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Case Series

Tumor response and the quality of life after isolated hypoxic pelvic perfusion for advanced G3 cervical cancer: A case series

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ABSTRACT

INTRODUCTION: We present a case series of three patients with advanced cervical cancer who either refused the standard of care systemic or chemoradiation treatment or did not benefit from it.
METHODS: We treated patients with isolated hypoxic pelvic perfusion (HPP).
RESULTS: Two patients achieved complete clinicopathologic response and one patient required surgical excision of the necrotic residual mass containing no viable cancer cells. There were no long-term systemic or local side effects. All patients are cancer free for up to 15 years after conclusion of treatment.
CONCLUSION: HPP is an effective option for treatment of advanced cervical cancer that generates rapid and onlasting remissions at low side effects. Gynecologic oncologists shall be aware of HPP to facilitate wider adaption of our technique.

1. Introduction

The treatment of advanced cervical cancer remains a challenging problem [1]. The present standard of care - chemoradiotherapy, followed by brachytherapy [2] - is associated with considerable toxicity [3]. The complete pathologic response rates with induction chemotherapy range from 11% to 20% [4]. There is no difference in survival benefit between chemotherapy, surgery, or radiotherapy alone [5], attributed to resistance of cancer cells to chemotherapy drugs and low peak concentration of these within a tumor. The isolated hypoxic perfusion overcomes these limitations. We present a case series of three patients with advanced cervical carcinomas, histologic grade G3 who refused standard of care treatment, and opted for isolated hypoxic pelvic perfusion (HPP). This current case series has been reported in line with the PROCESS criteria [6].

2. Methods

2.1. Isolated hypoxic pelvic perfusion technique

We expose the femoral artery and vein via a small incision under general anesthesia. Bilateral pneumatic cuffs are applied distal to the incision. We cannulate both vessels with three-channel stop-flow balloon catheters and use a guidewire to advance balloons above the bifurcation of the aorta and inferior vena cava at the same level under fluoroscopy (Fig. 1).

Then balloons are deflated, and patients receive 100% oxygen for 3–5 min. After that, Cisplatin, Adriamycin, and Mitomycin are rapidly infused via the arterial line, and balloons are reinflated to establish the isolated circuit for 15 min. We then deflate balloons and remove tourniquets while filtrating drugs out over the perfusion catheters for 30 min with 4 L of the filtrate to reduce systemic exposure. We remove catheters and repair vessels with running sutures. Investigations were performed in compliance with the principles of good clinical practice outlined in the Declaration of Helsinki and federal guidelines, and had approval by the Institutional Review Board. Informed consent was obtained from each participant or participant's guardian.

We herein present retrospective single cases treated in long-term intervals with the same method of isolated hypoxic pelvic perfusion performed by the corresponding author and his team in our private institution from 2005–2020.

Abbreviations: HPP, hypoxic pelvic perfusion; UICC, union internationale contre le cancer; MRI, magnetic resonance imaging; CT, computed tomography; FDG PET-CT, fluorodeoxyglucose positron emission tomography-computed tomography; DFS, disease-free survival; PFS, progression-free survival; QOL, quality of life.

