, inflammatory bowel disease-like findings (n=14, 46.7%), immune thrombocytopenic purpura (n=11, 36.7%), and autoimmune hemolytic anemia (n=9, 30.0%). A response to immunosupressive agents was observed in 15 (50%) patients. Ten patients underwent hematopoietic stem cell transplantation. Six patients were lost to follow-up due to a variety of complications.

Conclusion: Autoimmunity is frequently observed in patients with primary immunodeficiency. The possibility of primary immunodeficiency should be considered in patients with early-onset manifestations of autoimmunity, and these patients should be carefully monitored in terms of immunodeficiency development. Early diagnosis of primary immunodeficiency may provide favorable outcomes in terms of survival. (Turk Pediatri Ars 2016; 51: 186-92)

Keywords: Autoimmunity, autoimmune hemolytic anemia, inflammatory bowel disease, primary immunodeficiency

Introduction

Primary immune deficiency disorders (PID) are a group of genetic diseases characterized by recurrent infections. To date, at least 300 diferrent gene mutations have been found to lead to morbidity resulting in PID (1). Although they are known as rare diseases, recent investigations have shown that they occur more commonly than expected (2). In Turkey, the prevalence was found as 30.5/100 000 in a two-center study conducted in the Marmara and Egean regions (3). Autoimmunity is also frequently observed in additon to recurrent infections in PID (1). Disruption in central or peripheral regulatory mechanisms in T and/or B cells, increased antigen load due to recurrent infections,

Address for Correspondence: Safa Barış E-mail: safabaris@hotmail.com
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and inability to eliminate dead cells are blamed for the development of autoimunity (4-6). Briefly stated, disruptions in the steps of development of the immune system may lead to autoimmuntiy by disupting the mechanism of recognition and tolerance of self.

In some immune deficiencies, the first sign of disease may be autoimmunity. Especially in infancy, findings of autoimmunity should raise suspicion for primary immune deficiency even though infection has not yet been observed (7). Observation of autoimmunity alone in the beginning may prolong the time for making the diagnosis or may lead to the use of inappropriate therapeutic methods. In this context, pediatricians' awareness, especially of the relationship of early-onset autoimmunity with PID will improve the chances of early diagnosis of PID. In addition, knowledge of disease-specific mechanisms of autoimmunity will provide establishment of specific treatment. In this study, the autoimmunity variety, treatment options, and survival were evaluated in patients with PID who were genetically diagnosed and who had autoimmunity findings.

Material and Methods

In this study, the demographic properties and autoimmunity findings of PID patients who were diagnosed genetically and who had autoimmunity findings were examined retrospectively. Patients who had no genetic diagnosis, but who had autoimmunity findings and were being followed up with diagnoses of common variable immune deficiency, selective IgA deficiency, and combined immune deficiency were excluded from this study. Verbal consent was obtained from the patients and written informed consent was obtained from the parents for the recording of data. Ethics committee approval was obtained from the ethics committee of our university (09.04.2015, number: 09.2015.249).

Demographic and clinical properties

The current age, age at the time of diagosis, age at the time of the first symptoms, sex, consanguineous marriage, genetic diagnoses, clinical and laboratory findings, treatment methods, treatment responses, and survival data were examined.

Autoimmunity findings

The main autoimmunity findings examined included autoimmune hemolytic anemia (AHA), immune thrombocytopenic purpura (ITP), autoimmune thyroiditis, eczema, arthritis, lupus-like rash, inflammatory bowel disease (IBD)/IBD-like findings, adrenal failure, diabetes mellitus (DM), gastritis, hepatis, nephrotic syndrome, psoriasis, vitiligo, pericarditis, hypoparathyroidism, alopesia, cutaneous granuloma, and vasculitis. In addition, autoantibody positivity was also investigated.

Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences version 22.0 (SPSS Inc.; Chicago, IL, USA). Continuous variables among the descriptive statistics are expressed as mean±standard deviation (SD). Frequency analyses, , are expressed as number (n) and percentage (%).

Results

A total of 30 patients who were being followed up in our division because of immune deficiency, who were diagnosed genetically, and who had autoimmunity findings were evaluated. The demographic and clinical properties of the patients are shown in Table 1.

