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Mehmet Hakan Yetimalar[1], Derya Kilic[2], Seyran Yigit[3]

Uterine sarcomas: 7-year experience from a tertiary center

Mięsaki macicy: 7-letnie doświadczenie ośrodka o trzecim stopniu referencyjności

[1] Department of Obstetrics and Gynecology, Izmir Gozde Hospital, Izmir, Turkey
[2] Department of Obstetrics and Gynecology, Pamukkale University, Denizli, Turkey
[3] Department of Pathology, Izmir Katip Celebi University Ataturk Research and Trainig Hospital, Izmir, Turkey
Correspondence: Dr. Derya Kilic, Department of Obstetrics and Gynecology, Pamukkale University Medical School, Kinikli, Denizli, Turkey, tel.: +90 506 8654499, e-mail: deryakilic.md@gmail.com

Abstract

Uterine sarcomas are rare and aggressive gynecologic malignancies. Due to their rarity, histopathologic heterogeneity and molecular diversity, the optimal approach is still a matter of debate. Debulking surgery is still the mainstay of the treatment. But adjuvant treatment strategies remain controversial. In this study, we aimed to examine the clinical characteristics, histopathological features, tumoral behavior and recurrence patterns of patients diagnosed with uterine sarcoma at a tertiary referring center over a 7-year period. A total of 427 patients who were treated for uterine cancer between 2007 and 2014 were analyzed retrospectively. There were in total 20 patients diagnosed with uterine sarcoma. Median age of all patients diagnosed as uterine sarcomas was 50.5 years [interquartile range 11.5 (43.5–55)]. The median tumor size in these patients was 5.75 cm [interquartile range 4.38 (4.12–8.50)]. There were 5 patients with leiomyosarcomas, 10 patients with endometrial stromal sarcomas, 4 patients with undifferentiated uterine sarcomas and 1 patient with adenosarcoma. Despite our limited data, we presented our retrospective series over a period of 7 years. Prospective data and further insights are needed to better understand the tumor biology and improve treatment modalities.

Keywords: uterine sarcoma, leiomyosarcoma, carcinosarcoma, endometrial stromal sarcoma

Streszczenie

Mięsaki macicy to rzadkie i agresywne nowotwory kobiecego narządu rozrodczego. Z uwagi na rzadkość występowania, różnorodność histopatologiczną i zróżnicowanie molekularne tych nowotworów optymalny sposób leczenia pozostaje przedmiotem dyskusji. Podstawą leczenia w dalszym ciągu jest zabieg cytoredukcji, natomiast metody leczenia uzupełniającego nadal budzą kontrowersje. Celem pracy było dokonanie oceny cech klinicznych i histopatologicznych oraz zachowania się nowotworów i schematów ich nawracania u pacjentek leczonych w ośrodku o trzecim stopniu referencyjności w okresie obejmującym 7 lat. Analizą retrospektywną objęto łącznie 427 pacjentek leczonych z powodu raka macicy w latach 2007–2014. U 20 pacjentek rozpoznano mięsaka macicy. Mediana wieku wszystkich pacjentek z rozpoznaniem mięsaka macicy wynosiła 50,5 roku [przedział międzykwartylowy 11,5 (43,5–55)]. Mediana wielkości guza u tych pacjentek wynosiła 5,75 cm [przedział międzykwartylowy 4,38 (4,12–8,50)]. W badanej grupie opisano 5 przypadków mięsaka gładkokomórkowego, 10 mięsaka podścieliskowego, 4 niezróżnicowanego mięsaka macicy oraz 1 przypadek gruczolakomięsaka. Pomimo dysponowania ograniczonymi danymi autorzy przedstawili retrospektywny przegląd przypadków obejmujący okres 7 lat. W celu lepszego zrozumienia biologii nowotworów oraz poprawy skuteczności metod leczenia niezbędne są dane z badań prospektywnych i dalsze analizy.

Słowa kluczowe: mięsak macicy, mięsak gładkokomórkowy, mięsakorak, mięsak podścieliskowy

INTRODUCTION

Uterine sarcomas are rare gynecologic malignancies with a poor prognosis. They account for approximately 1% of gynecologic malignancies and 3–7% of uterine malignancies with an estimated 5-year survival rate of 40% for all stages[1,2]. Because of their rarity, it is hard to perform large prospective studies and there is scarce data that defines the risk factors, clinicopathological characteristics, prognostic factors, recurrence patterns and treatment options of uterine sarcomas.

Many systems have been proposed for the classification of these tumors[3,4]. The College of American Pathologists classifies uterine sarcomas mainly as leiomyosarcomas (LMS), endometrial stromal sarcomas (ESS), undifferentiated uterine sarcomas (USS) and adenosarcomas (AS)[4]. Historically, due to the biphasic morphology with a carcinoma and a sarcoma component, uterine carcinosarcomas were classified under the uterine sarcomas. From this perspective, they were termed as mixed mesodermal sarcomas. However, they are now classified as high-grade endometrial cancers. Supporting this, there is a current consensus of Cancer Genome Atlas Research Network regarding monoclonal evolution of carcinosarcomas originally from the epithelium via epithelial mesenchymal transition[5].

