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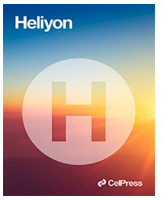

Primary versus secondary cutaneous endometriosis: Literature review and case study☆

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ABSTRACT

Cutaneous endometriosis, characterized by the presence of endometrium or endometrial-like tissue outside of the uterine cavity, is an uncommon and chronic disease. Depending on a patient's history, cutaneous endometriosis is classified as either primary cutaneous endometriosis (PCE) or secondary cutaneous endometriosis (SCE). We report a case of SCE presenting with the classic triad of previous caesarean section, subcutaneous nodules at the site of the scar, and pain associated with menstruation. Considering histopathology as the standard, we confirmed a diagnosis of cutaneous endometriosis by ultrasound and histopathology. Furthermore, we compared and analyzed the clinical characteristics of PCE and SCE, the study included 20 and 14 patients with cutaneous endometriosis diagnosed with PCE and SCE respectively. In the PCE group, the mean age of patients at the onset was 33.7 years, while it was 40.6 years in the SCE group. The mean disease-duration time of PCE was shorter than that of SCE (1.3 vs. 2.8 years, $P > 0.05$). The most common clinical presentation of PCE and SCE was a nodule (90% vs. 86%). The PCE was mainly bleeding with pain (45%), whereas the SCE of only pain and bleeding with pain accounted for the same proportion (45%). The most common sites of PCE and SCE were in the umbilical region (90% vs. 57%, $P < 0.05$). In our study, some statistically significant difference was found between different types of CE and it may contribute to improve clinicians' understanding of the disease, and perform early diagnosis and treatment.

1. Introduction

Endometriosis was first described by Rokitansky almost 150 years ago. It refers to the presence of endometrial tissue outside of the uterine cavity. It affects 6 to 10% of women of reproductive age and associated with complaints of pelvic pain and infertility. Cutaneous endometriosis (CE), a form of endometriosis located in the skin, is a rare entity [1]. According to its origin, it is divided into primary cutaneous endometriosis (PCE) and secondary cutaneous endometriosis (SCE) [2].

CE is so rare in dermatology that dermatologists fail to diagnose and treat it in a timely manner, delaying the diagnosis and treatment of patients. Furthermore, although great discrepancies exist in PCE and SCE clinical features and prognoses, no clinical study focusing on the characteristics of the two. Therefore, we delineated one SCE case and review 34 cases that were performed on PubMed

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case reports of CE in the past 10 years, including 20 PCE and 14 SCE cases. The objective of this study is to evaluate the clinical and epidemiological characteristics of patients with PCE and SCE.

2. Methods

Our search terms include cutaneous, comparison, Endometriosis, PCE and SCE. We included studies that met the following inclusion criteria: (1)The case includes the patient's complete clinical data; (2)The author categorizes CE explicitly. No language or geographic restrictions were imposed. Two of us (Q.-F.H and J.B) independently screened the search results and assessed eligibility by reading the patient data. We checked the full text of eligible literatures and included literatures that met the inclusion criteria. Disagreement was resolved by consulting another one of us (X.-P.H.). We delineated one SCE case and review 34 cases that were performed on PubMed case reports of CE in the past 10 years, including 20 PCE and 14 SCE cases.

Characteristic information including age, gynecological history, previous history, disease duration, lesion, the site of the lesion, symptom, cyclicity, treatment, recurrence was obtained from literature. Statistical analyses were conducted using SPSS (version 26.00) and Microsoft Excel 2019 (Microsoft Corporation, Redmond, WA, USA) software. Categorical data were expressed as numbers and percentages in the obtained data. Chi-square test was used for the comparison of the data obtained by counting.Continuous variables were expressed as mean ± standard deviation (SD) or median (range). Differences between samples following non-normal distributions were tested using the Mann–Whitney *U* test. Differences between paired samples were tested using the Wilcoxon test. Independent *t*-test was used for the data following normal distribution. Statistical significance was set as $P < 0.05$.