Genetic diagnoses

Eighteen different genetic diagnoses were observed in the patients. These included X-linked immune dysregulation, polyendocrinopathy, enteropathy syndrome (IPEX) (n=5, 16.7%), autoimmune lymphoproliferative syndrome (ALPS) (n=3, 10.0%), lipopolysaccharide-responsive beige-like anchor protein deficiency (LRBA) (n=3, 10.0%), Di-

Table 1. Demographic and clinical properties of the patients

Demographic and clinical properties		
Sex, n, (%)	Female	5 (16.7)
	Male	25 (83.3)
Current age (Mean±SD) (years)		10.56±8.02
Age at the time of first symptoms (Mean±SD) (months)		8.96±14.64
	IPEX (n=5)	4.40±4.72
	ALPS (n=3)	4.33±3.21
	Di George (n=3)	2.33±2.30
	LRBA (n=3)	6.00±0.00
	DOCK8 (n=2)	6.00±0.00
	RAG1 (n=2)	34.00±36.76
Age at the time of genetic diagnosis (Mean±SD) (months)		82.55±84.71
Consanguineous marriage, n, (%)		16 (53.3)
Treatment response of autoimmune findings, n, (%)		15 (50.0)
Bone marrow transplantation, n, (%)		10 (33.3)
Mortality, n, (%)		6 (20.0)

ALPS: autoimmune lymphoproliferative syndrome; DOCK8: dedicator of cytokinesis 8; IPEX: immune dysregulation, polyendocrinopathy, enteropathy, X-linked; LRBA: lipopolysaccharide-responsive beige-like anchor protein; RAG: recombination-activating gene

George syndrome (DGS) (n=3, 10.0%), atypical RAG1 deficiency (n=2, 6.7%), DOCK8 deficiency (n=2, 6.7%), CD19 deficiency (n=1, 3.3%), loss of function mutation of the *PI3KR1* gene (n=1, 3.3%), gain of function mutation of the *PIK3CD* gene (n=1, 3.3%), interleukin (IL)-10 receptor deficiecny (n=1, 3.3%), autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy (APECED) (n=1, 3.3%), excessive gain of function mutation of the *STAT1* gene (n=1, 3.3%), protein kinase C, delta (PRKCD) deficiecny (n=1, 3.3%), IL-21 receptor deficiency (n=1, 3.3%), chronic granulomatous disease (CGD) (n=1, 3.3%), Wiskott-Aldrich syndrome (WAS) (n=1, 3.3%), ataxia telengiectasia (n=1, 3.3%), and RAG2 deficiency (n=1, 3.3%). Autoimmune findings were observed in 12 of 30 (40%) patients at the initial presentation. The diagnoses of these patients were as follows: IPEX, ALPS, LRBA deficiency, RAG1 deficiency, DGS, PRKCD deficiency, IL-10 receptor deficiency, and RAG2 deficiency.

Autoimmunity findings, treatment, and survival

The autoimmuninty properties observed through the diagnoses of the patients are shown in Table 2. The most common autoimmunity findings included IBD/IBD-like findings (n=14, 46.7%), ITP (n=11, 36.7%) and AHA (n=9, 30.0%) (Figure 1). The cutaneous findings observed in the patients are shown in Figure 2. Laboratory findings revelead that the direct Coombs test was positive in 9 (30.0%) patients, antinuclear antibiody (ANA) was positive in 5 (16.7%) patients, and thyroid autoantibodies were positive in 4 (13.3%) patients. Antiplatelet antibodies were tested in one of eleven patients who had thrombocytopenia, and were found positive. Autoantibody positivity was not found in 10 patients (33.3%). The agents used to treat autoimmunity findings varied in each patient and these included intravenous immunoglobulin, corticosteroids, sirolimus, rituximab, cyclophosphamide, hydroxychloroquine, azathioprine, mycophenolate mofetil, cyclosporin, methotrexate, etanercept, and thyroid hormone. Splenectomy was performed in a patient who had treatment-resistant chronic thrombocytopenia. The survival rate was 70% (n=7) in 10 patients who underwent bone marrow transplantation. The causes of death in six patients who were lost included graft versus host disease (GvHD), sepsis, acute respiratory distress syndrome (ARDS), intracranial hemorrhage, and intracranial mycotic aneursm. The therapies, treatment responses, and clinical prognoses of the patients are presented in Table 2.

