

# Primary Clear Cell of Abdominal Wall, A Case Report

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## ABSTRACT

**Background:** Endometriosis occurring in a surgical scar is well recognized and occurs mainly in patients with a history of hysterectomy or caesarean section. Scar endometriosis as well as endometriosis at other sites, can undergo malignant change. Clear cell carcinoma of the endometrium is a very rare and highly malignant neoplasm that accounts for less than 5% of endometrial carcinoma.

**Case presentation:** We report a very rare case of clear cell adenocarcinoma arising from endometriosis of the abdominal scar. We must pay more attention on the following points in the surgical treatment of clear cell carcinoma: (1) Extensively resect tumors as far as possible; (2) Surgical treatment of clear cell carcinoma would easily result in poor wound healing especially in the patients receiving chemotherapy or radiotherapy because of extensive soft tissue stripping.

**Conclusion:** The patient died only 25 months after she was first diagnosed with the cancer.

**Lessons:** This case highlights the difficulties in preoperative diagnosis as well as the poor prognosis of these tumors.

Accurate diagnosis of a lump within a scar is important to define the prognosis and treatment.

These therapeutic principles are increasingly being applied to patients presenting with tumors greater than 5

cm and negative lymph nodes or even smaller tumors who are considered to have operable disease and a better outcome. Early recognition and prompt treatment can be essential to these patients' survival.

**Keywords:** Endometriosis, Clear cell carcinoma, Case report, Abdominal wall, Caesarean section

**Abbreviations:** PET: Positron-Emission Tomography; FDG: Fluoro Deoxy Glucose; SUV max: Maximum Standard Uptake Value; CT scan: Computed Tomography Scanner; Ki67: Antigen Ki-67; Napsin A: Napsin A Aspartic Peptidase; KRAS: KRAS proto-oncogene; GTPase; BRAF: B-Raf Proto-oncogene Serine/Threonine kinase; ERBB2: erb-b2 Receptor Tyrosine Kinase 2; CT-NNB1: Catenin Beta 1; PTEN: Phosphatase and Tensin Homolog; PIK3CA: Phosphatidylinositol-4,5-bisphosphate 3-Kinase Catalytic subunit Alpha; ARID1A: AT-Rich Interaction Domain 1A; PPP2R1A: Protein Phosphatase 2 Scaffold Subunit Alpha; Ca125: Cancer Antigen 125; Pax-8: Paired box gene 8; TP53: Tumor Protein 53; Ki67: Ki67 Antigen; PR: Progesterone Receptor; ER: Estrogen Receptor; HIFU: High-Intensity Focused Ultrasound; CS: Caesarean Section

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## INTRODUCTION

Abdominal wall endometriosis is one of the major extra pelvic sites and usually is highly related to abdominal surgeries and obstetric and gynecological procedures like a cesarean section, hysterectomy, amniocentesis, tubal ligation, appendectomies, umbilical hernioplasties and laparoscopic trocar tracts. Endometriosis occurring in surgical abdominal scar has been mainly documented after caesarean section (CS) or hysterectomy (0.03 upto 0.4%) and its malignant transformation is very rare: Clear cell histology accounts for only 4.5% of extra gonadal endometriosis-associated malignancies, while representing the most common histotype in case of parietal localization (Ferrandina G, *et al.*, 2018; Van Gorp T, *et al.*, 2008).

We report a very rare case of clear cell adenocarcinoma arising from endometriosis of the scar. However, ovarian cancer is known to develop in 0.3%-1.6% of women with endometriosis, and endometriosis is observed in 4%-29% of patients with ovarian cancer, which suggest the association between endometriosis and ovarian cancer (Kim HS, *et al.*, 2014). The majorities of carcinomas derived from endometriosis are of endometrioid or clear cell histologic type, in some series accounting for 70% of the subtypes (Fàbregas FE, *et al.*, 2014).

This suggests that addition of bevacizumab to paclitaxel plus carboplatin for patients with clear cell carcinoma could be a very important treatment strategy (Komiyama S, *et al.*, 2019).

## CASE PRESENTATION

Here, we report a 43-year-old woman, gravida1, para1, with

a history of uneventful caesarean delivery presented with increasing pain and a rapid growing mass in her cesarean section scar. She had no major health problems and her only surgery was a cesarean section for complete placenta previa during her first pregnancy in 2003.

