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Vaccine-derived varicella zoster infection in a kidney transplant recipient after zoster vaccine live administration

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ABSTRACT

A 49-year-old kidney transplant recipient, presented with a skin rash, and interstitial infiltrates three weeks after receiving a live attenuated varicella-zoster vaccine. Varicella-zoster Oka-vaccine strain was detected in plasma by polymerase chain reaction and sequencing analysis targeting open reading frame 62 (ORF 62). She was treated successfully with intravenous acyclovir. Our case report supports the current contraindication of live attenuated varicella-zoster vaccine in the solid-organ transplant recipients. Recombinant subunit varicella-zoster vaccine may be the vaccine of choice in these patients; nevertheless, further information is required to establish its safety, efficacy, and optimal timing.

1. Introduction

In recent decades, there has been a considerable increase in the number of solid organ transplant (SOT) recipients. Given their immunosuppression status, these patients are particularly prone to infectious complications; therefore, routine immunization for vaccine-preventable diseases is of paramount importance [1]. More than 90% of adults in the USA have a history of varicella-zoster virus (VZV) infection (establishing lifelong latency) [2]. Up to 8–11% of SOT recipients may experience VZV reactivation in the first years following SOT, with an increased risk of complications such as postherpetic neuralgia (PHN) and disseminated Herpes Zoster (HZ) [2,3].

Currently, there are two HZ vaccines licensed for immunocompetent adults ≥50 years: a live attenuated VZV vaccine (ZVL [Zostavax®, Merck]), and more recently an adjuvanted recombinant subunit VZV vaccine (RZV, [Shingrix®, GlaxoSmithKline]) [3,4]. ZVL is contraindicated after SOT due to the theoretical risk of uncontrolled replication of the vaccine virus (Oka-vaccine strain [vOka]); nevertheless, data about safety in this population is limited [3,5,6]. On the other hand, RZV does not confer this risk and, consequently, it may be a safer option for the immunocompromised host [3]. Here we report a case of a kidney transplant recipient who received ZVL and developed vaccine-derived disseminated HZ. This case supports the current contraindication of ZVL in the solid organ transplant population.

2. Case report

A 49-year-old woman presented to the emergency room with fever and a skin rash without any other accompanying symptom. Her past medical history was significant for kidney transplantation (four years prior) and diabetes mellitus. She was receiving azathioprine (75 mg q.d.), tacrolimus (4 mg b.i.d.), prednisone (5 mg q.d.), and metformin (500 mg q.d.). ZVL was indicated three weeks before the onset of symptoms by her primary care physician. On physical examination, her vital signs were as follows: pulse rate 84/min, blood pressure 110/70 mmHg, respiratory rate 18/min, and SpO2 94% on room air. The rash was distributed in the trunk,

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neck, and head and was characterized by vesicles, papules, and crusts (Fig. 1A–C). The remaining of the physical examination was normal. Laboratory data showed an acute kidney injury (KDIGO stage 1), and bicytopenia (white blood cell count of 2.1 × 109/L [lymphocytes of 0.11 × 109/L]; hemoglobin 11.1 g/dL, platelets 292 × 109/L). A chest X-ray revealed bilateral interstitial infiltrates (Fig. 1D and E). Plasma was positive for VZV by PCR. Disseminated HZ was diagnosed, and high-dose intravenous acyclovir (10 mg/kg three times a day) was administered. The patient had a favorable treatment response; she did not develop new vesicular lesions and was discharged after ten days of acyclovir treatment.

We identified the vOka strain using a DNA sequencing analysis as previously described (7). DNA was purified from a whole blood sample using a DNeasy Blood & Tissue Kit (QIAGEN, Germany) according to the manufacturer's instructions. We performed a PCR targeting ORF 62 with previously described primers and conditions [7]. The PCR products were extracted using a QIAquick kit (QIAGEN, Germany) and were sequenced in the 3500 Genetic Analyzer (Applied Biosystems) using a BigDye Terminator v3 Cycle Sequencing kit (Applied Biosystems, USA). We compared the nucleotide sequences with those available in the GenBank database (accession number KU926314.1) using BLAST tools (https://blast.ncbi.nlm.nih.gov/Blast.cgi). ORF 62 sequencing analysis revealed vaccine-specific single-nucleotide polymorphisms (C instead of T) at positions 105,705, 107,136, and 107,252, corroborating the vaccine-type strain.