Discussion

Although the typical characteristic of primary immunodeficiencies is recurrent infections, autoimmunity is observed as a predominant finding in some immune deficiencies (8). Among these diseases, APECED, ALPS, IPEX, IPEX-like syndromes (CD25 and STAT5b deficiency, LRBA deficiency, CTLA4 deficiency, gain of function mutation of the *STAT1* gene), IL-10/IL-10 receptor deficiency and newly defined Phospholipase C-gamma-2–related autoantibody deficiency and immune dysregulation (PLAID) are characterized by autoimmunity. In addition, autoimmunity findings may also be observed during the course of the disease in common variable immune deficiency (CVID), hyper IgM syndrome, X-linked agammaglobulinemia, selective IgA deficiency, CKGD, severe combined immune deficiencies, WAS, and complement deficiencies. The main mechanisms blamed for autoimmunity in primary immune deficiencies include escape of T cells, which react to cells of the organism from central and peripheral supressive steps; disruption in pathways that affect programmed cell death; abnormal function of regulatory T cells; and the inability to eliminate abnormal B cells in the bone marrow or in peripheral tissues (4, 5, 9).

Among our patients, autoimmunity was observed most commonly in IPEX. In IPEX, autoimmunity may be observed in many organs before the age of one year as a result of regulator T cell disruption (10). Autoimmunity findings, which may be observed in IPEX, include type 1 DM, thyroiditis, autoimmune cytopenias, eczema, autoimmune enteropathy, hepatitis, nephrotic syndrome, interstitial nephritis, and arthritis (11). In our patients, eczema, hemolytic anemia, hypothyroidism, diarrhea, Type 1 DM, gastritis, hepatitis, and nephrotic syndrome were observed. In four of five patients, autoimmunity was observed in the early months of life as the first finding. In 45% of the cases of IPEX described in the literature, the findings occured in the neonatal period, and even at birth in 11 patients (11). Therefore, autoimmune involvement, especially of multiple organs in the early period necessitates the suspicion of IPEX, which is one of the primary immune deficiencies even if infection has not yet developed. In STAT5b deficiency, which is defined as similar to IPEX, IL-2 receptor mutation, gain of protein function mutation of the *STAT1* and *STAT3* genes, CTLA4 deficiency and LRBA deficiency, disruptions in signal pathways responsible for regulatory T cell function have also been identified (12-16). In our patients who had LRBA deficiency and gain of protein function mutation of the *STAT1* gene, hemolytic anemia, IBD/IB-like findings, alopecia, thrombocytopenia, and hypothyroidism were detected.

In autoimmune polyendocrinopathy, candidiasis and ectodermal dystrophy, autoimmune involvement of many organs is observed because of the inability to eliminate T cells, which react to the organism during development in the thymus as a result of mutation in the autoimmune

Table 2. Autoimmunity findings, treatment methods and prognoses by the diagnoses of the patients

