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Case Report

Vaccine-related influenza virus B infection in a child with an undiagnosed B-cell acute lymphoblastic leukemia

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ABSTRACT

We report a case of Influenza type B (lineage Yamagata) infection in a child who received the live attenuated influenza virus vaccine before being diagnosed with B-cell acute lymphoblastic leukemia. The patient developed a mild disease that persisted for 18 days and resolved without antiviral treatment. The prolonged infection of an attenuated virus in an immunocompromised host might pose a risk of reversion or evolution to a more pathogenic strain. Prompt prevention, identification, and monitoring of similar cases are desirable to avoid the development of severe illness, which could complicate patient management.

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Introduction

Influenza is a highly contagious airborne disease caused by Influenza type A and type B viruses [1]. Influenza is one of the most common infectious diseases and occurs in seasonal epidemics [2] causing an acute febrile illness with variable degrees of systemic symptoms, ranging from mild fatigue to respiratory failure and death [3]. Although it is a preventable disease, influenza is one of the main public health concerns worldwide, and during the last decade, awareness towards influenza virus diagnosis and monitoring increased [4]. Live attenuated influenza vaccine (LAIV) is an intranasally administered vaccine that is very effective in children and adolescents and does not show relevant side effects. LAIV contains cold-adapted, temperature-sensitive, attenuated influenza viruses whose moderate replication rate usually prevents them from reaching disease-inducing concentrations. However, in some risk subjects, the vaccine might represent a threat to the patient developing a symptomatic infection followed by potential complications [5]. Here, we report a vaccine-related influenza B/Yamagata infection in a vaccinated child before the diagnosis of B-cell acute lymphoblastic leukemia.

Case

On November 25, 2022, a 6-year-old girl was admitted to the Pediatric Onco-Hematology Division of the Padova University Hospital with a diagnosis of severe anemia (Hb 7.9 g/dl) and thrombocytopenia (9000/µL). The patient's medical history indicated that the patient was a second child, born at term from eutocic delivery. The patient was diagnosed at birth with an interventricular septum defect without hemodynamic consequences and has been under follow-up at the Pediatric Cardiology Clinic of the Padova University Hospital. To date, no corrective surgery has been planned. Perinatal growth rate, height-weight, and psychomotor development were normal. Vaccinations were administered according to the Italian childhood immunization schedules. Her parents deny allergies, but since the patient was born, she suffered from atopic dermatitis.

On November 18, 2022, following the extraction of a deciduous tooth, the patient experienced significant gingival bleeding, requiring two stitches. Four days later, the patient received the intranasal antiflu vaccination with live attenuated influenza virus (LAIV) and developed a fever that night, one of the potential adverse events reported for LAIV [6]. On November 24, the patient experienced persistent gingival bleeding following the spontaneous loss of another deciduous tooth. Hemostasis was achieved through cauterization. To investigate the origin of the bleeding, blood tests were performed, revealing severe anemia and thrombocytopenia. Conse-

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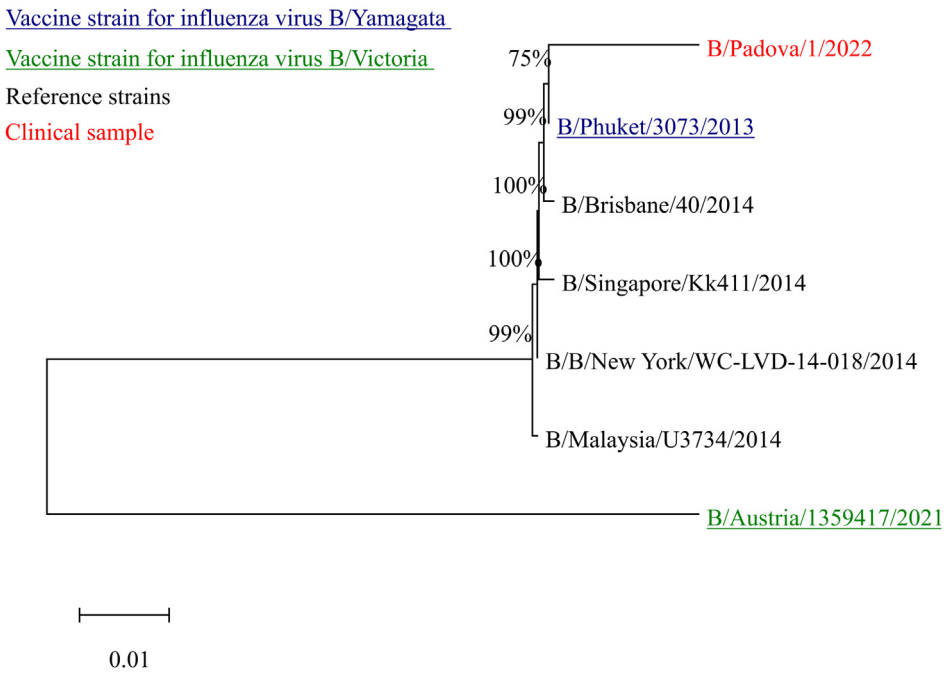