She complained of pain and swelling at the lower end of her abdominal scar during menstruation which started shortly after the surgery. She had not taken hormonal therapy. On physical examination, a large firm mass was palpated in the lower abdominal wall in the region underlying the incision in November 2017. Plain scan and enhanced scan of abdominal CT showed a 49 × 45 mm low-density shadow in the left rectus muscle (Figure 1). Serum carbohydrate antigen 125 was 21.6 Ku/L.

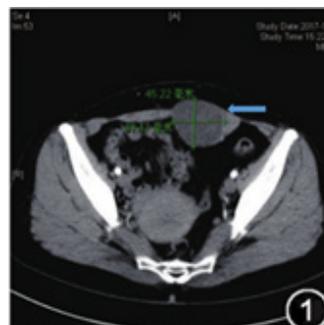
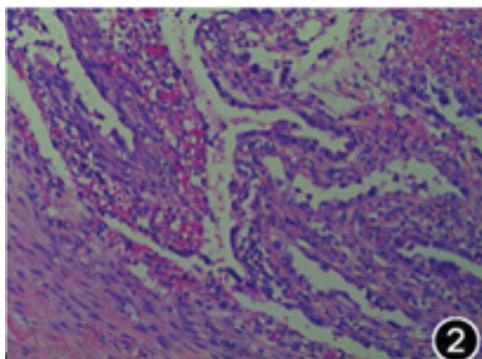


Figure 1: Abdominal CT section, 45 × 22 mm, in 2017

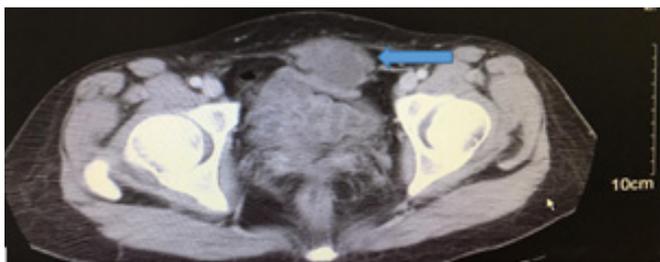
Based on these findings, we made a preoperative diagnosis of scar endometriosis. During the dissection of anterior abdominal wall, lot of fibrosis was observed with a mass of pale colored very adherent to surrounding structures on left rectus sheath involving the rectus muscle as well, it was excised and sent for histopathological analysis. The pathology from specimen showed adenocarcinoma in situ with immunohistochemistry: Cytokeratin +++++, Ca125+++, Pax-8+++, TP53+, Ki67 expression 30%+, PR(-), ER(-), and Napsin A (+).

Findings were consistent with clear cell carcinoma of ovarian epithelial cell origin, with endometriosis lesions noted in close proximity of the clear cell adenocarcinoma (Figure 2). Positron emission tomography-computed tomography (PET-CT) examination suggested soft tissue nodules in the left rectus. Increased cortical glucose metabolism was detected by PET-CT studies. The maximum standardized uptake value (SUV max) of the lesion was 3.2 g/ml. Fusion transversal image of the PET/CT showing a soft tissue lesion with moderately increased glucose metabolism (maximum standardized uptake value (SUV max) 9.7 g/ml 47 min post-injection of 175 MBq (FDG) in the left rectus.



**Figure 2: The observation under the histological microscope showed densely arranged tumor cells, growing as a crumby structure and diffuse appearance, with hyperchromatic and large nuclei, and abundant cytoplasm. HE × 20**

The patient underwent hysterectomy and bilateral adnexectomy with pelvic lymph node dissection in December 2017. She was treated with chemotherapy, but the cancer recurred locally in January 2018, and the patient subsequently received multiple agents secondary to progression. The induction chemotherapy consists of four cycles of paclitaxel 135 mg/m<sup>2</sup> and carboplatin (area under the curve=6) every 3 three weeks, by continuous intravenous infusion on days 2 to 4 every 3 weeks (Figure 3). After 4 cycles, the patient was reluctant to continue the chemotherapy.