Diagnosis	Autoimmunity properties	Autoimmune tests	Treatment	Prognosis
CD 19 deficiency	Psoriasis	ANA	IVIG, PUVA	Living
PI3KR1 mutation	ITP, arthritis, IBD/IBD-like findings		IVIG, steroid, methotrexate, etanercept, splenectomy, sirolimus	Living
PIK3CD mutation	IBD/IBD-like findings		IVIG, steroid, sirolimus	Living
IL-10 receptor deficiency	IBD/IBD-like findings		Azathioprine, steroid, cyclosporin	BMT/living
APECED	Hypothyroidism, adrenalitis, vitiligo	Anti TPO	Steroid, Levotyroxine	Living
STAT1 mutation	ITP, Hypothyroidism	Anti TPO	Levothyroxine, IVIG	Exitus/intracranial mycotic aneurism
PRKCD deficiency	Eczema, ITP, SLE-like eruption, IBD/IBD like findings	ANA, anti SSA, antiribosomal p protein	IVIG, hydroxychloroquine	Living
LRBA deficiency	AHA, ITPI	ANA, direct Coombs	Steroid, cyclosporin, mikofenolat mofetil, IVIG	BMT/living
LRBA deficiency	ITP, IBD/IBD-like findings		Steroid, IVIG	Living
LRBA deficiency	IBD/IBD-like findings, alopecia		Steroid, IVIG	Living
IL-21 receptor deficiency	SLE-like eruption	Lupus anticoagulant	IVIG, hydroxychloroquine	Exitus/sepsis
DOCK8 deficiency	Eczema, AHA	Direct Coombs	IVIG, steroid, rituximab	BMT/living
DOCK8 deficiency	Eczema, Vasculitis		Steroid, cyclophosphamide	BMT/living
DGS	AHA, ITP	Direct Coombs	IVIG	Living
DGS	ITP	ANA	IVIG	Living
DGS	ITP		IVIG	Living
KGH	Pericarditis, hepatitis		Steroid	BMT/Exitus/ GVHH
RAG1 deficiency	AHA, SLE-like eruption, IBD/IBD-like findings	Direct Coombs	Rituximab, hydroxychloroquine, IVIG, colchicine	Living
RAG1 deficiency	Hypothyroidism, DM, vitiligo	ATG, anti-islet cell antibody	Levothyroxine, IVIG	BMT/living
IPEX	Eczema, AHA, IBD/IBD-like findings	Direct Coombs, anti-enterocyte cell antibody	Steroid, cyclosporin	BMT/living
IPEX	IBD/IBD-like findings, hepatitis, nephrotic syndrome	ANA	Azathioprine, steroid	Exitus/ARDS
IPEX	Eczema, AHA, hypothyroidism, DM	Anti-TPO, direct Coombs	Steroid, sirolimus	BMT/intracranial hemorrhage/exitus
IPEX	IBD/IBD-like findings	Anti-enterocyte cell antibody	Steroid, sirolimus	BMT/ARDS/exitus
IPEX	IBD/IBD-like findings, gastritis	Antiparietal cell antibody	Sirolimus	Living
WAS	Eczema, ITP, IBD/IBD-like findings	Anti-platelet antibody	IVIG, rituximab, eltrombopag	Living
ALPS	AHA, ITP	ANA, direct Coombs	Steroid, IVIG, sirolimus	Living
ALPS	AHA, ITP	Direct Coombs	Steroid, cyclosporin	Living
ALPS	AHA, IBD/IBD-like findings	Direct Coombs	IVIG, G-CSF	Living
RAG2 deficiency	IBD/IBD-like findings		Subcutaneous IVIG, steroid	BMT/living
Ataxia telangiectasia	Cutaneous granuloma		IVIG, hydroxychloroquine	Living

ALPS: autoimmune lymphoproliferative syndrome; ANA: anti-nuclear antibody; APECED: autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy; ATG: anti-thyroglobulin antibody; DGS: DiGeorge syndrome; DM: diabetes mellitus; DOCK8: dedicator of cytokinesis 8; GVHH: graft versus host disease; IL: interleukin; IPEX: immune disregulation, polyendocrinopathy, enteropathy, X-linked; IVIG: intravenous immunglobulin; CGD: chronic granulomatous disease; BMT: bone marrow transfer; LRBA: lipopolysaccharide-responsive beige-like anchor protein; PIK3CD: phosphatidylinositol 3-kinase, catalytic, delta; PI3KR1: phosphatidylinositol 3-kinase, regulatory subunit 1; PRKCD: protein Kinase C, Delta deficiency; PUVA: psoralen Ultra-Violet A; RAG: recombination-activating gene; SLE: systemic lupus erythematosus; STAT1: signal transducer and activator of transcription 1; TPO: thyroid peroxidase; WAS: Wiskott-Aldrich syndrome

