Case Report

Rubella vaccine associated cutaneous granulomatous disease as initial manifestation of an inborn error of immunity: a case report

Shari Schroven [a], Michal Ulicki [a], Marieke De Bruyne [b], Jeroen Van Kampen [c], Carolien Bonroy [d], Vasiliki Siozopoulou [a], Victoria Bordon [d], Julie Leysen [a], Filomeen Haerynck [b,d], Koen Vanden Driessche [a]

[a] University Hospital Antwerp, Edegem, Belgium
[b] Center for Medical Genetics, Ghent University and Ghent University Hospital, Ghent, Belgium
[c] Erasmus MC, Department of Viroscience, Rotterdam, The Netherlands
[d] University Hospital Ghent, Ghent, Belgium

shari_schroven@hotmail.com ; koen.vandendriessche@uza.be

Keywords

iVDRV; rubella; PID; inborn error of immunity

Abstract

Immunodeficiency-related vaccine-derived rubella virus cutaneous granulomatous disease as the initial manifestation of an inborn error of immunity is rare. We present a case of a 17-month-old girl with a skin eruption, which started three weeks after a routine measles, mumps, and rubella vaccination. Immunofluorescence staining and PCR and sequencing confirmed the presence of rubella virus (vaccine strain). Whole exome-based primary immunodeficiency panel revealed a homozygous *UNC13D* 12-bp deletion, associated with familial hemophagocytic lymphohistiocytosis.

Introduction

Immunodeficiency-related vaccine-derived rubella virus (iVDRV) cutaneous granulomatous disease is a rare condition. The largest case series to date describes 66 patients with iVDRV (1). These patients are associated with multiple different inborn errors of immunity (see table 1), but mostly with ataxia telangiectasia (1-6).

We present a previously healthy toddler with iVDRV cutaneous granulomatous disease as initial manifestation of familial hemophagocytic lymphohistiocytosis (HLH).

Table 1.: Inborn errors of immunity described in iVDRV patients in current literature (1-6)

Ataxia telangiectasia
Nijmegen breakage syndrome
Cartilage–hair hypoplasia
XLA
MHC class II deficiency
Coronin-1A deficiency
Marden-Walker syndrome
CVID
NEMO
DNA ligase 4 deficiency
Artemis deficiency
WHIM syndrome
X-SCID
Griscelli syndrome type 2
Familial hemophagocytic lymphohistiocytosis types 2, 3 and 5

Case report

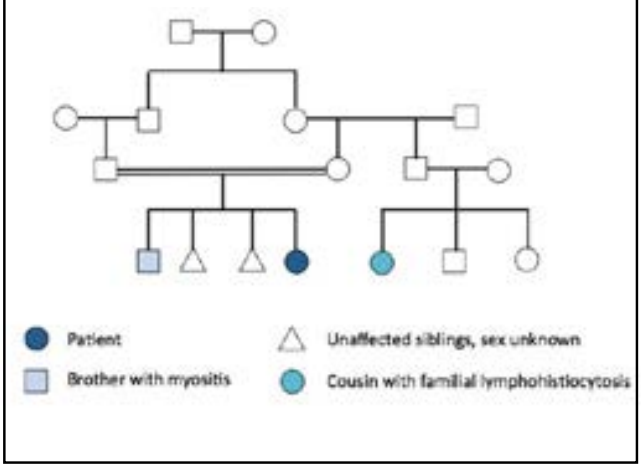
A 17-month-old girl was referred to our hospital by her dermatologist, with a non-itchy eruption of skin lesions on arms, legs and face since a few months. She had no accompanying symptoms and had not been sick when the rash started.

Her personal history was uneventful, except for a few ear and throat infections for which she had been treated with antibiotics. Aphthous mouth ulcers during an infectious episode with fever were also reported.

The appearance of the lesions coincided with the introduction of toddler milk and happened three weeks after our patient's 12-month vaccinations (measles, mumps, and rubella (MMR) vaccine and pneumococcal conjugate vaccine).

