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Four Pregnancies Following Chemotherapy and Pelvic Radiotherapy During Adolescence for Undifferentiated Vulvar Sarcoma: A Case Report

Akari Inazuki [1], Shun Yasuda [2], Momoka Yamauchi [2], Keisuke Yoshida [2], Tsubasa Hobo [3], Takahiro Omoto [2], Chihiro Okoshi [2], Tsuyoshi Murata [2], Akiko Yamaguchi [2], Hideki Sano [4], Keiya Fujimori [2]

1. Obstetrics and Gynecology, Shirakawa Kosei General Hospital, Shirakawa, JPN 2. Obstetrics and Gynecology, Fukushima Medical University, Fukushima, JPN 3. Obstetrics and Gynecology, Takeda General Hospital, Aizuwakamatsu, JPN 4. Pediatric Oncology, Fukushima Medical University, Fukushima, JPN

Corresponding author: Shun Yasuda, room335@fmu.ac.jp

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Abstract

Pregnancy outcomes following chemotherapy and pelvic radiation therapy for undifferentiated vulvar sarcoma during childhood, adolescence, and young adulthood have not been reported. We report the case of a woman who, at the age of 15 years, underwent chemotherapy with vincristine, actinomycin D, and cyclophosphamide (an alkylating agent), together with pelvic photon radiotherapy (45 Gy in 25 fractions; estimated uterine exposure, approximately 15 Gy), for this tumor. At the age of 25 years, she delivered a male infant at 36 weeks and subsequently developed postpartum hemorrhage due to uterine atony, from which she recovered. At the age of 27 years, her second pregnancy ended in miscarriage at 10 weeks, and her third pregnancy later that year ended in miscarriage at 19 weeks, accompanied by clinically suspected placenta accreta. During her fourth pregnancy, at the age of 30 years, she received specialist care from the first trimester, underwent elective prophylactic cervical cerclage, and delivered a male infant at 37 weeks without recurrent second-trimester pregnancy loss. Although uterine volume, uterine blood flow, and myometrial fibrosis were not directly assessed, radiation-associated changes in uterine and cervical function may have contributed to impaired uterine contractility, cervical insufficiency, and abnormal placentation. This case highlights the perinatal risks faced by childhood cancer survivors. A term delivery followed prophylactic cervical cerclage in the fourth pregnancy; however, this single observation does not establish the efficacy of cerclage in this setting. Further research in this population is warranted.

Categories: Obstetrics/Gynecology, Radiation Oncology, Oncology
Keywords: alkylating agents, cancer survivor, cervical insufficiency, perinatal complications, radiotherapy (rt)

Introduction

With advances in cancer treatment, the number of cancer survivors has increased, including individuals who underwent cancer treatment during childhood, adolescence, or young adulthood [1]. We report the pregnancy outcomes of a woman who received chemotherapy and radiation therapy at the age of 15 years for undifferentiated vulvar sarcoma. To the best of our knowledge, pregnancy outcomes following treatment for this rare malignancy in the childhood, adolescent, and young adult (C-AYA) population have not been previously reported. This case contributes to the limited body of evidence on reproductive and perinatal outcomes among C-AYA cancer survivors treated with both alkylating agent-based chemotherapy and pelvic radiation therapy.

Case Presentation

Cancer diagnosis and management

Menarche occurred at the age of 12 years. At the age of 15 years, the patient presented with a one-month history of left vulvar swelling, erythema, and induration. After approximately two weeks of evaluation at a local clinic, she was referred to our department because of a progressively enlarging vulvar mass. Physical examination revealed an approximately 8-cm firm, irregular, tender, erythematous mass. MRI demonstrated the mass and left inguinal lymphadenopathy (Figure *1*). Tumor excision and left inguinal lymph node biopsy established the diagnosis of INI-1-negative undifferentiated vulvar sarcoma.

