Double Trouble in an Adult Patient with UNC13D mutation: EBV-Associated Lymphoproliferation and Kaposi Sarcoma

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Dear Editor,

Epstein-Barr virus (EBV) also known as HHV-4 and human herpes virus-8 (HHV-8) are members of the Gammaherpesviridae subfamily. Among these viruses that replicate in lymphoblastoid cells, EBV remains dormant in lymphoid cells, whereas HHV-8 remains dormant in monocytes and B cells.[1] EBV is present in more than 90% of the adults globally, and may cause a variety of clinical manifestations. Children and healthy adults with primary infections typically have no symptoms or develop self-limiting infectious mononucleosis.[2] To a lesser extent, in immunocompetent individuals, EBV-related immune dysregulation may result in chronic active EBV infection, hydroa vacciniforme, and severe mosquito bite hypersensitivity. Proliferation of EBV may result in T/NK cell systemic proliferative disease. Malignant transformation may result in gastric carcinoma, nasopharyngeal carcinoma, extranodal T/NK cell lymphoma, or Burkitt lymphoma.[3]

In patients with inborn errors of immunity (IEI), EBV may cause severe infectious mononucleosis, hemophagocytic lymphohistiocytosis, B-cell systemic lymphoproliferative disease, diffuse large B-cell lymphoma, Hodgkin lymphoma, and smooth muscle sarcoma.[3]

HHV-8 may be associated with fever and maculopapular rash in immunocompetent children whereas it may cause Kaposi sarcoma (KS) which is an angioproliferative mesenchymal neoplasm. HHV-8 also may cause primary effusion lymphoma or Castleman's disease in immunocompromised hosts.[4]

The UNC13D which is the causative gene for familial hemophagocytic lymphohistiocytosis (FHL3), encodes a protein called unc-13 homolog D, also known as MUNC13-4. MUNC13-4 is a member of the UNC13 family. Contact-dependent cellular cytotoxicity by NK cells and CD8+ cytotoxic T lymphocytes (CTLs) is one of the key effector mechanisms of the immune system against intracellular pathogens such as viruses and intracellular bacteria. MUNC13-4 that is expressed in NK cells and CTLs, is involved in vesicle priming and its deficiency results in defective exocytosis despite polarization of lytic granules and docking with the plasma membrane.[5]

Here, we present an adult patient presenting with EBV-associated lymphoproliferative disease and Kaposi sarcoma whom genetic analysis by whole exome sequencing (WES) revealed a compound heterozygous mutation in the UNC13D gene.

Table 1. Immunological evaluation of the patient

	Patiens values	Referance range
Complete Blood Cell		
Hb (g/dL)	11.2	14.0-17.4gr/dL
WBC (/mm^3)	5600	4500-11000/mm^3
ANC (/mm^3)	3200	1800-7700/mm^3
ALC (/mm^3)	1400	1400-3300/mm^3
Platelets (/mm^3)	148000	150-400/mm^3
Immunoglobulins (mg/dL)		
IgA	13	139-378 mg/dL
IgG	493	913-1884 mg/dL
IgM	30	88-322 mg/dL
Total IgE (kU/L)	10.7	7-698 kU/L
Lymphocyte subgroups (% and absolute numbers)		
CD3	82%	56-84
	1148	1000-2200
CD4	48%	31-52
	672	530-1300
CD8	32%	18-35
	448	330-920
CD16+56	16%	3-22
	224	70-480
CD19	0	6-23
	0	110-570
CD27	49%	17.5-46.5

