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Authors

Chang, Sandy Y
Bisht, Anjali
Faysman, Karolina
et al.

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Vaccine-Associated Measles in a Hematopoietic Cell Transplant Recipient: Case Report and Comprehensive Review of the Literature

Sandy Y. Chang,¹ Anjali Bisht,² Karolina Faysman,³ Gary J. Schiller,³ Daniel Z. Uslan,^{1,2} and Ashrit Multani¹ 

¹Division of Infectious Diseases, Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California, USA, ²Clinical Epidemiology and Infection Prevention, UCLA Health, Los Angeles, California, USA, and ³Division of Hematology-Oncology, Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California, USA

Measles is a worldwide viral disease that can cause fatal complications in immunocompromised hosts such as hematopoietic cell transplant (HCT) recipients. The live attenuated measles, mumps, and rubella (MMR) vaccine is generally contraindicated post-HCT due to the risk for vaccine-associated measles. This, combined with decreasing vaccination rates due to vaccine hesitancy and the coronavirus disease 2019 pandemic, raises significant concerns for a measles resurgence that could portend devastating consequences for immunocompromised hosts. Multiple guidelines have included criteria to determine which HCT recipients can safely receive the MMR vaccine. Here, we report a case of vaccine-associated measles in a HCT recipient who met guideline-recommended criteria for MMR vaccination. The objective of this article is to query these criteria, highlight the importance of MMR vaccination, and comprehensively review the literature.

Keywords. hematopoietic cell transplant; immunocompromised; measles; MMR vaccine; vaccine.

CASE REPORT

A 22-year-old man with pre-B-cell acute lymphoblastic leukemia underwent myeloablative allogeneic hematopoietic cell transplantation (HCT) from a HLA-identical unrelated donor using a peripheral blood allograft 4 years prior to presentation. His post-HCT course was complicated by acute graft-vs-host disease (GVHD) of the skin, eyes, gastrointestinal tract, and

liver requiring intensified immunosuppression with tacrolimus, itacitinib, and prednisone. After clinical resolution of GVHD, all iatrogenic immunosuppression was discontinued on day +1335.

Due to the patient's concerns regarding recent measles outbreaks and because he met 2009 American Society for Blood and Marrow Transplantation (ASBMT), 2013 Infectious Diseases Society of America (IDSA), and 2017 National Comprehensive Cancer Network (NCCN) guideline criteria for immunization, he received the measles, mumps, and rubella (MMR) vaccine on day +1408 (73 days after discontinuing immunosuppressive medications). Nine days postvaccination, he presented to the Hematology and Oncology Clinic with fevers up to 40°C (104°F), sore throat, nonproductive cough, and tender cervical lymphadenopathy. Twelve days postvaccination, he returned to the Hematology and Oncology Clinic after an asymptomatic, faint pink, maculopapular rash developed on his face and spread to his torso and upper extremities (Figure 1). He did not have conjunctivitis or coryza. He denied any recent measles exposures, sick contacts, or international travel.

After consultation with Transplant Infectious Diseases, Clinical Epidemiology and Infection Prevention, and the Los Angeles County Department of Public Health, a diagnostic evaluation for vaccine-derived measles was performed. Serum measles immunoglobulin M antibody was positive and immunoglobulin G antibody was negative (Los Angeles County Public Health Laboratory, Los Angeles, California). Measles RNA was detected by polymerase chain reaction in urine and throat specimens (Los Angeles County Public Health Laboratory). Viral genotyping by sequence analysis confirmed the strain to be genotype A (vaccine-derived) measles (California Department of Public Health Viral and Rickettsial Disease Laboratory, Richmond, California). He received a single dose of intravenous immunoglobulin (IVIg) 400 mg/kg. His symptoms resolved without sequelae. Despite his attendance at the Hematology and Oncology Clinic where other vulnerable individuals with solid tumor malignancies, hematologic malignancies, and HCT recipients were also present, no secondary cases occurred.