She was the fourth child of healthy consanguineous parents of Moroccan descent; none of whom showed a similar rash, but her adolescent brother suffered from unexplained persistent mild myositis with elevated creatine kinase. Her cousin presented with familial lymphohistiocytosis when she was three months, for which she received an allogeneic hematopoietic stem cell transplantation (HSCT). A family tree of her family is shown in figure 1.

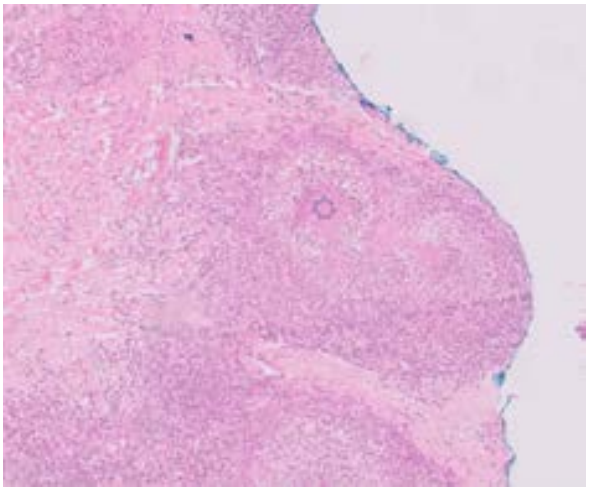
Figure 1 : *Patient's family tree*
The double line between our patient's parents emphasizes the consanguinity. Other than her cousin, no other family members have been tested to date



Before being referred to our hospital, she had already been seen by a dermatologist, who performed a blood test and a skin biopsy. Blood test showed no abnormalities except for a positive antinuclear factor (ANF) screening (1/160 titer). Skin biopsy demonstrated discrete lichenoid dermatitis with superficial and deep inflammatory infiltrates with numerous plasma cells and the formation of some granulomas with central necrosis (fig 2). These histological findings were consistent with a chronic infectious process, but additional immunohistochemical examination could not reveal an etiological cause.

She had already been treated with a betamethasone cream for two weeks, without any improvement of the rash.

Figure 2 : *Skin biopsy*
The biopsy showed granulomas with central necrosis (marked with a star) in the subcutis



On clinical examination we saw scattered pink-purple scaly papules and plaques (5-10 millimeters in diameter) with an occasional pustule, on both arms and legs and a few on the face (fig 3 (a-b)). Trunk and abdomen were spared. When the lesions healed, they left punched out scars (fig 3 c). Clinical examination was otherwise normal except for a geographic tongue.

Microscopy and/or culture on new skin biopsies were negative for general bacteria, fungi, spirochetes, *Leishmania*, and mycobacteria, including *M. tuberculosis* and *M. leprae* PCR. Serology was negative for *B. henselae*, syphilis, EBV, CMV, HIV, hepatitis viruses and parvovirus, as was a quantiferon test for tuberculosis. Because Behçet's disease, sarcoidosis, Wegener's granulomatosis, and Churg-Strauss syndrome were also considered, HLA B51, ACE and ANCA were determined but all results returned negative except for a weakly positive c-ANCA (1/20). There were however no signs of vasculitis, also not in repeat biopsies. The histopathology was not consistent with pityriasis lichenoides et varioliformis acuta (PLEVA), nor with pityriasis lichenoides chronica (PLC), and also not with Langerhans cell histiocytosis.

Chronic granulomatous disease was excluded by respiratory burst testing and further immunological screening showed a normal thymus gland, normal immunoglobulin levels and normal numbers of lymphocyte subsets, including maturation series.

Prolidase deficiency, that can present with scattered skin ulcerations, was excluded by the absence of imidodipeptides in the urine.