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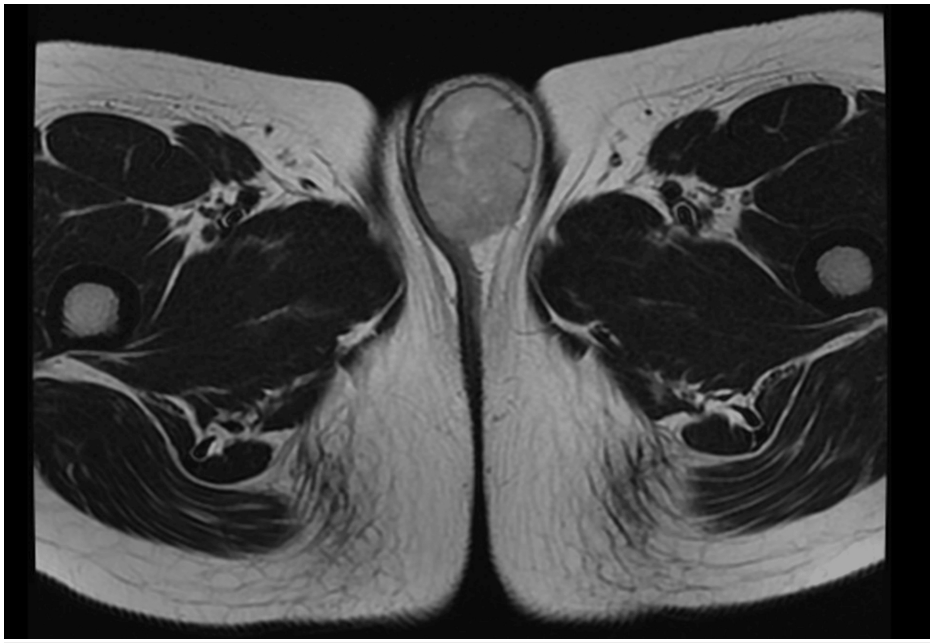


FIGURE 1: MRI scan of an 8-cm vulvar tumor at the age of 15 years

T2-weighted imaging shows an 8 cm tumor in the left vulva at the 2 o'clock position, with left inguinal lymphadenopathy.

MRI: magnetic resonance imaging

Postoperative positron emission tomography revealed metastasis confined to the left inguinal lymph nodes, necessitating left inguinal lymphadenectomy followed by pelvic radiation therapy (Figure *2*). Photon radiotherapy was delivered using 10-MV X-rays from a linear accelerator through opposed anterior-posterior fields encompassing the left inguinal lymph node region and vulvar tumor bed. The total prescribed dose was 45 Gy in 25 fractions, with an estimated uterine exposure of 15 Gy. Chemotherapy consisted of nine cycles of vincristine, actinomycin D, and cyclophosphamide, with dose reductions beginning in the sixth cycle, followed by one cycle of irinotecan plus vincristine. The total cumulative dose of cyclophosphamide was 17.6 g/m^2. According to the patient, the entire treatment course was completed within approximately one year.

