Rubella Virus–Associated Granulomas in Immunocompetent Adults—Possible Implications
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Granulomas are inflammatory infiltrates consisting primarily of macrophages, histiocytes, and lymphocytes that contain and limit insulting agents. They often develop in response to chronic infection, but may also be a manifestation of type IV delayed-type hypersensitivity reaction in response to noninfectious agents, including drugs and foreign bodies. Whenever microbial or noninfectious causes of granulomas cannot be identified, granulomas are defined as idiopathic.

Granulomatous lesions involving the skin or other organs are particularly common among patients with inborn errors of immunity (IEI), for which their overall prevalence is estimated to be 1% to 4%. This prevalence is highest among patients with combined immune deficiency (CID), common variable immunodeficiency (CVID), and chronic granulomatous disease.1 Furthermore, while granulomas involving sinopulmonary, gastrointestinal, and other visceral locations are more common in patients with CVID and chronic granulomatous disease, the skin represents the primary site of granulomatous manifestations in patients with CID.1

In this issue of JAMA Dermatology, Wanat et al2 report the presence of rubella virus (RuV) in idiopathic skin granulomas from 4 clinically immunocompetent adults. In 3 of these cases, vaccine-derived RuVs were detected, whereas wild-type RuV was present in the fourth patient.2

Rubella is typically a mild disease, but when contracted during pregnancy, it may cause miscarriage or serious birth defects, collectively termed congenital rubella syndrome (CRS). Before development of the RuV vaccine, during a major rubella epidemic in Europe and the US from 1962 to 1964, CRS left more than 11,000 infants with deafness, more than 3500 with blindness, and nearly 2000 with intellectual disability.3 In rare cases, persistent RuV infection in adults is associated with an increased risk of Fuchs uveitis, encephalitis, and arthritis. Vaccination with the RA27/3 vaccine strain, with multiple nucleotide and amino acid substitutions, such that the term immunodeficiency-related vaccine-derived rubella viruses (iVDRVs) has been coined.3

Sequencing of the viral genome has demonstrated that different populations of iVDRVs (each harboring different nucleotide variants) may coexist in the same patient, with a progressive increase in the number of nucleotide substitutions per RuV genome with time after vaccination.10 Compared with the parental RA27/3 vaccine strain, amino acid substitutions often involve RuV antigenic epitopes that are recognized by antibodies and cytotoxic CD8+ T cells that are induced on immunization. These amino acid changes might facilitate escape of the virus from immune responses and promote RuV persistence in the host.10 Presence of high titers of anti-RuV antibodies (including immunoglobulin M antibodies) in immunocompromised patients with iVDRV-associated granulomas from the US many years after rubella had been declared eliminated in the region strongly suggests ongoing persistence and replication of the vaccine virus.

Association Between RuV and Cutaneous Granulomas
In 2014, Bodemer et al4 performed high-throughput sequencing of cutaneous granulomatous biopsies and identified the presence of RuV RNA in 3 patients with CID. These findings were confirmed by reverse-transcriptase polymerase chain reaction and immunofluorescence. Sequence alignment revealed similarity to the RA27/3 strain. Since then, multiple studies have confirmed the presence of RuV in granulomatous lesions of patients with IEI, especially in those with various forms of CID,5-7 but also in patients with antibody deficiencies, defects of innate immunity, primary cytotoxic defects, and acquired forms of immunodeficiency.8,9 Importantly, sequencing of RuV RNA isolated from skin granulomas of patients with immunodeficiency has confirmed derivation from the RA27/3 vaccine strain, with multiple nucleotide and amino acid substitutions, such that the term immunodeficiency-related vaccine-derived rubella viruses (iVDRVs) has been coined.4

The iVDRV-associated granulomas most often affect the skin of the limbs (especially around the site of vaccine administration), the face, and the buttocks, but have also been demonstrated in various organs (liver, spleen, lymph nodes, lungs, and bone marrow). Their onset varies from a few months to more than 10 years after administration of the vaccine. Although spontaneous healing can be observed, granulomas often persist and may lead to tissue destruction. To my knowledge, no effective medical therapy is available to cure RuV-associated granulomas besides hematopoietic stem cell transplant when indicated by the clinical severity of the underlying immunodeficiency.7

Outstanding Questions in Understanding RuV-Associated Granulomas
Along with previous demonstrations of RuV-associated granulomas, the study by Wanat et al2 prompts several questions.
Is iVDRV Actually Causing Granulomas, or Is It a Bystander in the Inflammatory Process?

