Warts and DADA2: a Mere Coincidence?

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To the Editor,

In 2014, deficiency of adenosine deaminase 2 (DADA2), caused by biallelic loss-of-function mutations in the adenosine deaminase 2 gene (*ADA2*) (previously known as cat eye chromosome region 1 [*CECR1*]), was identified as an autosomal recessive autoinflammatory disorder [1, 2]. Until now, over 65 mutations have been described [1–35]. Biallelic homozygous and compound heterozygous mutations but also copy number variations have been reported. The mutations are found across the entire gene (Supplemental Fig. S1). CADD (‘Combined Annotation Dependent Depletion’) scores, an in silico tool combining various annotations, and the allele frequencies for the reported mutations are listed in Supplemental Table S1. A CADD score above the mutation significance cutoff (MSC) for a given gene is suggestive of but does not prove pathogenicity. In some patients with DADA2 (diagnosis based upon absent plasma ADA2 deaminase activity or protein levels with a compatible clinical phenotype), a single deleterious mutation has been identified, leaving room to suspect an intronic or

promoter region mutation, a cryptic mutation, or a mutation in a regulatory gene [36]. The originally described chronic autoinflammatory phenotype with vasculopathy (ranging from livedo reticularis and polyarteritis nodosa to ischemic and hemorrhagic stroke) extends to include lymphoproliferation and other hematological manifestations, as well various degrees of immunodeficiency, with associated infections [12, 13, 17, 23, 25, 26]. Anemia (including Diamond-Blackfan-like anemia and pure red cell aplasia), thrombocytopenia, leucopenia with neutropenia and/or lymphopenia, and associated hypogammaglobulinemia have all been reported in DADA2 patients. TNF-alpha blockade is the first-line treatment though a large cohort description is awaited. Hematopoietic stem cell transplantation cures the hematological and immunological phenotype as reported in a cohort of 14 patients [23, 37]. The pathophysiology of DADA2 is still enigmatic. ADA2 is mainly expressed and excreted by monocytes. Zavialov et al. have described that both ADA1 and ADA2 increase the proliferation of monocyte-activated CD4+ T cells and that ADA2

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induces T cell-dependent differentiation of monocytes into macrophages and stimulates macrophage proliferation [38, 39].

The immunodeficiency and spectrum of infection susceptibility observed in DADA2 are still poorly described. Severe or complicated herpesvirus infections are a notable feature in a substantial proportion of patients [13]. However, warts have not been explicitly described previously as an important problem in DADA2. We describe here two patients of unrelated kindreds who were referred for immune evaluation due to refractory cutaneous warts. The study was approved by the Ethical Committee of UZ Leuven and by the IRB of NIAID. Patients and/or parents have given written informed consent for study and publication.

Case 1

A 4-year-old boy was referred to the immunology clinic for recalcitrant warts on foot soles and hand palms as well as mollusca. The warts were refractory to cryotherapy, excision, cauterization, topical acetyl salicylic acid, and topical imiquimod. There were verrucae on the sole of the feet, the dorsal hands, the dorsal arms, trunk, and legs (Fig. 1a). Unfortunately, human papilloma virus (HPV) molecular genotyping was not performed. Mollusca were present all over the body except for the face. He is the second child of non-consanguineous parents of European descent. At the age of 9 months, he had suffered from severe primary varicella zoster virus infection. Also, he had presented with an infant-onset recurrent macular erythema with pathology revealing dermal perivascular T-lymphocytic infiltration. Vaccination with the live measles vaccine and conjugated pneumococcal vaccine at age 1 year had resulted in a pronounced febrile episode. Moreover, the boy had a history of pneumonia at the age of 18 months, recurrent otitis media until the age of 2 years, intractable diarrhea, and fatigue. At the age of 4 years, IVIG therapy was started with a favorable effect on number and size of warts and mollusca. Four months later, the patient switched to SCIG and the macular erythema disappeared. At the age of 6 years, he presented with knee pain. MRI valuation revealed enhancement of the medial head of the gastrocnemius around the vasculature suggestive of edema due to vasculitis. At the age of 7 years, the patient had severe autoimmune anemia and thrombocytopenia which was initially treated, unsuccessfully, with corticosteroids and was only responsive to rituximab. Weekly etanercept was started together with prophylactic antibiotics. Mollusca and warts have since reappeared though less extensive than at presentation. Neutropenia and fatigue persist despite etanercept treatment. His brain MRI is normal at the time of writing.