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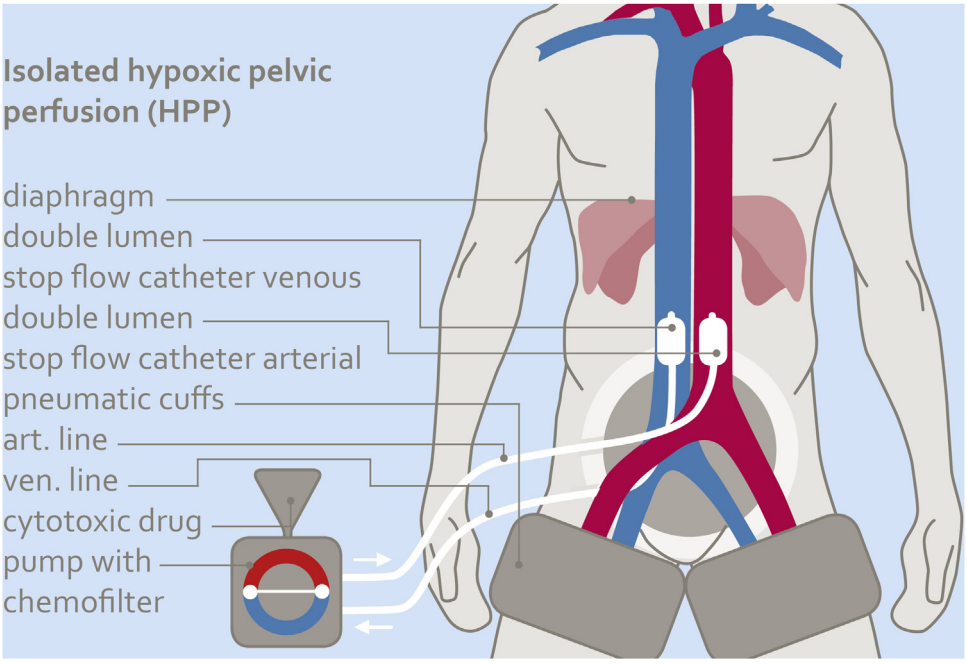

Fig. 1. Scheme of hypoxic isolated pelvic perfusion b Contrast imaging of pelvic vessels after balloon blocking.

2.2. Case 1

The first case is a 48-year-old patient with advanced cervical cancer UICC, stage IVA, metastatic to presacral lymph nodes. The histology confirmed squamous cell carcinoma, grade G3. The exploratory laparotomy confirmed rectal invasion.

She received two cycles of Carboplatin and Taxol in May of 2005. MRI of the abdomen and pelvis in June of 2005 revealed a 3.1 × 1.8 × 2.8 cm mass infiltrating the dorsal vaginal vault, right rectouterine plica up into the rectum, and presacral soft tissues on the left (Fig. 2a, b). The patient refused chemoradiotherapy.

The patient underwent three cycles of HPP with 50 mg of Cisplatin, 30 mg of Adriamycin and 20 mg of Mitomycin each cycle.

CT of the abdomen and pelvis from September of 2005 after two cycles of HPP demonstrated extensive calcifications in the cervix and uterus (Fig. 2c, d). MRI of the abdomen and pelvis from December of 2005 after two additional HPP cycles demonstrated residual necrotic cervical mass (Fig. 2e, f).

We performed radical hysterectomy in February of 2006 confirming the complete pathologic response. The patient received one adjuvant cycle of HPP with 50 mg of Cisplatin, 30 mg of Adriamycin and 30 mg Mitoxantrone. We followed the patient with an annual MRI which demonstrated no evidence of recurrence. The patient has been disease-free for fifteen years. There was no evidence of systemic toxicities.

2.3. Case 2

The second case is a 46-year-old patient with advanced cervical cancer, UICC stage IIIA, involving parametrium and vagina. She was diagnosed after presenting to her gynecologist with pelvic pain.

MRI from August of 2012 demonstrated a cervical mass 3.43 × 4.06 cm. CT of the abdomen and pelvis from April of 2013 revealed a 3.86 × 5.83 cm cervical mass (Fig. 3a). There was no evidence of metastatic disease. The attending gynecologic oncologist informed the patient that she has an inoperable disease. The patient self-referred to our clinic shortly after.

After the first two cycles of HPP with 50 mg of Cisplatin, 30 mg of Adriamycin, and 15 mg Mitomycin each, the gynecological examination revealed a small cervix with scarring and no evidence of tumor in the cervix or vagina. The parametria contained palpable scar tissue with improved mobility. The patient had no pain.

The patient received one additional cycle of HPP in June of 2013. MRI of the abdomen and pelvis from May of 2013 after two HPP cycles demonstrated residual cervical mass 1.89 × 2.34 cm (Fig. 3b).

FDG PET-CT performed in August of 2013 revealed normal cervix with no metabolic activity. There was no evidence of disease on the follow up FDG PET-CT in August of 2014 (Fig. 3c, d).

The patient has been disease-free for seven years.

