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MAJOR ARTICLE

Association of GATA2 Deficiency With Severe Primary Epstein-Barr Virus (EBV) Infection and EBV-associated Cancers

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Background. Most patients infected with Epstein-Barr virus (EBV) are asymptomatic, have nonspecific symptoms, or have self-limiting infectious mononucleosis. EBV, however, may result in severe primary disease or cancer.

Methods. We report EBV diseases associated with GATA2 deficiency at one institution and describe the hematology, virology, and cytokine findings.

Results. Seven patients with GATA2 deficiency developed severe EBV disease. Three presented with EBV infectious mononucleosis requiring hospitalization, 1 had chronic active EBV disease (B-cell type), 1 had EBV-associated hydroa vacciniforme–like lymphoma with hemophagocytic lymphohistiocytosis, and 2 had EBV-positive smooth muscle tumors. Four of the 7 patients had severe warts and 3 had disseminated nontuberculous mycobacterial infections. All of the patients had low numbers of monocytes, B cells, CD4 T cells, and natural killer cells. All had elevated levels of EBV in the blood; 2 of 3 patients tested had expression of the EBV major immediate-early gene in the blood indicative of active EBV lytic infection. Mean plasma levels of tumor necrosis factor α, interferon γ, and interferon gamma-induced protein 10 were higher in patients with GATA2 deficiency than in controls.

Conclusions. *GATA2* is the first gene associated with EBV hydroa vacciniforme–like lymphoma. GATA2 deficiency should be considered in patients with severe primary EBV infection or EBV-associated cancer, especially in those with disseminated nontuberculous mycobacterial disease and warts.

Keywords. GATA2; Epstein-Barr virus; hydroa vacciniforme; chronic active Epstein-Barr disease; Epstein-Barr virus smooth muscle tumors.

Most infections with Epstein-Barr virus (EBV) in children are asymptomatic or result in nonspecific symptoms. In contrast, EBV infection in adolescents and young adults frequently results in infectious mononucleosis. Although disease resolves within 2–4 weeks in most patients with EBV infectious mononucleosis, in a prospective study of 150 patients, 21% had fatigue that persisted for 2 months, 13% had fatigue at 6 months, and 29% had persistent cervical lymphadenopathy at 6 months [1]. Patients with certain polymorphisms in HLA-A01 [2] or interleukin 10 [3] may have more severe disease after primary infection. EBV is also associated with several cancers, including Burkitt lymphoma, Hodgkin and non-Hodgkin lymphoma, and smooth muscle tumors in immunocompromised persons.

Mutations in *GATA2* underlie the syndrome of sporadic monocytopenia and mycobacterial infection, dendritic cell, B-cell, and natural killer (NK) cell cytopenia, Emberger syndrome, and familial acute myelogenous leukemia/myelodysplastic syndrome [4–7]. GATA2 deficiency is also associated with fungal infections as well as with a number of severe virus infections, including human papillomavirus infection [4, 8–10], herpes simplex virus [8, 9, 11, 12], varicella-zoster [8, 11, 13], and cytomegalovirus (CMV) [4, 8, 11, 12]. Two cases of EBV-positive smooth muscle tumors have been reported in patients with GATA2 deficiency [9, 14], and 1 case of low-level EBV viremia without documented EBV disease [15]. Here we report 5 additional cases of severe EBV infections, including severe primary infections, chronic active EBV disease, and hydroa vacciniforme–like lymphoma with EBV-associated hemophagocytic lymphohistiocytosis.

CASE REPORTS

Severe EBV Infectious Mononucleosis

Patient 1 was a 16-year-old Hispanic girl with a history of severe primary EBV infection. At 5 years of age, she presented with neutropenia while seronegative for EBV and CMV. One

