Journal of Clinical Immunology (2019) 39:26–29
https://doi.org/10.1007/s10875-019-0590-7

LETTER TO EDITOR

Childhood Hodgkin Lymphoma: Think DADA2

Fahad Alabbas[1,2] · Ghaleb Elyamany[2,3] · Omar Alsharif[1] · Michael Hershfield[4] · Isabelle Meyts[5]

Received: 27 September 2018 / Accepted: 3 January 2019 / Published online: 14 January 2019

To the Editor

Deficiency of adenosine deaminase 2 (DADA2) is a recently described inborn error of immunity caused by biallelic deleterious mutations in adenosine deaminase 2 (*ADA2*) gene (formerly known as *CECR1)*. It is an auto-inflammatory disorder characterized by fevers and vasculopathy, ranging from livedo racemosa over Raynaud phenomenon and digital necrosis to lacunar ischemic stroke. Cytopenia (e.g., pure red cell aplasia), mild immunodeficiency, and chronic liver disease are also part of the phenotype [1]. Over 170 DADA2 cases have been reported; however, the pathophysiology of DADA2 is still ill defined [2, 3]. Adenosine deaminase 2 (ADA2) may play a role in endothelial integrity and induces differentiation of monocytes into macrophages. Steroids, cyclosporine, tacrolimus, azathioprine, and mycophenolate mofetil have been unsuccessful in controlling the disease. The mainstay of treatment is TNF-inhibition with etanercept/infliximab/adalimumab as it controls fever and vasculopathy and prevents further strokes. Recently, hematopoietic stem cell transplantation (HSCT) has been shown to be a definitive cure of vascular, hematological, and immunological manifestations [4].

With male predominance, Hodgkin lymphoma (HL) represents only 6% of childhood cancer. Risk factors of HL include a history of Epstein-Barr virus (EBV) infection, high standard of living in early childhood, underlying congenital or acquired immunodeficiency disorders, autoimmune diseases, and rare hereditary syndromes. Familial HL accounts for 4.5% of HL cases and can be ascribed to genetic susceptibility and shared environmental factors. The usual presentation of HL is with painless cervical lymphadenopathy and mediastinal mass. Subdiaphragmatic presentation is rare and hepatosplenomegaly is associated with advanced HL [5].

The association of DADA2 with lymphoproliferation is well known (Table 1); splenomegaly and lymphadenopathies have been described in 30% and 10% of cases, respectively. Autoimmune lymphoproliferative syndrome (ALPS) like disease has been reported in several cases. A single patient with multicentric Castleman disease was shown to have DADA2. Moreover, T cell large granular lymphocyte leukemia (T-LGL) like condition was associated with DADA2. Springer et al. reported an adult patient with DADA2 who suffered from HL during early childhood. However, no details were available on the HL episode [5, 17, 18].

Herein, we describe two siblings with DADA2 who presented with familial HL. The first patient (P1) is the third child of Saudi first-degree cousin parents. At the age of 5 years, P1 was referred for investigation of hepatosplenomegaly. He was otherwise well with growth along the fifth centile. Complete blood count (CBC) showed mild lymphopenia; other lab results were normal (Table 2). A few months later, he developed non-tender mobile cervical lymph nodes enlargement. Viral serology, including EBV, was negative. Histopathological examination of excisional cervical lymph node biopsy revealed the diagnosis of HL, mixed cellularity type without other histological features suggestive of other than HL. Bone marrow (BM) biopsy was done as work up for HL and confirmed absence of malignant BM invasion.

P1 was staged as HL IIIB and started on intermediate risk protocol ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide). However,

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10875-019-0590-7) contains supplementary material, which is available to authorized users.

✉ Fahad Alabbas
Fmabbas@psmmc.med.sa

[1] Department of Pediatric Hematology/Oncology and Bone Marrow Transplant, Prince Sultan Military Medical City (PSMMC), Sulimaniyah RD, Riyadh 12233, Saudi Arabia

[2] Prince Sultan Military Medical City (PSMMC), Riyadh, Saudi Arabia

[3] Department of Central Military Laboratory and Blood Bank, Prince Sultan Military Medical City (PSMMC), Riyadh, Saudi Arabia

[4] Department of Medicine and Biochemistry, Duke University Medical Center, Durham, NC, USA

[5] Department of Pediatrics, Department of Microbiology and Immunology, University Hospitals Leuven, Leuven, Belgium

