

CASE REPORT

A case of complete uterine prolapse complicated by cervical squamous cell carcinoma likely unrelated to HPV

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Abstract

Background: The coexistence of advanced uterine prolapse and progressive cervical cancer is extremely rare, with its onset mechanism unknown and treatment strategies yet to be established. **Case:** This article documents a case of clinical stage IIIC2r cervical squamous cell carcinoma combined with complete uterine prolapse classified as Pelvic Organ Prolapse-Quantification stage IV, which was left untreated for 20 years. Vaginal surgery was scheduled due to severe nocturnal pain caused by pelvic organ prolapse, resulting in a dramatic improvement in quality of life. Immunohistochemical staining of the pathological specimen revealed a patchy pattern for p16, indicating that the tumor was likely a human papillomavirus (HPV)-unrelated squamous cell carcinoma. HPV-unrelated squamous cell carcinoma is exceptionally rare, and it is suspected that prolonged external chronic irritation and inflammation caused by untreated pelvic organ prolapse may have contributed to the development of cervical cancer in this case. **Conclusions:** The pathogenesis of uterine prolapse complicated by cervical cancer is a unique condition, and its management requires tailored treatment strategies considering disease severity.

Keywords

Uterine prolapse; Vaginal surgery; HPV-unrelated cervical cancer; Squamous cell carcinoma; p16 expression

1. Introduction

Cervical cancer is the fourth-leading cause of cancer morbidity and mortality in women worldwide. According to 2022 World Health Organization statistics, it is estimated that, despite the expansion of cervical cancer screening and vaccination, 662,044 new cases of cervical cancer occur annually worldwide, resulting in 348,709 deaths [1]. More than 90% of cervical cancers are primarily caused by human papillomavirus (HPV); meanwhile, less than 5% of cervical cancers are unrelated to HPV [2].

Pelvic organ prolapse (POP) is a very common disease in adults; however, the combination of uterine prolapse and cervical cancer is extremely rare, with a prevalence of only 0.14–1.00% [3]. The majority of these cases are reported to be squamous cell carcinoma, although the mechanism of its development remains unknown [4]. Furthermore, there is currently no recommended treatment strategy for cervical cancer complicated by uterine prolapse. In this report, we present a case of complete uterine prolapse complicated by advanced cervical squamous cell carcinoma (SCC) unlikely related to HPV.

2. Case presentation

An 80-year-old G1P1 woman had experienced symptoms of uterine prolapse for approximately 20 years but had left it untreated. Several months prior to presentation, she experienced worsening lower abdominal and perineal pain, and was unable to self-reduce the prolapse. She consulted her primary care physician, who referred her to our department. She also complained of frequent and difficult urination. She had never undergone cervical cancer screening. Her medical history included hypothyroidism, hypertension, and transient ischemic attack (TIA), for which she was administered thyroid hormones and aspirin.

Physical examination revealed stage IV complete uterine prolapse, with an ulcerated mass measuring >10 cm in diameter with an irregular arising from the anterior lip of the cervix. The Pelvic Organ Prolapse Quantification (POP-Q) classification was C + 12 (Fig. 1). The right parametrium was firm, suggesting possible parametrial invasion, but did not reach the right pelvic side wall. Biopsy of the tumor revealed keratinizing SCC.

Magnetic resonance imaging revealed prolapse of the uterus and bladder outside the pelvis. A large tumor was observed in the anterior vaginal wall, extending to the vicinity of the ex-



FIGURE 1. Preoperative examination. A mass with a coarse, irregular surface accompanied by hemorrhage and ulceration was present on the portion of the uterine cervix that had prolapsed beyond the vaginal introitus.

ternal urethral orifice. Multiple punctate low-signal intensities were observed within the bladder, indicating numerous bladder calculi (Fig. 2A). On positron emission tomography-computed tomography, fluorodeoxyglucose uptake was observed in the cervical tumor and the right obturator and para-aortic lymph nodes (Fig. 2B), suggesting metastasis. A diagnosis of International Federation of Gynecology and Obstetrics (FIGO) stage IIIC2r was made. Bilateral hydroureter was present, and while tumor invasion into the ureters was not evident, the possibility of this being due to bladder prolapse was considered (Fig. 2A). Blood tests showed an elevated SCC antigen level of 8.3 ng/mL, a blood urea nitrogen level of 17 mg/dL, creatinine level of 0.45 mg/dL, and an estimated glomerular filtration rate of 97.6 mL/min, indicating preserved renal function.