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month, later she was hospitalized with fever, cervical lymphadenopathy, fatigue, headache, and facial rash. Her EBV immunoglobulin M test was positive, and her blood EBV DNA level by polymerase chain reaction (PCR) was 11 000 copies/mL. Her CD4 count was 257 cells/μL, and B and NK cells were nearly absent (Table 1). A bone marrow biopsy showed myeloid hypoplasia. Computed tomography showed cervical and mediastinal lymphadenopathy, enlarged tonsils, and ground glass opacities in the lungs, but no hepatosplenomegaly. The patient was discharged but readmitted 3 days later with worsening sore throat, malaise, and dehydration. Her blood PCR EBV level was 44 000 copies/mL. Cervical lymph node biopsy findings were consistent with acute EBV infection or chronic active EBV disease. The bone marrow remained hypocellular with scattered cells positive for EBV RNA. The patient received corticosteroids for 4 months. Five months after her illness began, her blood EBV DNA level was 360 copies/mL. Her course was complicated by methicillin-resistant *Staphylococcus aureus* at the site of an intravenous catheter, right hand cellulitis, and right-sided otitis media. After discharge, she had buttock and abdominal wall abscesses and a urinary tract infection. She has had recurrent respiratory tract infections, and at age 15 years she developed unilateral Bell palsy. She has had persistently elevated EBV DNA levels in the blood, most recently 9800 copies/mL.

Patient 2 was a 28-year-old white woman. She presented at age 19 years with fever, nausea, vomiting, cervical lymphadenopathy, and sore throat; infectious mononucleosis was diagnosed. This was accompanied by anemia and severe fatigue with intermittent fevers for 3 months, a 20-lb (9 kg) weight loss, and 3 hospitalizations for dehydration and anorexia. She had persistently elevated blood EBV DNA levels for 8 years after her primary infection. During childhood she had oral aphthous ulcers and a submandibular abscess requiring drainage, molluscum contagiosum, and sinusitis requiring surgery. Two years after her primary EBV infection, she had fever of unknown origin for 6 months with anemia and neutropenia. The next year she had *Salmonella* diarrhea followed by chronic diarrhea and arthralgias. She had chronic warts on her fingers, toes, and genital area with intraepithelial neoplasia at biopsy. Six years after her initial EBV infection, she underwent a vulvectomy for intraepithelial neoplasia associated with genital warts. The next year a bone marrow biopsy showed hypocellularity, trisomy 8, monocytopenia, B lymphopenia, and cells containing EBV RNA. She received interferon (IFN) α for 5 months, but her blood EBV DNA level by PCR was 20 600 copies/mL. The next year she received a haploidentical hematopoietic cell transplant from an unaffected sister, which was complicated by skin graft-vs-host disease (GVHD). Immediately after transplantation, her blood EBV DNA level was undetectable by PCR. At present, 1 year after transplantation, her blood EBV DNA level is low positive or undetectable.

Patient 3 was a 28-year-old white woman and the identical twin of patient 2. She had presented at age 24 years with fever, weight loss, cervical lymphadenopathy, and streptococcal pharyngitis, and infectious mononucleosis was diagnosed. She was treated with prednisone for 2 weeks. She had anemia, thrombocytopenia, orthostatic hypotension, weight loss, alopecia, and fatigue for 6 months. Elevated levels of EBV DNA persisted in the blood after primary infection. She developed oral aphthous ulcers and chronic warts on her hands, feet, and genitalia. Bone marrow biopsy showed trisomy 8 and hypocellularity. She was treated with IFN-α, but treatment was discontinued owing to fever and fatigue. Another bone marrow biopsy 2 years later showed atypical megakaryocytes, severe monocytopenia, B-cell lymphopenia, and absent NK cells, consistent with GATA2 deficiency. She subsequently developed herpes zoster and postherpetic neuralgia. The next year, she received a haploidentical hematopoietic cell transplant from the same unaffected sister as patient 2. Six months before transplantation, her blood EBV DNA level was 6050 copies/mL. Immediately afterward, EBV DNA was undetectable. Her transplant course was complicated by mild GVHD involving the skin and gastrointestinal tract. Six months after transplantation, her blood EBV DNA level was low positive or undetectable.

Chronic Active EBV

Patient 4 was a 22-year-old white man who had been hospitalized at age 20 years with fever, fatigue, chills, night sweats, weight loss, and an axillary mass. He had pancytopenia and hepatosplenomegaly, positive monospot test results, EBV viral capsid antigen immunoglobulin M antibody, and elevated EBV DNA levels in the peripheral blood. *Mycobacterium abscessus* was isolated from his blood, skin, and lymph nodes. In addition to antimycobacterial agents, he was treated with IFN-γ, but this was discontinued owing to adverse effects. A splenectomy was performed for persistent pancytopenia. Scattered EBV-positive B cells were noted in the spleen and a splenic hilar lymph node. Sorting of peripheral blood mononuclear cells (PBMCs) into B-, T-, and NK cell populations showed that EBV was predominantly in B cells. Chronic active EBV disease, B-cell type, was diagnosed. Despite treatment, the patient had persistent mycobacterial infection and eventually stopped therapy and died.