Finally, a causal relation with the MMR vaccine was considered because mother emphasized that the skin eruption appeared three weeks after vaccination. Both immunofluorescence staining (Centers for Disease Control and Prevention, Atlanta, US) and PCR (Erasmus MC, Rotterdam, NL) confirmed the presence of Rubella virus in the granulomas (fig 4). Nested PCR identified a 285nt fragment that belonged to the World Health Organization rubella vaccine genome. Basic Local Alignment Search Tool (BLAST) analysis matched this fragment with the RA 27/3 vaccine strain. PCR was negative for mumps and measles virus.

A micro-array analysis revealed no large deletions or duplications. A whole exome-based primary immunodeficiency panel revealed a known homozygous UNC13D 12-bp deletion (c.1828_1839del, p.(Arg610_Gln613del)), associated with familial HLH, previously found in her cousin. Functional testing (CD107a upregulation) confirmed a significant decreased degranulation in natural killer (NK) cells and CD8+ T-lymphocytes.

Awaiting HSCT, our patient was started on monthly intravenous immunoglobulins to prevent infections. Based on a study of Perelygina et al., in which one out of seven similar patients showed good response and two out of seven showed no improvement but a clinical stabilization on nitazoxanide, a broad-spectrum antiparasitic drug for which also antiviral activity is reported, including in vitro activity against Rubella virus, our patient also received this treatment (7). After starting with oral nitazoxanide (250 mg twice daily), skin lesions seemed to dry out and fewer new ones seemed to appear. Ribavirin, remdesivir, favapirivir and galedesivir were also considered but not started because either too expensive, too toxic or too experimental.

She recently received an allogenic HSCT with good engraftment. Soon after the HSCT, we observed a gradual involution of the skin lesions.

Figure 3 : *Clinical pictures of skin rash*
The images show the skin rash in its different stages: scaly papules and plaques at the moment of eruption (a and b) which form punched out lesions after healing (c).

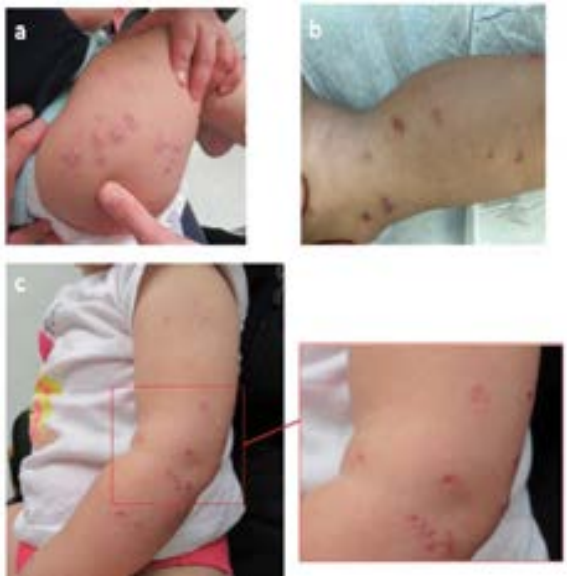
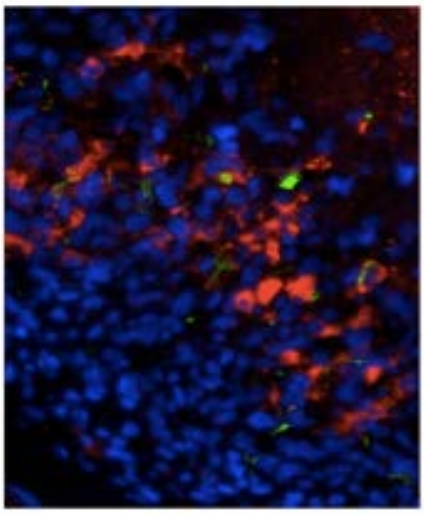


Figure 4 : *Histological immunofluorescent staining for rubella virus capsid in skin biopsy*
Double immunofluorescent staining was performed with RV capsid mouse monoclonal antibody (red), and CD206 M2 macrophage-specific rabbit monoclonal antibody (green). The nuclei are colored blue.