Concurrent chemoradiotherapy was initially considered; however, although analgesics such as non-steroidal anti-inflammatory drugs and acetaminophen were used, adequate pain relief was not achieved. In addition, the cervical tumor had enlarged, making reduction of the uterus with a pessary impossible. Several concerns were considered in treatment planning. First, prolonged radiotherapy may be

required for pain relief; second, even if the tumor responded, subsequent reparative procedures, such as hysterectomy, vaginal wall reconstruction, and vaginal closure, would be difficult because of radiation-induced fibrosis; and third, uterine mobility during radiotherapy could result in deviation of the irradiation field and hinder the planned treatment. Therefore, after a comprehensive assessment and consultation with the Department of Radiation Oncology, we decided to proceed with transvaginal surgery. Vaginal hysterectomy and colpocleisis were performed under general anesthesia. During the surgery, tumor invasion of the right ureter was observed near the ureterovesical junction, with a width of approximately 2 cm. An emergency urology consultation was required, and ureteroureterostomy was performed transvaginally. The surgery lasted 8 h and 51 min, with a blood loss of 1660 mL. The patient required a high-risk surgery involving four units each of packed red blood cells and fresh frozen plasma.

The postoperative course was uneventful, and the patient was discharged home on the 15th postoperative day. The preoperative Pelvic Floor Disability Index was 231.25 and decreased to 90.66 at 3 months postoperatively, indicating