Due to the histopathologic heterogeneity and molecular diversity of sarcomas, the optimal treatment approach is still a matter of debate. Biological and molecular differences between the subsets of uterine sarcomas are evident and this may appear to affect their behavior. Debulking surgery is still the mainstay of treatment, but adjuvant treatment strategies remain controversial. The main problem is that a vast majority of these tumors relapse, even at early stages[6,7]. Chemotherapy and radiotherapy are not the standard of care for all these subsets in the adjuvant setting, particularly at early stages as the improvement of survival has not been well established[8,9]. Some features of these tumors are assumed as prognostic factors including mitotic count, grade, necrosis and stage, but there is no generalized prognostic algorithm for uterine sarcomas[10].

In this study, we aimed to assess clinical characteristics, histopathological features, tumoral behavior, recurrence patterns and survival outcomes of patients at a tertiary referring center during a 7-year period between 2007 and 2014 in order to contribute to the existing data.

MATERIALS AND METHODS

A retrospective study was designed and performed after Institutional Ethical Board clearance was obtained. The cohort was limited to patients who had histological diagnosis of sarcomas of the uterus. All patients were treated in a tertiary gynecologic oncology center between 2007 and 2014. Demographic data, age, systemic diseases, laboratory test results (tumor markers), tumor characteristics, surgical information, postoperative treatment data, recurrence pattern and survival outcomes were obtained from the hospital medical record system.

Age was grouped as <50 and ≥50 years. All patients underwent surgery with or without adjuvant treatment. Surgical procedures were classified into four categories as simple hysterectomy and bilateral salpingo-oophorectomy (TAH + BSO), TAH + BSO and pelvic lymphadenectomy, TAH + BSO and pelvic + para-aortic lymphadenectomy and debulking surgery with extensive metastasectomy. Standardized lymphadenectomy was performed according to the GOG surgical procedure recommendations in all patients who underwent surgical staging[11]. Patients without surgical treatment due to medical comorbidities and those who required neoadjuvant chemotherapy were excluded from the study.

Chemotherapy regimes were grouped as paclitaxel, carboplatin + paclitaxel, pegylated liposomal doxorubicin and other. Radiotherapy options were grouped as external beam radiotherapy (EBRT), vaginal brachytherapy (VBRT) and combination of these two.

All pathological specimens were evaluated at the same center. For tumor characteristics; subtype, mitotic count, necrosis, atypia, grade, stage, tumor size, lymph node metastasis, and stage were collected. Tumor size was classified into three groups: <5, 5–9.9 and 10 cm. Mitosis count was evaluated according to criteria of French Federation of Cancer Centres (FNCLCC) grading of soft tissue sarcomas[12].

Tumor stage was retrospectively determined on the basis of surgical and pathological findings using the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system for uterine cancers[11]. Adequate lymphadenectomy was defined as the GOG surgical procedure recommendations appropriate in the analyzed time period[13].

The recurrence pattern and the site of the recurrence were also analyzed.

The time during and after primary treatment with no clinical or imaging signs of relapse or progression was defined as progression-free survival (PFS) and the time from the date of diagnosis to the date of the last follow-up was defined as overall survival (OS). The data on the follow-up period was also collected and analyzed.

Statistical analyses

Statistical analyses were performed using the SPSS software package, version 21 (Computing Resource Centre, Santa Monica, California, USA). Descriptive statistics were used to report patient demographics. Demographic and clinical data were presented with contingency tables.

RESULTS

A total of 427 patients who were treated for uterine cancer between 2007 and 2014 were analyzed retrospectively. According to the inclusion criteria defined in Materials and Methods section, 20 patients diagnosed with uterine sarcoma were eligible for our analyses.

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	LMS (*n* = 5)	ESS (*n* = 10)	USS (*n* = 4)	AS (*n* = 1)
Age [years]:				
• median	51.0	44.0	67.5	55
• <50	2 (40%)	7 (70%)	0 (0%)	0 (0%)
• ≥50	3 (60%)	3 (30%)	4 (100%)	1 (100%)
Menopausal status:				
• premenopausal	2 (40%)	6 (60%)	0 (0%)	0 (0%)
• postmenopausal	3 (60%)	4 (40%)	4 (100%)	1 (100%)
AS – adenosarcoma; **ESS** – endometrial stromal sarcoma; **LMS** – leiomyosarcoma; **USS** – undifferentiated stromal sarcoma.				

Tab. 1. The clinical presentation of uterine sarcoma groups

According to the histological subgroup evaluation, there were 5 patients diagnosed as leiomyosarcoma, 10 patients diagnosed as endometrial stromal sarcoma, and 5 patients in the other subgroup (1 patient with AS and 4 patients with undifferentiated uterine sarcoma). Diabetes and/or hypertension/metabolic syndrome were diagnosed in 4 patients. Among uterine sarcomas, 16 patients were assigned to stage 1, none of the cases to stage 2, 1 case to stage 3 and 3 cases to stage 4, according to the FIGO 2009 criteria.

Overall, the median age and tumor size of the patients is the uterine sarcoma group was 50.5 years [interquartile range 11.5 (43.5–55)] and 5.75 cm [interquartile range 4.38 (4.12–8.50)], respectively. All patients in the USS subgroup were postmenopausal. However, most of the cases in the ESS subgroup were premenopausal. The clinical characteristics of the sarcoma group are summarized in Tab. 1.