2.4. Case 3

The third case is a 63-year-old patient with cervical cancer, UICC stage III, grade G3. She had curettage and conization in December of 2017, pathologic stage pT1b1, cN0, cMx, L1, V1, R1. She refused guideline-based therapy and started naturopathic treatment instead. CT of the abdomen and pelvis performed in November of 2019 revealed metastatic disease in the iliac lymph nodes bilaterally, and bulky cervix with deep infiltration of myometrium.

The patient presented to our clinic with recurrent vaginal bleeding in February of 2020. CT abdomen and pelvis and FDG PET-CT performed in February of 2020 confirmed a highly metabolic cervical lesion 3.61 × 4.29 cm (Fig. 4a, b). The patient decided to proceed with HPP.

We performed HPP with 50 mg of Cisplatin, 30 mg of Adriamycin, and 15 mg Mitomycin each on March and April of 2020. The vaginal bleeding stopped by the time of the second procedure. The CT of the abdomen and pelvis performed in May of 2020 revealed a 2.90 × 3.24 cm residual cervical lesion.

The patient received one additional HPP cycle in June of 2020. There is no evidence of systemic toxicities.

FDG PET-CT performed in September of 2020 demonstrated no abnormal metabolic activity within the cervix (Fig. 4c, d).

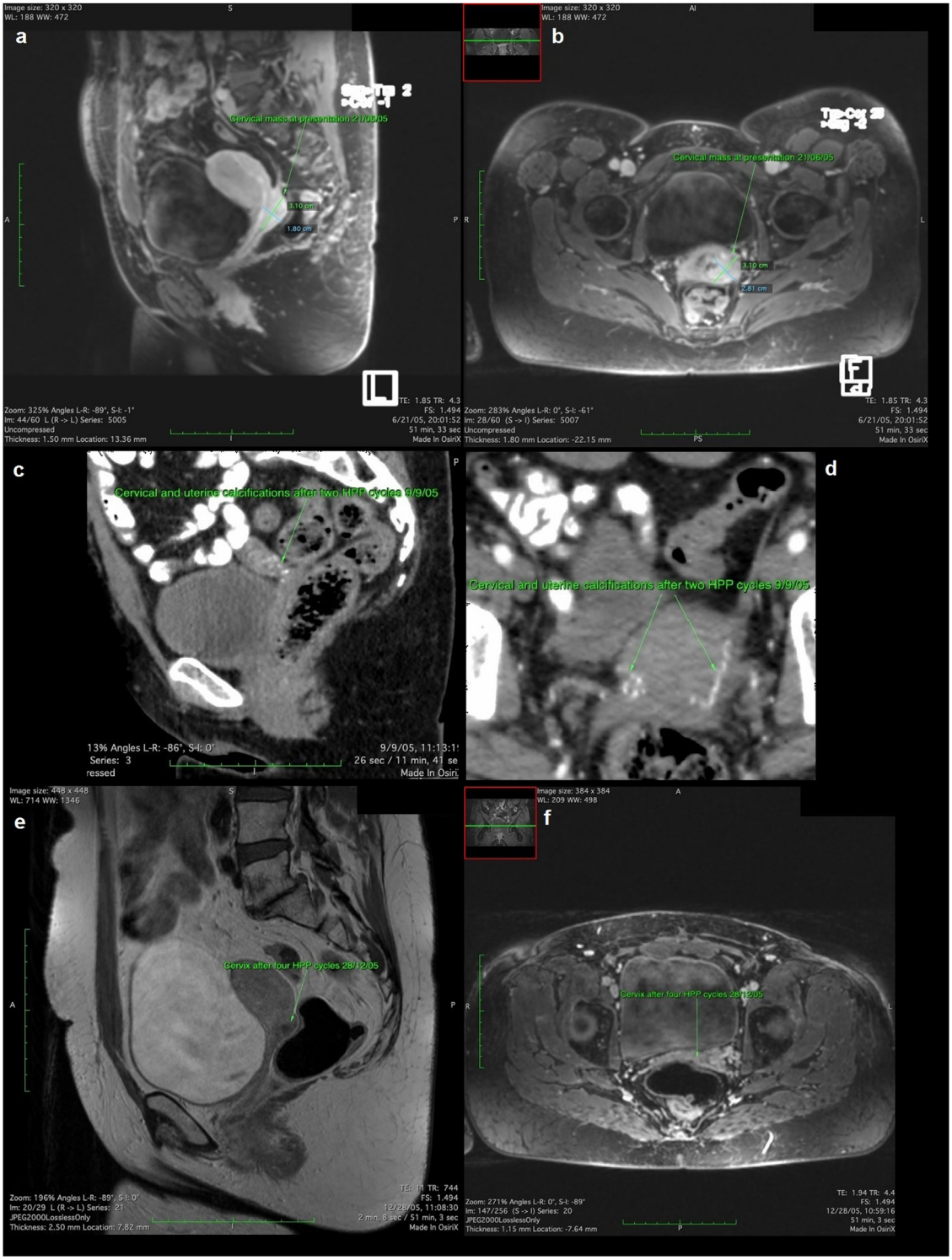

Fig. 2. (a, b) Cervical mass at presentation, (c, d) Extensive calcifications in the cervix and uterus after two HPP cycles, (e, f) Residual cervical mass after four HPP cycles.