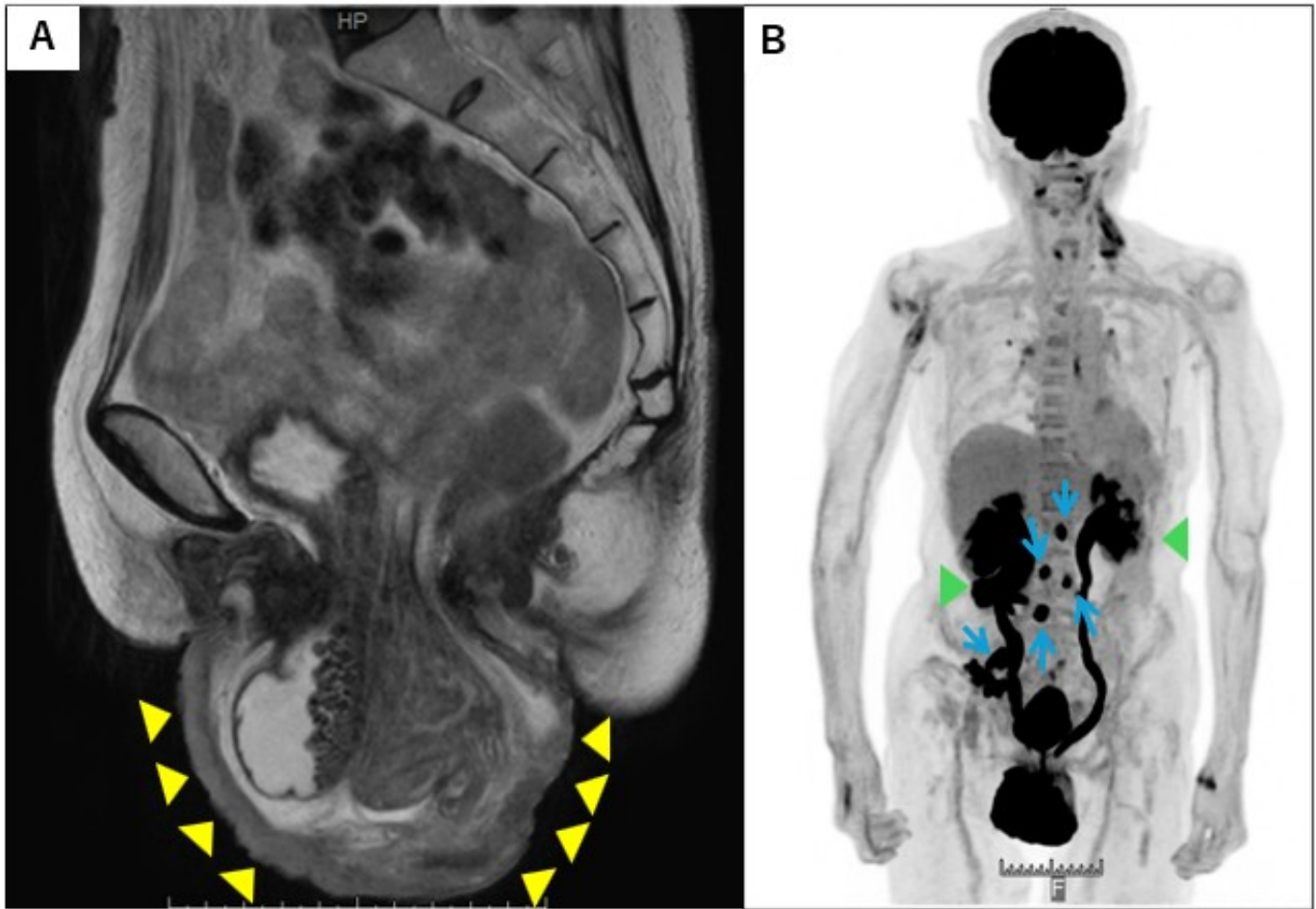


FIGURE 2. Preoperative images. (A) Magnetic Resonance Imaging (MRI) axial T2-weighted image, and (B) Positron Emission Tomography-Computed Tomography (PET-CT) image. Yellow arrow-heads show the cervical tumor, green arrow-heads show the bilateral hydronephrosis, and blue arrows show the FDG uptake by the para-aortic and right obturator lymph nodes.

a significant improvement in pelvic floor function and contributing to an improvement in activities of daily living. Post-operative radiation therapy was planned; however, computed tomography performed on the 20th postoperative day revealed splenic and multiple liver metastases, leading to the decision for systemic therapy.

The pathological diagnosis of the excised specimen was keratinizing SCC (Fig. 3), pT3BpNx, with positive lymphovascular invasion and surgical margins. Immunohistochemical staining of p16 in tumor cells revealed a patchy pattern (Fig. 4A), suggesting that the tumor was unlikely to be HPV-related. Additionally, p53 overexpression was observed in the invasive areas of the carcinoma, suggesting *p53* mutation in the tumor cells (Fig. 4B).

Paclitaxel-carboplatin (TC) plus pembrolizumab therapy was initiated on the 45th postoperative day owing to increased tumor expression of programmed death-ligand 1, and the metastatic lesions showed a partial response. After completing six cycles of TC plus pembrolizumab, the patient was switched to maintenance therapy with pembrolizumab monotherapy. Twelve months have passed since the initiation of maintenance therapy, and the lesion remains reduced in size.

3. Discussion

This case involves advanced stage IIIC cervical cancer, for which concurrent chemoradiation therapy (CCRT) is the standard treatment, as per the National Comprehensive Cancer Network (NCCN) guideline [5]. However, due to severe pain caused by pelvic organ prolapse requiring early symptom relief, and concerns that anatomical distortion and mobility could significantly impact radiation therapy planning, potentially leading to decreased radiation response rates and increased adverse events in healthy organs, a surgical approach involving resection and perineal reconstruction was prioritized.

According to a systematic review [4], among 78 cases of cervical cancer-associated uterine prolapse, only 12 (15.3%) cases were advanced stage III or higher, with the majority being early-stage cancers. This report suggests that surgery-based treatments contribute to a better prognosis compared with radiotherapy (RT)-based treatments. However, there are currently no detailed descriptions of the treatment provided for stage III or higher cases. Therefore, it remains unclear whether prioritizing surgical treatment leads to improved prognosis in patients with stage III or higher cervical cancer.