Table 1 Reports of lymphoproliferation associated with DADA2

Lymphoproliferative manifestation [reference]	DADA2 patients affected	Associated mutation
Splenomegaly ± lymphadenopathy [2, 4, 6–16]	± 30%	A109D/Y453C
		G47A/Y453C
		R169Q/deletion
		G47A/H112Q
		R169Q/Y453C
		M1T/I93T
		G47R/G47R
		R169Q/R169Q
		Homozygous 22q11.1 deletion (IL17RA and *ADA2*)
		V458D/V458D
		C408Y/c.542+1G>A
		R169Q/M243R
		c.973-1G>A/c.973-1G>A
		H112Q/H112Q
		R49Afs*13/R49Afs*13
		D261Pfs*2/D261Pfs*2
		N370K/G358R
		Y220X/Y220X
		R49fs/R169Q
		R169Q/M1T
		G47V/H112Q
		G49fs/splice site
		R169Q/L311R
Autoimmune lymphoproliferative like disorder [6, 13]	Reported in 2 patients	c.882-2A>G/c.882-2A>G
		R169Q/R169Q
T-LGL [14]	Reported in 2 patients	R169Q/R169Q
Castleman disease [17]	Reported in 1 patient	G47R/G47R
Lymphoma [18]	Reported in 1 patient	c.973-2A>G/V458D

re-evaluation of HL after 2 cycles of chemotherapy revealed slow early response, for which treatment was upgraded to chemotherapy DECA (dexamethasone, etoposide, cisplatin, cytarabine) making a total of 6 cycles, in addition to involved field radiation therapy. HL therapy was complicated by multiple febrile neutropenia episodes and chest infections. Three months after finishing HL therapy, mild splenomegaly persisted and the patient suffered from moderate pancytopenia necessitating regular transfusions. Malignancy was excluded by BM examination and positron emission tomography-computed tomography study. Results for viral blood PCRs as well as inherited BM failure gene panel were negative.

P1 was then started on prednisone 2 mg/kg/day, which resulted in regression of splenomegaly and decreased need of transfusions. However, steroids could not be weaned and he remained on prednisone 0.5 mg/kg every other day. His condition was complicated by recurrent infections in the form of chest infection, cellulitis, and skin abscess around the port-a-catheter that were treated with intravenous antibiotics. Immunological evaluation then revealed hypogammaglobulinemia. Whole exome analysis identified (at Centogene laboratory) a homozygous variant in *ADA2* gene c.1447_1451del, (p.Ser483Profs*5). This variant was private and predicted pathogenic by SIFT, PolyPhen2, AlignGVD, Mutation Taster, by creating a shift in the reading frame resulting in a premature stop codon. The variant was confirmed by Sanger sequencing and also detected in the sibling of the index patient in a homozygous state. Functional validation by dried plasma spot assay of ADA2 enzyme activity revealed undetectable level compatible with ADA2 deficiency. Magnetic resonance imaging did not show brain vasculopathy. P1 remained stable for 3 years on small dose of prednisone, monthly intravenous immunoglobulin (IVIG) and *Pneumocystis jirovecii* (PJ) prophylaxis. He then showed lower blood counts (anemia, thrombocytopenia, and lymphopenia), persistent splenomegaly and failure to thrive, in addition to chronic lung disease. After confirmation of DADA2, etanercept 5 mg/kg/week was started to control disease

Table 2 Laboratory findings of both patients

Investigations at presentation	P1	P2	Age adjusted reference range
Peripheral blood cell counts			
White blood cells	4.5	3.8	5–14.5 × 10^9/l
Neutrophils	2.6	1.5	1.6–9 × 10^9/l
Lymphocytes	1.2	1.7	2.2–9.8 × 10^9/l
Hemoglobin	8.8	10.5	11.5–15.5 g/dl
Platelets	225	181	150–450 × 10^9/l
Liver function tests			
Total bilirubin	23	4	0–17 umol/l
Alanine transaminase	32	39	2–40 u/l
Alkaline phosphatase	236	253	0–269 u/l
EVB serology (anti-EBNA)			
EBV IgG antibodies	Positive	Positive	N/A
EBV IgM antibodies	Negative	Negative	N/A
Investigations at diagnosis of DADA2			
ADA2 activity	Undetectable	Undetectable	57.7–271 mU/g protein
Immunoglobulin levels			
IgG	0.6	5.72	6.6–16.2 g/l
IgA	< 0.2	0.37	0.5–2.5 g/l
IgM	1.1	< 0.2	0.45–2.44 g/l

N/A not applicable

progression. Given limited time of treatment, we cannot comment on control of the cytopenia.