DISCUSSION

The measles vaccine was first licensed for use in the United States in 1963. Subsequently, measles incidence declined rapidly and it was declared eliminated in the United States in 2000 [1, 2]. However, measles incidence and deaths have been increasing globally, particularly in low- and middle-income countries where vaccination rates have regressed since 2010 and are far from the Global Vaccine Action Plan targets [2–11]. Vaccination rates have declined further during the coronavirus

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Correspondence: Ashrit Multani, MBBS, Division of Infectious Diseases, Department of Medicine, David Geffen School of Medicine at UCLA, 10833 Le Conte Ave, CHS 52-215, Los Angeles, CA 90095-1688, USA (amultani@mednet.ucla.edu).

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Figure 1. Maculopapular rash due to vaccine-associated measles.

disease 2019 pandemic, heightening serious concerns for a measles resurgence [2, 9, 10, 12, 13].

Belonging to the *Paramyxoviridae* family, measles virus is a single-stranded, negative-sense, enveloped RNA virus that exists worldwide. As an airborne infection, measles is the most contagious transmissible viral disease known, with a single case resulting in an average of 12–18 secondary cases in susceptible persons [1]. Measles can occur in fully vaccinated persons either due to absence of immunization (primary vaccine failure) or due to waning immunity (secondary vaccine failure) [5, 14, 15]. Wild-type measles classically manifests with a prodrome lasting 2–4 days consisting of fever and at least 1 of the “3 C’s” (cough, coryza, and conjunctivitis) [1]. Usually between 2 and 4 days after fever onset, the typical erythematous maculopapular rash appears first on the face and head, and then spreads to the trunk and extremities [1]. The rash then fades in the order in which it appeared, usually resolving within 7 days after onset in uncomplicated cases [1]. Koplik spots (small bluish-white plaques on the buccal mucosa) are considered pathognomonic and appear in up to 70% of cases [1]. In relation to rash onset, they present 1–2 days before and may persist for 1–2 days after [1]. Measles generally resolves without sequelae. However, rare but devastating consequences such as measles inclusion body encephalitis (MIBE), subacute sclerosing panencephalitis, Hecht’s giant cell pneumonia (GCP), and death can occur in specific vulnerable populations, including immunocompromised hosts such as HCT recipients [1]. Measles has been shown to compromise acquired immunity to prior infections and vaccinations, highlighting the additional benefits of measles vaccination in

its ability to preserve existing protection against other pathogens [16, 17]. Measles outbreaks also place a significant financial burden on a health care system that is already under duress, with a median total cost per outbreak of \$152 308 (range, \$9862–\$1 063 936) [18]. Of note, the 2019 measles outbreak in Washington was estimated to have an overall societal cost of \$3.4 million [19].

To identify published cases of vaccine-associated measles, a systematic electronic search of PubMed and Google Scholar using the keywords “measles vaccine,” “measles, mumps, and rubella vaccine,” “MMR vaccine,” and “vaccine-associated measles” without date or language restrictions was conducted. Vaccine-associated measles is a rare occurrence, with 66 laboratory-confirmed cases in measles vaccine recipients (including our patient) published to date (Table 1) [20–38]. Cases were confirmed by genotyping or by the combination of another diagnostic methodology (eg, culture, antigen, or serology) in conjunction with clinical criteria (eg, measles-like illness occurring soon after measles vaccination, absence of known exposures, and/or lack of secondary cases), thereby rendering the diagnosis of vaccine-associated measles far more likely than wild-type measles. Of these, 3 had severe complications including MIBE, GCP, and/or death, and all had an underlying immunocompromising condition [20, 21, 23–25]. The remaining 63 (95.5%) cases were self-limiting and resolved without sequelae. The only other published case of vaccine-associated measles in a HCT recipient was a 5-year-old boy whose clinical manifestations resolved without complications [30]. Additional cases have also been suspected clinically to be vaccine-associated but were not microbiologically-confirmed [39–42]. Choe et al reported that patients with vaccine-associated measles may be less likely to develop the “3 C’s” than patients with wild-type measles, and therefore suggested that these findings may help differentiate wild-type measles from vaccine-associated measles [32]. However, our case report and literature review do not support this hypothesis. Ultimately, laboratory confirmation is required to distinguish between the 2, which is critical to inform infection prevention and control practices including contact tracing [22, 29, 30, 35, 43]. Importantly, including our patient, no laboratory-confirmed secondary cases of vaccine-associated measles have been reported [30, 44]. One brief case report of possible brother-to-sister transmission of measles after MMR vaccination was described, but this was a clinical diagnosis that was not microbiologically-confirmed [42].