In the current case, intraoperative findings revealed accidental ureteral invasion, necessitating additional high-risk surgery

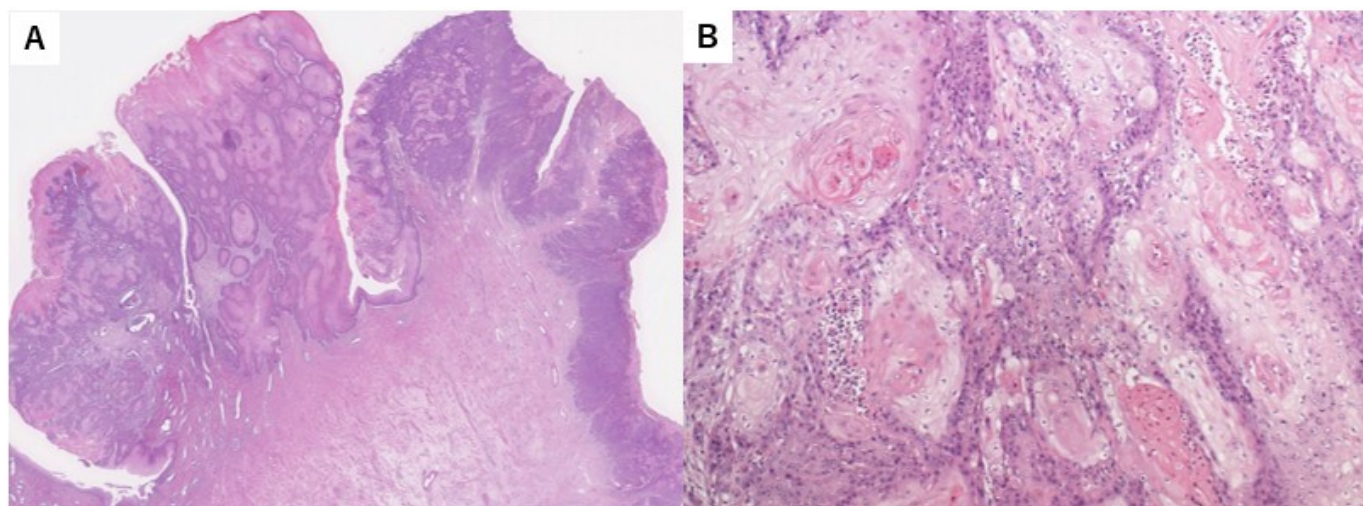


FIGURE 3. Pathological findings of the cervical tumor. Hematoxylin and eosin staining at weak magnification ($\times 40$, A) and strong magnification ($\times 200$, B).

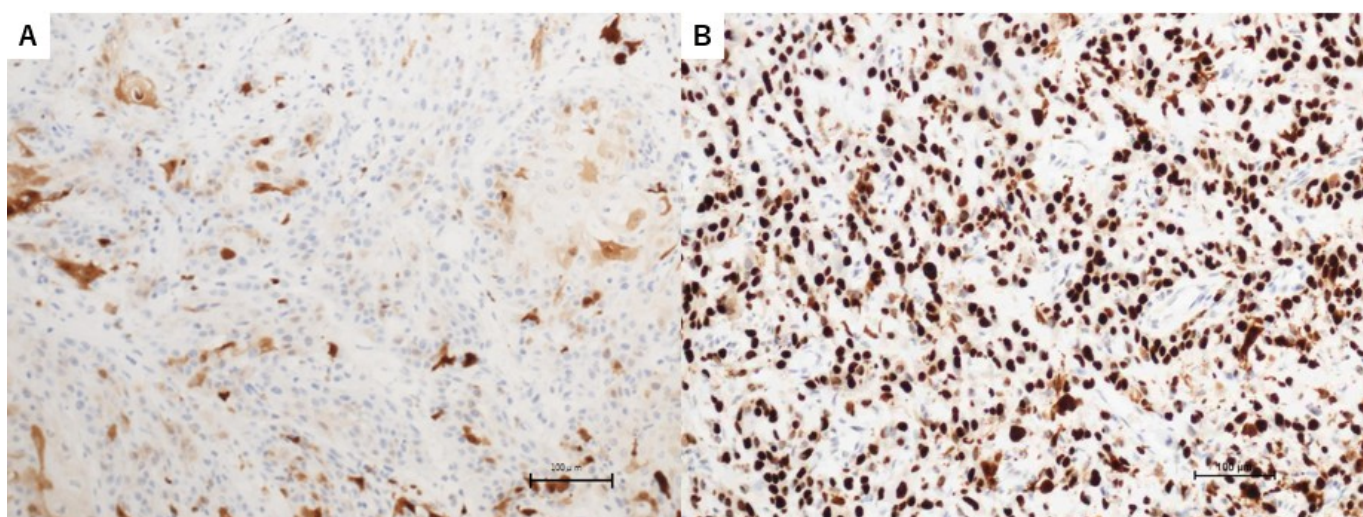


FIGURE 4. Immunohistochemical staining. (A) p16 expression in the cervical tumor ($\times 200$). (B) p53 expression in cervical tumor cells in the area of stromal invasion ($\times 200$).