EBV Hydroa Vacciniforme–like Lymphoma and Hemophagocytic Lymphohistiocytosis

Patient 5 was a 24-year-old Cantonese woman who reported a vesicular eruption associated with sun exposure from age 10 to 16 years. At age 20 years she was hospitalized with fever, cervical and mediastinal lymphadenopathy, neck pain, weight loss, dyspnea, and splenic lesions. A lymph node biopsy showed necrosis, and she was treated with corticosteroids. A urine test was positive for *Histoplasma* antigen, resulting in treatment with itraconazole, but cultures were negative for *Histoplasma*. The

Table 1. Patients With GATA2 Deficiency and Severe Primary Epstein-Barr Virus (EBV) Infection or EBV-Associated Cancers

	Severe EBV Infectious Mononucleosis			Chronic Active EBV Disease	Hydroa Vacciniforme–like Lymphoma/HLH	EBV-Positive Smooth Muscle Tumors	
Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Race/sex	Hispanic/female	White/female	White/female	White/male	Asian/female	Hispanic/female	Asian/male
Age at onset of EBV disease, y	6	19	23	20	20	41	24
Age at death, y (cause of death)	Alive	Alive	Alive	22 (mycobacterial infection)	Alive	46 post-HSCT viral infection; *Staphylococcus aureus* bacteremia and candidemia; respiratory failure	Alive
Symptoms	Fever, lymphadenopathy, fatigue	Fever, fatigue, sore throat, lymphadenopathy, anorexia	Fever, fatigue, cervical lymphadenopathy, anorexia, streptococcal pharyngitis	Fever, fatigue, night sweats, lymphadenopathy	Blistering rash in sun-exposed areas, then fever, diffuse lymphadenopathy, necrotizing lesions in nonexposed areas	Fever, fatigue, dyspnea, weight loss	Fever, fatigue, anorexia, weight loss
Other infections and cancers	HSV stomatitis; MRSA cellulitis	HPV; HSV stomatitis; *Salmonella* enteritis; *Neisseria meningiditis* sepsis	HPV; HSV stomatitis	*Mycobacterium abscessus*	*Enterococcus faecium* bacteremia; *Mycobacterium avium complex*; histoplasmosis; EBV T-cell lymphoma of lung	HPV, *M. avium complex*, HSV esophagitis; chronic monomyelocytic leukemia	HPV, *Mycobacterium szulgai*, *M. avium* complex; recurrent bacterial pneumonia
EBV therapy	Corticosteroids	HSCT	HSCT	None	Corticosteroids, etoposide, alemtuzumab for HLH; HSCT	HSCT	HSCT
EBV-positive tissues	Bone marrow, lymph node	No biopsies	No biopsies	Lymph node, spleen	Skin, lung, small and large intestine, skeletal muscle, CSF	Orbital tissue, liver, colon, uterus	Liver
Peak EBV DNA in blood, copies/mL	44 000	20 600	8900	2770[a]	6.4 million	ND	3350
EBV type	1	ND	ND	ND	1	1	ND
EBV gene expression in blood	Positive for *EBNA1* and *BZLF1*; negative for *EBNA2*, and *LMP1*	ND	ND	ND	Negative for EBNA1, BZLF1, EBNA2, and LMP1	BZLF1; negative for EBNA1, EBNA2, and LMP1	ND
IgG, mg/mL	1570[b]	3150	1940	966[b]	550[b]	610[b]	1090[b]
Cell count, cells/μL							
Lymphocytes	1796[b]	280	290	499	170	402	340
Monocytes	29	0	20	6	30	0	0
CD3 T cells	1773[b]	272	289	198	247	396	339
CD4 T cells	257	182	192	288	49	124	175
CD8 T cells	964	70	86	277[b]	192[b]	234[b]	145
B cells (CD20)	2	1	2	1	2	2	1
NK cells $CD3^{-}CD16^{+}$	22	8	0	3	12	4	0
GATA2 mutation	c.1187G > A R396Q missense	c.988C > T R330X (stop) null	c.988C > T R330X (stop) null	c.1061C > T T354M missense	Unialleleic expression; heterozygous for genomic SNPs exon 2bp 55A > C and exon 3 c.15C > G, hemizygous by cDNA sequence	c.1192 C > T R398W missense	C.1186 C > T R396W missense
Patient No.	14.I.1 [8]	39.I.2 [8]	39.I.1 [8]	19.II.1 [8]	Patient 14 [16]	1.II.1 [8, 9]	42.I.1 [8, 14]