All patients in the uterine sarcoma group underwent surgery. Surgical findings, histopathological features and management data of the cases were evaluated separately and are presented individually in Tabs. 2–4.

Leiomyosarcomas

Five patients with LMS were managed. The treatment modalities and recurrence pattern of patients with LMS are represented in Tab. 2.

The median tumor diameter of leiomyosarcomas was 5.50 cm [interquartile range 2.75 (5.00–7.75)]. The maximum tumor size was 9.5 cm and the minimum tumor size was 5 cm. Two out of 5 patients underwent lymphadenectomy. Para-aortic lymphadenectomy was performed in 1 of these 2 patients. None of the patients had lymph node metastases and none of the patients presented with an extrauterine disease. The details of adjuvant treatment modalities and recurrence patterns are shown in Tab. 2.

One out of 5 patients had no recurrence during her follow-up period of 32 months. All other patients had recurrences, which were treated by surgery alone, surgery with chemotherapy and radiotherapy, chemotherapy alone and radiotherapy alone.

Endometrial stromal sarcomas

Ten patients with ESS were managed. Among these patients, 1 patient was diagnosed with high grade ESS and 9 patients were diagnosed with low grade ESS. The treatment modalities and recurrence pattern of the patients with ESS were summarized in Tab. 3.

The median tumor diameter was 4.25 cm [interquartile range 4.50 (3.00–7.50)]. Tumor size were analyzed in three groups: <5, 5–9.9 and 10 cm (Tab. 2). The maximum tumor size was 10 cm and the minimum tumor size was 1 cm. The median number of removed pelvic/para-aortic lymph nodes in 5 patients was 49 [interquartile ranged 11 (44–55)]. The details of adjuvant treatment modalities and recurrence patterns are shown in Tab. 3.

Among 10 patients, 3 patients were lost to follow-up. For the other patients, the mean follow-up period was 25.14 ± 16.42 months. One had experienced recurrence at 24 months of her follow-up, which was treated by surgery with chemoradiotherapy. All the other patients had no recurrences during their follow-up period.

Undifferentiated uterine sarcomas and adenosarcomas

Four patients with USS and 1 patient with AS were managed. The treatment modalities and recurrence patterns for the group are presented in Tab. 4.

The median tumor diameter in patients with USS was 7.00 cm [interquartile range 8.25 (6.25–14.5)]. The maximum tumor size was 17 cm and the minimum tumor size was 6 cm. The median number of removed pelvic lymph nodes was 23.50 [interquartile range 43 (8.75–51.75)] in 5 patients. Among these patients, pelvic/para-aortic

No.	Age	Tumor size	Mitosis count	Stage	Surgery	Adj. CT	Adj. RT	Recc.	Recc. site	DFS
1	48	5 cm	2	1A	TAH + BSO	+	VBRT	+	Inguinal LAP	40
2	54	6 cm	3	1B	TAH + BSO + pelvic/para-aortic LND	-	VBRT	+	Lung	26
3	53	5.5 cm	3	1A	TAH + BSO + pelvic LND	-	-	+	Vagina	12
4	46	9.5 cm	3	1B	TAH + BSO	-	VBRT + EBRT	-	-	-
5	51	5 cm	3	1B	TAH + BSO	+	-	+	Lung	26

Adj. CT – adjuvant chemotherapy; **Adj. RT** – adjuvant radiotherapy; **DFS** – disease-free survival; **EBRT** – external beam radiotherapy; **LAP** – lymphadenopathy; **Recc.** – recurrence; **Recc. site** – recurrence site; **TAH + BSO** – simple hysterectomy and bilateral salpingo-oophorectomy; **TAH + BSO + pelvic LND** – TAH + BSO and pelvic lymphadenectomy; **TAH + BSO + pelvic/para-aortic LND** – TAH + BSO and pelvic + para-aortic lymphadenectomy; **VBRT** – vaginal brachytherapy.

Tab. 2. Treatment modalities and recurrence patterns in patients with leiomyosarcoma

No.	Age	Tumor size	Grade	Stage	Surgery	Adj. CT	Adj. RT	Recc.	Recc. site	DFS	Follow-up time [months]
1	45	1 cm	Low-grade	1A	TAH + BSO						Lost to follow-up
2	61	5 cm	Low-grade	1A	TAH + BSO + pelvic/para-aortic LND	-	-	-			13
3	50	7 cm	3	1A	TAH + BSO + pelvic/para-aortic LND	-	-	-			48
4	52	4 cm	3	1B	TAH + BSO + pelvic/para-aortic LND	-	VBRT + EBRT	+	Abd.	24	29
5	45	4.5 cm	Low-grade	1A	TAH + BSO + pelvic/para-aortic LND	-	-	-		-	12
6	43	3 cm	Low-grade	1B	TAH + BSO		VBRT + EBRT		-		47
7	39	3 cm	Low-grade	1A	TAH + BSO	-	-	-			Lost to follow-up
8	33	10 cm	Low-grade	1A	TAH + BSO	-	VBRT + EBRT	-			11
9	42	9 cm	Low-grade	3B	Debulking	+ (Caelyx)	-	-			16
10	38	4 cm	Low-grade	3B	Debulking						Lost to follow-up

Abd. – abdominal; **Adj. CT** – adjuvant chemotherapy; **Adj. RT** – adjuvant radiotherapy; **DFS** – disease-free survival; **EBRT** – external beam radiotherapy; **Recc.** – recurrence; **Recc. site** – recurrence site; **TAH + BSO** – simple hysterectomy and bilateral salpingo-oophorectomy; **TAH + BSO + pelvic/para-aortic LND** – TAH + BSO and pelvic + para-aortic lymphadenectomy; **VBRT** – vaginal brachytherapy.

