Brief report

IgG4-related disease and B-cell malignancy due to an *IKZF1* gain-of-function variant

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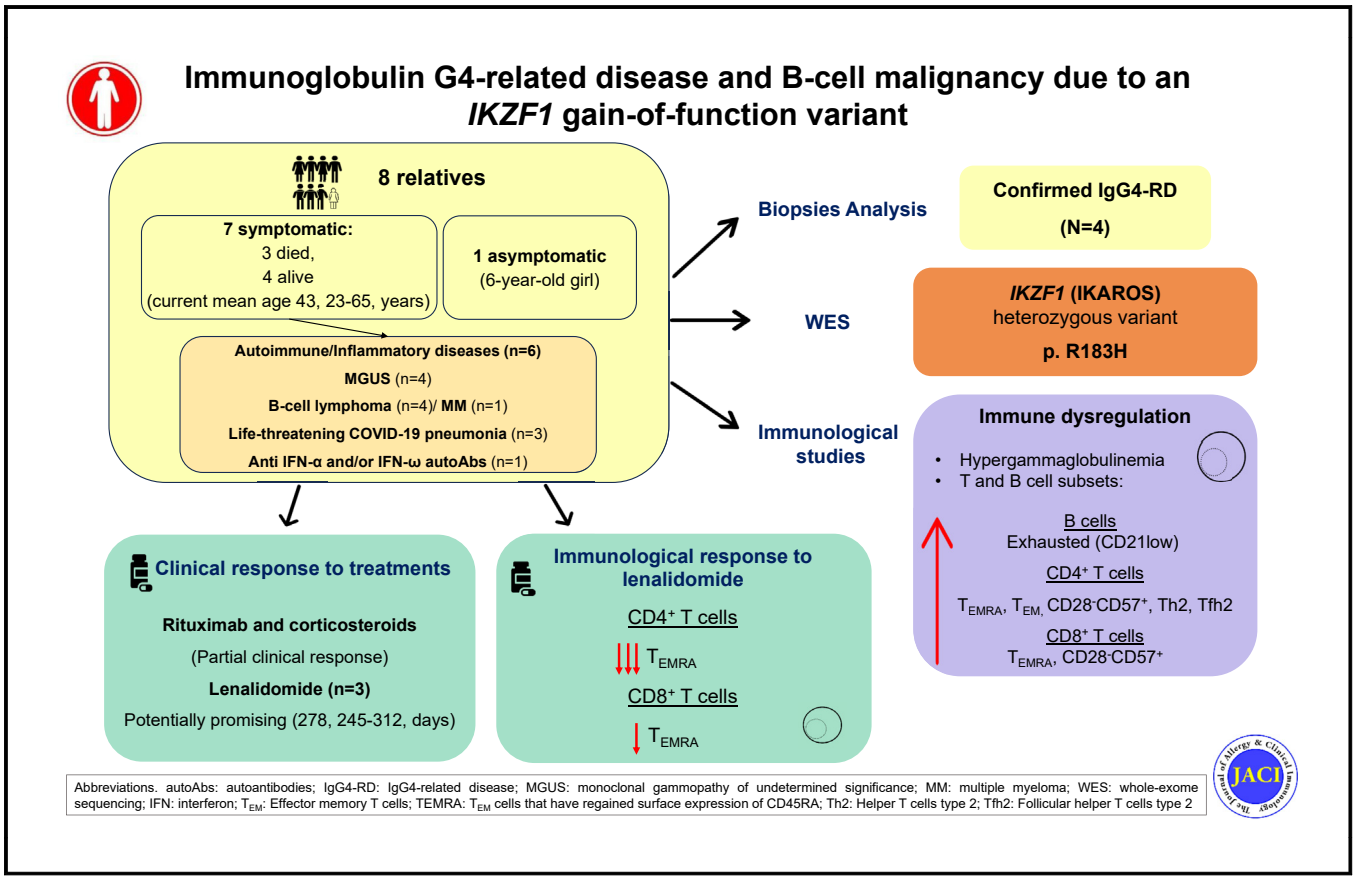
GRAPHICAL ABSTRACT



Capsule summary: Heterozygosity for gain-of-function *IKZF1* variants causes immune dysregulation, with a predisposition to autoimmunity/inflammation, immunoglobulin G4–related disease, and B-cell malignancy. Partial clinical responses to rituximab were observed, generally leading to a predisposition to recurrent infections. Lenalidomide is a potentially promising treatment for these patients.

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IgG4-related disease and B-cell malignancy due to an *IKZF1* gain-of-function variant

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Background: Monoallelic loss-of-function *IKZF1* (IKAROS) variants cause B-cell deficiency or combined immunodeficiency, whereas monoallelic gain-of-function (GOF) *IKZF1* variants have recently been reported to cause hypergammaglobulinemia, abnormal plasma cell differentiation, autoimmune and allergic manifestations, and infections.

Objective: We studied 7 relatives with autoimmune/inflammatory and lymphoproliferative manifestations to identify the immunologic disturbances and the genetic cause of their disease.

Methods: We analyzed biopsy results and performed whole-exome sequencing and immunologic studies.