Blood analysis showed intermittent neutro- and monocytopenia and microcytic anemia. IgG2, IgM, and

switched memory B cells were low at that time (Table 1). Total T, B, and NK cell numbers and subsets were normal. NK cell function was normal. Anti-protein and anti-polysaccharide vaccine response was normal.

The severe viral phenotype with eczema and associated neutro- and monocytopenia initially made us consider DOCK8 and GATA2 deficiency. DOCK8 expression was normal. No mutations were found in *DOCK8*, *DOCK2*, *GATA2*, or *CXCR4*. The MRI results of the patients' knee at the age of 6 led to the suspicion of DADA2, which was confirmed by low plasma ADA2 activity (1.1 mU/g protein on plasma spot, range DADA2 patients 0.04–17.2 mU/g protein; M. Herschfield lab). The exons and intron-exon boundaries of *ADA2* were evaluated by Sanger sequencing for the index patient. A splice site variant c.973 -2A>G was found and segregation analysis showed paternal inheritance. This mutation was previously reported and shown to result in non-sense mediated RNA decay [25]. CGH array failed to identify a deletion in *ADA2*. cDNA amplification of *ADA2* of the family showed a deletion of exon 9 (c.1240_c.1442 del) in the index patient and his mother. To find the second disease causing allele, whole genome sequencing (WGS, Macrogen) was performed for the index patient. Although WGS confirmed the splice variant c.973 -2A>G, we were unable to identify the breakpoint for the exon 9 deletion. Based on the low ADA plasma level, the molecular findings and the clinical phenotype, the diagnosis of DADA2 was made and the patient was started on etanercept as stated above. Both parents had ADA plasma activity levels in the range reported in carriers. The patient's sister was subsequently also diagnosed with DADA2, based upon absent plasma spot ADA2 activity. She shares the splice mutation and exon 9 deletion with her brother and she suffers from intermittent arthralgia and Raynaud's phenomenon (Fig. 1b). She is not receiving any treatment.

Case 2

The patient is a 28-year-old Caucasian male. He was born to non-consanguineous parents and reported being well in early childhood with the exception of recurrent sinusitis and otitis media requiring tympanostomy tubes around the age of 4 years. The frequency of ear infections improved thereafter. Around 10 years of age, he developed warts on his feet, which progressed to involve his hands over the next decade. Unfortunately, HPV molecular genotyping was not performed. The warts were recalcitrant to cryotherapy, cauterization, blister beetle juice, laser therapy, topical imiquimod, squaric acid, and duct tape. More recent trials with topical cidofovir have had minimal effect. A trial of weekly pegylated interferon-alpha (IFN- α) at a dose of 80 mcg was discontinued due to neutropenia (neutrophil count from

Fig. 1 **a** Extensive mollusca on legs and arms of patient 1. **b** Extensive verrucae on fingers including subungual, foot, and toes of patient 2. **c** Pedigree from patient 1. **d** Pedigree from patient 2

$2960 \times 10^9/L$ to $0.83 \times 10^9/L$ after 3 doses) and mild thrombocytopenia (baseline $175 \times 10^9/L$ to $100 \times 10^9/L$), malaise, and depression. He had molluscum contagiosum infection in the groin, which resolved around 10 years of age without any specific intervention. There was no history of other recurrent viral infections such as herpes or zoster, of pneumonia, meningitis, or fungal infection. Other medical history was notable for eczema, worse on the hands, and medication allergies to doxycycline and sulfa drugs. He does report migraines associated with strenuous activity, for which brain imaging has been normal. Otherwise, he denied a history of arthralgia, arthritis, myalgia, skin nodules or livedo, and seizures. The physical exam was notable only for bulky skin-colored warts on the lateral and dorsal fingers and dorsal hands including periungual skin. There were mosaic verrucae on the left forefoot extending to the plantar surface of the left great toe, second toe, and left heel. There were several smaller verrucous papules on the right plantar foot (Fig. 1c).