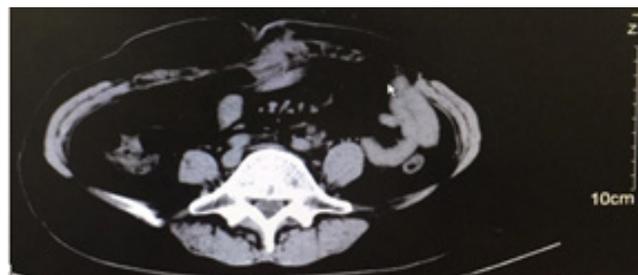
**Figure 3: Abdominal CT section, 40 × 35 mm, local tumor recurrence in 2018 (Kim HS, et al., 2014)**

High-Intensity Focused Ultrasound (HIFU) continues to receive increased attention as a therapeutic tool in the treatment of cancer and other tissue abnormalities. She received HIFU, but the tumor continued to grow. Radiotherapy was performed with a total dose of 45 Gy

plus Anlotinib and the tumor shrank remarkably in November 2018.

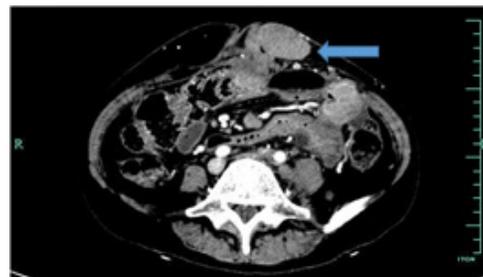
A month after radiotherapy, she developed severe intestinal obstruction and had to stop treatment. A physical examination revealed a hard right abdominal mass, and a subsequent CT scan detected a large abdominal tumor, which was suspected to be a clear cell carcinoma in May 2019. The patient underwent abdominal wall tumor resection once again and she continued to take the targeted drug Anlotinib orally. The goal of surgery has to be to achieve complete excision of the tumor with wide (negative) margins (>=2 cm) using frozen section pathology analysis during surgery. Abdominal wall reconstruction was successfully carried out by placing a double-layer synthetic mesh (Vicryl) in a tension-free manner, and the skin was closed over it.

Even though the patient continued with treatment, the tumor recurred at the left surgical site and the tumor size increased (Figure 4). She underwent a third operation.



**Figure 4: Abdominal CT section, after third operation in 2019 (Horton JD, et al., 2008)**

She got a fever; temperature reached highest values of 39. She was admitted to the hospital with a diagnosis of adhesive intestinal obstruction in November 2019. CT scan showed a hypermetabolic abdominal wall mass (60 × 50 mm), non-hypermetabolic enlarged right pelvic lymph node with no evidence of distant metastases (Figure 5).



**Figure 5: Abdominal CT section, 60 × 50 mm, local tumor recurrence in 2019 (Hitti IF, et al., 1990)**

Since the patient was rapidly deteriorating palliative care was given. She was admitted to hospital and surgically treated but died of adhesive intestinal obstruction 22 months after the clear cell carcinoma diagnosis.

## DISCUSSION

In 1925, Sampson described the first case of malignant transformation of ovarian endometriosis, and defined three criteria for the diagnosis of malignant transformation of endometriosis:

- (1) Demonstration of both neoplastic tissue and endometriosis within the tumor,
- (2) Histological appearance resembling endometrial stroma surrounding characteristic glands, and
- (3) No other primary tumor site (Sampson JA, 1925).

However, a mass in the scar tissue with symptoms of cyclic pain syn-

chronously with menses and a positive history of cesarean section may be nearly pathognomonic. Patient in this study met Sampson's criteria. Dissemination of endometrial tissue during a cesarean section or uterine surgery is biologically plausible because of the opportunity to inoculate the abdominal wall with endometrial cells from a hysterotomy (Horton JD, *et al.*, 2008; Ecker AM, *et al.*, 2014; Zhang P, *et al.*, 2019). As shown in *Table 1*, the histological characteristics of malignant transformation in endometriosis of the abdominal wall are primarily represented by clear cell carcinoma. Thirty-five cases of abdominal wall clear cell carcinoma have been recorded from 1986 to 2019 *table 1*. In all cases, patients underwent a cesarean section. Abdominal wall endometriosis describes the involvement of ectopic endometrial tissues

superficial to the peritoneum of the abdominal wall, including lesions secondary to a surgical incision and spontaneous lesions (Ecker AM, *et al.*, 2014; Zhang P, *et al.*, 2019; Taburiaux L, *et al.*, 2014). The use of a tissue retrieval bag might help to prevent endometriosis implants.