Results: Disease onset occurred at a mean age of 25.2 years (range, 10-64, years). Six patients suffered from autoimmune/inflammatory diseases, 4 had confirmed IG4-related disease (IgG4-RD), and 5 developed B-cell malignancies: lymphoma in 4 and multiple myeloma in the remaining patient. Patients without immunosuppression were not particularly prone to infectious diseases. Three patients suffered from life-threatening coronavirus disease 2019 pneumonia, of whom 1 had autoantibodies neutralizing IFN-α. The recently described *IKZF1* GOF p.R183H variant was found in the 5 affected relatives tested and in a 6-year-old asymptomatic girl. Immunologic analysis revealed hypergammaglobulinemia and high frequencies of certain lymphocyte subsets (exhausted B cells, effector memory CD4 T cells, effector memory CD4 T cells that have regained surface expression of CD45RA and $CD28^{-}CD57^{+}$ $CD4^{+}$ and $CD8^{+}$ T cells, T_H2, and Tfh2 cells) attesting to immune dysregulation. Partial clinical responses to rituximab and corticosteroids were observed, and treatment with lenalidomide, which promotes IKAROS degradation, was initiated in 3 patients.

Conclusions: Heterozygosity for GOF *IKZF1* variants underlies autoimmunity/inflammatory diseases, IgG4-RD, and B-cell malignancies, the onset of which may occur in adulthood. Clinical and immunologic data are similar to those for patients with unexplained IgG4-RD. Patients may therefore benefit from treatments inhibiting pathways displaying IKAROS-mediated overactivity. (J Allergy Clin Immunol 2024;■■■:■■■-■■■.)

Key words: *Primary immunodeficiency, inborn errors of immunity, IKAROS, IKZF1, gain-of-function, IgG4-related disease, lymphoma, multiple myeloma, allergy*

Abbreviations used

COVID-19:	Coronavirus disease 2019
CTL:	Cytotoxic T cell
GOF:	Gain-of-function
IEI:	Inborn errors of immunity
IgG4-RD:	IgG4-related disease
IKZF1/IKZF3:	IKAROS family zinc finger 1/3
ITP:	Immune thrombocytopenia
MM:	Multiple myeloma
PC:	Plasma cell
T_{EM}:	Effector memory T cell
T_{EMRA}:	T_{EM} cells that have regained surface expression of CD45RA
Tfh:	Follicular helper T cells

INTRODUCTION

Studies of the pathogenesis of several inborn errors of immunity (IEI) have revealed that different variants of the same

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gene can cause different clinical conditions, thereby paving the way for the implementation of pathway-specific treatments.[1,2]

IKAROS family zinc finger 1, encoded by *IKZF1*, is an essential zinc finger transcription factor that guides lymphocyte differentiation and development.[3] Patients heterozygous for loss-of-function *IKZF1* variants present with hypogammaglobulinemia and a wide range of clinical manifestations, depending on the genetic defect concerned, ranging from limited susceptibility to infectious diseases to early-onset combined immunodeficiency; autoimmunity and hematological malignancies have also been reported.[3] Monoallelic variants of the zinc finger domain 3 of *IKZF1* with gain-of-function (GOF) behavior were recently reported in 7 patients with hypergammaglobulinemia; lymphoproliferative, autoimmune, and allergic manifestations; and recurrent infections.[4]

RESULTS AND DISCUSSION

We studied a multiplex family from the Canary Islands (Spain) in which 7 relatives suffering from inflammatory, autoimmune, and lymphoproliferative diseases were identified (Table I; see Fig E1 and the "Patients and Methods" section in this article's Online Repository at www.jacionline.org). Disease onset occurred at a mean age of 25.2 years (range, 10-64 years). Three patients suffered from autoimmune cytopenia, and 6 patients suffered from other autoimmune/inflammatory diseases. Extensive IgG4-positive infiltration of polyclonal plasma cells (PCs), meeting the diagnosis of IgG4-related disease (IgG4-RD),[5] was observed in biopsy specimens from 4 patients (Table I; Fig 1). IgG4-RD is a fibroinflammatory disorder resulting from dysregulation of the immune system, with specific $gG4^+$ PC[5,6] infiltration in diverse organs or anatomic sites. Several other episodes of inflammatory or autoimmune diseases affecting organs and tissues often involved in IgG4-RD were observed in the patients (Table I). However, it is challenging to distinguish IgG4-RD from other rheumatic diseases, and we were therefore unable to confirm IgG4-RD in at least some of these episodes because of incomplete data.[5,6] Five patients developed a B-cell hematological malignancy (lymphoma in 4 patients and multiple myeloma [MM] in 1 patient), and monoclonal gammopathy was documented in 4 patients (Table I). Four of the 5 affected adults had abnormally high IgE levels (Table II). Symptomatic atopy was observed in 2 patients, who had IgE specific for several house dust mites, with 1 of these patients displaying multiple allergies (see text and Table E1 in this article's Online Repository at www.jacionline.org). However, the prevalence of rhinitis, asthma, and positive house dust mite allergy test results has been reported to be high in the Canary Islands.[7] Viral serologies performed to 5 patients suggest that the patients were able to mount specific antibody responses (Table E2). The patients did not seem to be particularly prone to infectious diseases, although numerous recurrent and severe infections secondary to treatments with rituximab and for lymphoma were documented. Six episodes of mild coronavirus disease 2019 (COVID-19) and 3 of life-threatening COVID-19 pneumonia were documented in 6 patients (Table I). One of the 5 patients tested had neutralizing antibodies against IFN-α;[8] this patient suffered from mild COVID-19, severe COVID-19 pneumonia, and hypoxemic pneumonia due to respiratory syncytial virus. Immune thrombocytopenia (ITP) and marked lymphoproliferation of a retroperitoneal adenopathic conglomerate were documented after vaccination with an mRNA COVID-19 vaccine in 2 of the 5 patients vaccinated. ITP, although rare, has been shown to occur following immunization against various infectious diseases, particularly after vaccination against severe acute respiratory syndrome coronavirus 2 in individuals with a history of ITP.[9] COVID-19 vaccine–associated lymphadenopathy is accompanied by reactive T- and B-cell hyperplasia, which has also been reported in individuals with recent anti-CD20 treatment, albeit with a lower incidence.[10] Temporal relationships suggested that these episodes might be adverse events attributable to the vaccine, and a possible role of mRNA vaccines in the induction of antispike IgG4 antibodies and IgG4-switched memory B cells cannot be ruled out.[11] However, it is difficult to establish causal relationships between a vaccine and adverse events, particularly in patients with a history of lymphoproliferation and autoimmunity, and it is therefore not possible to draw any definitive conclusions here.