According to the 2009 ASBMT, 2013 IDSA, and 2017 NCCN guidelines, the live attenuated MMR vaccine can be administered to seronegative HCT recipients who are >2 years post-HCT, with neither chronic GVHD nor ongoing immunosuppression, and if at least 8–11 months (or earlier if there is a measles outbreak) have elapsed since the last dose of IVIG [45–47]. These recommendations are based on studies showing the efficacy and safety of MMR

Table 1. Summary of Published Cases of Laboratory-Confirmed Vaccine-Associated Measles in Measles Vaccine Recipients

First Author, Year [Reference]	No. of Case	Age	Underlying Condition(s)	Time From MMR Vaccine to Symptom Onset	Clinical Manifestations (No. [%])	Outcome
Mawhinney, 1971 [20]	1	10 months	Dysgammaglobulinemia	7 days	Fever, rash, GCP	Death
Monafo, 1994 [21]	1	17 months	SCID	2 months	Fever, rash, hepatitis, GCP	Death
Kobune, 1995 [22]	1	1 year	NS	7 days	Fever	Recovery
Angel, 1998 [24]	1	20 years	HIV/AIDS (CD4 ⁺ T-lymphocyte count undetectable)	330 days	Fever, night sweats, chills, cough, weight loss, GCP	Recovery
Bitnun, 1999 [25]	1	21 months	CD8 ⁺ T-lymphocyte deficiency, dysgammaglobulinemia	8.5 months	Fever, irritability, vomiting, MIBE	Death
Jenkin, 1999 [26]	1	17 months	NS	15 days	Fever, rash	Recovery
Goon, 2001 [27]	1	14 months	HIV (CD4 ⁺ T-lymphocyte count 570 cells/ μ L)	10 days	Fever, anorexia, diarrhea, rash	Recovery
Berggren, 2005 [28]	1	13 months	None	10 days	Fever, cough, coryza, conjunctivitis, rash, anorexia, cervical LAD, Koplik spots	Recovery
Nestibo, 2012 [29]	1	15 months	None	12 days	Fever, irritability, cough, conjunctivitis, rash, cervical LAD	Recovery
Hau, 2013 [30]	1	5 years	HCT	6 days	Fever, cough, coryza, conjunctivitis, rash	Recovery
Murti, 2013 [31]	1	2 years	None	37 days	Fever, cough, coryza, conjunctivitis, rash	Recovery
Choe, 2014 [32]	40	12–23 months	NS	7–14 days	Fever (34 [85%]), rash (38 [95%]), cough (14 [35%]), coryza (17 [43%]), conjunctivitis (4 [10%])	Recovery
Kurata, 2014 [33]	1	23 years	None	18 days	Fever, rash, coryza, conjunctivitis, Koplik spots	Recovery
Sood, 2017 [34]	1	13 months	None	9 days	Fever, cough, coryza, rash	Recovery
Xu, 2017 [35]	8	8 months–26 years	NS	4–11 days	Fever (8 [100%]), rash (8 [100%]), cough (3 [38%]), conjunctivitis (3 [38%]), coryza (2 [25%]), Koplik spots (2 [25%]), LAD (1 [13%])	Recovery
Churchill, 2018 [36]	1	40 years	Postpartum	10 days	Fever, cough, rash, malaise, myalgia	Recovery
Miauton, 2020 [37]	1	35 years	RRMS (on natalizumab)	7 days	Fever, rash, myalgia, fatigue	Recovery
Yu, 2020 [38]	2	11–53 months	NS	8–10 days	Fever (2 [100%]), rash (2 [100%])	Recovery
Chang (2021, present case)	1	22 years	ALL, HCT	9 days	Fever, sore throat, cough, cervical LAD, rash	Recovery