Abbreviations: cDNA, complementary DNA; CSF, cerebrospinanal fluid; EBV, Epstein-Barr virus; HLH, hemophagocytic lymphohistiocytosis; HPV, human papilloma virus; HSCT, hematopoietic stem cell transplant; HSV, herpes simplex virus; IgG, immunoglobulin G; MRSA, methicillin-resistant *Staphylococcus aureus*; ND, not determined; NK, natural killer; SNPs, single nucleotide polymorphisms.

[a] Expressed in EBV DNA copies/10^6 cells.

[b] Values within normal range; all other laboratory values in these rows are abnormal.

patient was hospitalized with fever and treated with high-dose prednisone and azathioprine. The next year she had a perforated small intestine and underwent partial small-bowel resection. She was hospitalized again with panniculitis and treated with high-dose steroids and intravenous immunoglobulin for presumed Weber-Christian disease. A perforation of her large intestine necessitated subtotal colectomy, ileal resection, and right-sided ileostomy.

The patient subsequently had 2 cerebral ischemic infarcts with left-sided weakness. She was found to have disseminated *Mycobacterium avium* complex and was treated with clarithromycin and ethambutol. She was hospitalized with deep venous thromboses, pulmonary embolism, vertebral compression fracture (presumably due to long-term cortico steroids), multiple deep skin ulcers (Figure 1*A* and 1*B*), and osteomyelitis. She was later readmitted with diffuse ulcerations in the small intestine. Her peripheral blood showed neutropenia, lymphopenia, and reduced numbers of B cells and NK cells; she also had hypogammaglobulinemia. Multiple biopsies showed EBV-positive hydroa vacciniforme–like lymphoma involving the colon and skin (Figure 1*C* and 1*D*) with a clonal T-cell population. Computed tomography showed splenic infarcts and a perisplenic abscess, which was drained. Echocardiography showed vegetations on the mitral valve, presumed to be marantic. A bone marrow biopsy showed hemophagocytosis and a T-cell clone. The marrow was hypocellular with EBV-positive T-cells and B-cell lymphopenia (Figure 1*E–J*).

Fever, markedly elevated ferritin levels, thrombocytopenia, anemia, hypertriglyceridemia, and low NK cell counts led to a clinical diagnosis of hemophagocytic lymphohistiocytosis. The patient received dexamethasone, etoposide, and alemtuzumab. She had T-cell clones in the blood and cerebrospinal fluid and an EBV-positive T-cell lymphoma of the lung. EBV DNA was found in peripheral blood T cells (2 022 000 copies/10^6 T cells) and B cells (18 410 000 copies/10^6 B cells). She received a haploidentical hematopoietic cell transplant from her unaffected sister. Her course was complicated by GVHD involving the liver. Four months before transplantation, her blood EBV DNA was 1 541 800 copies/mL; immediately afterward, it was about 1400 copies/mL. Since transplantation, there has been no evidence of lymphoma, the level of EBV DNA in the patient's blood has generally been in the low thousands/ml range, and most of the virus has been in B cells.

