Rubella virus vaccine-induced granulomas: a case in children with ataxia-telangiectasia

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Abstract

Ataxia telangiectasia (AT) is a rare autosomal recessive primary immunodeficiency disorder (PID) resulting from a mutation in the ATM gene involved in DNA repair. We describe the case of a young girl with cutaneous granulomas that developed after childhood vaccinations. Immunohistochemistry revealed granulomas induced by the rubella virus vaccine. This finding raises the question of the safety of live rubella vaccine strains in immunocompromised children.

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Introduction

Ataxia telangiectasia (AT) is a complex disorder with multiple phenotypic features and variability in the severity of symptoms between affected patients.[1] The development of cutaneous granulomas in AT is a known phenomenon, less common than in other primary immunodeficiency disorders (PIDs) such as DICV (common variable immunodeficiency disorder) and Nijmegen breakage syndrome, and is usually considered to be a response to a microbial trigger or a consequence of immune dysregulation.[2]

Case Report

A six-year-old girl with AT was referred to our hospital with a 4-year history of well-demarcated and infiltrated erythematous-squamous plaque measuring 5x3 cm on the anterior aspect of the left leg and a 1-year history of a similar plaque on the left forearm (Figures 1 and 2). The lesions were ulcerated and non-tender with a gradual extension. Physical examination revealed hepatosplenomegaly.

Biology showed low levels of LB CD19$^+$, LT CD4$^+$, and LT CD8$^+$ with hyper IgM immunophenotype (deficiency of IgA and IgG and normal IgM) despite immunoglobulin cures started one year ago. No cytopenia was associated.

Skin biopsy excluded a neoplasic lesion and confirmed the diagnosis of non-sarcoid granuloma. The specimen showed granulomatous dermal inflammation with necrotizing epithelioid and giant cells. No infectious agent was identified by conventional methods. Abdominal ultrasound and whole-body magnetic resonance imaging showed multiple supra- and infra-diaphragmatic adenomegaly, pulmonary nodules, and hepatosplenomegaly with micronodules. The patient's parents objected to sampling of deeper lesions to confirm extracutaneous granuloma. A myelogram was performed, and blood disorders were excluded.

The child has received all required live vaccines prior to the diagnosis of PID. Immunochemistry (IHC) of the skin biopsy, using a monoclonal anti-rubella capsid antibody (Abcam 34749), demonstrated the presence of rubella virus capsid within the granulomas (Figure 3). The diagnosis of rubella vaccine-induced cutaneous granulomas was made. The skin lesions did not respond to topical corticosteroids.

Discussion

Cutaneous granulomas in PIDs represent a recognized complication, yet their incidence in individuals with AT is relatively low, affecting less than 10% of patients.[2] As the search for responsible microorganisms or antigens is frequently unsuccessful, granulomas are often considered immune dysregulation, and a correlation

with a hyperIgM immunoglobulin phenotype has been reported.[3,4] Recent investigations have identified rubella as a primary virus strongly linked to cutaneous granulomas in immunocompromised children, substantiated by the absence of viral detection in biopsies from healthy skin.[5] A case report of rubella granuloma (RG) due to wild type in AT illustrates the fact that it is not vaccine strain-specific.[6] Skin RG can appear weeks to decades after infection or vaccination, typically before the age of two, and progresses slowly over the years.[5,6,7] It is characterised by well-defined erythematous-squamous papular lesions with atrophic centres, usually localised to the trauma-prone area, which can cause significant morbidity with possible local tissue destruction.[4] Extracutaneous lesions have been described in two studies of patients with PID, showing that the spleen, liver, bones and lungs are the most commonly affected sites.[4,5] These findings align with our case, suggesting a potential visceral process underlying the splenic and pulmonary nodules observed in our patient.