Nine months after the diagnosis of P1, his younger brother (P2) presented at the age of 5 years with hepatosplenomegaly and generalized lymphadenopathy (Table 2). Lymph node biopsy revealed the histopathological diagnosis of classical HL, lymphocyte-rich subtype without other than features of HL. BM study was negative for malignancy. Compared to P1, staging of HL in P2 identified a stage IIIA HL. Hence, chemotherapy (ABVE-PC protocol) without radiotherapy was given for 4 cycles and showed rapid early response. Similar to his sibling, whole exome analysis identified the same mutation (a homozygous variant in *ADA2* gene c.1447_1451del). This variant was again confirmed by Sanger sequencing and also for him, dried plasma spot analysis of ADA2 enzyme activity showed undetectable level. Other homozygous variants of unknown significance common to the two patients are listed in the supplement (Table E1). After the diagnosis of DADA2, screening for serum immunoglobulin levels showed hypogammaglobulinemia. P2 remains in remission of HL after chemotherapy and free of infection or inflammatory signs. Therefore, he is not on IVIG or anti-TNF-alpha until the time of writing the paper.

These cases are interesting for several reasons. First, we present a novel mutation causing DADA2. More importantly, this is the first detailed description of HL in DADA2. Given that lymphoproliferation is an important phenotype in DADA2 and given the previous note of a single case of childhood HL [18] and T-LGL, we hypothesize that the link between DADA2 and HL is likely to be causative. WES failed to identify any other pathological or likely pathological mutations to the two patients. In addition to that, the pedigree was not suggestive of a second independent disease in the family although indeed in a highly consanguineous background this might be the case. Moreover, the publication of another patient [18] and the fact that various "benign" lymphoproliferative conditions are part of the DADA2 phenotype, suggests that this rare childhood malignancy is indeed related to DADA2. The site of the mutation is located near the end of the protein. Although we did not test the expression of the protein or any truncated form, the ADA2 enzyme activity was absent in plasma suggesting a deleterious effect. The plasma enzymatic activity assay for ADA2 is at present a widely accepted test for establishing disease. Also, undetectable level of ADA2 is likely to be associated with more severe disease manifestations. However, a true phenotype-genotype correlation has not been established up until now.

Unfortunately, the precise physiological role of ADA2 and hence the pathophysiology of DADA2 is at present still enigmatic. FAS-mediated apoptosis has been tested in a limited number of patients [2]. Therefore, it is hard to hypothesize on the pathogenesis of lymphoproliferation or HL in DADA2. The presentation with different forms of HL and subdiaphragmatic involvement at a young age as well as the uncommon course with many infectious complications and development of cytopenia raised suspicion and led to

identification of DADA2. It is a matter of debate if the patient should be listed for HSCT. Indeed HSCT is a hazardous yet potentially curative treatment in refractory cytopenia in DADA2 [4]. Further studies are needed to establish whether long-term anti-TNF treatment will be able to prevent malignant lymphoproliferation in DADA2.

In summary, we report familial HL in two children with a novel deleterious mutation in *ADA2* and alert the hemato-oncologist to the possibility of DADA2 as an underlying diagnosis in childhood HL. Judicious exclusion of DADA2 is indeed warranted in familial HL and in the HL patient with an aberrant course and additional symptoms/signs, as it is potentially important both for genetic counseling as well as for optimal treatment.

Acknowledgments We would like to thank Saudi Society of Blood and Marrow Transplantation (SSBMT) for support and enhance hematology research in the KSA.

Authorship Wrote the manuscript: Alabbas F, Elyamany G, and Meyts I. Contributed to the writing of the manuscript: Alsharief O and Hershfield M. Agree with manuscript conclusions: Alabbas F, Elyamany G, and Meyts I. Made critical revisions and approved final version: Alabbas F and Meyts I. All authors reviewed and approved the final manuscript.

Funding Information This work was supported by the SANAD Children's Cancer Support Association and SANAD Research Grants Program (grant number: RGP-2017-02).