3. Case report

A 39-year-old female patient presented with a history of a subcutaneous mass in the lower-left abdominal region to our dermatology department. The occupation of patient was recorded as teacher in Southwest China. The subcutaneous mass, without erosion or ulcers, was a caesarean scar mass under the skin. She complained that the lump was accompanied by a slight pain, and that the pain worsened around the time of menstruation. The patient had a history of chronic urticaria, which was relieved by the occasional use of loratadine. She underwent a cesarean section eight years ago, and we observed a linear scar in her lower-left abdominal region. In addition, she underwent myomectomy to remove a myoma six months ago. She denied a history of dysmenorrhea and abortion. Upon physical examination, she had no obvious abnormalities in the heart, lungs, or abdomen, and no palpable swelling of the superficial lymph nodes. She presented with a subcutaneous nodule of approximately 1 cm diameter under the hypogastrium, and she frequently experienced painful menstruation. The surface of the nodule was normal, and there was no ulceration or bleeding (Fig. 1). Ultrasonography showed a hybrid echo-mass about 1.1 × 1.0 cm, with an irregular shape, a well-defined border, and 3 mm from the body surface in the subcutaneous soft tissue (Fig. 2). Based on the patient's history of cesarean section, nodule under the scar and cyclical pain, secondary cutaneous endometriosis was initially considered. A mass of about 1 cm diameter, surrounded by a 1 cm wide margin of normal tissue, underwent resection and was sent for histopathological examination. Histopathology with hematoxylin-eosin confirmed the diagnosis of CE (Fig. 3) and histopathology of the nodule revealed endometrial glands, consisting of a single layer of monomorphous cuboidal cells, with an endometrial stroma (Figs. 4 and 5). The patient recovered well after the operation, and no pain occurred in the follow-up.

4. Results

A comparison of the clinical features of PCE and SCE in the 34 cases reviewed are summarized in Table 1, including 20 PCE and 14 SCE. And Detailed clinical data of the patients as in Table 2 and Table 3. Patients classified as PCE had a higher mean age of onset than those classified as SCE (33.7 vs. 40.6 years, $P > 0.05$). The mean disease-duration time of PCE was shorter than that of SCE; however, there was no significant difference between them (1.3 vs. 2.8 years, $P > 0.05$). The most common clinical presentation of PCE and SCE

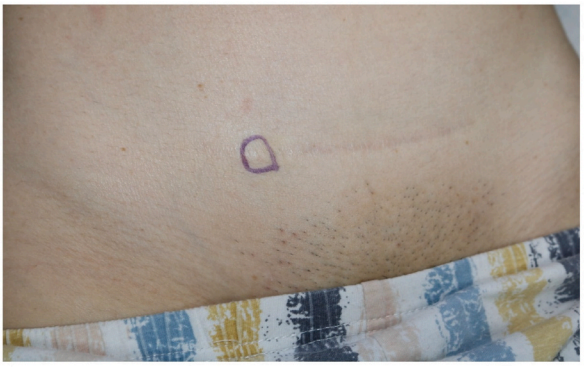

Fig. 1. Showing subcutaneous mass observed during pre-operation.

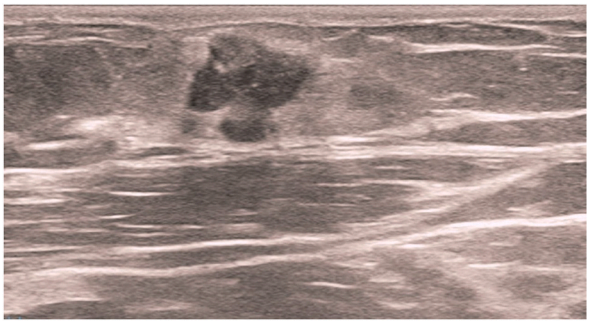

Fig. 2. Ultrasonic image.

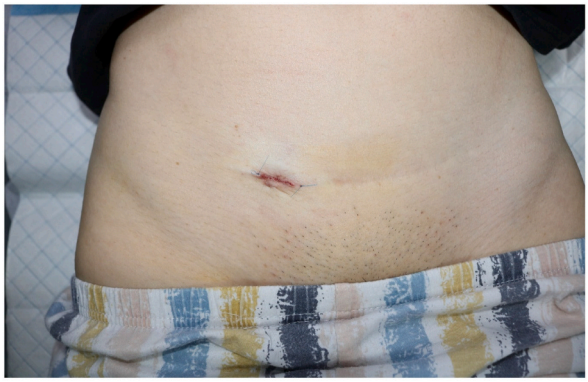

Fig. 3. Postoperative wounds.