Figure 1. Phylogenetic tree of the influenza B/Yamagata HA gene. Subclades-specific reference strains are in black; the vaccine strain for B/Yamagata is in underlined blue and the vaccine strain for B/Victoria is in underlined green; the study sequence is in red.

quently, the patient was admitted to the hospital for further investigations.

On admission, the patient appeared in good general condition. Physical examination revealed pale skin and mucous membranes, a heart murmur 2/6 at the left sternal border, and an enlarged liver and spleen of a harder consistency than normal but not painful or red. There was also laterocervical and inguinal lymphadenopathy (maximum size of 1 cm). On November 28, a bilateral bone marrow aspiration was performed, and precursor B-cell acute lymphoblastic leukemia was diagnosed. Due to a temperature rise and the high circulation levels of respiratory syncytial virus and influenza viruses, a nasopharyngeal swab was performed on November 25 to screen for respiratory tract pathogens using the Panther Fusion ® SARS-CoV-2/Flu A/B/RSV Assay. Results indicated a positive test for the influenza B virus. Surprisingly, the following real-time RT-PCR test for lineage determination indicated an infection by influenza type B of the Yamagata lineage, which has not been detected since March 2020 [7]. Several consecutive nasopharyngeal swabs were positive for influenza B/Yamagata, indicating a slower clearance rate compared to immunocompetent subjects. Considering the patient's general condition and mild symptoms, no antiviral therapy was administrated. The first negative result for influenza virus was obtained on December 19, 2022. To better investigate the origin of the influenza B/Yamagata affecting the patient, Sanger sequencing was performed on a portion of the hemagglutinin (HA) gene using the nasopharyngeal swab collected on December 2, which had the highest amount of viral RNA. Results showed a high similarity between the virus detected in the clinical swab and the influenza virus strain B/Phuket/3073/2013-like genotype contained in the LAIV (Figure 1). Our data suggest that the patient's clinical condition allowed for a prolonged persistence of the attenuated vaccine strain, resulting in mild clinical signs.

Discussion

Seasonal influenza vaccination is an important strategy for reducing the burden of disease, particularly in specific population groups, such as young children [4]. LAIV was introduced in Italy in the 2020-2021 season and was licensed for use in people aged 2 to 18 years [8]. Although the safety of the vaccine is supported by many studies in health individuals, there is also evidence that its administration to children with cancer did not cause any deterioration in their illnesses, further supporting the safety of LAIV [9]. However, among the recommendations, LAIV should not be administrated to people with weakened immune systems (such as oncologic patients) to avoid the risk of developing symptomatic infection and potential complications [5].

By combining molecular diagnostic data with nucleotide sequence analyses of the HA gene, we demonstrated an infection originating from the vaccine influenza B/Yamagata strain in a girl with B-cell acute lymphoblastic leukemia. This situation represented a significant risk, as the patient also had a congenital interventricular septum defect, and heart diseases, like immunosuppression, are included among the comorbidities associated with a higher risk of severe influenza complications [10]. Fortunately, the course of the infection was mild, and it was unnecessary to adopt antiviral therapies.

In conclusion, this case report underscores the importance of carefully evaluating all situations in which immunosuppression might be possible, as in the case of the described patient, before proceeding with LAIV administration to avoid the risk of potential complications.

Declarations of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical statement

Ethical approval is not required. Informed consent to publication of the completely anonymized data was obtained from the patient's parents.

Author contributions

GDP, CS, and CDV conceived and designed the study. GDP, SDS, EL, and VC collected data and drafted the paper. CDV, EL, EF, IC, and CS revised the paper. MGP and AB enrolled the patient and provided consent from the patient's parents. All co-authors contributed to the interpretation of the findings, critically revised subsequent versions, approved the final version, and agreed to submit it for publication.

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