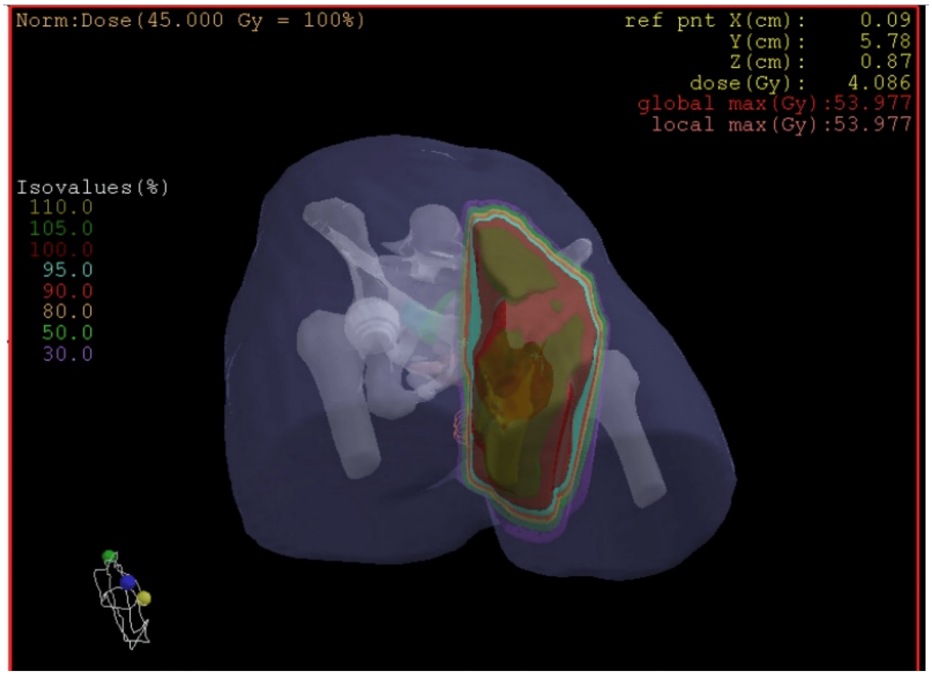


FIGURE 2: Radiation field for undifferentiated vulvar sarcoma

The patient underwent radiation therapy with a total of 45 Gy in 25 fractions to the left pelvic cavity. Isodose lines are normalized to the prescribed dose of 45 Gy (100%), and the global maximum dose within the plan was 54.0 Gy. The estimated radiation dose to the uterus was approximately 15 Gy; the dose metric and the dose distribution within the uterus could not be retrospectively verified.

Subsequently, she developed radiation-induced cystitis, for which she required hyperbaric oxygen therapy for two months. The symptoms first appeared at the age of 16 years. She underwent follow-up every six months for five years and annually thereafter, primarily using MRI or computed tomography, with no evidence of disease recurrence. Menstruation remained regular until the age of 19 years, when irregularities prompted a single course of Kaufmann therapy. Regular menstruation was subsequently restored and continued spontaneously until her first pregnancy at the age of 25 years.

First pregnancy (25 years of age)

The patient conceived naturally and received prenatal care locally, with gestational age determined by first-trimester crown-rump length measurement. At 30 weeks and six days of gestation, she was referred to our department because of a short cervix and was hospitalized. At 36 weeks and four days, she vaginally delivered a male infant weighing 2,522 g (-0.126 SD). Placental pathology revealed no evidence of chorioamnionitis.

Following delivery, she developed postpartum hemorrhage due to uterine atony, which was managed conservatively with uterine massage, uterotonics (oxytocin and methylergometrine), and fluid resuscitation. Given her treatment history and the complications of preterm birth and postpartum hemorrhage due to uterine atony, early obstetric consultation in future pregnancies was advised. The infant has demonstrated normal growth and development.

Second pregnancy (27 years of age)

The second pregnancy ended in a first-trimester miscarriage at 10 weeks of gestation, which was managed by dilation and evacuation at another hospital. No investigation into the cause of the miscarriage, including cytogenetic analysis of the products of conception, was performed.

Third pregnancy (27 years of age)

The third pregnancy was also conceived naturally. Although she had been advised to attend our department as soon as pregnancy was confirmed, she first presented without symptoms at 17 weeks and five days of gestation after referral from a local clinic. Initial examination unexpectedly revealed cervical dilation with prolapsed fetal membranes and amniotic fluid sludge, prompting admission on the same day. Transvaginal ultrasonography at 18 weeks and four days confirmed the findings observed at admission (Figure *3*). Conservative management included strict bed rest, intravenous ritodrine hydrochloride for tocolysis, and close monitoring; however, cervical dilation progressed. The pregnancy was complicated by increasing

membrane prolapse and ended in miscarriage at 19 weeks and two days. Placental pathology confirmed chorioamnionitis (Blanc stage II; Redline maternal inflammatory response stage 2, grade 1). Placenta accreta was suspected because of retained placental tissue and persistent bleeding, necessitating forceps-assisted removal; however, a portion of the placenta remained adherent. At 32 days postpartum, the patient presented with heavy vaginal bleeding, and MRI revealed retained placental tissue and a pseudoaneurysm (Figure 4). Uterine artery embolization was performed, followed by spontaneous expulsion of the remaining placental tissue at 43 days postpartum. The patient continued annual oncologic surveillance, with no evidence of disease recurrence. Menstruation remained regular, and she expressed a desire for another pregnancy.