The first studies on 5 relatives (Table II) revealed hypergammaglobulinemia, with high IgG4 levels in 2 patients. Patients had normal or slightly low levels of B cells and natural killer cells, and low to high numbers of $CD4^+$ T cells and $CD8^+$ T cells. Whole-exome sequencing was performed on the 5 affected relatives, who were found to be heterozygous for a missense variant of *IKZF1* affecting nucleotide position g.50382666 (GRCh38p13) in exon 5 (c.769G>A, p.R183H) (Fig E1). This variant was recently reported by Hoshino et al[4] in 4 affected patients (mean age at disease onset, 21.7 years) and 1 asymptomatic 16-year-old boy from 3 families. The variant is GOF because it increases the DNA-binding ability of the encoded IKAROS variants, thereby increasing the expression of the genes concerned.[4] We also performed whole-exome sequencing analysis on 5 asymptomatic relatives. Four of these asymptomatic adult relatives did not carry the variant. However, 1 asymptomatic 6-year-old girl (patient IVA) with high IgG and IgA levels, but no changes in counts for B, T, and natural killer cells, was also heterozygous (Fig E1).

Hoshino et al[4] noted a marked infiltration of $IgG4^+$ PCs in the biopsy specimens of 3 patients with the *IKZF1* p.R183H variant. Our data highlight the predisposition to IgG4-RD in patients with the p.R183H variant. Hoshino et al[4] also reported the p.R183C GOF variant of *IKZF1* in 3 patients with an early disease onset (mean age, 1.17 years). None of their 8 patients had suffered from a hematologic malignancy or monoclonal gammopathy.[4] However, this may reflect the younger ages at which their patients were studied (mean age, 27 years; range, 11-49 years), given that our patients developed B-cell malignancies at a mean age of 47 years (range, 23-64 years). Nevertheless, they found the *IKZF1* GOF variant p.R183C in 1 patient from a series of 1838 patients with MM. We cannot exclude the possibility that additional environmental or genetic factors common to our patients account for their susceptibility to B-cell malignancies, but no variants known to confer a predisposition to B-cell malignancies, particularly for *MYD88*, *CD79B*, *TBL1XR1*, *BRCA2*, *NCOR1*, *KLF2*, *FAS*, *CCND3*, and *BRWD3*,[12,13] were detected in whole-blood DNA from our patients.

An extended analysis of lymphocyte subsets from 4 adult patients (Fig 2) showed immune dysregulation and chronic activation: all patients had high proportions of exhausted ($CD21^{low}$ $CD38^{low}$) B cells; T cells were skewed toward $CD4^+$ effector memory T cells (T_{EM}) and terminally differentiated $CD4^+$ and $CD8^+$ T_{EM} cells (T_{EMRA}, $CD45RA^+$), and the proportions of $CD28^-CD57^+$ $CD4^+$ and $CD8^+$ T cells were significantly

TABLE I. Clinical and epidemiological data and treatments in relatives heterozygous for the p.R183H variant of *IKZF1*