3. Discussion

SOT recipients are at higher risk of HZ, have an earlier age of presentation, and are more likely to present complications such as multi-organ involvement (i.e., pneumonia, hepatitis, encephalitis) and PHN; therefore, immunization against HZ is of paramount importance [1]. Both currently available vaccines (i.e., ZVL and RZV), have been shown to be effective for PHN and HZ prevention in the non-immunocompromised [3,4]. On the other hand, the recommendations for their use in the SOT scenario are mainly

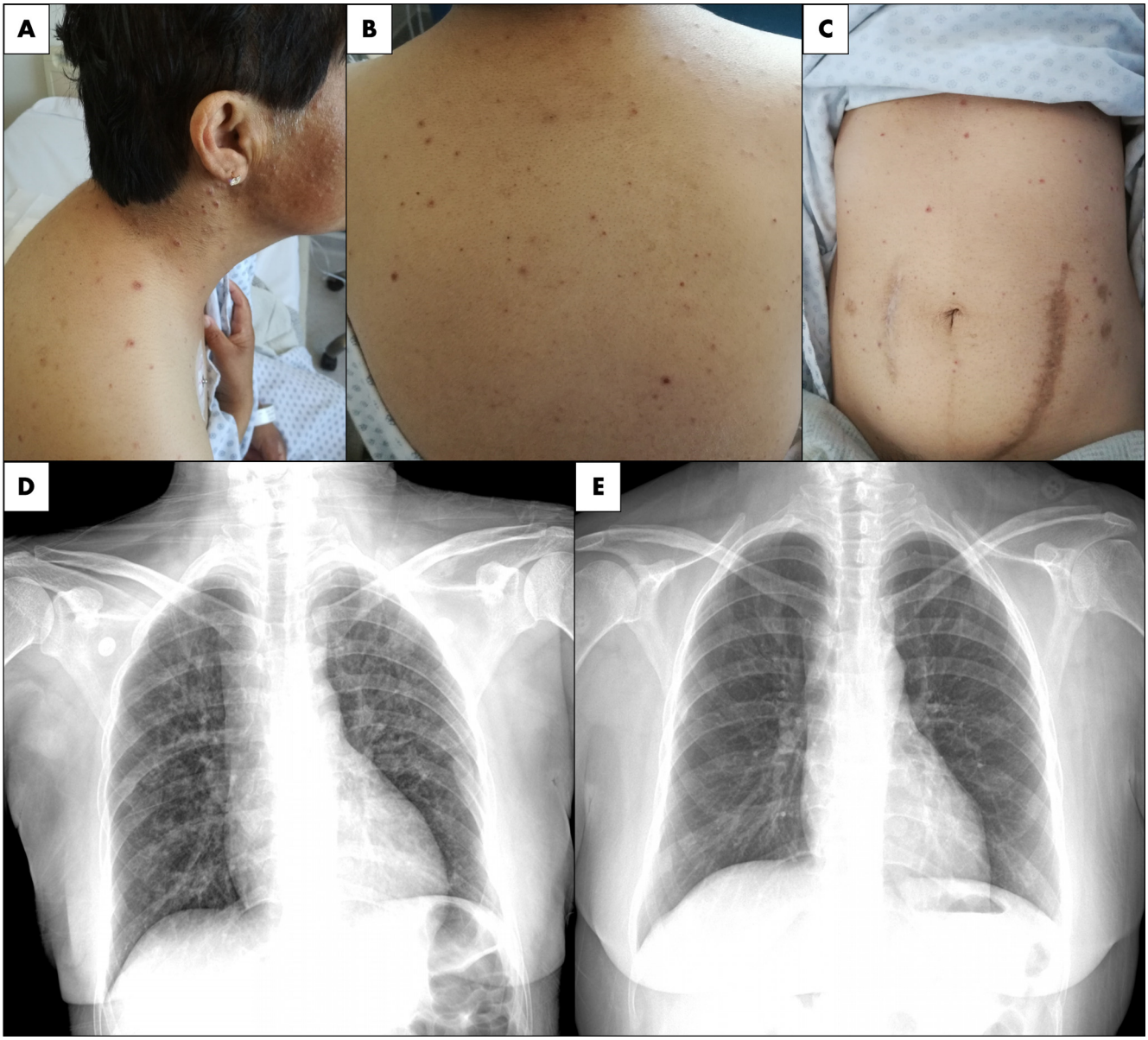

Fig. 1. A vesicular rash in different stages of development distributed on the face (A), trunk, and abdomen (B, C) in a kidney allograft recipient secondary to vOka-strain infection after herpes-zoster vaccination. (D) A chest X-ray revealed bilateral interstitial infiltrates; a chest X-ray taken one year before is depicted for comparison (E).

based on expert recommendations. Remarkably, in Mexico, there are no specific recommendations for special populations including the SOT recipients, a fact that may contribute to the misuse of some vaccines by general practitioners who are responsible for the immunization of most of the population.