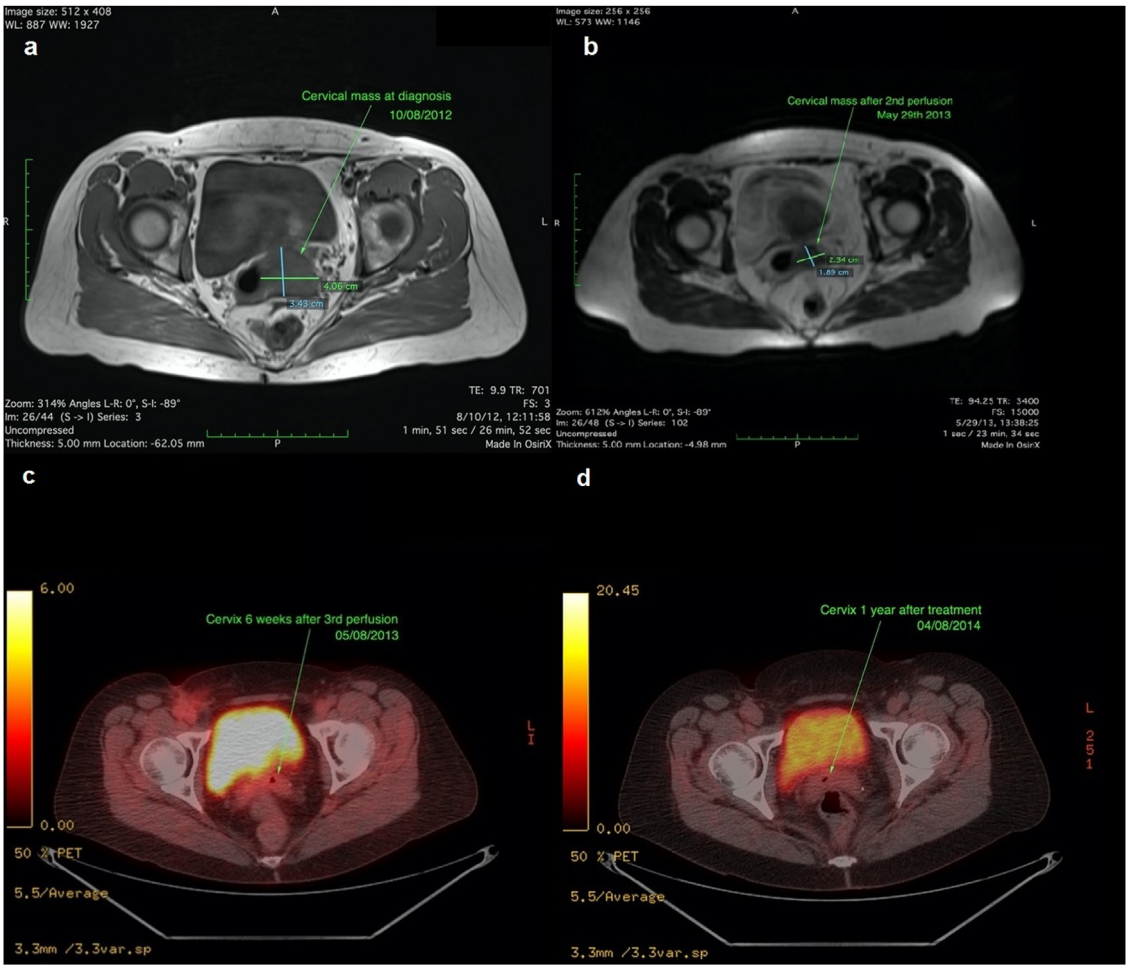

Fig. 3. (a) Cervical mass at diagnosis in August of 2012 (left) and (b) after the 1st HPP, (c, d) FDG PET-CT two months after 3rd treatment (left) and one year after (right).

3. Discussion

Chemoradiotherapy, followed by intracavitary brachytherapy, is the standard of care for the treatment of advanced cervical cancer. The long-term disease-free survival (DFS) is 85–90%. Unfortunately, it is associated with significant morbidity due to the toxicity of platinum-based regimens and the mutilating effect of radiotherapy. These include vaginal dryness, ureteral strictures, vesicovaginal and rectovaginal fistulas, lymphostasis, and lymphocele. None of these side effects have occurred in our patients.

The DFS after cisplatin-based chemoradiotherapy and radical surgery is superior to induction chemotherapy and subsequent radical surgery [7]. The intensity-modulated radiation therapy reduced toxicity by almost 50%, although it still results in severe side effects in approximately 30% of the cases [8].

There were multiple efforts to investigate if induction chemotherapy is sufficient to achieve an adequate response and assure resectability [9]. The meta-analysis of radical surgery with or without induction chemotherapy did not demonstrate induction chemotherapy's effect on DFS or progression-free survival (PFS) [10]. Several small studies demonstrated comparable results with intra-arterial infusions of chemotherapeutic drugs [11,12].

Hence, there is a need for alternative approaches to achieve optimal PFS, DFS, and quality of life (QOL).

We demonstrated that isolated hypoxic perfusion, followed by chemo-filtration, allows higher drug penetration into the tumor, leading to durable responses after three or four treatment cycles without significant systemic toxicities. The use of immune checkpoint inhibitors in select patients may further enhance response [13–15].

Although we routinely perform isolated hypoxic perfusion for various cancers, we rarely see patients with gynecological tumors, primarily treated by gynecologic oncologists. The presented cases demonstrated excellent results in advanced cervical cancer, which is often the case with arterial chemotherapy and isolated hypoxic perfusion in other tumor types [16–19].

4. Conclusions

We demonstrated the efficacy of HPP in achieving complete and durable clinical and radiologic remission with no identifiable signs of systemic toxicity.

There is a need for a prospective randomized study comparing the current standard of care and isolated hypoxic perfusion.