Abbreviations: ALL, acute lymphoblastic leukemia; GCP, giant cell pneumonitis; HCT, hematopoietic cell transplantation; HIV, human immunodeficiency virus; LAD, lymphadenopathy; MIBE, measles inclusion body encephalitis; MMR, measles, mumps, and rubella; NS, not specified; RRMS, relapsing-remitting multiple sclerosis; SCID, severe combined immunodeficiency.

vaccination in HCT recipients [48]. Our patient met the criteria established in the ASBMT, IDSA, and NCCN guidelines but acquired measles via vaccination nonetheless. While he fortunately did not suffer any severe adverse consequences, questions were raised regarding the safety of the MMR vaccine in HCT recipients who meet these guideline-recommended criteria. Carpenter and Englund offered a slightly different approach by suggesting it would be considered safe to give the MMR vaccine when HCT recipients are at least 2 years out from HCT, at least 1 year off systemic immunosuppressive therapy, and at least 8 months out from any prior IVIG dose (also known as the “2-1-8” Rule) [49]. Since our patient

had received the MMR vaccine only 73 days after discontinuation of iatrogenic immunosuppression, he would have been ineligible to receive the MMR vaccine according to the “2-1-8” Rule.

The resurgence of measles has led to a closer examination of the relative benefits and risks of MMR vaccination in immunocompromised hosts such as HCT recipients. However, data on this are scarce. A systematic review by Croce et al evaluating the safety and efficacy of live vaccines in immunocompromised hosts included 152 HCT recipients who received the MMR vaccine within 2 years post-HCT [50]. Twenty-seven of these patients were receiving immunosuppressive therapy at the time

of vaccination [50]. A limitation of this review is that many of the included studies did not document whether adverse events were observed. One child who had undergone high-dose chemotherapy and autologous stem cell rescue had relapse of her underlying disease after MMR vaccination, but the relative time points of each event were unknown [50]. Multiple studies showed clinical protection from measles and immunogenicity to measles ranging from 33% to 78%, but these studies were heterogeneous in regard to patient population, timepoint post-HCT, iatrogenic immunosuppression at the time of vaccination, and immunogenicity assessment [50]. Because of these and other limitations, the authors concluded that the identified data were not sufficiently robust to change the currently available international vaccination recommendations on live vaccines under immunosuppression or within 2 years post-HCT [50].

Knowledge of the online ecology of vaccine views can help combat the dangers of homemade remedies, falsehoods, dismissal of expert advice, and antivaccination beliefs before they become dominant in a decade as predicted [51, 52]. Because vaccine hesitancy is largely related to distrust of the medical community and concerns regarding vaccine safety, greater communication is urgently needed to build trust based on scientific evidence and transparency. There should be increased awareness about publicly available resources such as the Centers for Disease Control and Prevention's Wide-ranging Online Data for Epidemiological Research (WONDER) interface that can provide up-to-date information regarding vaccine safety by evaluating reports submitted to the Vaccine Adverse Event Reporting System [52, 53]. While adverse events have been associated with the MMR vaccine, it has an acceptable safety profile and the risks of a natural measles infection far outweigh the risks associated with MMR vaccination for eligible persons [1].

Measles can lead to serious complications in immunocompromised hosts such as HCT recipients, and the MMR vaccine may not be safe and effective for the vast majority of this population. To protect these vulnerable individuals, there is a pressing need to optimize vaccination rates in eligible persons, particularly their close contacts [54]. Compared to current ASBMT, IDSA, and NCCN guideline-recommended criteria, the "2-1-8" Rule deserves further study as a strategy for MMR vaccination of HCT recipients [49].

Notes

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Patient consent statement. The patient's written consent was obtained. The University of California, Los Angeles Institutional Review Board approval was not required due to this study not constituting human subjects research.

Potential conflicts of interest. All authors: No reported conflicts of interest.

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