EBV Smooth Muscle Tumors

Patient 6 was a 46-year-old Hispanic woman [9] with EBV-positive leiomyosarcomas of the left posterior orbit and chronic myelomonocytic leukemia who underwent allogeneic bone

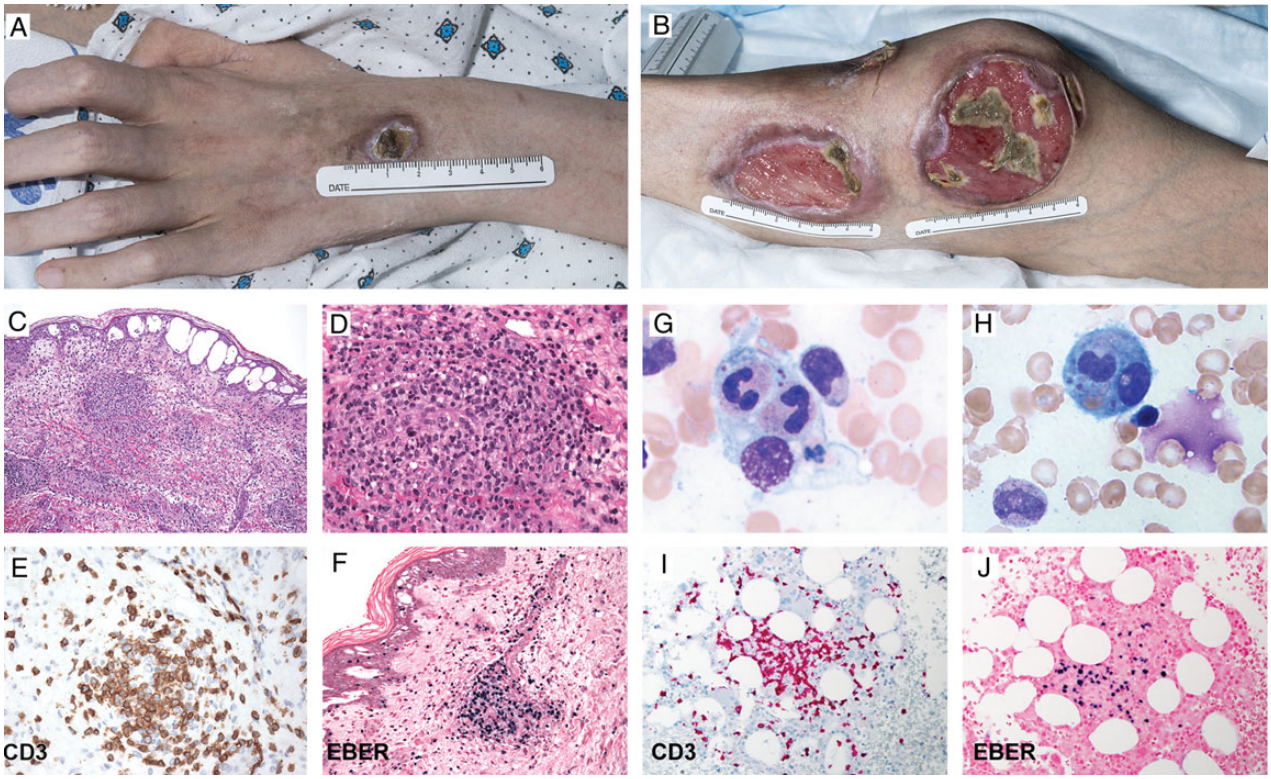

Figure 1. *A, B,* Skin lesions in patient 5 due to Epstein-Barr virus (EBV)–positive hydroa vacciniforme–like lymphoma. *C–F,* Hematoxylin-eosin staining show fluid-filled vacuoles in the epidermis (*C*) and a dense lymphocytic infiltrate (*D*), CD3 T cells (*E*), and EBV-encoded RNA (EBER)–positive cells in the skin (*F*). *G, H,* Hemophagocytosis. *I,* CD3 T cells. *J,* EBER-positive cells in the bone marrow.

marrow transplantation and died of respiratory viral infection. Sorting of stored PBMCs into B- and T-cell populations showed that EBV was predominantly in B cells. EBV-positive leiomyosarcomas of the posterior orbit, colon, uterus, and liver were found at autopsy.

Patient 7 was a 27-year-old Filipino man [14] with EBV-positive smooth muscle tumors of the liver and an elevated blood EBV DNA level (3350 copies/mL) who received an HLA-matched hematopoietic stem cell transplant from his sister. Six months before transplantation, his blood EBV DNA level was 3350 copies/mL; immediately afterward, it was undetectable. His liver lesions resolved, he developed mild skin GVHD, and the level of EBV DNA in his blood has been low positive or undetectable.