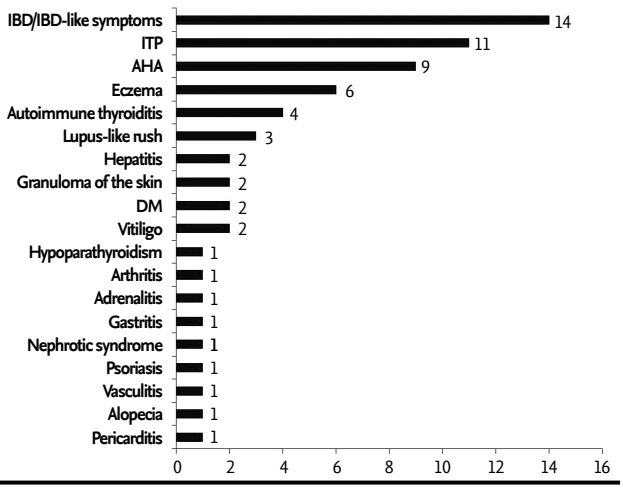

Figure 1. Autoimmunity findings observed in the patients

DM: diabetes mellitus; IBD: inflammatory bowel disease; ITP: immune thrombocytopenic purpura; AHA: autoimmune hemolytic anemia

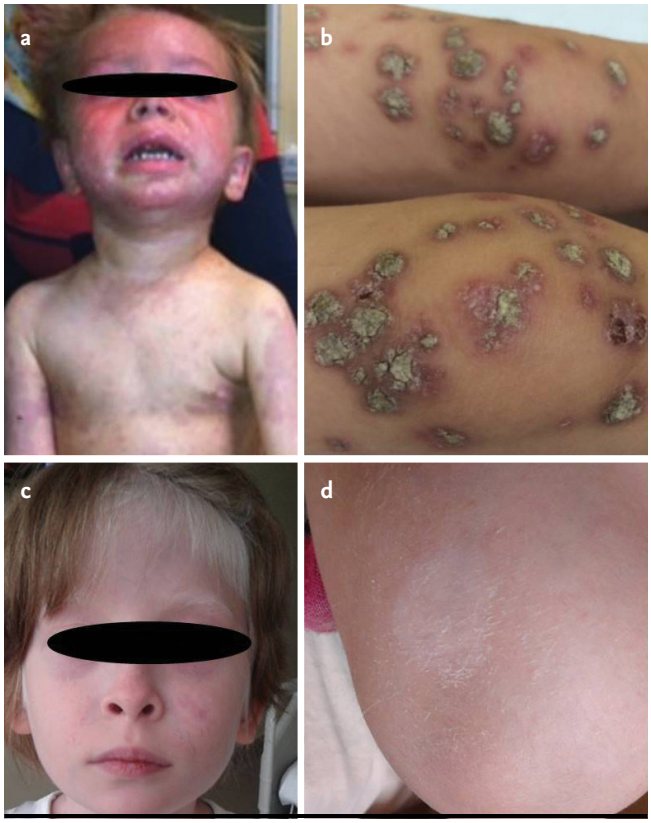

Figure 2. a-d. Examples of cutaneous findings observed in the patients lupus-like eruption on the face and body in the patient who had PRKCD deficiency (a) cutaneous granulomas in the patient who had ataxia telangiectasia (b) vitiligo findings on the face, hair and leg of the patient who had *RAG1* mutation (c, d)

regulatory gene (*AIRE*) (17, 18). Hypoparathyroidism, hypothyroidism, adrenal failure, chronic atrophic gastritis, pernicious anemia, autoimmune hepatitis, and vitiligo are among the findings observed in this disease in which autoimmune reaction is observed against many endocrine organs (19). Hypoparathyroidsm, hypothyroidism, adrenal failure, and vitiligo were observed in our patients.

It is thought that autoimmunity observed in DiGeorge syndrome is caused both by disruption in expression of the *AIRE* gene, and decreased variety and number of regulatory T cells as a result of abnormal thymus development (20). Autoimmune disease may be observed with a rate of 8.5% in DiGeorge syndrome. The most common autoimmune findings include reduction in cell counts (ITP, AHA, neutropenia), hypothyroidism and arthritis, respectively (21). In our patients, hematologic disorders also predominated as an autoimmunity finding.