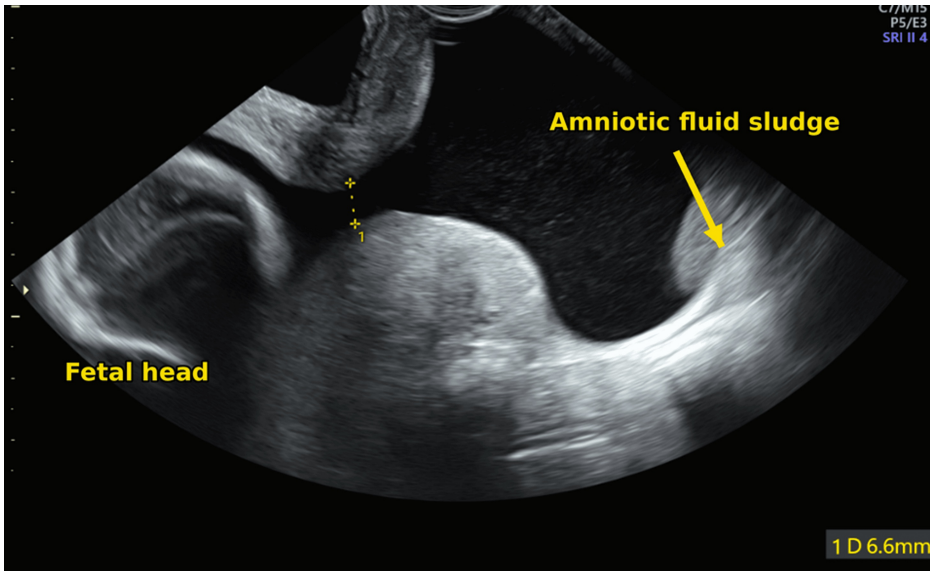


FIGURE 3: Transvaginal ultrasound findings during the third pregnancy

A transvaginal ultrasound scan at 18 weeks and four days of gestation shows cervical dilation to 6.6 mm and amniotic fluid sludge. These findings were already present at admission at 17 weeks and five days but were better visualized and documented on this later scan.



FIGURE 4: Postpartum MRI performed 32 days after delivery following heavy vaginal bleeding

Gadolinium-enhanced T1-weighted imaging shows retained placental tissue in the uterine cavity.

MRI: magnetic resonance imaging

Fourth pregnancy (30 years of age)

The fourth pregnancy was conceived naturally. In contrast to the third pregnancy, the patient attended our department during the first trimester, presenting at 10 weeks and three days of gestation, when gestational age was confirmed by crown-rump length measurement. Transvaginal ultrasonography showed a cervical length of 27 mm. Given the anticipated risk of cervical insufficiency, elective prophylactic cervical cerclage (Shirodkar procedure) was performed at 12 weeks and five days of gestation, before any further cervical changes were observed. The cervix subsequently shortened to the level of the suture (approximately 15 mm in length); however, no second-trimester pregnancy loss occurred. Pelvic MRI at 35 weeks and four days showed no findings suggestive of placenta accreta, and the cerclage suture was removed at 36 weeks and two days. As spontaneous labor did not occur, labor was induced at 37 weeks and two days. Vacuum extraction was performed because of prolonged fetal heart rate deceleration during the second stage of labor. A male infant weighing 2,366 g (-1.26 SD) was delivered, with Apgar scores of 8 and 9. The umbilical artery and vein pH values were 7.377 and 7.430, respectively. The patient's obstetric status was updated to gravida 4, para 2. The neonate required brief admission to the neonatal intensive care unit for transient respiratory distress but was subsequently discharged. The maternal postpartum course was uncomplicated, with no recurrence of the significant postpartum hemorrhage experienced during the first pregnancy. Both surviving children have demonstrated normal growth and development.

Written informed consent for publication of this case report was obtained from the patient and documented in her medical record.

Discussion

This case describes a woman who underwent chemotherapy and pelvic radiation therapy during adolescence and subsequently experienced four pregnancies. Pregnancy outcomes following treatment for undifferentiated vulvar sarcoma in the C-AYA population have not been previously reported, and the available evidence on reproductive outcomes in this population is derived largely from survivor cohort studies [1,2]. Although cancer treatment outcomes have improved, fertility and perinatal complications remain major concerns [2,3].

Alkylating agents, particularly cyclophosphamide, are associated with diminished ovarian reserve and infertility [4,5]. Cyclophosphamide was the only alkylating agent administered to our patient; therefore, her cumulative dose of 17.6 g/m² corresponds to a cyclophosphamide equivalent dose (CED) of 17,600 mg/m². In a European case-control study involving 1,332 female C-AYA cancer survivors, a CED exceeding 7,121 mg/m² was associated with a significantly increased risk of fertility impairment. The CED stratum encompassing our patient's exposure (>13,274-20,618 mg/m²) was associated with an odds ratio of 2.7 (95% confidence interval, 1.5-4.7) [5]. Nevertheless, she experienced only transient menstrual irregularities, which resolved following a single course of Kaufmann therapy. Such recovery of regular menstruation may be less common in patients with comparable treatment exposure, as prolonged or permanent amenorrhea has been reported in similar populations [6].