Tab. 3. Treatment modalities and recurrence patterns in patients with endometrial stromal sarcoma

metastasis was observed in 1 patient (20%) after total pelvic/para-aortic lymph node dissection. There was no lymph node metastasis in the patient with AS. Extrauterine tumor was observed in 2 (40%) patients. The details of adjuvant treatment modalities and recurrence pattern are shown in Tab. 4. Among 5 patients, 1 patient was lost to follow-up. All of the other patients had no recurrences during their follow-up period.

DISCUSSION

This was a retrospective study conducted in order to contribute to the existing data as these tumors are rare and obscure, although limited by a small sample size. Even early stage diseases tend to relapse and have a propensity to the distant metastasis[6,14,15]. Unfortunately, there is no effective preoperative diagnostic test for uterine sarcomas[15,16]. In addition, no pathognomonic features have been defined for imaging modalities[17].

There is a lack of evidence on prognostic factors and ideal treatment modalities. Surgery remains the mainstay of the treatment of uterine sarcomas, but there is a lack of data about optimal adjuvant interventions. Apart from the high grade endometrial cancers, total pelvic and/or paraaortic lymphadenectomy is not a part of surgical treatment in early stage disease unless suspicious lymphadenopathy exists[18]. It was documented in larger series that LMS is the most common type of uterine sarcomas. Patients with ESS tend to be younger than other groups, which is in concordance with the findings in our study.

Nusrath et al. presented 11 cases of uterine sarcomas treated in their tertiary care center during an 8-year period.

No.	Age	Tumor size	Hystologic type	Stage	Surgery	Adj. CT	Adj. RT	Recc.	Recc. site	Follow-up period [month]
1	75	7 cm	USS	1B	TAH + BSO + pelvic LND	-	-	-	-	18
2	77	6 cm	USS	1B	TAH + BSO + pelvic LND	-	VBRT + EBRT	-	-	24
3	55	7 cm	USS	3C	TAH + BSO + pelvic/para-aortic LND	+ (carbo-taxan)	VBRT + EBRT	-	-	10
4	60	17 cm	USS	4B	Debulking					Lost to follow-up
5	55	11 cm	AS	1B	TAH + BSO + pelvic LND	-	-	-	-	4

Adj. CT – adjuvant chemotherapy; **Adj. RT** – adjuvant radiotherapy; **AS** – adenosarcoma; **DFS** – disease-free survival; **EBRT** – external beam radiotherapy; **Recc.** – recurrence; **Recc. site** – recurrence site; **TAH + BSO** – simple hysterectomy and bilateral salpingo-oophorectomy; **TAH + BSO + pelvic LND** – TAH + BSO and pelvic lymphadenectomy; **TAH + BSO + pelvic/para-aortic LND** – TAH + BSO and pelvic + para-aortic lymphadenectomy; **USS** – undifferentiated stromal sarcoma; **VBRT** – vaginal brachytherapy.

Tab. 4. The treatment modality and recurrence pattern of patients with undifferentiated uterine sarcoma and adenosarcoma

Clinical presentation, histopathological and recurrence patterns were investigated in their article. Among their patients; 4 were ESS, 6 were LMS and 1 was AS. The median age of patients was 53 and 49 years in the ESS and LMS group, respectively. Similar to our study, all patients with LMS were stage 1 in their report. The majority of their study group had a recurrence in a very short time, almost a 1-year period. Although it is not statistically significant, they reported that patients with tumor less than 5 cm (stage 1A) had a better survival than those with tumor size of more than 5 cm (stage 1B), and the survival of patients who received adjuvant therapy did not differ significantly. Two patients with ESS were stage 1, and 2 patients with ESS were stage 4 and the patient with AS was stage 1 in their study group. Apart from our study there was no patient with USS[19].

Kyriazoglou et al. retrospectively analyzed patients treated for uterine sarcomas in their institution over a period of 17 years. In their data, there were 51 patients with LMS, 3 with high-grade ESS, and 5 with USS. In their study group, increased mitotic index was the only recognized independent significant prognostic factor in the multivariate analysis. Their study group was heterogeneous and no significant impact of adjuvant therapy could be drawn as a result, which is in line with other studies[20]. Further insights are needed for the adjuvant treatment of uterine sarcomas. There is also a lack of data for the ideal treatment modalities. European Organisation for Research and Treatment of Cancer (EORTC 55874) randomized control trial for early stage sarcoma, which aimed to compare radiation versus no further treatment, was remarkable at this point. In this study, no difference was found either in local control or survival outcomes[21]. A French sarcoma group evaluated the impact of additional adjuvant chemotherapy to radiotherapy (RT) or RT alone. The study was conducted in patients with completely surgically resected carcinosarcomas and uterine sarcomas and found moderate improvement in PFS rates, but no improvement in OS rates[22]. According to the guideline of the German Society for Gynecology and Obstetrics (Deutsche Gesellschaft für Gynäkologie und Geburtshilfe e. V., DGGG) and the Austrian Society of Gynecology and Obstetrics (Österreichische Gesellschaft für Gynäkologie und Geburtshilfe, OEGGG), RT should not be performed after complete resection of a stage I/II LMS[15].