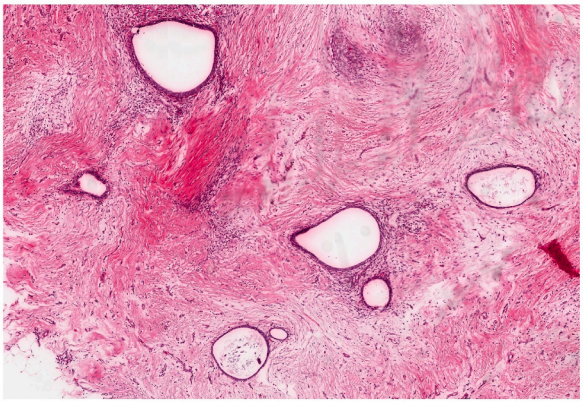

Fig. 4. Hematoxylin-eosin staining × 40.

was a nodule, and both had bleeding and pain. The PCE was mainly bleeding with pain (45%), whereas the SCE of only pain and bleeding with pain accounted for the same proportion (45%). There were significant differences in the distribution of lesions between the two groups, but the most common sites of PCE and SCE were in the umbilical region (90% vs. 57%, $P < 0.05$). Only one case of CE occurred in the upper arm, left iliac region, and groin, respectively. In this case, the lesion was also located in the umbilical cord.

5. Discussion

Endometriosis is a chronic and benign disease characterized by the presence of endometrium or endometrial-like tissue outside of the uterine cavity, and endometrial implants located in the abdominal wall are referred to as CE, a rare, hormone-dependent disease, which is divided into PCE and SCE. Of note, SCE is also called “iatrogenic endometriosis” because it is mainly associated with previous surgery, most commonly cesarean section [2].

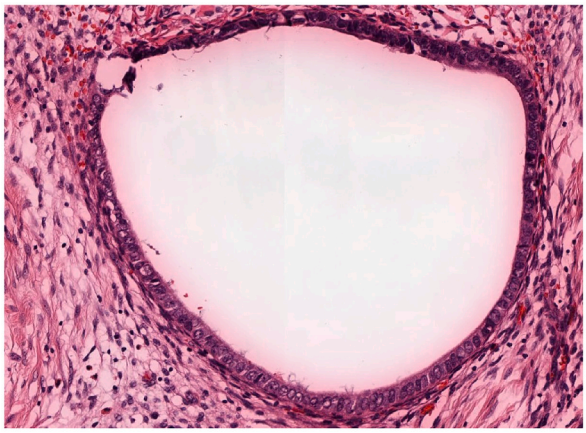

Fig. 5. Hematoxylin-eosin staining × 200.

Table 1
Clinical features of PCE and SCE.

Table 1 Clinical features of PCE and SCE

	Primary cutaneous endometriosis	Secondary cutaneous endometriosis	P value
Patients, n (%)	20（58.8）	14（41.2）	
Previous abdominal surgery, n (%)	0	14（100）*	
Age (year), mean ± SD	33.7 ± 8.4	40.6 ± 11	P>0.05
Disease duration (year), mean ± SD	1.3 ± 1	2.2 ± 2.8	P>0.05
Lesion			
Nodule, n (%)	18（90）	12（86）	P>0.05
Papule, n (%)	2（10）	1（7）	
Fistula, n (%)	0	1（7）	
Symptom			
No symptom, n (%)	3（15）	3（21）	
Only bleeding, n (%)	1（5）	3（21）	P>0.05
Only pain, n (%)	7（35）	4（29）	
Bleeding and pain, n (%)	9（45）	4（29）	
Cyclicity			
Yes, n (%)	12（60）	10（71.4）	P>0.05
No, n (%)	8（40）	4（28.6）	
The site of the lesion			
Umbilical region, n (%)	18（90）	8（57）	
Hypogastrium（excluding umbilical region ）, n (%)	0	5（36）	P<0.05
Groin, n (%)	1（5）	0	
The upper arm, n (%)	1（5）	0	
Left iliac region, n (%)	0	1（7）	

*Previous abdominal surgery：hysterectomy、cesarean section、laparoscopic salpingectomy