METHODS

Patients

All patients signed consents and were enrolled in protocols approved by the institutional review boards of the National Institute of Allergy and Infectious Diseases and the National Cancer Institute.

EBV Gene Expression and EBV Typing

To determine the pattern of EBV latency in the blood, RNA was isolated from PBMCs, complementary DNA was produced using reverse-transcriptase, and PCR was performed across spliced exons of 3 EBV latency genes (EBV *EBNA1, EBNA2,* and *LMP1*) and the *BZLF1* major immediate-early gene and actin (a positive control) [17, 18]. Southern blotting was performed using the PCR products and phosphorus 32–labeled DNA probes for each of the EBV genes. EBV type 1 or 2 was determined using PCR [19].

Cytokine Levels, in Situ Hybridization for EBV, and EBV Loads

Serum cytokines (interleukin 1β [IL-1β]; interleukin 2, 6, 10, 17A, 17E, 17F, 21, and 22; interferon gamma-induced protein 10 [IP-10]; IFN-γ, tumor necrosis factor [TNF] α; and macrophage inflammatory protein-1β) were measured using Luminex 200 instrumentation (Luminex Corporation) with Multiplex assay kits (Millipore Corporation). The assays were performed and analyzed with the Bio-Plex manager 5.0 software (Bio-Rad Laboratories) using a Logistic-5PL regression method. In situ hybridization for EBV-encoded RNA 1 was performed on fixed paraffin-embedded sections [20].

RESULTS

EBV DNA Level, Gene Expression, and EBV Typing in Blood

The median EBV DNA level in our patients was 14 750 copies/mL; in contrast, it was 117 copies/mL in 44 other EBV-seropositive patients with GATA2 insufficiency (a subset of those reported elsewhere [8]). In situ hybridization of tissues from patients 1, 4, 5, 6, and 7 was positive for EBV-encoded RNA. Four patterns of EBV latency gene expression have been reported, ranging from type 0, with no latency genes expressed, to type 3, with expression of EBV *EBNA1, EBNA2,* and *LMP1*. PBMCs from patient 1 expressed EBV *EBNA1* but no other latency genes, whereas patients 5 and 6 showed no expression of EBV latency genes. Patients 1 and 6 showed EBV *BZLF1* expression consistent with lytic infection in PBMCs. EBV protein expression in tissues was performed using antibodies to LMP1, EBNA2, and BZLF1 in patients 4 and 5, for whom sufficient tissue was available. A lymph node from patient 4 and multiple tissues from patient 5 were negative for expression of each of the 3 EBV latency proteins tested. Two types of EBV have been reported, types 1 and 2; the latter has been shown to have a predilection to infect T cells [19]. Each of the patients tested (patients 1, 5, and 6) had EBV type 1.

Cytokines Levels in Patients With GATA2 Deficiency and EBV Disease

Mean plasma levels of TNF-α were significantly higher in patients with GATA2 deficiency and EBV disease (mean, 55.7 pg/mL) than in healthy controls (mean, 36.7 pg/mL; $P = .02$). Similarly, mean plasma levels of IP-10 were higher in patients with GATA2 deficiency than in controls (mean, 4402.8 vs 419.6 pg/mL; $P = .04$), and levels of IL-1β were lower (mean, 1.0 vs 7.78 pg/mL; $P = .01$). Levels of IFN-γ were higher in patients with GATA2 deficiency and EBV disease than in controls, but the difference did not reach statistical significance.

DISCUSSION

Certain genetic disorders are associated with severe EBV disease but generally not with other infections. These include mutations in *SH2D1*, *BIRC4*, *ITK*, *MAGT1*, and *CD27* [21, 22]. Other genes, such as *PRF1, PIK3CD, CORO1A,* and *STK4* are associated with EBV disease and other infections. Here we report that mutations in *GATA2* are associated with severe primary EBV disease or EBV-associated cancers, along with other infections and cancers. In addition to having severe EBV disease, these patients had severe infections with herpes simplex virus, human papillomavirus, and nontuberculous mycobacteria. Five of the 7 patients underwent hematopoietic stem cell transplantation; 4 of them are alive.