The body of evidence concerning adjuvant computed tomography (CT) is also controversial. The result of a recent meta-analysis seeking for the effect of adjuvant CT in early stage LMS conducted on national cancer database was coherent with no survival improvement in comparison to observation/failed to prolong survival[23]. And even in advanced stages after cytoreductive surgery it is still a matter of debate whether treatment contributes to any improvement in survival or not[24,25]. National Comprehensive Cancer Network (NCCN) and ESMO guidelines recommend adjuvant CT for high risk patients with uterine sarcoma[6]. Hormonal therapy have been suggested to be efficacious in the treatment of ESS, but there is a lack of data regarding the optimal usage[26]. According to the guideline of DGGG and OEGGG, adjuvant CT should not be generally administered and it should depend on the presence of other risk factors[15].

It is also remarkable that the molecular patterns of these tumors are totally different[26,27]. In a large retrospective series including 419 patients with uterine sarcomas, the stage of disease was reported as the most important prognostic factor for all tumor types. The authors emphasized that there are determinant differences in survival between uterine sarcoma subtypes. Leiomyosarcomas and ESS can be divided into different groups[14]. Characterization of a molecular prognostic panel might be especially useful for guiding therapeutic interventions for these patients.

CONCLUSION

Uterine sarcomas are group of gynecologic malignancies which shows histopathologic and molecular diversity. This marked heterogeneity within uterine sarcoma subtypes warrants an individualized treatment approach. Most of the patients are diagnosed in early stages and surgery is in the cornerstone of the therapy. Optimal adjuvant therapy on the other hand is yet to be defined. Along with the accumulated data on management, centralization of treatment is crucial for an improvement in prognosis

Conflict of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1. Hosh M, Antar S, Nazzal A et al.: Uterine sarcoma: analysis of 13,089 cases based on surveillance, epidemiology, and end results database. Int J Gynecol Cancer 2016; 26: 1098–1104.
2. Noone AM, Howlader N, Krapcho M et al. (eds.): SEER Cancer Statistics Review, 1975–2015. National Cancer Institute, Bethesda, MD. Available from: https://seer.cancer.gov/csr/1975_2015/ [based on November 2017 SEER data submission, posted to the SEER web site, April 2018].
3. Lu Z, Chen J: [Introduction of WHO classification of tumours of female reproductive organs, fourth edition]. Zhonghua Bing Li Xue Za Zhi 2014; 43: 649–650.
4. Otis C, Ocampo A: Protocol for the Examination of Specimens from Patients with Sarcoma of the Uterus. College of American Pathologists, 2013. Available from: http://www.cap.org/apps/docs/committees/cancer/cancer_protocols/2013/UterineSarcomaProtocol_3000.pdf [cited: 29 April 2014].
5. Cherniack AD, Shen H, Walter V et al.; Cancer Genome Atlas Research Network: Integrated molecular characterization of uterine carcinosarcoma. Cancer Cell 2017; 31: 411–423.
6. ESMO/European Sarcoma Network Working Group: Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014; 25 Suppl 3: iii102–iii112.
7. Mancari R, Signorelli M, Gadducci A et al.: Adjuvant chemotherapy in stage I–II uterine leiomyosarcoma: a multicentric retrospective study of 140 patients. Gynecol Oncol 2014; 133: 531–536.

8. Gronchi A, Stacchiotti S, Verderio P et al.: Short, full-dose adjuvant chemotherapy (CT) in high-risk adult soft tissue sarcomas (STS): long-term follow-up of a randomized clinical trial from the Italian sarcoma group and the Spanish sarcoma group. Ann Oncol 2016; 27: 2283–2288.

9. Roque DR, Taylor KN, Palisoul M et al.: Gemcitabine and docetaxel compared with observation, radiation, or other chemotherapy regimens as adjuvant treatment for stage I-to-IV uterine leiomyosarcoma. Int J Gynecol Cancer 2016; 26: 505–511.

10. Hanley KZ, Birdsong GG, Mosunjac MB: Recent developments in surgical pathology of the uterine corpus. Arch Pathol Lab Med 2017; 141: 528–541.

11. Kim HS, Song YS: International Federation of Gynecology and Obstetrics (FIGO) staging system revised: what should be considered critically for gynecologic cancer? J Gynecol Oncol 2009; 20: 135–136.

12. French Federation of Cancer Centers Sarcoma Group – Tumor Differentiation Score by Histologic Type. In: Fletcher CDM, Bridge JA, Hogendoorn PCW et al. (eds.): WHO Classification of Tumours of Soft Tissue and Bone. 4th ed., IARC Press, Lyon 2013; Coindre JM: Grading of soft tissue sarcomas: review and update. Arch Pathol Lab Med 2006; 130: 1448–1453; Hasegawa T: Histological grading and MIB-1 labeling index of soft-tissue sarcomas. Pathol Int 2007; 57: 121–125; Coindre JM, Trojani M, Contesso G et al.: Reproducibility of a histopathologic grading system for adult soft tissue sarcoma. Cancer 1986; 58: 306–309.