CE is a rare entity, and reported prevalence rates of associated PCE range from 0.5% to 1%. SCE occurs in 3.5% of patients who undergo gynecologic surgery, is extremely rare, and accounts for 0.03%–0.15% of all endometriosis cases [3]. The exact etiology and pathogenesis of CE remain unclear, but endometriosis is associated with autoimmune diseases, including systemic lupus erythematosus, Sjogren's syndrome, ulcerative colitis, etc. Cellular immunity and humoral immunity are closely linked. Studies have shown that patients with endometriosis have decreased cell-mediated immunity and increased humoral immune response [4]. And CE may be related to three hypotheses. The most widely accepted is the "classical migration" or "retrograde menstruation" hypothesis, that is, due to the menstrual blood reflux or implantation of endometrial cells during cesarean section and other gynecological operations of target organs. The second and third theories termed "induction" or "coelomic metaplasia" and "retrograde lymphatic flow," are also considered to be involved in the pathogenesis of CE [5]. The first hypothesis was obviously verified by SCE. All patients with SCE had a history of surgery (14 patients, 100%), that is to say, endometrial cells transplanted into the skin at the time of surgery caused SCE [3]. CE often occurs in women of reproductive age [1], and the mean age of onset was 35.4 ± 2.33 years [6]. There was no difference in the mean age between PCE and SCE (Table 1). The PCE and SCE are both located in the umbilical region. Earlier studies suggested that the cause for umbilical region as a prevalent location in PCE was umbilicus acts as a physiological scar with a predilection for endometrial tissue [7]. Because endometrial cells are transplanted during the operation, caesarean section scars are one of the most frequent locations in SCE [1].

Table 2
Clinical datas of PCE.

Cases Study	Age (year)	Gynecological history	Previous history	Disease duration (year)	Lesion	The site of the lesion	Symptom	Cyclicity	Treatment	Recurrence
Wan et al. [17]	29	N/A	N/A	1.0	Nodule	Umbilical region	Only pain	Yes	Surgical operation	N/A
Bittar et al. [18]	20	N/A	N/A	1.0	Nodule	Umbilical region	Bleeding and pain	Yes	Surgical operation	No
Batista et al. [2]	24	N/A	N/A	2.0	Nodule	Umbilical region	Only pain	No	Contraceptive	No
Brown et al. [19]	26	Hypermenorrhea dysmenorrhea	N/A	3.0	Papule	Umbilical region	Bleeding and pain	Yes	Leuprolide	No
Alibrahim et al. [20]	40	Abortion	N/A	3.0	Nodule	Umbilical region	Bleeding and pain	Yes	Surgical operation	N/A
Loh et al. [21]	38	N/A	N/A	2.0	Nodule	Umbilical region	Bleeding and pain	Yes	Surgical operation	No
Gin et al. [22]	31	Dysmenorrhea	N/A	0.1	Papule	Umbilical region	Bleeding and pain	No	Surgical operation	N/A
Hansadah et al. [5]	24	Abnormal uterine bleeding	Pelvic endometriosis	2.0	Nodule	Umbilical region	Bleeding and pain	Yes	Surgical operation	N/A
Mohaghegh et al. [23]	37	N/A	Ovarian endometriosis	1.5	Nodule	Umbilical region	No	No	Surgical operation	N/A
Chamli et al. [24]	33	Dysmenorrhea	N/A	3.0	Nodule	Umbilical region	No	No	N/A	N/A
Genovese et al. [25]	42	Dysmenorrhea infertility	Pelvic endometriosis	0.1	Nodule	Umbilical region	Only pain	No	Surgical operation	No
Chen et al. [26]	40	N/A	Hernia	0.3	Nodule	Groin	No	No	Surgical operation	No
Pandey et al. [27]	32	N/A	N/A	0.5	Nodule	The upper arm	Only pain	No	Surgical operation	No
Pourang et al. [28]	34	Infertility	N/A	0.3	Nodule	Umbilical region	Only bleeding	No	Surgical operation	N/A
Buljan et al. [29]	51	N/A	N/A	0.3	Nodule	Umbilical region	Only pain	Yes	Surgical operation	N/A
Van den Nouland et al. [30]	44	Oral contraceptive	N/A	1.0	Nodule	Umbilical region	Bleeding and pain	Yes	Surgical operation	N/A
Jamani et al. [31]	47	Dysmenorrhea	N/A	1.0	Nodule	Umbilical region	Bleeding and pain	Yes	Surgical operation	N/A
Pramanik et al. [32]	33	Infertility	N/A	0.7	Nodule	Umbilical region	Bleeding and pain	Yes	Surgical operation	No
Ojong et al. [33]	23	N/A	N/A	2.0	Nodule	Umbilical region	Only pain	Yes	N/A	N/A
Kourouma et al. [34]	26	N/A	N/A	0.8	Nodule	Umbilical region	Only pain	Yes	Surgical operation	N/A