ZVL is a live-attenuated vaccine that contains 14 times higher titers of the vOka/Merck strain than the varicella virus vaccine live (VARIVAX®; Merck, USA) [3]. In the non-immunocompromised, ZVL has 51% efficacy against HZ and 65% for PHN, but the effect against HZ declines over 4–8 years [4]. In the pre-SOT period, the Infectious Diseases Society of America only recommends its use for non-severely immunocompromised SOT candidate's ≥60 years old or varicella-positive candidates (i.e., persons with a history of varicella or zoster infection or are VZV seropositive with no previous doses of VZV vaccine) aged 50–59 years if the SOT is not anticipated within 4 weeks [1]. Recently, a randomized, placebo-controlled phase I trial showed that ZVL is safe and immunogenic among adults' ≥18 years with end-stage renal disease when administered with a minimum of 4 weeks before renal transplantation. During the study period, there was no evidence of cases with rash illnesses, changes in anti-HLA antibodies, or graft rejections [8]. Nevertheless, further studies are required to confirm these results, and to assess ZVL efficacy in this specific scenario.

In the post-transplant period, immunization with live virus vaccines (including ZVL) may result in an uncontrolled vaccine strains replication; consequently, they are generally not administered in these patients; however, data to support this practice is limited [1,6]. A recent systematic review examined the evidence about safety and efficacy of live vaccinations in the immunocompromised population. They identified 339 SOT recipients with a history of live virus vaccines administration, 192 of them were against varicella but none for HZ. Among the formers, 7.3% developed infection through the vaccine strain without complications [6]. Despite being the same vaccine strain (vOka), this information is not extractable to ZVL given its higher concentration. Moreover, most of the varicella virus vaccine live use in SOT recipients' reports belonged to the pediatric population [6].

A randomized, placebo-controlled study that assessed the safety, tolerability, and immunogenicity of ZVL in individuals receiving chronic/maintenance systemic corticosteroid therapy (prednisone 5–20 mg/day) for ≥2 weeks, showed that ZVL was immunogenic and well tolerated, with no proven episodes of vaccine-strain related infections [9]. Notwithstanding, subjects were not eligible if they were receiving other concomitant immunosuppressive therapies; the most common scenario for the SOT population. Finally, a review of ZVL post-marketing safety experience with information following 10 years of its use with >34 million doses distributed identified 18 cases of disseminated HZ secondary to the vOka vaccine-strain; of them, 7 had a history of immunosuppressive conditions and/or therapy (none SOT recipients), one with a fatal outcome [10]. This information in addition to our case-report confirms the possibility of uncontrolled vOka strain replication with the potential of organ involvement (e.g., pneumonia).

RZV is a subunit vaccine composed by the recombinant VZV glycoprotein E and the AS01B adjuvant system; it has an approximate efficacy of 90% against HZ, and PHN and it is minimally affected by aging [4]. Consequently, with RZV there is no concern for inducing vaccine-strain disease; hence it may be suitable for the SOT population [8]. Currently, the Advisory Committee on Immunization Practices recommends the use of RZV in persons under low-dose immunosuppressive therapy (e.g., prednisone <20 mg/day) and persons anticipating immunosuppression but, due to the lack of evidence, it does not make a recommendation for the immunocompromised including SOT recipients [11]. Recently a randomized, double-blind, placebo-controlled phase 3 trial, established that RZV was effective and well tolerated among autologous HSCT recipients [12]. Nevertheless, more information about safety, immunogenicity, efficacy, and potential for sensitization to HLA is needed before its wide use in the SOT population.

In conclusion, our case report supports the current contraindication of ZVL in the SOT recipients. RZV may be the vaccine of choice in these patients; nevertheless, further information is required to establish its safety, efficacy, and optimal timing. Regarding the pre-transplant period, further studies are required to establish which option (ZVL or RZV) is safer and translates into better immunogenicity.

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Authors contributions

EOB, JCR, and APDL took care of the patient, made the evidence revision and wrote the manuscript. FLV and MBDV made the molecular analysis and contributed to writing the manuscript. All Authors reviewed and approved the final version of the manuscript.

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Patient consent

A written informed consent was obtained from the patient.

Conflict of interest statement

The authors declare no conflicts of interest to disclose.
All authors attest they meet the ICMJE criteria for authorship.

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