13. Whitney CW, Spirtos N: Gynecologic Oncology Group Surgical Procedures manual. Gynecologic Oncology Group, Philadelphia 2010.

14. Abeler VM, Røyne O, Thoresen S et al.: Uterine sarcomas in Norway. A histopathological and prognostic survey of a total population from 1970 to 2000 including 419 patients. Histopathology 2009; 54: 355–364.

15. Denschlag D, Ackermann S, Battista MJ et al.: Sarcoma of the Uterus. Guideline of the DGGG and OEGGG (S2k Level, AWMF Register Number 015/074, February 2019). Geburtshilfe Frauenheilkd 2019; 79: 1043–1060.

16. Amant F, Coosemans A, Debiec-Rychter M et al.: Clinical management of uterine sarcomas. Lancet Oncol 2009; 10: 1188–1198.

17. Thomassin-Naggara I, Dechoux S, Bonneau C et al.: How to differentiate benign from malignant myometrial tumours using MR imaging. Eur Radiol 2013; 23: 2306–2314.

18. SGO Clinical Practice Endometrial Cancer Working Group; Burke WM, Orr J, Leitao M et al.: Endometrial cancer: a review and current management strategies: part I. Gynecol Oncol 2014; 134: 385–392.

19. Nusrath S, Bafna S, Rajagopalan R et al.: Uterine sarcomas: experience from a tertiary cancer care center from India. Indian J Surg Oncol 2019; 10: 342–349.

20. Kyriazoglou A, Liontos M, Ziogas DC et al.: Management of uterine sarcomas and prognostic indicators: real world data from a single-institution. BMC Cancer 2018; 18: 1247.

21. Reed NS, Mangioni C, Malmström H et al.; European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group: Phase III randomised study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas stages I and II: an European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group Study (protocol 55874). Eur J Cancer 2008; 44: 808–818.

22. Pautier P, Floquet A, Gladieff L et al.: A randomized clinical trial of adjuvant chemotherapy with doxorubicin, ifosfamide, and cisplatin followed by radiotherapy versus radiotherapy alone in patients with localized uterine sarcomas (SARCGYN study). A study of the French Sarcoma Group. Ann Oncol 2013; 24: 1099–1104.

23. Littell RD, Tucker LY, Raine-Bennett T et al.: Adjuvant gemcitabine-docetaxel chemotherapy for stage I uterine leiomyosarcoma: trends and survival outcomes. Gynecol Oncol 2017; 147: 11–17.

24. Bogani G, Fucà G, Maltese G et al.: Efficacy of adjuvant chemotherapy in early stage uterine leiomyosarcoma: a systematic review and meta-analysis. Gynecol Oncol 2016; 143: 443–447.

25. Hensley ML, Ishill N, Soslow R et al.: Adjuvant gemcitabine plus docetaxel for completely resected stages I–IV high grade uterine leiomyosarcoma: results of a prospective study. Gynecol Oncol 2009; 112: 563–567.

26. Serkies K, Abacjew-Chmyłko A, Wieczorek-Rutkowska M et al.: Aromatase inhibitor therapy for endometrial stromal sarcoma – two-centre experience. Ginekol Pol 2018; 89: 607–610.

27. Bacalbasa N, Balescu I, Dima S et al.: Prognostic factors and survival in patients treated surgically for primary and recurrent uterine leiomyosarcoma: a single center experience. Anticancer Res 2015; 35: 2229–2234.

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Gülşah Selvi Demirtaş

Cesarean scar pregnancy management: medical or surgical? When and which? A literature review

Postępowanie w przypadku ciąży w bliźnie po cięciu cesarskim: leczenie farmakologiczne czy chirurgiczne? Kiedy i jak? Przegląd piśmiennictwa

Gynecologic Oncology Clinic, Tepecik Education and Research Hospital, İzmir, Turkey
Correspondence: Gülşah Selvi Demirtaş, Gynecologic Oncology Clinic, Tepecik Research and Education Hospital, 35000 İzmir, Turkey, tel.: +905337271512, e-mail: drg.selvi@gmail.com

Abstract

Aim: The aim of this study was to compare the effectiveness of treatment methods and to highlight treatment debates of cesarean scar pregnancy in the light of the current literature. **Materials and methods:** A total of 55 cesarean scar pregnancy patients from 39 English, free full-text available case reports published between year 2010 and 2020 were analyzed. The patients were treated with various treatment methods. The most commonly used methods, complications, and treatment failures were evaluated. Cases with uterine dehiscence, rupture, acute abdomen, placental abnormalities, trophoblastic diseases, heterotopic pregnancies, twin pregnancies, and emergency surgeries were excluded from the analysis. **Results:** Overall, 55 patients from 39 case reports were included in the analysis. Of these cases, 24 were treated with methotrexate (14 patients systemically, 9 systemically methotrexate plus local potassium chloride, 1 methotrexate plus mifepristone). Surgical management was performed in 31 patients, and involved: dilatation and suction curettage, laparoscopy, uterine artery embolization, laparotomy, hysteroscopy, high intensity focused ultrasound, bilateral uterine artery balloon catheter insertion, obliteration of the feeding artery with fibrin sealant, and cesarean section. Two of the cesarean scar pregnancies were continued and cesarean section plus hysterectomy was performed at 35 weeks gestation. **Limitations of the study:** Dependence of the analysis on anecdotal case reports and series is the main limitation of this study. Therefore, there is a need for larger prospective series comparing treatment options and outcomes. Another limitation that precludes us from definitive conclusions is the heterogeneity in the methods of laboratory measurements, the quality of ultrasonography equipment, and the experience of surgeons. **Conclusion:** In conclusion, although there has been no established consensus on the management of scar line pregnancies in the literature, current literature indicates that one size does not fit and that it is reasonable to plan the treatment according to the patients' characteristics. Ultrasonography is valuable in diagnosis and choosing a treatment modality. It is also crucial to determine the type of scar line pregnancy before planning the treatment.