Previous observations and the study by Wanat et al² found that most of the Bradford Hill criteria are met to suggest causality of RuV in the pathogenesis of granulomatous lesions. However, lack of adequate animal models represents a major obstacle to obtain experimental evidence that persistence (and possibly intrahost evolution) of RuV may actually be associated with granuloma formation. Larger natural history studies are necessary to address whether RuV represents the cause of granuloma or is simply a bystander in the process.

Which Mechanisms May Contribute to the Development of RuV-Associated Granulomas?

Previous studies had found that compromise of cell-mediated immunity, particularly T-cell lymphopenia and defects of cell-mediated cytotoxic effects, may play a key role.⁴-⁷,⁹ Wanat et al² propose that neutralizing anticytokine antibodies may also contribute to the development of RuV-associated granulomas in otherwise immunocompetent individuals. This is an interesting hypothesis that needs to be tested. Type I interferons (IFNs), including IFN-α and IFN-β, play a key role in containing viral replication. Autoantibodies that neutralize IFN-α have recently been demonstrated in 15% of patients with life-threatening COVID-19¹¹ and apparently healthy individuals who developed serious adverse reactions to the yellow fever vaccine.¹² Whether such autoantibodies are present in patients with RuV-associated granulomas and whether they may facilitate persistence of the virus remains to be seen. Interestingly, the frequency of anti-type I IFN antibodies is higher in elderly individuals,¹¹ in whom granulomatous lesions may be seen more often.

What Are the Natural Reservoirs of iVDRV That Allow Persistence of the Virus Over Time?

Detailed immunofluorescence studies of granulomatous lesions in immunocompromised hosts have detected RuV capsid antigen within M2 macrophages (an immunoregulatory type of macrophages involved in tissue repair) and neutrophils and occasionally within epidermal keratinocytes.⁸,¹³ It has been proposed that macrophages and neutrophils residing in the bone marrow may serve as a reservoir of the virus.⁸ Presence of the virus in the macrophages is consistent with what has been observed in persistently infected patients with CRS.¹⁴ However, neutrophils have too short a lifespan to be attributed the role of long-term reservoir. It seems more plausible that they engulf viral antigens released on cell death. The possibility that Langerhans cells in the skin may participate in persistence of the virus should be also considered, because the vaccine is most frequently administered in the upper arm, where granulomatous lesions appeared in the patients described by Wanat et al.²

Can RuV-Associated Granulomas Also Occur in Immunocompetent Individuals?

The study by Wanat et al² suggests that RuV-associated granulomas are not restricted to individuals with clinically evident immune compromise. However, while none of the individuals described by Wanat et al² had a history of infections consistent with immunodeficiency, laboratory test results revealed immune abnormalities in all of them, suggesting altered immune competence. Along with previous observations in patients with IEI, these data raise the possibility that immunological abnormalities may be required for the development of RuV-associated granulomas. Additional studies in the general population are needed to provide definitive evidence that RuV-associated granulomas may also develop in fully immunocompetent individuals.

Can Wild-Type RuV Also Be Detected in Cutaneous Granulomas?

One of the 4 patients described by Wanat et al² harbored wild-type RuV in his granulomatous lesions. Another case of wild-type RuV-associated granulomas was recently reported in a nonimmunized adult with CVID.¹³ However, derivatives of the RuV vaccine strain were detected in all other cases identified so far. Elimination of rubella in many countries worldwide makes it difficult to estimate the real risk of developing wild-type RuV-associated granulomas.

Is There a Risk of Viral Dissemination From Patients With Granulomatous Lesions to Susceptible Individuals, and What Could the Consequences of Such Dissemination Be?

It should be emphasized that the development of RuV-associated granulomatous skin lesions is exceedingly rare, RuV has been infrequently (and at low levels) isolated from nasopharyngeal secretions of patients with RuV-associated granulomas,¹⁰ and there are to my knowledge no cases of proven dissemination to susceptible individuals reported to date. Although rubella was declared eliminated from North and South America in 2015, it is still present in other regions of the world. While use of live-attenuated vaccines (including measles and mumps-attenuated viruses) is contraindicated in patients with substantial immune compromise, the rarity of RuV-associated granulomas in immunocompetent individuals is outweighed by the benefits of universal RuV immunization. Therefore, no changes in immunization policies are warranted at this time. Additional studies in larger cohorts of patients (including clinically and immunologically competent adults) are needed to investigate the mechanisms, frequency, and possible consequences of RuV persistence.

ARTICLE INFORMATION

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