Discussion

Inborn errors of immunity (IEI) are genetic defects causing problems with the immune system, usually manifesting as an increased susceptibility to infectious diseases, autoinflammatory diseases, allergy, or autoimmunity. They were considered to be rare conditions, but nowadays the prevalence of IEI is estimated around 1/1000 – 1/5000 (8). With improving genetic techniques, which also become more accessible and affordable, new IEIs are being discovered at a rapid rate, with more than 400 IEIs known until today (9).

This growing genetic knowledge is also very important with regard to treatment, because a correct genetic diagnosis can alter the treatment course. For example, some IEIs are known to respond very well to a stem cell transplant, while others do not.

IEIs typically present with recurrent and/or chronic infections. Depending on the type of IEI, these infections can be due to common or opportunistic pathogens. Some IEIs don't present with the typical infection, but rather with failure to thrive, severe atopy, autoinflammatory disease, or autoimmune disease.

In our case, we searched for the presence of rubella because the patient's mother pointed out that the rash started three weeks after vaccination and because a literature search suggested iVDRV as a possibility. After confirmation of the presence of rubella virus in the granulomas, an inborn error of immunity was a likely diagnosis.

Most patients with immunodeficiency-related vaccine-derived rubella virus cutaneous granulomatous disease (iVDRV) reported in literature were associated with ataxia telangiectasia (AT), but our patient did not meet the diagnostic criteria for AT since she did not have a decreased IgA, nor an increased radiosensitivity or an elevated α-fetoprotein. Other inborn errors of immunity associated with iVDRV (table 1) were also unlikely, for example cartilage-hair hypoplasia (because she had a normal stature), Marden Walker syndrome (due to the absence of contractures) and X-linked agammaglobulinemia (she had normal gammaglobulin levels).

Adenosine deaminase deficiency and urine nucleoside phosphorylase deficiency, two immunodeficiencies caused by a genetic defect of the purine salvage pathway that result in severe combined immunodeficiency (SCID), were also ruled out (2,3).

Hemophagocytic lymphohistiocytosis (HLH) is a potentially life threatening condition caused by an uncontrolled immune activation. It can occur both in a familial (genetic) or sporadic form and it is important to distinguish between the two, since many of the genetic forms can be treated by allogeneic hematopoietic cell transplantation (10). Our patient had a confirmed genetic mutation associated with familial HLH, but did not yet develop a clinically active HLH.

Allogeneic hematopoietic stem cell transplantation (HSCT) is still the only curative treatment for HLH. HSCT has a higher rate of success when performed pre-emptively rather than with active disease. Therefore, pre-emptive treatment is often recommended in patients with proven genetic abnormalities, but taking into account that HSCT isn't without risk, not every patient with a genetic form of HLH should undergo this treatment preventively (11). In our case the patient had a *UNC13D* mutation, associated with familial HLH-3, in which central nervous system involvement is more common (12,13).

According to a review by Amirifar et al, in which they describe the characteristics of 322 patients with a *UNC13D* mutation, dermatological disorders appear in 25% of these patients but the type of cutaneous abnormalities was not further specified (14).

Gro et al and Murphy et al report in total five patients with a similar clinical presentation and a *UNC13D* mutation (6,15). In three of these patients rubella virus was also detected.

As mentioned before, the patient's brother suffered from myositis, which developed after he received the second MMR vaccine. He was invited for further testing. We emphasized that other family members, with similar consanguinity, should be screened before administering live-attenuated vaccines.

Conclusion

Immunodeficiency-related vaccine-derived rubella virus (iVDRV) cutaneous granulomatous disease is a rare complication following live-attenuated rubella vaccination. It is associated with different types of inborn errors of immunity, so further investigation is warranted when coming across this clinical presentation. Thinking about an IEI when complications arise after live-attenuated vaccination is the most important take home message from this case, as well as to always trust a mother's instinct, because most pediatricians know that they often tend to be right.

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Conflict of interest

The authors declare that they have no conflict of interest in the subject matter or materials discussed in this manuscript.

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