In the case series (*Table 1*), the average age was 46.8 years (range37-60). The interval from cesarean section to the onset of abdominal wall endometriosis was 16.1 years (range1-37). The median duration of lower abdominal pain lasted for 10 years since cesarean section, and abdominal endometriosis may have already developed during that period. These patients, with surgical birth history (cesarean section) and pelvic endometriosis diagnosed for over 10 years, presented with progressive abdominal pain.

**Table 1: Summary of studies included in the review**

Reference	Year Reported	Patient age, Y	Tumor Pathology	Previous Gynecological Surgery	Delay, Y	Coexisting Endometriosis	Tumor Size, cm	Treatment	Patient Outcomes	Months
Schnieber Agner-Kolb (Schnieber D, Wagner-Kolb D, 1986)	1986	40	ccc	1CS	15	NA	NA	Surgery+RT+progestins	DOD	18
Hitti (Hitti IF, <i>et al.</i> , 1990)	1990	46	ccc	2CS	14	NA	6	Surgery+RT	NED	30
Miller (Miller DM, <i>et al.</i> , 1998)	1998	38	ccc+Margins: close	1h+1a+1CS	8	yes	4	Surgery+-CIS-based CT+RT	NED	60
Park (Park SW, <i>et al.</i> , 1999)	1999	56	ccc	2CS	24	NA	5	Surgery+RT	NA	NA
Ishida (Ishida GM, <i>et al.</i> , 2003)	2003	56	ccc	2CS	22	yes	10	Surgery+-CIS-based CT	DOD	24
Sergent (Sergent F, <i>et al.</i> , 2006)	2006	45	Ccc+Margins: 1 cm free	2CS+2excision of nodules	25	yes	20	Surgery	DOD	6
Alberto (Alberto VO, <i>et al.</i> , 2006)	2006	38	ccc	1CS+BSO	11	yes	6	Surgery+Carbo/Ptx CT+RT	NA	NA
Razzouk (Razzouk K, <i>et al.</i> , 2007)	2007	46	ccc+LN: 1 positive	2CS+2 excision of nodules	26	NA	>20	GnRh analogue without benefit+Surgery+Carbo/Ptx CT(benefit)	DOD	6
Rust (Rust MM, <i>et al.</i> , 2008)	2008	42	Ccc+Margins: 1 mm free	3CS	5	yes	5	Surgery	NA	NA
Bats (Bats AS, <i>et al.</i> , 2008)	2008	38	Ccc+Margins: 2 mm free	1CS+1 excision of nodules	13	NA	10	NACT (carbo/PTX) No benefit+Surgery	NED	4
Williams (Williams C, <i>et al.</i> , 2009)	2009	53	Ccc+Inguinal LN: 7 positive/11 Pelvic LN: 8 positive/14	1CS	17	yes	25	Surgery+CT(-Carbo/PTX*4)	DOD	11
Bourdel (Bourdel N, <i>et al.</i> , 2010)	2010	43	Ccc+Pelvic LN: Multiple positive	2CS+1 excision of nodules	20	yes	NA	Surgery+CT(-Carbo/PTX*4)+RT	DOD	22
Yan (Yan Y, <i>et al.</i> , 2011)	2011	41	ccc	2CS+2 excision of nodules	5	yes	9	Progestins without benefit +Surgery+CT	NED	24
Li (Li X, <i>et al.</i> , 2012)	2012	49	ccc	1CS	26	yes	9	Surgery+CT(-Carbo/PT*6)	NED	8