	Patient							
Characteristics	**IB**	**IC**	**IIA**	**IIC**	**IIIA**	**IIIB**	**IIIE**	**IVA**
Current age (y)	73 (deceased)	ND (deceased)	65	59 (deceased)	44	41	23	6
Age (y) at disease onset	64	ND	34	16	10	14	13	Asymptomatic
IgG4-RD/B-cell malignancy (age at onset [y])	IB-DLBCL (64)	Multiple myeloma (ND)	IgG4-R bilateral MD (34)*/submandibular lymphoplasmacytic lymphoma and MG IgA (43)	IgG4-R noncaseating granulomatous lymphadenitis (55)/MG IgG (44), DLBCL (58)	IgG4-R MD (10)/MG IgM and DLBCL (23)	MG IgA (27)	IgG4-R bilateral sclerosing dacryoadenitis and polyadenopathies with lymphoid follicular hyperplasia (13)	
Cytopenia	ES (ITP and AIHA)				ITP (10)	ITP (14)		
Other autoimmunity/ inflammation	Suspicion of autoimmune cholangitis†	ND	Pancreatitis with lymphocytic infiltration (47) Suspicion (no biopsy) of interstitial lung disease (48), alopecia areata (64) Chronic pansinusitis	HS (16), lymphadenopathies (34), left dacryoadenitis (40), retroperitoneal fibrosis (47) Chronic pansinusitis	Chronic maxillary sinusitis	Large-vessel necrotizing granulomatous lymphocytic vasculitis in the lower limbs (26),‡ alopecia areata Chronic pansinusitis	Chronic pansinusitis	
Infections	ND	ND	Recurrent URT and LRT infections, septic shock (adulthood)§	Recurrent and severe infections (mostly cutaneous), septic shock, and ARDS (adulthood)‖	Recurrent URT and LRT infections (adulthood)¶	Recurrent URT and LRT infections (adulthood)#	No	
SARS-CoV-2 infection and vaccination	Died before the pandemic	Died before the pandemic	Mild COVID-19 (December 2021, March 2022), severe COVID-19 pneumonia (February 2023) Vaccine ChAdOx1-S (2 doses)	Mild COVID-19 (January 2021), severe COVID-19 pneumonia (January 2022) Vaccine BNT162b2 (2 doses), followed by lymphoproliferation/ lymphadenitis and renal insufficiency	Mild COVID-19 (December 2021), severe COVID-19 pneumonia (March 2023) Vaccine BNT162b2 (1 dose), followed by ITP	Mild COVID-19 (December 2021) Vaccine BNT162b2 (2 doses)	Mild COVID-19 (December 2021) Vaccine BNT162b2 (2 doses)	No vaccination
N-autoAb anti–IFN-α and/or anti–IFN-ω and/or IFN-β	ND	ND	Negative	ND	Positive for IFN-α (10) and IFN-α (100)	Negative	Negative	Negative
Treatments eliciting a response**	ND	ND	RTX + corticosteroids, lenalidomide	RTX, rituximab + bendamustine, corticosteroids + methotrexate	RTX, lenalidomide	Corticosteroids, RTX	Corticosteroids, mycophenolate mofetil RTX, lenalidomide	
Treatments for B-cell malignancies	ND	ND	Radiotherapy (worsening), CHOP, auto-HSCT	R-mini-CHOP	R-CHOP, auto-HSCT			

AIHA, Autoimmune hemolytic anemia; *ARDS*, acute respiratory distress syndrome; *BNT162b2*, mRNA monovalent BNT162b2 COVID-19 vaccine (Pfizer-BioNTech); *ChAdOx1-S*, recombinant chimpanzee adenovirus ChAdOx1-S COVID-19 vaccine (AstraZeneca); *CHOP*, cyclophosphamide, doxorubicin, vincristine, and prednisone; *ES*, Evans syndrome; *HS*, hidradenitis suppurativa; *HSCT*, hematopoietic stem cell transplantation; *IB-DLBCL*, immunoblastic diffuse large B-cell lymphoma; *IFN-α (10)*, IFN-α2 at 10 ng/mL; *IFN-α (100)*, IFN-α2 at 100 pg/mL; *LRT*, lower respiratory tract; *MD*, Mikulicz disease; *MG*, monoclonal gammopathy; *N-autoAb*, neutralizing autoantibodies; *ND*, no data; *R-CHOP*, rituximab plus CHOP; *R-mini-CHOP*, rituximab and reduced dose CHOP; *RTX*, rituximab; *SARS-CoV-2*, severe acute respiratory syndrome coronavirus 2; *URT*, upper respiratory tract.

*The patient was diagnosed with Sjögren syndrome, negative for antinuclear antibodies as well as for autoantibodies anti-double stranded DNA, anti-ribonucleoproteins, anti-extractable nuclear antigens, anti-Sm, anti-Ro and anti-La., at the age of 34 y. A recent reanalysis of a biopsy from a salivary gland confirmed the diagnosis of IgG4-related MD.

†No autoantibodies were analyzed and no biopsy was performed.

‡Negative for antineutrophil cytoplasm antibodies, with scarce neutrophils.

§After rituximab treatment and treatment for lymphoma; septic shock during mobilization for autologous HSCT.

‖Secondary to rituximab and to neutropenia induced by bendamustine and bortezomib; fatal septic shock and acute respiratory distress syndrome while treated with R-mini-CHOP for lymphoma.

¶Secondary to rituximab treatment and R-CHOP treatment for lymphoma.

#On rituximab treatment.

**Only treatments with at least a partial response in autoimmune and inflammatory diseases are indicated.

higher than normal. An analysis of the expression of chemokine receptors in $CD4^+CD45RA^-CXCR5^-$ T_H cells and $CD4^+CD45RA^-CXCR5^+$ follicular helper T cells (Tfh) revealed an increase in the proportions of T_H2 and Tfh2 cells. Similar alterations were observed in the patients described by Hoshino et al,[4] although these patients displayed no increase in the proportions of $CD21^{low}CD38^{low}$ B, $CD4^+$ T_{EMRA}, and $CD28^-CD57^+$ $CD4^+$ T cells, possibly because of the greater mean age of our patients. Higher levels of circulating T_H2 and Tfh2 cells, and of $CD28^-CD57^+$ $CD4^+$ and $CD8^+$ T_{EM} cells have been reported in patients with IgG4-RD.[14-16] The phenotype of $CD4^+$ and $CD8^+$ $CD28^-CD57^+$ T cells from patients with IgG4-RD resembled that of *bona fide* effector cytotoxic T cells (CTLs), and their $CD28^-CD57^+$ $CD8^+$ T cells displayed an upregulation of IKZF1