EBV DNA levels in the blood were elevated in all patients tested. The virus was detected in multiple tissues including the bone marrow, lymph nodes, and spleen in persons without EBV-associated cancers. Three patients had EBV-associated cancers, 2 with smooth muscle tumors and 1 with hydroa vacciniforme–like lymphoma and T cell lymphoma. In these 3 patients the virus was detected in multiple tissues, including the liver, eye, lung, and small and large intestine. GATA2 deficiency is the first genetic disorder reported to be associated with EBV hydroa vacciniforme–like lymphoma.

We found significantly elevated plasma levels of IP-10 (a chemokine induced by IFN-γ) and TNF-α in patients with GATA2 deficiency and EBV disease. Levels of IFN-γ were higher in patients with GATA2 deficiency with EBV disease, but did not

reach statistical significance. Both TNF-α and IFN-γ are Th1 cytokines significantly elevated in patients with chronic active EBV disease [20].

GATA2 is a transcription factor important for both cellular immune responses and possibly for controlling latency of herpesviruses. Latent human CMV infection in CD34 progenitor cells results in up-regulation of GATA2 [23]. Expression of 2 human CMV latency genes, *UL144* and *LUNA*, depends on GATA2 binding sites in their promoters [24]. Of 6 predicted GATA2 binding sites in EBV, one is located in a latency promoter, the Cp promoter for the EBNA latency proteins. Thus, it is possible that in the presence of reduced levels of GATA2, virus latency may be impaired, resulting in more virus replication with severe primary EBV infection. At present it is unknown what role GATA2 plays in latency in other herpesviruses. The presence of EBV lytic gene expression (*BZLF1*) in the peripheral blood of 2 of 3 patients with GATA2 deficiency tested implies that these patients had difficulty maintaining EBV in a latent state.

GATA2 is expressed in hematopoietic progenitors but generally not in primary B cells or B-cell cancers except classic Hodgkin lymphoma; in the latter there was no relationship between GATA2 expression and EBV positivity [25]. Thus, EBV disease associated with GATA2 insufficiency is probably due to impaired immune surveillance against EBV due to reduced numbers and/or function of T and NK cells, rather than an effect of GATA2 transcription in EBV-infected B cells.

All of the patients reported here had low numbers of monocytes, CD4 T, B, and NK cells. Monocytes may be important for control of EBV based on their ability to secrete cytokines, such as interleukin 1, that can enhance immune responses or their differentiation into dendritic cells that present viral antigens to the immune system. EBV infection of monocytes inhibits their differentiation into dendritic cells [26] and the virus encodes a protein, BCRF1, that inhibits production of interleukin 1α, IL-1β, TNF-α, and interleukin 6 by monocytes [27]. CD4 cells from persons with EBV infectious mononucleosis or those infected with EBV in the past recognize both EBV lytic and latency proteins to control proliferating virus-infected cells [28–30]. The observation that our patients had low levels of IL-1β is consistent with their monocytopenia; however, their elevated levels of IFN-γ and TNF-α imply that they had sufficient CD4 T-cell function to generate these cytokines. Thus, low levels of monocytes and CD4 T cells in patients with GATA2 deficiency may impair immune surveillance to EBV.

NK cells are also important for control of primary EBV infection [31–33]. Patients with infectious mononucleosis and higher NK cell counts have lower EBV loads in the blood [34]. Tonsillar NK cells produce IFN-γ and inhibit EBV transformation and EBV-induced B-cell proliferation in culture [35]. Patients with congenital NK cell deficiencies have been reported to have severe EBV infections [36]. Mace and colleagues [12] showed that NK cells from persons with GATA2 deficiency and severe virus infections have impaired cytotoxicity and diminished numbers of $CD56^{bright}$ NK cells, the precursors for terminal cytotoxic $CD56^{dim}$ NK cells. Furthermore, 2 patients with GATA2 deficiency had improved NK cell function in response to IFN-α therapy [12], suggesting that IFN-α may be beneficial for some patients with viral diseases associated with GATA2 deficiency. Thus, the reduced numbers of NK cells in patients with GATA2 deficiency may predispose to severe primary EBV infection or reduced immunosurveillance against EBV, resulting in an increased propensity for EBV-associated cancers.

These cases identify *GATA2* as an important regulator of EBV infection and control, and suggest that GATA2 deficiency should be considered in cases of prolonged primary EBV infection and certain EBV-associated cancers.

Notes

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