Pelvic irradiation, particularly at doses exceeding 5-10 Gy, poses significant risks to uterine volume, vascularization, and elasticity, potentially affecting fertility and pregnancy outcomes [7-10]. A recent French cohort study of 1,159 female childhood cancer survivors with a history of radiotherapy, in whom uterine radiation doses were individually reconstructed, demonstrated an association between higher uterine radiation doses and adverse pregnancy outcomes. Among pregnancies in women with a median uterine radiation dose exceeding 20 Gy, the combined proportion of ectopic pregnancies, spontaneous abortions, and medically indicated pregnancy terminations was 39%, compared with 12% in the French general population [11]. Although the estimated uterine dose in our patient was approximately 15 Gy, the specific dosimetric parameters and dose distribution within the uterus could not be retrospectively verified, limiting direct comparison with that study. Doses to the uterine cervix and ovaries were likewise not reconstructed. Because the opposed anterior-posterior fields encompassed the left inguinal region and vulva, the cervix was closer to the field border than the uterine corpus and may have received a higher radiation dose, whereas ovarian exposure was likely lower. However, neither exposure can be quantified retrospectively. Nevertheless, our patient experienced pregnancy losses and postpartum hemorrhage, highlighting the need for careful obstetric management following pelvic irradiation.

The patient's pubertal stage at the time of treatment was not recorded. However, irradiation of a uterus that has already attained adult dimensions may preserve its responsiveness to steroid hormones and its capacity to support pregnancy [12]. In this patient, irradiation was delivered approximately three years after menarche, by which time pubertal uterine growth is largely complete [13]. The timing of irradiation relative to pubertal development influences subsequent uterine growth and function [14].

Across the four pregnancies, the earlier gestations were complicated by preterm labor and postpartum hemorrhage due to uterine atony in the first pregnancy, a first-trimester miscarriage at 10 weeks in the second pregnancy, and a second-trimester pregnancy loss accompanied by cervical dilation, membrane prolapse, and clinically suspected placenta accreta in the third pregnancy. These complications are consistent with previous reports linking radiation exposure to myometrial fibrosis, impaired uterine contractility, and abnormal placentation [15-18] (Figure *5*). The cause of the first-trimester miscarriage in the second pregnancy was not investigated, and fetal chromosomal abnormalities, which account for most first-trimester pregnancy losses irrespective of treatment history, cannot be excluded. Exposure to alkylating agents may also impair oocyte quality and thereby contribute to early pregnancy loss [4,5], although neither mechanism can be established in this case. Fibrotic cervical changes have been associated with cervical insufficiency in childhood cancer survivors [19].

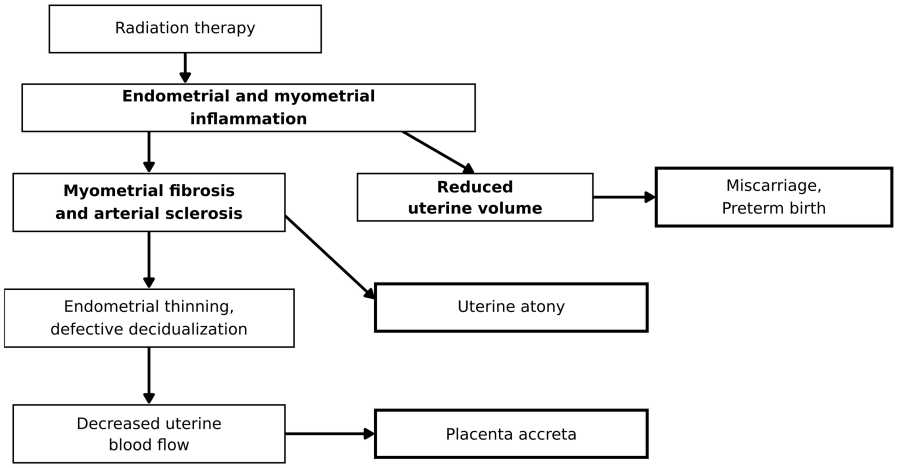


FIGURE 5: Proposed mechanisms by which pelvic radiation therapy may affect labor and delivery

Schematic summary of mechanisms reported in the literature that may link pelvic irradiation to the obstetric complications observed in this patient. The pathways shown are hypothetical for the present case and were not directly assessed.