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests

References

1. Meyts I, Aksentijevich I. Deficiency of adenosine deaminase 2 (DADA2): updates on the phenotype, genetics, pathogenesis, and treatment. J Clin Immunol. 2018;38(5):569–78.
2. Zhou Q, Yang D, Ombrello AK, Zavialov AV, Toro C, Zavialov AV, et al. Early onset stroke and vasculopathy associated with mutations in ADA2. N Engl J Med. 2014;370(10):911–20.
3. Navon Elkan P, Pierce SB, Segel R, Walsh T, Barash J, Padeh S, et al. Mutant adenosine deaminase 2 in a polyarteritis nodosa vasculopathy. N Engl J Med. 2014;370(10):921–31.
4. Hashem H, Kumar AR, Muller I, Babor F, Bredius R, Dalal J, et al. Hematopietic stem cell transplantation rescues the hematological, immunological and vascular phenotype in DADA2. Blood. 2017;130(24):2682–8.
5. Linabery AM, Erhardt EB, Fonstad RK, Ambinder RF, Bunin GR, Ross JA, et al. Infectious, autoimmune and allergic diseases and risk of Hodgkin lymphoma in children and adolescents: a children's oncology group study. Int J Cancer. 2014;135(6):1454–69.
6. Van Eyck L Jr, Hershfield MS, Pombal D, Kelly SJ, Ganson NJ, Moens L, et al. Hematopoietic stem cell transplantation rescues the immunologic phenotype and prevents vasculopathy in patients with adenosine deaminase 2 deficiency. J Allergy Clin Immunol. 2015;135(1):283–7 e5.
7. Fellmann F, Angelini F, Wassenberg J, Perreau M, Arenas Ramirez N, Simon G, et al. IL-17 receptor a and adenosine deaminase 2 deficiency in siblings with recurrent infections and chronic inflammation. J Allergy Clin Immunol. 2016;137(4):1189–96.
8. Van Montfrans JM, Hartman EA, Braun KP, Hennekam EA, Hak EA, Nederkoorn PJ, et al. Phenotypic variability in patients with ADA2 deficiency due to identical homozygous R169Q mutations. Rheumatology (Oxford). 2016;55(5):902–10.
9. Westendorp WF, Nederkoorn PJ, Aksentijevich I, Hak AE, Lichtenbelt KD, Braun KP. Unexplained early-onset lacunar stroke and inflammatory skin lesions: consider ADA2 deficiency. Neurology. 2015;84(20):2092–3.
10. Schepp J, Proietti M, Frede N, Buchta M, Hubscher K, Rojas Restrepo J, et al. Screening of 181 patients with antibody deficiency for deficiency of adenosine deaminase 2 sheds new light on the disease in adulthood. Arthritis Rheumatol. 2017;69(8):1689–700.
11. Ben-Ami T, Revel-Vilk S, Brooks R, Shaag A, Hershfield MS, Kelly SJ, et al. Extending the clinical phenotype of adenosine deaminase 2 deficiency. J Pediatr. 2016;177:316–20.
12. Caorsi R, Penco F, Grossi A, Insalaco A, Omenetti A, Alessio M, et al. ADA2 deficiency (DADA2) as an unrecognised cause of early onset polyarteritis nodosa and stroke: a multicentre national study. Ann Rheum Dis. 2017;76(10):1648–56.
13. Alsultan A, Basher E, Alqanatish J, Mohammed R, Alfadhel M. Deficiency of ADA2 mimicking autoimmune lymphoproliferative syndrome in the absence of livedo reticularis and vasculitis. Pediatr Blood Cancer 2018;65(4). https://doi.org/10.1002/pbc.26912.
14. Trotta L, Martelius T, Siitonen T, Hautala T, Hamalainen S, Juntti H, et al. ADA2 deficiency: clonal lymphoproliferation in a subset of patients. J Allergy Clin Immunol. 2018;141(4):1534–7.
15. Rama M, Duflos C, Melki I, Bessis D, Bonhomme A, Martin H, et al. A decision tree for the genetic diagnosis of deficiency of adenosine deaminase 2 (DADA2): a French reference centres experience. Eur J Hum Genet. 2018;26:960–71. https://doi.org/10.1038/s41431-018-0130-6.
16. Arts K, Bergerson JRE, Ombrello AK, Similuk M, Oler AJ, Agharahimi A, et al. Warts and DADA2: a mere coincidence? J Clin Immunol. 2018;38:836–43. https://doi.org/10.1007/s10875-018-0565-0.
17. Van Nieuwenhove E, Humblet-Baron S, Van Eyck L, De Somer L, Dooley J, Tousseyn T, et al. ADA2 deficiency mimicking idiopathic multicentric Castleman disease. Pediatrics. 2018;142(3):e20172266. https://doi.org/10.1542/peds.2017-2266.
18. Springer JM, Gierer SA, Jiang H, Kleiner D, Deuitch N, Ombrello AK, et al. Deficiency of adenosine deaminase 2 in adult siblings: many years of a misdiagnosed disease with severe consequences. https://doi.org/10.3389/fimmu.2018.0136.