Initial laboratory testing was notable for mild hypogammaglobulinemia (Table 1). Lymphocyte subset analysis revealed a predominantly T cell lymphopenia with normal absolute numbers of B cells and NK cells. Further

immunophenotyping revealed decreased naïve and memory CD4 and CD8 subsets, as well as decreased memory B cells. NK function was normal. Vaccine responses included protective tetanus and diphtheria antibody levels. Post-immunization pneumococcal antibody levels were protective for 18/23 serotypes. Additionally, HIV serology was negative.

Whole exome sequencing for the patient and his parents revealed a homozygous R169Q mutation in *ADA2* in the patient. The kindred's pedigree is shown in Fig. 1d. The variant has been previously described in patients with *ADA2* deficiency [1, 2]. Consistent with the genetic diagnosis, the *ADA2* activity level was severely diminished at 0.04 mU/mL (reference range 4.8–27.2 mU/mL). He is being treated with etanercept for 8 months now, without improvement of the warts.

Discussion

Here, we report two DADA2 patients in whom recalcitrant warts and mollusca were a predominant phenotype. Verruca vulgaris and mollusca have not previously explicitly been

Table 1 Hematological and immunological phenotype of the patients

	Case 1 (UZ Leuven)					Case 2 (NIH)			
	Plasma ADA2 activity ADA2 mutation	1.1 mU/g (control reference range 74–271 mU/g) plasma spot, M. Hershfield c.973>2A>G/c.1240-?-1442+? Del	2 years	4 years	6 years	7 years	26 years	27 years	R169Q/R169Q 0.04 mU/mL (control reference range 4.8–27.2 mU/mL)
Age									
Immunoglobulines									
IgG (mg/dl)			669 (417–1300)*	757 (478–1129)*	Under SCIG 1390 (558–1254)*	Under SCIG 1350 (558–1254)*	504 (700–1600)- *	539 (700–1600)*	536 (700–1600)*
IgG2 (mg/dl)			30 (52–280)*	< 26 (72–340)*	290 (85–410)*	334 (85–410)*			
IgG3 (mg/dl)			19 (14–120)*	21 (13–133)*	42 (13–142)*	18 (13–142)*			
IgG4 (mg/dl)			< 0.7 (1.2–106)*	< 0.7 (1.7–158)	ND	ND			
IgA (mg/dl)			41 (23–124)*	33 (35–190)*	41 (29–384)*	150 (29–384)*	54 (70–400)*	67 (70–400)*	65 (70–400)*
IgM (mg/dl)			20 (33–128)*	96 (34–134)*	22 (34–142)*	7 (34–142)*	< 50 (40–230)*	20 (40–230)*	17 (40–230)*
IgE (mg/dl)							3.4 (0–90)	3.3 (0–90)	3.8 (0–90)
Specific antibodies									
Anti-Diphtheria Ab IgG (IU/mL)			ND	ND	ND	ND			> 1.00 (positive)
Anti-Haemophilus influenza Ab IgG (mg/L)			ND	ND	ND	ND			< 0.11 (negative)
Anti-Meningococcal IgG Ab (μg/mL)			ND	Adequate response	ND	ND			2/4 serotypes adequate
Anti-Pneumococcal Ab (mg/mL)			ND	ND	ND	ND			18/23 serotypes adequate
Anti-Tetanus Ab (IU/mL)			ND	ND	ND	ND			2.85 (positive)
Anti-Mumps Ab IgG			ND	ND	ND	ND			1.81 (positive)
Anti-Varicella-Zoster Virus IgG (Index)			1800 mU/ml (positive)	ND	710 AU/ml (positive)	930 mU/ml (positive)			0.9 (equivocal)
Measlesvirus IgG			2600 mU/ml (positive)	ND	1600 mU/ml (positive)	27.3 IU/ml (positive)			Negative
Rubellavirus IgG			11.9 IU/ml (positive)	ND	3.09 OD/cutoff (positive)	9500 AU/ml			
Parvovirus B19 IgG			ND	ND	ND	Positive			
Herpes simplex virus IgG			ND	ND	ND	211.8 mU/ml (positive)			
Hep A IgG			ND	ND	ND	ND			
Hep B virus surface IgG			23.5 mU/ml (positive)	Positive	Positive	ND			
Poliomyelitis type 1, 2, 3									
Lymphocytes subsets									
CD3+ cells (absolute number/μL)			1723 (900–4500)*			788 (700–4200)*	175 (714–2266)*	432 (714–2266)*	437 (714–2266)*