Keywords: cesarean section, ectopic pregnancy, cesarean scar pregnancy

Streszczenie

Cel: Celem badania było porównanie skuteczności metod leczenia ciąży w bliźnie po cięciu cesarskim ze szczególnym uwzględnieniem dyskusji dotyczących strategii terapeutycznych w świetle aktualnej literatury. **Materiał i metody:** Analizą objęto łącznie dane 55 pacjentek z rozpoznaniem ciąży w bliźnie po cięciu cesarskim z 39 dostępnych angielskojęzycznych pełnotekstowych opisów przypadków opublikowanych w latach 2010–2020. Pacjentki leczono z zastosowaniem różnych metod. Ocenie poddano najczęściej stosowane metody leczenia, powikłania oraz niepowodzenia terapeutyczne. Z analizy wykluczono przypadki rozejścia się macicy, pęknięcia macicy, ostrego brzucha, nieprawidłowości łożyska, chorób trofoblastycznych, ciąży bliźniaczej oraz zabiegów ze wskazań nagłych. **Wyniki:** Łącznie analizą objęto 55 pacjentek (39 opisów przypadków), w tym 24 pacjentki leczone metotreksatem (leczenie ogólnoustrojowe u 14, leczenie ogólnoustrojowe metotreksatem i miejscowe chlorkiem potasu u 9 pacjentek oraz leczenie metotreksatem i mifepristonem u 1 pacjentki). Leczenie operacyjne przeprowadzono u 31 kobiet i obejmowało ono: rozszerzenie i wyłyżeczkowanie próżniowe, laparoskopię, embolizację tętnicy macicznej, laparotomię, histeroskopię, technologię HIFU (zogniskowanej fali ultradźwiękowej o wysokiej częstotliwości), wprowadzenie balonu cewnika obustronnie do tętnic macicznych, obliterację tętnicy doprowadzającej klejem fibrynowym oraz cięcie cesarskie. Dwie ciąże w bliźnie po cięciu cesarskim kontynuowano do 35. tygodnia ciąży, w którym wykonano cięcie cesarskie z histerektomią. **Ograniczenia badania:** Głównym ograniczeniem badania było oparcie analizy na niepotwierdzonych opisach przypadków i seriach przypadków. Potrzebne są większe badania prospektywne dotyczące serii przypadków, porównujące różne opcje i wyniki leczenia. Kolejnym ograniczeniem, które nie pozwoliło na wyciągnięcie ostatecznych wniosków, był brak jednorodności w odniesieniu do metod pomiarów laboratoryjnych,

jakości sprzętu ultrasonograficznego i doświadczenia chirurgów. **Wniosek:** Podsumowując, pomimo braku ustalonego konsensusu dotyczącego postępowania w przypadku ciąży w bliźnie po cięciu cesarskim w piśmiennictwie, z przeglądu aktualnej literatury wynika, że nie ma rozwiązań uniwersalnych, a zatem uzasadnione jest planowanie leczenia zgodnie z indywidualną charakterystyką pacjentki. Ultrasonografia jest cennym narzędziem w diagnostyce i wyborze metody leczenia. Istotne jest również określenie rodzaju ciąży w bliźnie po cięciu cesarskim przed planowaniem leczenia.

Słowa kluczowe: cięcie cesarskie, ciąża ektopowa, ciąża w bliźnie po cięciu cesarskim

INTRODUCTION

Cesarean scar pregnancy (CSP) is a rare but unique and life-threatening type of ectopic pregnancy. This type of pregnancy was first defined by Larsen and Solomon[1]. One explanation of the pathophysiology includes disruption of the normal healing process of the isthmic wall by repeated trauma and poor vascularization in the scar that prevents optimal healing[2]. Cervical dilation in labor, prolonged duration of labor, or oxytocin augmentation are also considered factors that increase the risk of a large scar defect in non-pregnant women[3]. Along with the rising rate of cesarean section and improvements in sonographic imaging, the incidence of CSP has substantially increased worldwide[4–7]. CSP diagnosis has a critical importance due to its life-threatening feature. Undiagnosed ectopic pregnancy of any abnormal location remains an important cause of pregnancy-related deaths[8]. In the literature, several etiopathogenetic explanations were proposed. One of these is the suturing and closure technique. Roberge et al. reported that a locked single-layer suturing technique is associated with a fourfold increase in the risk of uterine rupture compared with the double-layer suturing technique[9]. Since no standard management protocol has been established for this rare life-threatening condition, each patient should be evaluated individually[10]. In this type of ectopic pregnancy, the gestational sac is partially or completely implanted in the cesarean section scar[11].