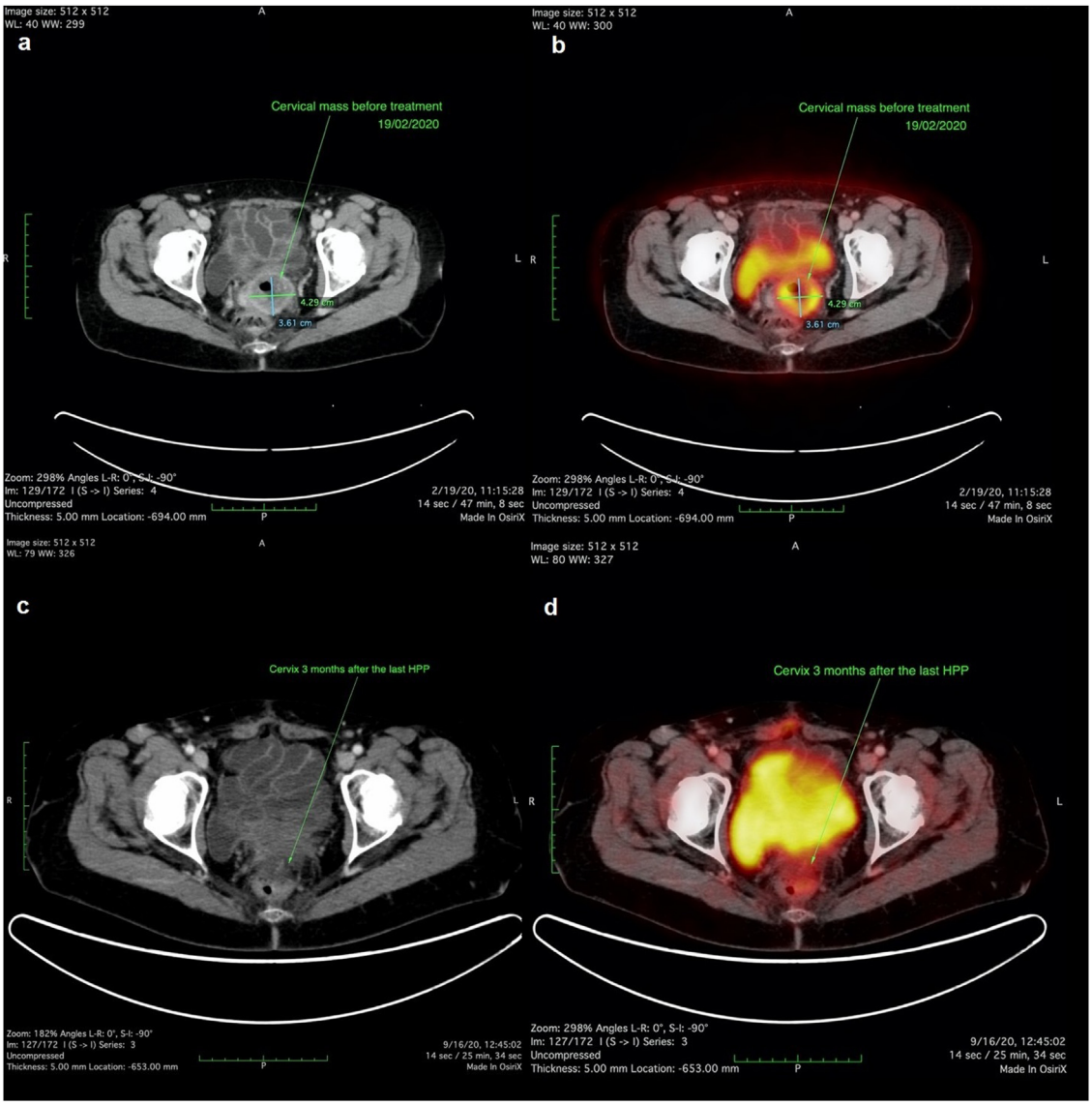

Fig. 4. (a, b) cervical mass before treatment on contrast-enhanced CT and FDG PET-CT, (c, d) cervix 3 months after the last HPP.

Conflicts of interest

The authors declare that there is no conflict of interest.

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Ethical approval

Ethic approvals was not required and patient-identifying knowledge was not presented in the report.

Consent

Written informed consent was obtained from the patients for publication of this case series and accompanying images. A copy of the written consents are available for review by the Editor - in-Chief of this journal on request.

Author contribution

Karl R. Aigner: Conceptualization, Writing, Review, Editing, Supervision - Original draft. Performed surgery/intervention.

Youri Lavinski: Review, Data Collection

Sabine Gailhofer: Review, Data Collection, Data Analysis, Performed surgery/intervention

Registration of research studies

1. Name of the registry: **Research Registry**
2. Unique identifying number or registration 10: **researchregistry6171**

3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com/browse-the-registry#home/registrationdetails/5f9816f33175a20015ca6caf/

Guarantor

All mentioned authors were involved in the preparation of this case series and accept full responsibility for the work, had access to the data and controlled the decision to publish.

Provenance and peer review

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