N/A, Not Available.

Table 3
Clinical datas of SCE.

Cases Study	Age (year)	Gynecological history	Previous history	Disease duration (year)	Lesion	The site of the lesion	Symptom	Cyclicity	Treatment	Recurrence
Gonzalez et al. [3]	39	N/A	Cesarean section	1.5	Nodule	Hypogastrium	Only pain	Yes	Surgical operation	No
Raffi et al. [35]	41	Abortion	Laparoscopic salpingectomy	0.4	Nodule	Umbilical region	Only pain	Yes	Surgical operation	N/A
Amir et al. [36]	32	N/A	Cesarean section	3.0	Nodule	Hypogastrium	Bleeding and pain	Yes	Surgical operation	N/A
Din et al. [37]	41	Pelvic endometriosis	Hysterectomy	0.5	Papule	Umbilical region	Bleeding and pain	No	Surgical operation	No
Costa et al. [4]	38	N/A	Laparoscopic salpingectomy	1.0	Nodule	Umbilical region	Only pain	Yes	N/A	N/A
Marsden et al. [38]	33	N/A	Cesarean section	1.5	Nodule	Hypogastrium	No	No	Surgical operation	N/A
Tajima et al. [39]	70	Endometrial adenocarcinoma	Cesarean section	2.8	Nodule	Umbilical region	No	No	Chemotherapy	N/A
Jaime et al. [40]	32	N/A	Cesarean section	0.3	Nodule	Umbilical region	No	No	N/A	N/A
Lopes et al. [41]	34	N/A	Cesarean section	6.0	Nodule	Left iliac region	Only bleeding	Yes	Surgical operation	N/A
Tognetti et al. [42]	29	N/A	Cesarean section	0.8	Nodule	Hypogastrium	Only pain	Yes	N/A	N/A
Shalin et al. [43]	47	Clear cell adenocarcinoma	Cesarean section	0.8	Nodule	Umbilical region	Bleeding and pain	Yes	Radiotherapy	N/A
Juneja et al. [44]	36	N/A	Cesarean section	11.0	Fistula	Umbilical region	Bleeding and pain	Yes	Surgical operation	N/A
Obata et al. [45]	60	Clear cell adenocarcinoma	Hysterectomy	1.0	Nodule	Umbilical region	Only bleeding	Yes	Surgical operation	N/A
Kocher et al. [46]	37	N/A	Cesarean section	0.5	Nodule	Hypogastrium	Only bleeding	Yes	Surgical operation	N/A

N/A, Not Available.

The clinical manifestation of CE is painful nodules associated with the menstrual cycle, which become enlarged during the menstrual cycle and shrink after menstruation [8]. As shown in this case, SCE may present with the classic triad of prior abdominal surgery, nodules at the scar site, and periodic pain [1]. CE can also present as bleeding or pain alone, as shown in Table 1. When the clinical manifestations are atypical, as seen in 50% of cases, CE can be confused with nodular malignant melanoma, metastatic tumors, pyogenic granuloma, keloid, hernia and so on [8–10]. Effective ancillary tests are necessary for the early diagnosis of CE, including non-invasive and invasive techniques. Non-invasive examinations such as ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) are helpful for the diagnosis of cutaneous endometriosis. US can be used as the initial imaging modality for SCE, mainly manifesting as hypo-echoic or anechoic lesions, and peripheral blood vessels can be observed at the scar site [1]. In this case, US puncture was used, and a hybrid echo-mass was observed in this case. MRI, used to identify hemorrhagic signals and distinguish between muscle and abdominal subcutaneous tissue, is helpful to determine the depth of skin lesions and to perform a preoperative evaluation [3]. Dermoscopy, a non-invasive, economical and emerging imaging modality, has also been applied to CE gradually. Preoperative dermoscopy showed a brownish background, a structureless area, and small red globular structures corresponding to irregular endometrial glands [11]. Dermoscopy of SCE reveals a dendritic appearance in areas of scarring (branching) and papillary surfaces (frugiform). A previous study considered that dermoscopy could not be used as a tool for a definitive diagnosis of CE [11]. A diagnosis of CE is dependent on histopathology, in which malignancy can be ruled out. There were irregular, round, and elongated cystic cavities in the dermis, and the capsule wall was composed of tall columnar epithelial cells arranged in a linear manner, with basophilic cytoplasm and a spindle-shaped matrix [12].