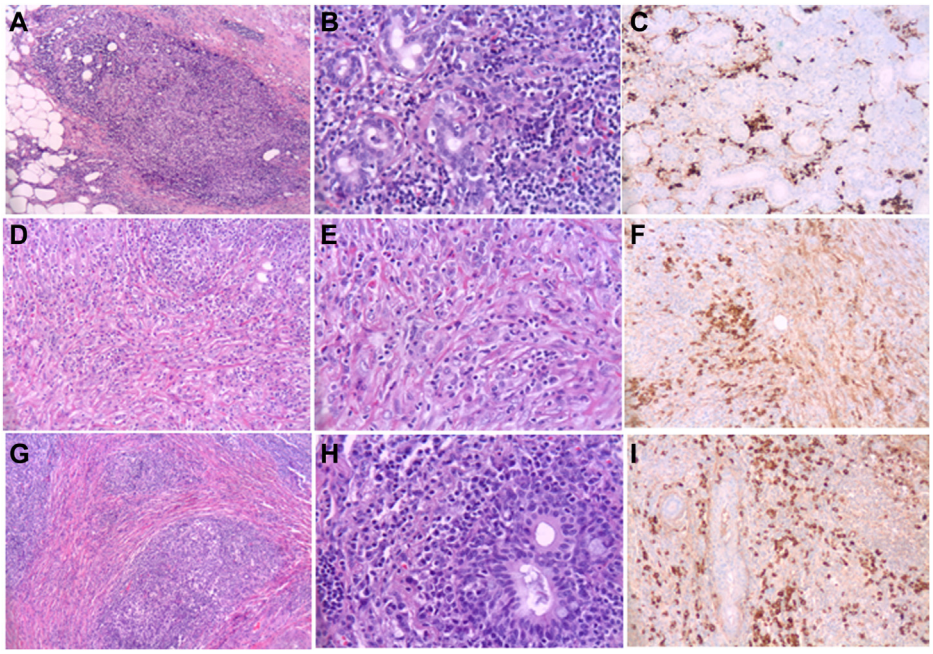

FIG 1. A-I, Immunohistochemistry of biopsy specimens from patients with IgG4-RD. Salivary glands from patients IIA (Fig 1, *A-C*) and IIIA (Fig 1, *D-F*) and a femoral lymph node from patient IIC (Fig 1, *G-I*) showing a lymphoplasmacytic infiltrate, prominent fibrosis, abundant scattered eosinophils, and abundant PCs (Fig 1, *A*, *B*, *D*, *E*, *G*, *H*), 60% (Fig 1, *C*), 70% (Fig 1, *F*), and 50% (Fig 1, *I*) of PCs being positive for IgG4.

TABLE II. Serum immunoglobulins and lymphocyte subpopulations in relatives heterozygous for the p.R183H variant in *IKZF1*

	Patient							Normal values	
Immunologic parameters	**IIA**	**IIC**	**IIIA**	**IIIB**	**IIIE**		**IVA**	**Adults**	**5 y old**
Serum immunoglobulins									
Age at evaluation (y)	46*	44†	23‡	21	15§	22‖	5		
IgG (mg/dL)	**2050**	**2140**	1120	1180	**1660**	**2576**	**1433**	700-1600	508-1201
IgA (mg/dL)	**440**	334	319	**860**	**547**	277	**601**	70-400	30-190
IgM (mg/dL)	77.4	98	**329**	70.3	116	*20.1*	121	40-240	36-203
Age at evaluation (y)	60‖	54†	38	35¶	17§	22‖	5		
IgG1	362	1055	874	*319*	1133	797	939	490-1140	370-1000
IgG2	422	509	281	*185*	567	382	295	150-640	72-340
IgG3	86	57	**188**	51	84	*28.5*	83.6	20-110	13-133
IgG4	73	15	**181**	9	21.17	**2100**	52.5	1-140	0-158
IgE (IU/mL)	**818**	**>2500**	**958**	*5.38*	**>2500**	**6300**	17.9	20-87	14-52
Lymphocyte subpopulations (cells/μL)									
Age at evaluation (y)	48	43	27	24‖	14	22‖	5		
T cells ($CD3^+$)	1975	**2980**	*893*	2106	1282	1399	2837	1000-2290	1400-3700
$CD4^+$ T cells ($CD3^+CD4^+$)	890	**2298**	*347*	1478	926	1216	1609	575-1525	700-2200
$CD8^+$ T cells ($CD3^+CD8^+$)	**1063**	539	557	627	285	148	1057	140-710	490-1300
Senescent/cytotoxic T cells ($CD3^+CD57^+$)	998	431	672	202	ND	134	324	22-401	—
B cells ($CD19^+$)	*65*	287	*74*	*0*	135	*0*	463	135-500	390-1400
NK cells ($CD3^-CD56^+$)	130	144	105	*67*	142	164	189	92-480	130-720
Markers of autoimmune lymphoproliferative syndrome									
DN TCR αβ (%)#	0.51	**3.24**	0.22	0.62	2.3	ND	ND	<2.5	
Serum IL-10 (pg/mL)	ND	ND	ND	ND	9.4	ND	ND	<10	
Vitamin B_{12} (pg/mL)	ND	ND	ND	ND	612	ND	ND	180-914	