Mert (Mert I, <i>et al.</i> , 2012)	2012	42	Ccc+Margins: Free	Tubal ligation, right ovariectomy	NA	NA	15	Surgery	NED	1	
		51	Ccc+Margins: Free	2CS	1	yes	6	Surgery	NED	31	
Shalin (Shalin SC, <i>et al.</i> , 2012)	2012	47	Ccc+ Pelvic LN: 2 positive/4 margins: Positive	1CS	10	yes	3	Surgery+- CIS-based CT*6+RT	NED	7	
Ijichi (Ijichi S, <i>et al.</i> , 2014)	2014	60	Ccc+ Margins: free	2CS	37	yes	4	Surgery	NED	23	
Heller (Heller DS, <i>et al.</i> , 2015)	2014	37	Ccc+LFN: Multiple LN positive	3CS	8	yes	18	Surgery	NED	5	
Aust (Aust S, <i>et al.</i> , 2015)	2015	47	Ccc+LN: 2 positive/48 Margins: free	1CS	16	yes	10	Surgery+CT(-Carbo/PTX)	NED	10	
Liu (Liu H, <i>et al.</i> , 2015)	2014	39	Ccc+Bladder: Positive	1CS+excision of nodules	5	yes	6	Surgery+CT(-Carbo/PTX*3)	DOD	12	
			Pelvic LN: 18 positive/21 Aortic LN: 6 positive /6 Inguinal LN: 8 positive/8								
Ferrandina, G (Ferrandina G, <i>et al.</i> , 2016)	2016	44	Ccc+Pelvic LN: 7 positive/14 Inguinal LN: 8 positive/11 Margins: free	1 CS	9	No	10.5×5.0×5.0	Surgery+CT(pegylated liposomal doxorubicin)	DOD	1	
Sosa (Sosa-Durán EE, <i>et al.</i> , 2016) Duran, E. E	2016	45	Ccc+negative margins	3CS	17	yes	11×8.0×8.0	Surgery+CT(-carboplatin plus paclitaxel)	NED	36	
Graur,F (Graur F, <i>et al.</i> , 2017)	2017	43	Ccc+ negative margins	1CS	22	yes	8×5	Surgery*2	NED	6	
Marques,C (Marques C, <i>et al.</i> , 2015)	2017	47	Ccc+negative margins	3CS	17	yes	11×8×8	Surgery*2+CT(-carboplatin plus paclitaxel)	NED	36	
Gentile JKA (Gentile JKA, <i>et al.</i> , 2018)	2018	42	Ccc+external iliac chain lymph node (1/8)	1CS	8	yes	10.6×4.7	Surgery	NED	8	
Shozo Yoshida (Yoshida S, <i>et al.</i> , 2018)	2018	53	Ccc+lymph node (8/61)	1CS	15	no	11.5×9.5	gemcitabine and carboplatin	NED	20	
Yen-Ling Lai (Lai YL, <i>et al.</i> , 2019)	2019	52	Ccc+negative margins	1CS+positive LN	19	NA	17.5	Surgery	Rucurrence	10	
	2019	56	Ccc+negative margins	1CS+1positive LN	33	NA	6.5	Surgery+CT(-carboplatin plus paclitaxel)	NED	3	
	2019	52	Ccc+negative margins	LSC	4	NA	7	Surgery+CT(-carboplatin plus paclitaxel)	NED	93	
	2019	56	Ccc+negative margins	1CS	21	NA	12	Surgery+CT(-carboplatin plus paclitaxel)	NED	5	
	2019	55	Ccc+positive margins	1CS+positive LN	24	NA	12.5	Surgery+CT(-carboplatin +paclitaxel)+bevacizumab	DOD	23	
	2019	45	ccc	1CS	20	NA	4.8	CT(carboplatin + paclitaxel*7+liposomal doxorubicin +carboplatin*1)+3DRT	Progression	7	

Tetsushi Tsuruga (Tsuruga T, <i>et al.</i> , 2019) present case	2019	49	ccc+negative margins	1LCS	15	yes	4	Surgery+CT(-carboplatin and paclitaxel)	NED	NA
	current	43	ccc+positive margins+positive LN	1CS	16	yes	6*5	Surgery+CT(-carboplatin +paclitaxel)+RT+Anlotinib	DOD	25

Note: NED: No Evidence of Disease; DOD: Died Of Disease; CCC: Clear Cell Carcinoma; CS: Cesarean Section; LCS: Laparoscopic Cesarean Section; CT: Chemotherapy; HT: Hormone Therapy; RT: Radiotherapy; NED: No Evidence Of Disease; DOD: Died Of Disease; NA: Not Available; 1h: Hysterotomy; 1a: Abortion; Carbo: Carboplatin, CIS: Cisplatin; PTX: Paclitaxel.

The large number of patients (72%) with the occurrence of symptoms, the advancement of tumors in our patients, metastases to lymph nodes, and one positive margin are probably connected with their short survival period. Patients with positive tumor margins and lymph nodes after tumor resection could be used as independent adverse prognostic factors.