Table 1 (continued)

	Case 1 (UZ Leuven)		Case 2 (NIH)	
	2965 (900–4500)*	1748 (700–4200)*	504 (714–2266)- *	
CD4+ cells (absolute number/ μ L)	1622 (500–2400)*	841 (500–2400)*	ND	389 (300–2000)*
CD8+ cells (absolute number/ μ L)	1233 (300–1600)*	794 (300–1600)*	ND	346 (300–1800)*
CD19+ cells (absolute number/ μ L)	638 (200–2100)*	252 (200–2100)*	ND	1 (200–1600)*
NK cells (absolute number/ μ L)	ND	269 (100–1000)*	ND	239 (90–900)*
Lymphocyte phenotyping (absolute number/ μ L)				
CD4/CD62L/CD45RA/CD3				
CD3/CD4/CD62L+CD45RA-				
CD3/CD4/CD62L-/CD45RA-				
CD4/CD62L-/CD45RA/CD3				
CD8/CD62L/CD45/CD3				
CD3/CD8/CD62L+/CD45RA-				
CD3/CD8/CD62L-/CD45RA-				
CD8/CD62L-/CD45RA/CD3				
CD20/CD27				
CD20/CD38				
CD20/CD10				
CD20/IgM-/CD38++				
CD20/IgM+/CD10+				
CD20/CD38/CD10+				
CD20/CD27/IgM+				
CD20/CD27/IgM-				
Hemoglobine (g/dl)	10.42 (11.5–13.5)*	10.3 (11.5–13.5)*	9.4 (11.5–13.5)*	9.6 (11.5–15.5)*
Hematocrit	0.318 (0.34–0.40)*	0.318 (0.34–0.4)*	0.304 (0.34–0.4)*	0.307 (0.34–0.4)*
Total white blood cell count ($\times 10^9$ /L)	6.21 (5.5–15.5)*	5.12 (5.5–15.5)*	5.83 (5.5–15.5)*	5.23 (4.5–13.5)*
Neutrophils ($\times 10^9$ /L)	2.2 (1.5–8.5)*	2.57 (1.5–8.5)*	3.31 (1.5–8.5)*	3.44 (1.8–8)*

Table 1 (continued)

	Case 1 (UZ Leuven)		Case 2 (NIH)	
Eosinophils ($\times 10^9/L$)	0.74 (0.3)*	1.12 (0.3)*	1.39 (0.3)*	0.99 (0.2)*
Monocytes ($\times 10^9/L$)	0.55 (0.5)*	0.45 (0.5)*	0.52 (0.5)*	0.41 (0.4)*
Lymphocytes ($\times 10^9/L$)	3 (2–8)*	1.9 (2–8)*	2 (2–8)*	1.8 (1.5–6.5)*
Platelets ($\times 10^9/L$)	385 (150–450)*	333 (150–450)*	389 (150–450)*	191 (150–450)*
			154 (161–347)*	175 (161–347)*
			2.74 (1.78–5.38)*	0.02 (0.04–0.54)*
			0.01 (0.04–0.54)*	0.01 (0.04–0.54)*
			0.45 (0.30–0.82)*	0.39 (0.30–0.82)*
			0.78 (1.32–3.57)*	0.74 (1.32–3.57)*
			0.46 (0.30–0.82)*	0.41 (0.30–0.82)*
			0.74 (1.32–3.57)*	0.74 (1.32–3.57)*
			167 (161–347)*	167 (161–347)*

*Normal ranges for age between brackets, aberrant values in bold

associated to DADA2, although 2 patients in the report by Schepp et al. suffered from “verrucosis” [13]. In both patients reported here, the presence of recalcitrant warts was the indication for referral to the immunodeficiency clinic. Indeed, extensive or recalcitrant warts should alert the physician to investigate for underlying primary immunodeficiency (PID). Warts can be the predominant manifestation or a less-consistent feature of other PIDs, a topic recently reviewed by J. Leiding and S. Holland [40].