In the fourth pregnancy, prophylactic cervical cerclage was performed in anticipation of cervical insufficiency. Although the cervix progressively shortened, no second-trimester pregnancy loss occurred, and the pregnancy reached 37 weeks. Two factors distinguished the fourth pregnancy from the third. As agreed with the patient following the third pregnancy, she attended our department during the first trimester rather than presenting only after membrane prolapse had occurred. Consequently, cerclage was performed electively before cervical dilation developed, rather than being attempted after dilation had occurred. The fourth pregnancy also followed a more stable course, without the progressive cervical dilation observed in the third pregnancy, although the indication for cerclage, based on her obstetric history, would have remained unchanged. Whether the earlier presentation, elective timing of cerclage, or differences in the clinical course of the pregnancy itself contributed to the outcome cannot be determined from a single case.

Importantly, fetal growth was relatively preserved, suggesting that endometrial receptivity and placental function were at least partially maintained. However, uterine elasticity and vascular remodeling may have been compromised [8], highlighting the distinction between the ability to conceive and the ability to sustain a pregnancy [16].

This case reinforces the importance of preconception counseling and risk assessment for C-AYA cancer survivors, including regular gynecological follow-up, uterine and ovarian imaging, and multidisciplinary perinatal planning [14,20]. Women with a history of pelvic radiation should be evaluated for uterine volume and blood flow and monitored for miscarriage, preterm labor, and postpartum hemorrhage [9,11,17]. Long-term follow-up guidelines for childhood and adolescent cancer survivors increasingly emphasize reproductive and perinatal health [20].

This report has several limitations, including its single-case nature and the absence of preconception imaging and hormonal data. Uterine volume, uterine blood flow, and myometrial fibrosis were not directly assessed, and abnormal placental adherence was not confirmed histologically. Although cervical insufficiency related to prior pelvic irradiation was suspected, the contribution of intra-amniotic inflammation or infection to the second-trimester pregnancy loss cannot be excluded, as placental pathology confirmed chorioamnionitis. Furthermore, the favorable outcome following prophylactic cervical cerclage does not establish its efficacy in this setting, and the respective contributions of chemotherapy and radiation therapy cannot be clearly delineated. Additionally, although the estimated uterine radiation dose was approximately 15 Gy, detailed dosimetric records were unavailable, preventing verification of the dose metric, assessment of dose heterogeneity within the uterus, and reconstruction of doses to the uterine cervix and ovaries. The patient's pubertal stage at the time of treatment was not recorded, and the cause of the first-trimester miscarriage in the second pregnancy was not investigated. Nonetheless, this case provides clinical insight into fertility and pregnancy outcomes among young vulvar sarcoma survivors following combined-modality treatment.

Conclusions

We describe the clinical courses and outcomes of four pregnancies in a woman who received alkylating agent-based chemotherapy and pelvic radiotherapy at the age of 15 years for undifferentiated vulvar sarcoma. The prescribed radiation dose was 45 Gy, with an estimated uterine exposure of approximately 15 Gy. Radiation-associated changes in uterine and cervical function may have contributed to her perinatal complications, although these changes were not directly assessed. Appropriate risk assessment, consideration of cervical cerclage, and preparedness for postpartum hemorrhage are critical when managing pregnancies in childhood cancer survivors. In this case, early engagement with specialist care facilitated the planning and elective performance of prophylactic cervical cerclage during the fourth pregnancy, and the pregnancy subsequently resulted in a term delivery without recurrent second-trimester pregnancy loss. This case highlights the need for further research and the development of guidelines for perinatal management in C-AYA cancer survivors.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Shun Yasuda, Akari Inazuki, Momoka Yamauchi, Akiko Yamaguchi, Keiya Fujimori

Acquisition, analysis, or interpretation of data: Shun Yasuda, Akari Inazuki, Keisuke Yoshida, Tsubasa Hobo, Takahiro Omoto, Chihiro Okoshi, Tsuyoshi Murata, Hideki Sano

Drafting of the manuscript: Shun Yasuda, Akari Inazuki, Takahiro Omoto, Tsuyoshi Murata, Akiko Yamaguchi

Critical review of the manuscript for important intellectual content: Shun Yasuda, Momoka Yamauchi, Keisuke Yoshida, Tsubasa Hobo, Takahiro Omoto, Chihiro Okoshi, Hideki Sano, Keiya Fujimori

Supervision: Shun Yasuda, Tsuyoshi Murata, Keiya Fujimori

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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