In the present study, univariate analysis suggested that patients with tumors larger than 5 cm had a shorter survival time when compared with patients that had tumors smaller than 5 cm.

On the other hand, some cases were reported to experience relatively longer disease-free and overall survival (longer than 30 months) (Hitti IF, *et al.*, 1990; Miller DM, *et al.*, 1998; Mert I, *et al.*, 2012; Sosa-Durán EE, *et al.*, 2016; Marques C, *et al.*, 2017; Lai YL, *et al.*, 2019); while recognizing that a more thorough molecular characterization could hopefully help define prognosis of this very rare condition, it has to be acknowledged that cases with better outcome presented with masses ranging between 4 and 9 cm, thus suggesting that a prompt recognition and treatment could make the difference.

In our case, abdominal CT can show a mass lesion involving the abdominal wall, a dilated small bowel loop with hyper enhancing and thickened wall, the involvement of the surrounding tissue. It is extremely difficult to detect early because of its deep location and lack of obvious clinical signs in its early stages. All patients underwent standardized preoperative assessment: Routine blood tests and tumor markers CEA and CA19-9 determination, abdominal UltraSound (US), Computed assisted Tomography (CT) scan, and when needed, Magnetic Resonance Imaging or Positron Emission Tomography (PET-CT). An abdominal CT scan revealed thickening of the abdominal wall and enlargement of the abdominal lymph nodes, but no evidence of distant metastasis in 2019.

Many epidemiologic studies supported a link between endometriosis and invasive epithelial ovarian cancer based on high prevalence and incidence of epithelial ovarian cancer and endometriosis. Unlike epithelial cells, endometriotic stromal cells are mutation free but contain widespread epigenetic defects that alter gene expression and induce a progesterone-resistant and intensely inflammatory environment, driven by estrogen via estrogen receptor-beta. The resulting increased estrogenic action in the stroma drives inflammation and sends paracrine signals to neighboring epithelial cells to enhance proliferation. Clear cell carcinoma of the endometrium is a rare type of endometrial cancer generally associated with an aggressive clinical behavior.

They are generally indolent, present in stage I (tumor confined to the ovary) and are characterized by specific mutations, including KRAS, BRAF, ERBB2, CTNNB1, PTEN PIK3CA, ARID1A, and PPP1A, which target specific cell signaling pathways. Due to the extremely low incidence of clear cell carcinoma, it is unlikely that randomized clinical trials can be feasible to establish the standard treatment of this disease. Even though an additional abdominal wall tumor resection was performed after 1.5 year from the initial operation, there are still remaining local tumor lesions and they are gradually enlarging in

size on a serial follow up CT. She received chemotherapy, including platinum-based regimens as adjuvant therapy, or at the time of disease progression (Table 1).The patient underwent four courses of tri-weekly chemotherapy with carboplatin and paclitaxel.

**CONCLUSION**

In our case, the clear cell carcinoma showed a very aggressive behavior with rapid local recurrence from which the patient survived only 24 months after diagnosis. We present a case of clear cell carcinoma directly arising from scar endometriosis after a cesarean section and review all 35 cases reported. The treating physician should keep in mind abdominal wall endometriosis as a possible cause of post cesarean section scar-related masses. Treatment of cancer patients with conventional therapies (chemotherapy, hormonal therapy, and radiation and Targeted therapy) respond initially well and experience prolonged tumor-free survival. After targeted therapy and radiotherapy, the tumor appeared to shrink significantly. Better understanding of the molecular mechanisms of tumor angiogenesis, especially in clear cell carcinoma, has led to the development of multiple targeted therapies to inhibit key effectors: Vascular Endothelial Growth Factor (VEGF), VEGF receptor.

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**AUTHORS' CONTRIBUTIONS**

JJ Zhai is involved in the management of the patient and wrote the case report. CH Chen was instrumental in imaging characterization. RB Ying was instrumental in imaging characterization.

HY Feng participated in the management of the patient and was instrumental in manuscript writing. All authors read and agreed to the final manuscript.

**CONSENT FOR PUBLICATION**

We have obtained consent to publish from the permissible relative (husband) of the patient since she passed away before the manuscript planning and writing.

**ETHICS APPROVAL AND CONSENT TO PARTICIPATE**

According to our institutional ethical committee, no explicit protocol is required for a retrospective collection of data.

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