In the first patient, diagnosis was based on low-plasma ADA2 activity. Sanger sequencing of *ADA2* showed only the c.973 -2A>G mutation, inherited from the father. Whole genome sequencing and CGH array (low probe density on *CECR1* locus) failed to reveal a second pathogenic mutation on the other allele. However, cDNA sequencing showed a deletion of exon 9 in the patients, the mother, and the affected sibling. In the second patient, whole exome sequencing revealed a known biallelic deleterious mutation in *ADA2* and plasma ADA2 activity was severely diminished. Because the immune mechanisms that rule immunity against warts, and even more so, mollusca, are ill defined, it is unclear whether the presence of recalcitrant warts in the reported patients are a co-incidental finding or rather directly related to the deficiency in ADA2 function. ADA2 deficiency may thus be a monogenic vasculopathy that is associated with an increased susceptibility to warts. Although HPV infection and immunization (and other viral infections) can trigger vasculitis flares, there are no causal links found for monogenetic vasculitis or autoinflammatory syndromes to our knowledge.

Mollusca contagiosa is caused by infection with a poxvirus whereas warts are local infections with human papilloma virus (HPV), both double-stranded DNA viruses [40]. HPV typically infects epithelial cells. There is evidence that T cells and NK cells are necessary in the control of HPV infections and mollusca, although the exact mechanism is unknown. For instance, patients with acquired immunodeficiency syndrome (AIDS) and CD4 lymphopenia can suffer from extensive mucosal and cutaneous warts. Also, activated CD4 and CD8 T cells can be found in regressing warts. In general, cytotoxic T cells and NK cells play an important role in controlling viral infections. In this report, the second patient had T cell lymphopenia (of both naïve and memory CD4 and CD8 subsets), which may have contributed to the refractory verrucosis. Both patients had normal NK cell numbers and function as tested by CD107a expression (case 1) and chromium⁵¹ release assay (case 2).

Next to cellular immunity, humoral responses to HPV can play a role even though the evidence here is even weaker [40]. Both patients had hypogammaglobulinemia (IgG2 and IgM deficiency in patient 1; IgG, IgA, IgM deficiency in the second patient) with overall normal anti-protein responses. Surprisingly, in patient 1, the warts and mollusca regressed upon start of IVIG and later SCIG.

As HPV and Poxvirus (Mollusca) are both dsDNA viruses, it is possible that in patients with ADA2 deficiency, there is a defect in sensing of these viruses or in the signaling pathways downstream of the viral sensing, which should lead to type I/III interferon responses. Both type I and type III IFN responses have been shown to play an important role in defense against warts and mollusca. The hypothetical defect may be enhanced by the reverse interference, viral-induced inhibition of interferon, that is characteristic of HPV and many other DNA viruses [41]. The possibility of increased susceptibility to infection with dsDNA viruses is in line with previous reports of severe HHV-6, HSV-1, CMV, and VZV infection [8, 13, 22, 37]. Interestingly, upon administration of IFN- α , patient 2 suffered severe side effects, whereas the warts did not improve. As in several DADA2 patients, a type I IFN-signature/very high serum IFN- α levels have been described, making it all the more striking that viral infections are an important feature of the disease [21, 42]. The recent hypothesis that ADA2 serves as a sensor for dsDNA or the older hypothesis that ADA2 might be an antiviral factor would be additional interesting research questions that at present remain unanswered [43, 44]. A deficient cross-talk between the endothelium in the skin vasculature and the keratinocyte and antigen presenting cells in the skin may further explain the increased susceptibility to warts in DADA2.

In conclusion, we report here two patients with ADA2 deficiency in whom recalcitrant warts and mollusca were the initial or predominant clinical presentation. Moreover, we report deletion of exon 9 as a novel mutation causative of DADA2. Severe viral infections should alert to potential DADA2, although the pathophysiology of this presentation is unclear at present. The optimal treatment of warts in DADA2 or in PID in general is still to be defined.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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