Numbers in bold and italics indicate values above and below the normal range, respectively.
DN, Double-negative; *ND*, no data; *NK*, natural killer.
*At diagnosis of lymphoma. At the age of 39 y, she had normal levels of IgG (1139 mg/dL) and high IgA levels (724 mg/dL).
†At the age of 47 y, IgG and IgA levels had increased to 2880 and 467 mg/dL, respectively.
‡On treatment with azathioprine.
§On treatment with prednisone plus mycophenolate mofetil.
‖On treatment with rituximab.
¶On treatment with prednisone, 2 y after the last dose of rituximab; at the time of analysis, she had normal numbers of B cells with low levels of switched memory B cells (4.2% of B cells), low IgG levels (519 mg/dL), and monoclonal gammopathy IgA (0.44 g/dL) with very high serum IgA levels (1170 mg/dL).
#The values shown are percentages of $CD3^+$ T cells that are $CD4^-CD8^-$ TCR $\alpha\beta^+$. The levels of DN T cells were found to be normal in subsequent studies for patients IIB (0.56%, 60 y), IID (1.29%, 54 y), IIIA (0.54%, 38 y), IIIB (0.43%, 35 y), and IIIE (1.15%, 17 y).

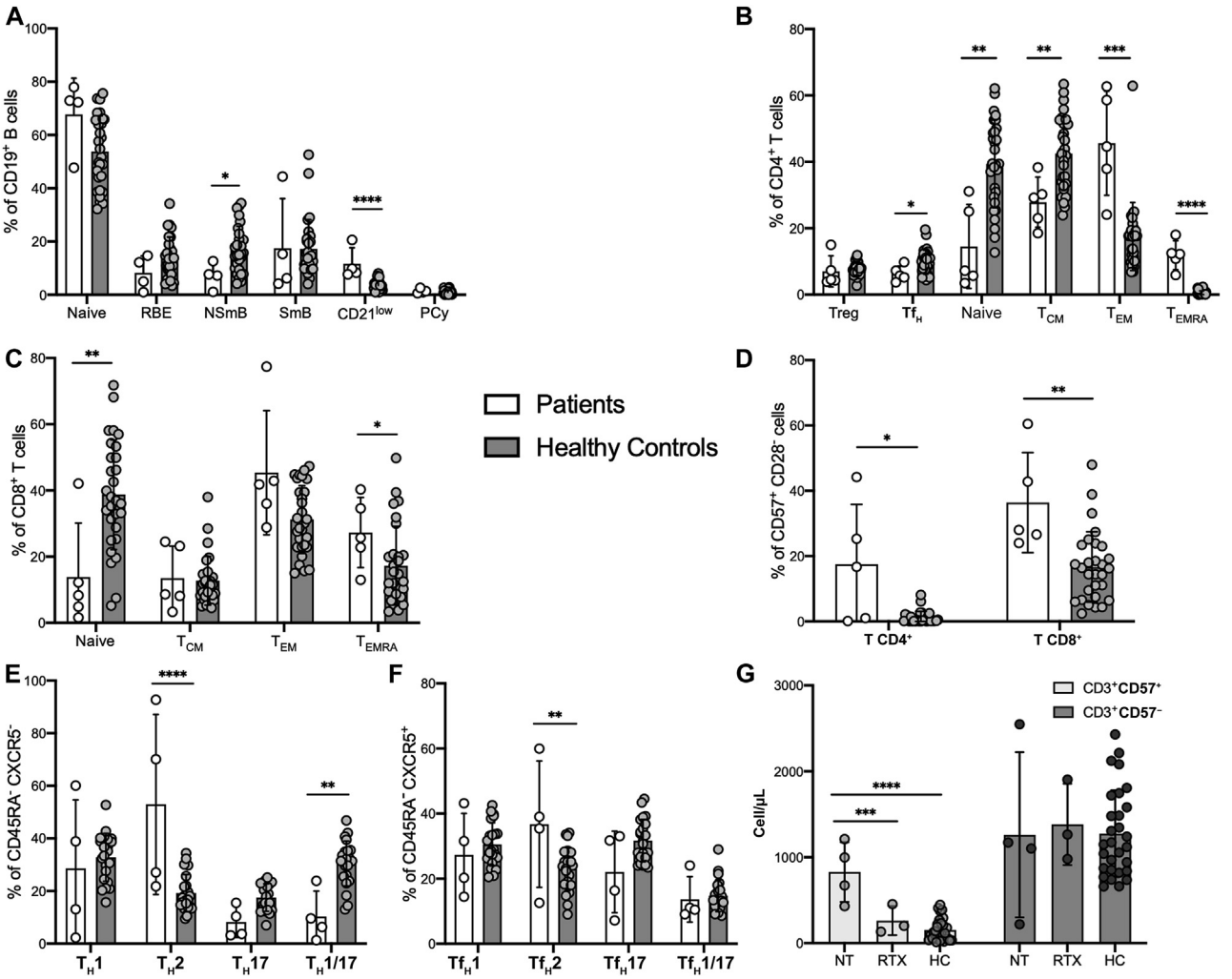

FIG 2. Lymphocyte subpopulations in affected adult patients and healthy controls. **A**, Relative frequencies of transitional (RBE), naive, nonswitched memory (NSmB), switched memory (SmB), exhausted ($CD21^{low}$), and plasmacytoid (PCy) B cells. **B** and **C,** Regulatory T (Treg) cells, Tfh CD4 T cells, and naive, central memory (T_{CM}), effector memory (T_{EM}), and terminal T_{EM} cells (T_{EMRA}, $CD45RA^+$) among $CD4^+$ and $CD8^+$ T cells. **D,** Senescent/cytotoxic ($CD57^+CD28^-$) $CD4^+$ and $CD8^+$ T lymphocytes. **E,** Frequencies of helper T-cell subsets. **F,** Frequencies of Tfh subsets. **G,** Frequencies of $CD57^+$ and $CD57^-$ T cells in patients on rituximab treatment (RTX), in patients without rituximab treatment (NT), and in healthy controls (HC). Data are presented as mean ± SD. $*P < .05$; $**P < .005$; $***P < .0005$; $****P < .0001$.