The presence of rubella vaccine capsid proteins in granuloma M2 macrophages suggests that macrophage tropism triggers granuloma formation, such as aberrant $CD8^+$ cytotoxic T cell response, profound T-cell deficiency, and abnormal cell repair DNA.[8]

To date, no treatment was known to be highly effective to cure RG. In patient with immunodeficiency, immunoglobulin therapy has no benefit. Nitazoxanide, while exhibiting antiviral activity against rubella virus in vitro, demonstrated limited efficacy when administered to patients.[9] Regression of RG was only seen after hematopoietic stem cell transplantation partly explained by the elimination of rubella-carrying neutrophils and monocytes.[10]

The diagnosis of RG is based on characteristic clinical features and skin biopsy with histopathology and IHC or PCR. In immunocompromised children, IHC or PCR should be performed on all idiopathic cutaneous granulomas to elucidate the aetiology and frequency of rubella virus involvement. Possibly, the rubella virus vaccine strain and wild type may be the etiology of cutaneous granulomatous dermatitis previously diagnosed as idiopathic. In most cases, the diagnosis of AT is made after the period of childhood vaccinations. Vaccine-induced cutaneous granulomas have not been seen with live attenuated measles, mumps or varicella vaccines.[7] Although rubella vaccination is recommended despite this potential late side effect, the occurrence of RG raises concerns about its safety.[2]

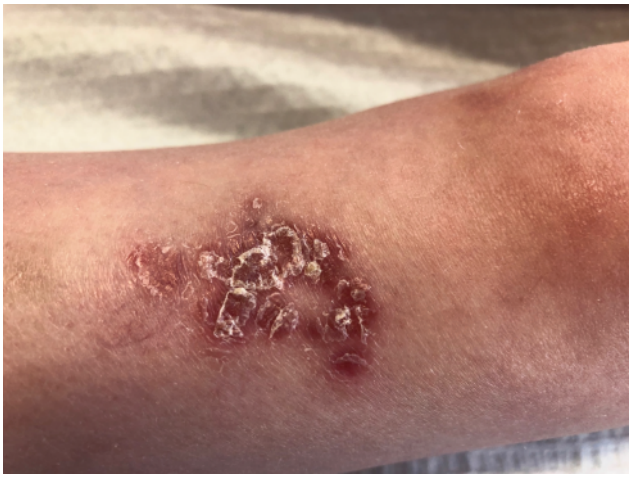

Figure 1. Macroscopic aspect of left leg cutaneous granuloma.

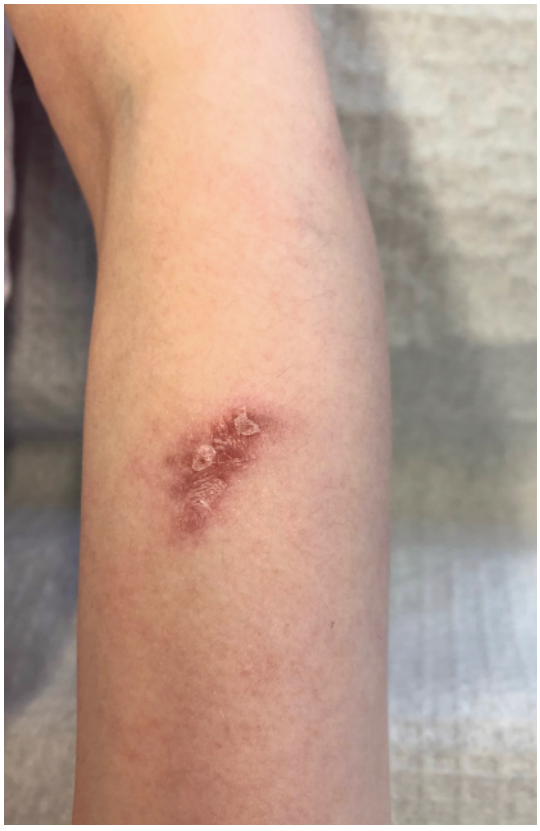

Figure 2. Macroscopic aspect of left forearm cutaneous granuloma.

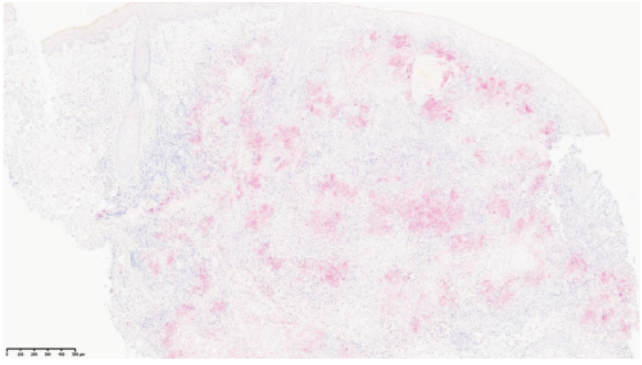

Figure 3. Immunohistochemical study with anti-Rubella antibody showing numerous positive foci within the granulomas (magnification x5).

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