involving ureteral resection. Considering bilateral hydroureter was thought to be caused by compression due to pelvic organ prolapse, the ureteral invasion of the cancer was masked. When hydroureter is observed in locally advanced cervical cancer with uterine prolapse, it is necessary to consider not only the possibility of uterine prolapse, but also the possibility of cancer ureteral invasion and to exercise caution when performing surgery.

Previous reports have documented cases in which RT for cervical cancer with complete uterine prolapse resulted in a favorable clinical course [3, 6]. Therefore, in cases where pain due to prolapse symptoms is acceptable, RT for locally advanced cervical cancer can be considered sufficiently tolerable.

The histological type of cervical cancer in the present case was SCC, although HPV infection was considered negative. HPV-DNA testing for cervical cancer is not covered under the Japanese health insurance system; therefore, genetic-level confirmation could not be performed in this case. In cervical SCC, negative expression of the p16 protein generally indicates that

HPV infection is unlikely to be involved in cervical cancer progression. However, in the current case, HPV-DNA was not examined and so, cannot be definitively classified as unrelated; therefore, the case was described as “likely HPV-unrelated”.

Table 1 (Ref. [3, 6–11]) summarizes previously reported cases of uterine prolapse complicated by cervical cancer, where the presence or absence of HPV infection was confirmed. Among them, three cases had stage III or IV cervical cancer: two of these underwent RT, and the other underwent surgery; all required highly invasive procedures.

Among these 15 cases, only 4 (27%) were positive for HPV infection. The histological type was diagnosed as SCC in 13 of the 15 cases, and 2 cases were described as verrucous carcinoma, which is a special type of highly differentiated SCC; thus, all the cases can be considered SCC. Considering that the HPV negativity rate in general cervical SCC is 2% [12], the HPV positivity rate is significantly lower in cervical SCC complicated by uterine prolapse. However, due to limitations in extracting previously reported cases, the number identified is likely smaller than the actual number of cases, and selection

TABLE 1. Previous reports investigating the presence or absence of HPV infection in cases of uterine prolapse complicated by cervical cancer.

Authors	Age	Histology	FIGO	HPV-DNA	p16	Prolapse duration (yr)	POP-Q	Treatment	Follow-up	Outcome
Lee <i>et al.</i> [6], 2022	74	Verrucous carcinoma	IIIC1r	–	n.d.	30	IV	CCRT → ARH/LS	19 mon	NED
Davidson <i>et al.</i> [7], 2024	81	Well-mod differentiated SCC	IB3	–	n.d.	Many	IV	ARH/Hartmann → CCRT	n.d.	n.d.
Chapman <i>et al.</i> [8], 2024	73	SCC	IB3	–	n.d.	10	IV	ARH/colpopexy → RT	12 mon	NED
Chapman <i>et al.</i> [8], 2024	83	Poorly differentiated SCC	IB3	–	n.d.	10	IV	ARH/colpopexy → RT	12 mon	NED
Kahn <i>et al.</i> [3], 2020	68	Keratinizing SCC	IIB	–	+	Many	IV	CCRT	12 mon	DOD
Dane <i>et al.</i> [9], 2009	86	Verrucous carcinoma	IB3	+	n.d.	n.d.	IV	VH	6 mon	NED
Waseem <i>et al.</i> [10], 2024	86	Well-mod differentiated SCC	IIB	–	–	50	IV	VH/colpocleisis	29 mon	NED
Waseem <i>et al.</i> [10], 2024	71	Poorly differentiated SCC	IB1	–	+	15	III	VH/colpocleisis	48 mon	NED
Waseem <i>et al.</i> [10], 2024	74	SCC	IA1	+	n.d.	1	II	VH/LS	11 mon	NED
Waseem <i>et al.</i> [10], 2024	85	SCC	IA1	+	n.d.	3	II	VH/colpocleisis	6 mon	NED
Waseem <i>et al.</i> [10], 2024	75	SCC	IA1	+	n.d.	15	II	VH/colpocleisis	2 mon	NED
Horn <i>et al.</i> [11], 2025	83	Keratinizing SCC	IB3	–	–	10	IV	ARH/colpectomy	4 mon	DOA
Horn <i>et al.</i> [11], 2025	78	Keratinizing SCC	IVA	–	–	8	IV	APE/LEER	14 mon	DOD
Horn <i>et al.</i> [11], 2025	70	Keratinizing SCC	IIIB	–	–	20	IV	RT	4 mon	DOD
Horn <i>et al.</i> [11], 2025	69	Keratinizing SCC	IIA2	–	–	n.d.	IV	ARH	20 mon	NED