and IKZF3.[14-16] These CTLs have been identified as the dominant cells infiltrating tissues in patients with IgG4-RD, where they may induce apoptotic cell death, whereas circulating $CD28^-CD57^+$ $CD8^+$ and $CD4^+$ CTLs are strongly correlated with disease severity.[14,16]

In patients with IgG4-RD, treatment with glucocorticoid and the depletion of B cells with rituximab result in clinical improvement and a striking decrease in the levels of circulating $CD28^-CD57^+$ CD4 T cells, presumably because activated B cells and plasmablasts can act as potent antigen-presenting cells at low antigen concentrations.[14-16] Our patients displayed at least partial clinical responses to both rituximab and glucocorticoids during autoimmune/inflammatory episodes (see Table E3 in this article's Online Repository at www.jacionline.org). Interestingly, in our patients, $CD57^+$ T-cell counts also decreased following rituximab treatment (mean age, 35.3 years; range, 22-60 years) relative to the levels in untreated patients (mean age, 39 years; range, 27-48 years) (Fig 2). IKZF1 forms heterodimers with other IKAROS family proteins,[3,4] and IKZF1 and IKZF3 are essential for the development of MM. Lenalidomide, which is used to treat patients with MM and other hematological malignancies, promotes the degradation of IKZF1/IKZF3,[17] and *in vitro* treatment with lenalidomide has been shown to correct the T_H2 and PC abnormalities caused by the GOF *IKZF1* R183H/C variants.[4] Lenalidomide treatment was initiated in patients IIA, IIIA, and IIIE with a minimum maintenance dose (10 mg daily, 21 d/mo), and these patients have now been treated for 312, 277, and 245 days, respectively. Rituximab treatment was ceased, but the patients are still receiving prednisone. Lenalidomide was well tolerated in patients IIA and IIIE, but patient IIIA developed transient severe neutropenia (300 polymorphonuclear granulocytes/μL) in the context of severe pneumonia due to respiratory syncytial virus; he was treated with 1 dose of filgrastim, with the interruption of lenalidomide treatment for 17 days, and his granulocyte levels