This suggested that excision of the lesion is the primary therapy for CE. The patient in the present case received timely complete surgical resection. Other studies suggested that surgical resection after reduction of the lesion with oral hormones may be an option for larger masses [13]. Some patients can be given nonsteroidal anti-inflammatory drugs (NSAIDs) to relieve pain when they feel is unbearable. Furthermore, hormones can reduce the size of the lesion by inhibiting the periodic proliferation of endometrial tissue. Medicines for CE include danazol, gonadotropin-releasing hormone (GnRH) agonists, progestins and oral contraceptives [14]. Danazol, a synthetic derivative of 17-a-ethinyl testosterone, is thought to work via inhibiting follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secretion. Caution should be given to the side effects of danazol, such as weight gain, acne, hairiness, and deepening of the voice. GnRH agonists, including leuprolide, goserelin, nafarelin, reduce the levels of FSH and LH by down-regulating the receptors in the anterior pituitary gland, thereby lowering ovarian steroids. In comparison with methotrexate danazol, GnRH have a smaller side effects, but attention also needs to be paid to the adverse side effects of GnRH. For example, GnRH an cause declined bone density [13]. When combination of hormone and operative treatment is used, it improves the markedly effective rate and reduces the recurrence rate [15]. The case reported herein was that following the subcutaneous injection of GnRH agonist, the nodule was surgically resected [16]. Among the 2 previously reported cases with treatment of CE, the treatment options were radiotherapy or surgery, no recurrence was seen by 7 months after the oral danazolin one case, and the patients who received GnRH was also no relapse after follow-up 2 months in another case [16]. Currently, there are no definitive guidelines for the time of administration of hormone therapy. The literature is scarce and mainly based on case reports, further research is needed. Current documentation on CE is mostly in the form of case reports. At present, there is a lack of large sample studies on the CE. And CE can be easily confused with other malignant tumors, leading to misdiagnoses and delayed treatment. Furthermore, primary versus secondary CE were found to differ in the present study. PCE and SCE may have distinct genomic determinants, and this may warrant further investigation. Therefore, this study can reduce recurrence and improve survival.

6. Conclusion

CE is a rare, benign condition, and there is no literature summarizing and comparing the clinical characteristics of PCE and SCE at present. The findings of our reported case will be of help to clinicians, as they indicate that CE should be suspected in females of bearing age, presenting with a painful or bleeding lesion associated with menstruation. This is especially true if there has been a previous cesarean section or hysterectomy. In addition, necessary auxiliary inspections should be improved further, and we should give the patient oral hormones or perform surgical resection when the diagnosis is confirmed.

We searched the literature by the PubMed database of the past 10 years. And the study focused retrospectively on clinical characteristics of CE patients. Another intriguing finding in the present study is the difference between PCE and SCE. There have differences among the two groups regarding age, illness duration, symptom,and lesion site. This is a retrospective case study, with certain limitations in terms of the research deficiencies and prospects. In general, as retrospective study is not always performed faultlessly, the clinical data obtained need critical analysis. Notably, some patients with missing data have been screened out during information collection, leading to selection bias. Furthermore, the relative rarity of CE limited our selection of patients. In addition, patients could not be well documented because of incomplete medical data, resulting in the failure to fully analyze the recurrence rates and therapeutic effects.

Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article.

Data availability statement

Data included in article/supplementary material/referenced in article.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided her written informed consent to participate in this study.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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