+, positive; –, negative; APE, anterior pelvic exenteration; ARH, abdominal radical hysterectomy; CCRT, concurrent chemoradiotherapy; DOA, dead of another disease; DOD, dead of disease; FIGO, International Federation of Gynecology and Obstetrics; LEER, laterally extended endopelvic resection; LS, lateral suspension; NED, no evidence of disease; n.d., no data; SCC, squamous cell carcinoma; VH, vaginal hysterectomy; HPV, human papillomavirus; POP-Q, Pelvic Organ Prolapse Quantification; RT, radiotherapy.

bias is probable. Therefore, the true HPV positivity rate in cervical cancer complicated by uterine prolapse may be higher than the 27% observed in this analysis.

HPV-unrelated SCC of the lower genital tract is often of the keratinizing type, and it has been suggested that p53 mutations may contribute to cancer progression [13]. In vulvar cancer, cases are classified into HPV-related and -unrelated cancer. HPV-unrelated cancer is thought to develop against a background of chronic inflammation, such as lichen sclerosis, and progresses to cancer via differentiated vulvar intraepithelial neoplasia (d-VIN). It has been found that p53 mutations occur at the stage of d-VIN [14]. Similarly, in uterine prolapse-associated cervical cancer, it has been reported that prolonged perineal contact irritation may lead to keratinization, ulceration, and repeated tissue repair, which potentially induces p53 mutations [11]. These features align with the characteristics of the present case, although direct causation cannot be established.

Among the 15 previous cases, 12 were classified as POP-Q stage IV complete uterine prolapse, indicating that a severe state of uterine prolapse had been left untreated for a prolonged period. This raises the hypothesis that chronic prolapse-related irritation may play a role in carcinogenesis; however, such an association remains speculative. Additionally, none of these cases had been conservatively managed with a pessary, which suggests that cervical friction beyond the perineum due to contact with clothing could contribute to cancer development. However, given that reports of HPV-unrelated SCC include cases without uterine prolapse [15], avoiding perineal contact irritation through conservative treatments, including pessary therapy, does not necessarily prevent the onset of cervical cancer. Overall, the present findings should be interpreted as hypothesis-generating rather than indicating a definitive causal mechanism.

Regarding HPV-unrelated SCC, it is desirable to accumulate cases, analyze clinical characteristics, and establish standard treatments. However, due to its rarity, it is currently necessary to carefully determine treatment strategies on a case-by-case basis. In the future, the accumulation of cases from multiple facilities and the analysis of clinical information will be highly anticipated.

4. Conclusions

Leaving severe pelvic organ prolapse untreated for many years may not only lower quality of life, but may be associated with cervical cancer development, independent of HPV infection. Treatment decision-making should be individualized based on a multidisciplinary approach.

AVAILABILITY OF DATA AND MATERIALS

The data are contained within the article.

AUTHOR CONTRIBUTIONS

NH—completed the case report and literature review. SS, KaF and RK—collected the data and reviewed the manuscript.

HK and KeF—supervised the data collection and reviewed the manuscript. All authors edited, read, and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethics approval was deemed unnecessary by the Kurashiki Central Hospital Ethics Committee. Written informed consent for publication of the case report and accompanying images was obtained from the patient.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. Although Naoki Horikawa is currently serving on the Editorial Board of this journal, he was not involved in the peer review process of this article and had no access to any information related to its evaluation. The entire editorial responsibility for this manuscript was delegated to MJ.

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