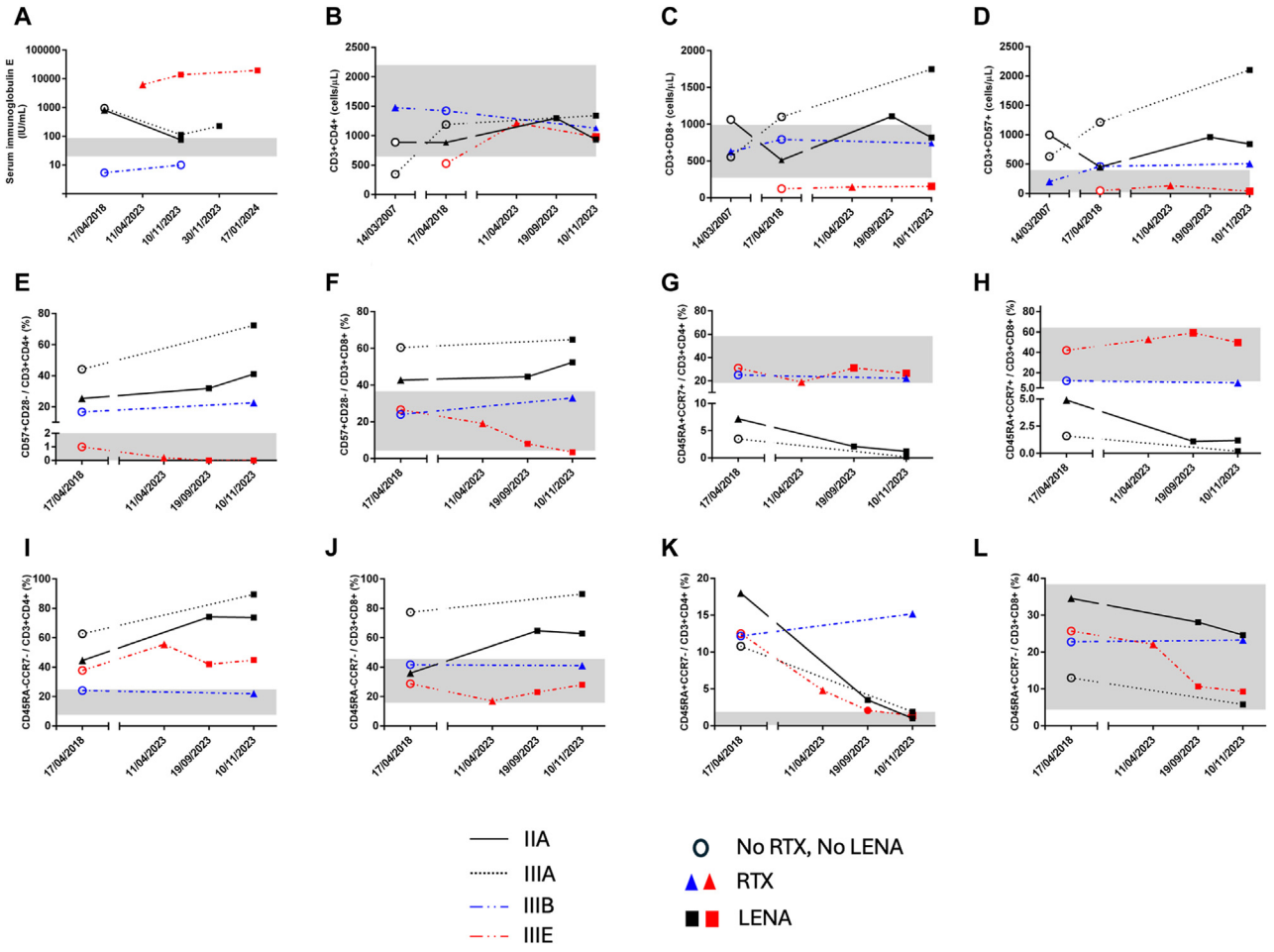

FIG 3. Serum IgE levels and lymphocyte subpopulations in affected adult patients treated with lenalidomide. **A,** Serum IgE levels. **B-D,** Counts of $CD4^+$ (Fig 3, *B*), $CD8^+$ (Fig 3, *C*), and $CD3^+CD57^+$ T cells (Fig 3, *D*). **E-L,** Relative frequencies of $CD57^+CD28^-CD4^+$ (Fig 3, *E*) and $CD8^+$ (Fig 3, *F*) T cells, naive $CD4^+$ (Fig 3, *G*) and $CD8^+$ (Fig 3, *H*) T cells, $CD4^+$ (Fig 3, *I*) and $CD8^+$ T_{EM} cells (Fig 3, *J*), and $CD4^+$ T_{EMRA} (Fig 3, *K*) and $CD8^+$ T_{EMRA} (Fig 3, *L*). Patients IIA, IIIA, and IIIE, but not patient IIIB, are on lenalidomide treatment. Shaded areas represent the 5th to 95th percentiles for healthy individuals. *LENA*, Lenalidomide; *RTX*, rituximab.

reached 3500 granulocytes/μL 10 days after administration of the dose of filgrastim. On physical examination, we observed a complete disappearance of the alopecia lesions in patient IIA, a disappearance of the residual sialadenitis in patient IIIA, and a large decrease in exophthalmos in patient IIIE (Table E3). The main finding for lymphocyte subpopulations common to these 3 patients was a marked decrease in the proportions of terminally differentiated T_{EMRA} $CD4^+$ and $CD8^+$ T cells on lenalidomide treatment (Fig 3).

The profile of circulating $CD4^+$ and $CD8^+$ T cells in our patients mimics that observed in patients with IgG4-RD, who also have a high risk of lymphoma.[18] The p.R183H and p.R183C IKAROS variants result in higher levels of T_H2 and PC differentiation, with the combined effect of promoting IgG4-RD and increasing IgE levels.[4] Clinically, IgG4-RD is most frequent in men older than 50 years, and most forms are nonfamilial. However, children, adolescents, and even monozygotic twins with IgG4-RD have been reported.[19] No genetic causes of IgG4-RD have yet been identified, and this condition is extremely rare in patients with IEI.[20-25] IgG4-RD and IEI due to *IKZF1* GOF variants appear to involve the same pathogenic mechanisms, but are not necessarily linked. Nevertheless, it is tempting to speculate that GOF *IKZF1* variants may underlie some cases of unexplained IgG4-RD and predisposition to B-cell malignancies. Larger cohorts and/or control trials will be required to evaluate lenalidomide tolerability and effectiveness. If lenalidomide is well tolerated and effective in the long-term for controlling IgG4-RD and/or the development of malignancies in our patients, then these patients would benefit from personalized medicine approaches aiming to inhibit pathways displaying IKAROS-mediated overactivation.

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All procedures were carried out according to the Declaration of Helsinki, and approval was obtained from the Ethics Committee of the Hospital Universitario de Gran Canaria Doctor Negrin and Hospital Universitario La Paz, Madrid. Informed consent was obtained from all individual participants included in the study.

Clinical implications: Heterozygosity for GOF *IKZF1* variants causes immune dysregulation, conferring predispositions to autoimmunity/inflammation, IgG4-RD, and B-cell malignancy. Partial clinical responses to rituximab were observed, generally resulting in a predisposition to recurrent infections. Lenalidomide treatment is potentially promising for these patients.

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