The Case

A fourty eight-years-old male was admitted to Hacettepe University Immunology Department due to lymphoma recurrence, recurrent sinopulmonary infections and herpes labialis during infectious episodes. He admitted to the hospital with complaints of fatigue and night sweating at 32 years of age. Imaging studies showed mediastinal lymphadenopathy (LAP), and the excisional biopsy of the LAP was compatible with anaplastic large cell lymphoma. The patient was treated with chemotherapy (6 cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) and radiotherapy. However lymphadenopathy reappeared in the inguinal area at the age of 42 years, and the excisional biopsy revealed recurrence of lymphoma and HHV-8 was found to be positive. He was treated with chemotherapy (6 cycles of R-CHOP). A cardiac pacemaker was inserted for heart failure that was developed possibly secondary to chemotherapeutics, especially anthracyclines. When the patient was 46 years old, lymph nodes appeared again in the neck. The results of the excisional lymph node biopsy from the neck were consistent with EBV-associated lymphoproliferative disease. The chest computed tomography revealed mediastinal LAP. The wedge resection of left lung upper lobe and pericardial biopsy were found to be consistent with EBV-associated reactive lymphoproliferation, with lymphoid infiltration of pericardial tissue and fluid. Abdominal ultrasonography showed a nodular lesion 2.5 cm in diameter in the splenic hilus. The positron emission tomography revealed multiple, conglomerated lymph nodes in the right upper jugular, right submandibular, right lower cervical, left maxillary, within the spleen, splenic, right iliac, intra-abdominal multiple areas, with high FDG uptake showing high probability of malignancy. In his follow-up, he suffered from recurrent sinopulmonary infections (3-4 times in the last one year). The parents were non-consanguineous. His physical examina-

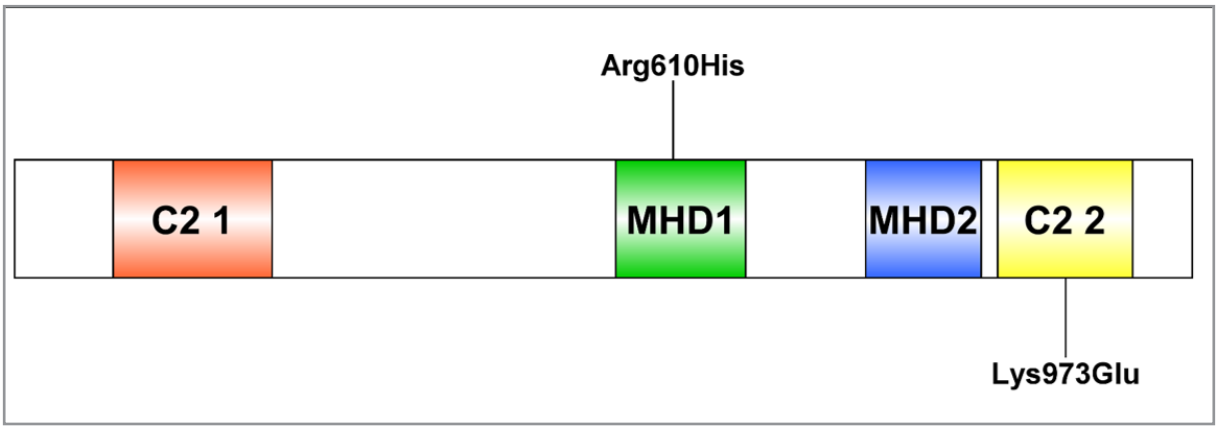

Figure 1. The compound heterozygous mutation of the patient in UNC13D gene

tion showed pale and sluggish appearance, painless, nonpruritic, hyperemic purpuric lesions on the neck, arms, abdomen and thigh with 1x1cm in diameter. The immunological evaluation shown in Table 1 revealed lymphopenia, hypogammaglobulinemia, low CD19 percentage and absolute counts. Immunoglobulin replacement therapy (400 mg/kg in every three weeks) and antibiotic prophylaxis with trimethoprim-sulphamethoxazole were initiated. EBV DNA in serum was 1.413.780 copies/mL. A skin biopsy which was performed to evaluate the lesions on the skin was found to be consistent with HHV8+ Kaposi sarcoma. Also, lymph node excisional biopsy revealed recurrence of anaplastic large cell lymphoma so ICE chemoterapy protocol (ifosfamide, carboplatin, etoposide) was initiated. Complete remission was achieved after 4 cycle ICE chemotherapy protocol and autologous stem cell transplantation was applied with BEAM (carmustine, etoposide, cytarabine, melphalan) chemotherapy regimen. A compound heterozygous mutation of c.1829G>A (p.R610H) and c.2917A>G (p.K973E) in the UNC13D gene was detected in whole exome sequencing (WES).The mutation was confirmed by Sanger sequencing (Figure 1).