Programmed cell death is very important in terms of the balance of the immune system and development of tolerance. Autoimmune lymphoproliferative syndrome (ALPS) is characterized by disruption in cell death. Autoimmunity is observed in approximately 70% of patients (22). The most common findings include autoimmune hemolytic anemia and autoimmune thrombocytopenia. Direct Coombs test-positive hemolytic anemia was found in all three of our patients who had a diagnosis of autoimmune lymphoproliferative syndrome and thrombocytopenia was found in two. Antiplatelet and anti-neutrophil antibodies, together with anti-erythrocyte antibodies detected with a positive direct Coombs test are the most common autoantibodies found in ALPS (23, 24).

Autoimmunity observed in CGD is thought to be triggered by a prolonged inflammatory response related with the inability of phagocytes with disrupted oxidative function to eliminate cellular remnants and antigens (25, 26). The most common autoimmunity finding in these patients is IBD. In addition, discoid lupus, arthritis, and ITP may be observed (4). In our patient, recurrent pericarditis and hepatitis were observed (27).

It is known that early-onset IBD is related with immune deficiencies. CGD, IL-10/IL-10 receptor deficiency, WAS, IPEX and IPEX-like diseases, and severe combined immune deficiencies are among these immune deficiencies (28). An underlying immune deficiency should be kept in mind, especially in the presence of very early-onset IBD (below age six months), consanguineous marriage or multiple family members affected, and in patients with unresponsiveness to treatment and accompanying autoimmunity, because stem cell transplantation will be among the therapeutic options other than ordinary IBD treatment, if immune deficiency is found (11, 29). In addition, therapeutic interventions directed to prevent infections may also affect survival. The initial finding in our patient with

IL-10 receptor deficiency was diarrhea. The symptoms started at the age of one month in this patient and stem cell transplantation was performed when no response to drugs used for IBD (azatyoprine, steroid, cyclosporin) was observed.

Cutaneous findings are frequently observed in primary immune deficiencies. The most common cutaneous finding is skin infections. In addition, eczema, erythrodermia, pigment changes, granuloma, vasculitic formations, and urticaria may also be observed (30). The main cutaneous findings observed in our patients included eczema, lupus-like cutaneous eruptions, vitiligo, granuloma, alopecia, and psoriasis. Although eczema is a frequent finding observed in childhood, severe eczema in early infancy may be a sign of *DOCK8* mutation, IPEX, and severe combined immune deficiencies. Cutaneous granulomas may be caused by infectious agents or occur as sterile granuloma in PID (30-33). Granuloma was observed in two of our patients who had ataxia telangiectasia and *RAG2* mutation.

Rapid genetic diagnosis of primary immune deficiencies in recent years has enabled development of specific therapies for new and present gene disorders. For example, use of CTLA4 protein (abatacept) has provided great benefit in controlling intestinal findings and other autoimmine diseases, because CTLA4 protein is also reduced in cases of LRBA deficiency (34). Sirolimus is another specific drug and has increased the survival rates to a great extent in patients with IPEX, PI3KR1, PIK3CD, LRBA and ALPS (35, 36). In our patients, both autoimmune findings and organomegaly (liver, lymph node, and spleen) were controlled with sirolimus treatment. Almost complete regression was observed in cutaneous findings with hydroxychloroquine in our patient with PRKCD deficiency in association with cutaneous involvement (37). Anti-CD20 (rituximab) treatment was found more successful than corticosteroid in our patient with DOCK8 in association with hemolytic anemia. Finally, it has been reported that autoimmunity findings could be controlled with ruxolitinib (Janus kinase inhibitor) in patients with gain of function *STAT1* mutation (38). As the mechanism of development of autoimmunity becomes clear, target-specific therapeutic opitions will increase gradually as observed in these examples.

In conclusion, autoimmunity occurs with different findings in various immune deficiencies independent of the mechanism. It should be kept in mind that early-onset autoimmunity findings and multiple autoimmunity may even be a sign of primary immune deficiency in patients who have not yet developed infection. This approach will increase the chance of early and accurate treatment and survival in these patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Marmara University School Medicine (04.09.2015- 09.2015.249).

Informed Consent: Verbal informed consent was obtained from patients and parents of patients who participated in this study.