Discussion

Here, we describe an adult male patient with compound heterozygous UNC13D mutation presenting with recurrent EBV-positive lymphoproliferation and Kaposi sarcoma. The mutations in UNC13D gene are known to cause FHL which is a heterogeneous autosomal recessive disorder caused by mutations also in PRF1 (FHL2), STX11 (FHL4), and STXBP2 (FHL5) genes. All of these genes are related to formation and function of secretory lysosomes within cytotoxic T lymphocytes (CTL) and natural killer (NK) cells. Different from the literature, our patient did not present with hemophagocytic lymphohistiocytosis (HLH) which is the characteristic presentation.[6,7]

Primary immunodeficiencies are a diverse collection of disorders with varying clinical manifestations. Our patient's presenting symptom was EBV-associated lymphoproliferation The number of genes associated with EBV susceptibility is increasing each year. Severe infectious mononucleosis, lymphoproliferation, HLH, and lymphoma with EBV should be a red flag for IEI. Among these IEI, XIAP, STX11, STXBP2, RAB27A, LYST, and PRF1 deficiencies cause HLH by disrupting T and NK cell cytotoxicity, whereas ITK, MAGT1, CTPS1, RASGRP1, DEF6, CD70, and TNFSF9 deficiencies cause B-cell lymphoproliferative disease and lymphoma by disrupting T cell activation and expansion. Both clinical presentations appear to be caused by SH2D1A, CD27, and TNFRSF9 deficiencies. Based on the presented case, relocating the UNC13D deficiency in this common overlap region may be reasonable.[7,8]

Kaposi's sarcoma, which was caused by HHV-8, was a second problem in the presented patient. The epidemic and iatrogenic forms of childhood KS result from a profound and acquired T cell deficiency. Recent studies have shown that classic KS of childhood can result from rare single- gene inborn errors of immunity, with mutations in WAS, IFNGR1, STIM1, and TNFRSF4.[9] Since UNC13D deficiency presenting with Kaposi's sarcoma has not been previously defined in the literature, we think that this information will contribute to the literature.

In recent years, it has been shown that secondary HLHs can emerge as a result of a variety of genetic defects. UNC13D mutations are shown to be associated with macrophage activation syndrome (MAS) in sJIA patients; especially polymorphims in key regulatory regions, has been demonstrated. In addition another study described a of UNC13D mutation in a patient with juvenile polymyositis with recurrent MAS.[10]

Despite the absence of consanguinity between the parents, the recurrent nature of the disease and resistance to treatment and coexistence of KS made a IEI with an EBV susceptibility highly probable. WES analysis revealed a compound heterozygous mutation in our patient. Compound heterozygous mutations in FHL patients are prevalent, as such mutations have been previously reported in the UNC13D gene.[11] Nevertheless, homozygous mutations are common in populations with consanguineous marriage.[12] We indicated that compound heterozygous and homozygous mutations occurred in approximately 48% and 37% of patients with FHL3, respectively.[5]

Although CHOP-like chemotherapy and rituximab can be used to treat EBV-related lymphoproliferation, these therapies are not always successful in treating the primary illness and commonly fail to control relapses.[13] The presented patient was treated with ICE chemoterapy protocol, and we started immunoglobulin replacement therapy since he had hypogammaglobulinemia and low CD19 which may be secondary to previous rituximab therapy. ASCT is a treatment option for lymphoma recurrences, however in cases where EBV positive or recurrent lymphoproliferative processes are present, allogeneic HSCT should be favored, as it was in our patient. New targeted immunotherapeutic approaches are needed for the better control of the severe immune dysregulation prior to HSCT.[7]

In conclusion, the presented case provided a novel insight into understanding a spectrum of EBV associated LPDs and Kaposi Sarcoma and demonstrated a different phenotype than classical HLH. Research should be done and precautions should be taken for other herpesviruses, such as HHV-8, in people with genetic abnormalities that predispose to EBV.

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