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References

1. Bousfiha A, Jeddane L, Al-Herz W, et al. The 2015 IUIS Phenotypic Classification for primary immunodeficiencies. J Clin Immunol 2015; 35: 727-38. [CrossRef]
2. Bousfiha AA, Jeddane L, Ailal F, et al. Primary immunodeficiency diseases worldwide: more common than generally thought. J Clin Immunol 2013; 33: 1-7. [CrossRef]
3. Kilic SS, Ozel M, Hafizoglu D, Karaca NE, Aksu G, Kutukculer N. The prevalences [correction] and patient characteristics of primary immunodeficiency diseases in Turkey-two centers study. Clin Immunol 2013; 33: 74-83. [CrossRef]
4. Maggadottir SM, Sullivan KE. The intersection of immune deficiency and autoimmunity. Curr Opin Rheumatol 2014; 26: 570-8. [CrossRef]
5. Saifi M, Wysocki CA. Autoimmune disease in primary immunodeficiency: At the crossroads of anti-infective immunity and self-tolerance. Immunol Allergy Clin North Am 2015; 35: 731-52. [CrossRef]
6. Arason GJ, Jorgensen GH, Ludviksson BR. Primary immunodeficiency and autoimmunity: lessons from human diseases. Scand J Immunol 2010; 71: 317-28. [CrossRef]
7. Carneiro-Sampaio M, Coutinho A. Early-onset autoimmune disease as a manifestation of primary immunodeficiency. Front Immunol 2015; 6: 185. [CrossRef]
8. Lehman HK. Autoimmunity and immune dysregulation in primary immune deficiency disorders. Curr Allergy Asthma Rep 2015; 15: 53. [CrossRef]
9. Cunningham-Rundles C. Autoimmunity in primary immune deficiency: taking lessons from our patients. Clin Exp Immunol 2011; 164: 6-11. [CrossRef]
10. Bennett CL, Christie J, Ramsdell F, et al. The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. Nat Genet 2001; 27: 20-1. [CrossRef]
11. Barzaghi F, Passerini L, Bacchetta R. Immune dysregulation,

polyendocrinopathy, enteropathy, x-linked syndrome: a paradigm of immunodeficiency with autoimmunity. Front Immunol 2012; 3: 211. [CrossRef]
12. Caudy AA, Reddy ST, Chatila T, Atkinson JP, Verbsky JW. CD25 deficiency causes an immune dysregulation, polyendocrinopathy, enteropathy, X-linked-like syndrome, and defective IL-10 expression from CD4 lymphocytes. J Allergy Clin Immunol 2007; 119: 482-7. [CrossRef]
13. Cohen AC, Nadeau KC, Tu W, et al. Cutting edge: decreased accumulation and regulatory function of CD41CD25(high) T cells in human STAT5b deficiency. J Immunol 2006; 177: 2770-4. [CrossRef]
14. Kuehn HS, Ouyang W, Lo B, et al. Immune dysregulation in human subjects with heterozygous germline mutations in CTLA4. Science 2014; 345: 1623-7. [CrossRef]
15. Verbsky JW, Chatila TA. Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) and IPEX-related disorders: an evolving web of heritable autoimmune diseases. Curr Opin Pediatr 2013; 25: 708-14. [CrossRef]
16. Milner JD, Vogel TP, Forbes L, et al. Early-onset lymphoproliferation and autoimmunity caused by germline STAT3 gain-of-function mutations. Blood 2015; 125: 591-9. [CrossRef]
17. Gardner JM, Fletcher AL, Anderson MS, Turley SJ. AIRE in the thymus and beyond. Curr Opin Immunol 2009; 21: 582-9. [CrossRef]
18. Finnish-German APECED Consortium. An autoimmune disease, APECED, caused by mutations in a novel gene featuring two PHD-type zinc-finger domains. Nat Genet 1997; 17: 399-403. [CrossRef]
19. Kisand K, Peterson P. Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy. J Clin Immunol 2015; 35: 463-78. [CrossRef]
20. Ferrando-Martínez S, Lorente R, Gurbindo D, et al. Low thymic output, peripheral homeostasis deregulation, and hastened regulatory T cells differentiation in children with 22q11.2 deletion syndrome. J Pediatr 2014; 164: 882-9. [CrossRef]
21. Tison BE, Nicholas SK, Abramson SL, et al. Autoimmunity in a cohort of 130 pediatric patients with partial DiGeorge syndrome. J Allergy Clin Immunol 2011; 128: 1115-7. [CrossRef]
22. Oliveira JB. The expanding spectrum of the autoimmune lymphoproliferative syndromes. Curr Opin Pediatr 2013; 25: 722-9. [CrossRef]
23. Kwon SW, Procter J, Dale JK, Straus SE, Stroncek DF. Neutrophil and platelet antibodies in autoimmune lymphoproliferative syndrome. Vox Sang 2003; 85: 307-12. [CrossRef]
24. Stroncek DF, Carter LB, Procter JL, Dale JK, Straus SE. RBC autoantibodies in autoimmune lymphoproliferative syndrome. Transfusion 2001; 41: 18-23. [CrossRef]
25. Sanford AN, Suriano AR, Herche D, Dietzmann K, Sullivan KE. Abnormal apoptosis in chronic granulomatous disease and autoantibody production characteristic of lupus. Rheumatology (Oxford) 2006; 45: 178-81. [CrossRef]
26. Kang EM, Marciano BE, DeRavin S, Zarember KA, Holland SM, Malech HL. Chronic granulomatous disease: overview and hematopoietic stem cell transplantation. J Allergy Clin Immunol 2011; 127: 1319-26. [CrossRef]
27. Barış S, Özen AO, Kıykım A ve ark. Kronik granülomatöz hastalıklı olgularımızın değerlendirilmesi. Asthma Allergy Immunol 2014; 12: 20-5.
28. Uhlig HH, Schwerd T, Koletzko S, et al. The diagnostic approach to monogenic very early onset inflammatory bowel disease. Gastroenterology 2014; 147: 990-1007. [CrossRef]
29. Engelhardt KR, Shah N, Faizura-Yeop I, et al. Clinical outcome in IL-10- and IL-10 receptor-deficient patients with or without hematopoietic stem cell transplantation. J Allergy Clin Immunol 2013; 131: 825-30. [CrossRef]
30. Relan M, Lehman HK. Common dermatologic manifestations of primary immune deficiencies. Curr Allergy Asthma Rep 2014; 14: 480. [CrossRef]
31. Chiam LY, Verhagen MM, Haraldsson A, et al. Cutaneous granulomas in ataxia telangiectasia and other primary immunodeficiencies: reflection of inappropriate immune regulation? Dermatology 2011; 223: 13-9. [CrossRef]
32. Schuetz C, Niehues T, Friedrich W, Schwarz K. Autoimmunity, autoinflammation and lymphoma in combined immunodeficiency (CID). Autoimmun Rev 2010; 9: 477-82. [CrossRef]
33. Nanda A, Al-Herz W, Al-Sabah H, Al-Ajmi H. Noninfectious cutaneous granulomas in primary immunodeficiency disorders: report from a national registry. Am J Dermatopathol 2014; 36: 832-7. [CrossRef]
34. Lo B, Zhang K, Lu W, et al. Autoimmure Disease. Patients with LRBA deficiency show CTLA4 loss and immune dysregulation responsive to abatacept therapy. Science 2015; 349: 436-40. [CrossRef]
35. Lucas CL, Zhang Y, Venida A, et al. Heterozygous splice mutation in PIK3R1 causes human immunodeficiency with lymphoproliferation due to dominant activation of PI3K. J Exp Med 2014; 211: 2537-47. [CrossRef]
36. Baris S, Schulze I, Ozen A, et al. Clinical heterogeneity of immunodysregulation, polyendocrinopathy, enteropathy, X-linked: pulmonary involvement as a non-classical disease manifestation. J Clin Immunol 2014; 34: 601-6. [CrossRef]
37. Kiykim A, Ogulur I, Baris S, et al. Potentially Beneficial Effect of Hydroxychloroquine in a Patient with a Novel Mutation in Protein Kinase Cδ Deficiency. J Clin Immunol 2015; 35: 523-6. [CrossRef]
38. Higgins E, Al Shehri T, McAleer MA, et al. Use of ruxolitinib to successfully treat chronic mucocutaneous candidiasis caused by gain-of-function signal transducer and activator of transcription 1 (STAT1) mutation. J Allergy Clin Immunol 2015; 135: 551-3. [CrossRef]