Vial et al. reported two different types of CSP: The first type is a superficial invasion of the amniotic sac into the scar with the progression of pregnancy into the cervicoisthmic space and uterine cavity, which is known as endogenous CSP (type I). The second type involves a deep implantation into the scar with progression toward the uterine myometrium and the serosal surface, and is referred to as exogenous CSP (type II)[12]. This type is particularly dangerous due to high risk of uterine rupture and hemorrhage[13]. Besides, management options for these types of CSP have not been established yet[14]. Therefore, a guideline is needed to establish a standardized safe and effective management. In this literature review, the effectiveness of treatment methods was compared and the debates on the management were highlighted.

MATERIALS AND METHODS

A total of 55 cesarean scar pregnancy (CSP) patients from 39 English, free full-text available case reports published between 2010 and 2020 were analyzed. Reviews and clinical trials were excluded. Patients were treated with various treatment methods. The most commonly used treatment methods, complications, and treatment failures were evaluated. Cases with uterine dehiscence, rupture, acute abdomen, placental abnormalities, trophoblastic diseases, heterotopic pregnancies, twin pregnancies, and emergency surgeries were excluded from the analysis.

Treatment methods

Local or systemic injection of methotrexate (MTX) has been widely used for medical treatment. Local treatment is considered to be more effective than systemic treatment[15]. Besides, medical treatment is not preferred in some situations. Advanced gestational age, high level of serum β-subunit of hCG gonadotropin (beta-hCG), and positive fetal cardiac activity. The type of CSP is also important for selecting the candidates. Unfortunately, there are no established management protocols depending on the type of CSP. Surgical treatment includes dilatation and suction curettage (C), laparoscopy (L/S), uterine artery embolization (UAE), laparotomy (L/T), hysteroscopy (H/S), high-intensity focused ultrasound (HIFU), bilateral uterine artery balloon catheter insertion, obliteration of feeding artery with fibrin sealant, and hysterectomy.

RESULTS

All patients in this analysis were hemodynamically stable and had no acute abdomen during admission to the hospital. In all cases, the diagnosis was made based on ultrasound examination. In 45 patients, an embryo with a cardiac activity was documented. Among all, 24 patients were treated with MTX [14 patients systemically, 9 systemically MTX, and local potassium chloride (KCL), 1 MTX and mifepristone]. Surgical treatment included dilatation and C, L/S, UAE, L/T, H/S, HIFU, bilateral uterine artery balloon catheter insertion, obliteration of the feeding artery with fibrin sealant, cesarean section. One of the reports documents a 41-year-old CSP patient with a live birth. At 38 weeks, the baby was safely delivered during a three-hour-long cesarean section operation. Placenta previa was observed. Hysterectomy was performed after delivery due to the massive bleeding. In another case report of a 32-year-old patient, pregnancy was continued and cesarean section was performed with hysterectomy at 35 weeks gestation due to bleeding.

Conservative treatment	Number of patients	Treatment failure	Complication
Only MTX: • local • systemic • local + systemic Total	 3 10 1 14	 2 2 0 4 (28.5%)	 0 0 0 0
MTX + KCL	9	0	0
MTX + mifepristone	1	0	0
MTX – methotrexate; **KCL** – potassium chloride.			

Tab. 1. Conservative treatments with MTX

Surgical treatment	Number of patients	Treatment failure	Complication
C: • only C • C + MTX • C + Foley catheter Total	 1 4 1 6	 1 (100%) 0 0 1 (100%)	 0 0 0 0
L/S: • only L/S • L/S + MTX • L/S + vasopressin • L/S + UAE Total	 6 1 2 1 10	 1 (16.6%) 0 0 0 1	 0 0 0 0 0
L/T	3	0	0
H/S + MTX	1	0	0
UAE: • UAE + MTX • UAE + L/S + H/S • UAE + C Total	 1 1 1 3	 0 0 0 0	 0 0 1 1
HIFU: • HIFU + C + MTX • HIFU + mifepristone Total	 3 1 4	 1 (33.3%) 0 1 (33.3%)	 0 0 0
Local MTX + KCL + bil. UABCI + C + Foley catheter	1	1	0
OFAFS	1	0	0
C/S + hysterectomy	2	0	0
C – suction curettage; **MTX** – methotrexate; **L/S** – laparoscopy; **UAE** – uterine artery embolization; **L/T** – laparotomy; **H/S** – hysteroscopy; **HIFU** – high-intensity focused ultrasound; **KCL** – potassium chloride; bil. **UABCI** – bilateral uterine artery balloon catheter insertion; **OFAFS** – obliteration of the feeding artery with fibrin sealant; **C/S** – cesarean section.			

Tab. 2. Surgical treatments

The rates of treatment failures are shown in Tabs. 1 and 2. The most frequently used treatments, i.e. MTX and laparoscopy, were also compared in terms of outcome (Tabs. 3 and 4). They were found to be comparable with respect to success rates ($p = 0.9$). Medical and surgical treatments were compared in terms of treatment failure, but no statistical significance was detected ($p = 0.273$). Also, the comparison of treatment types in terms of beta-hCG levels, cesarean section number, abortion number, parity, and gravida, revealed no statistically significant differences ($p = 1$, $p = 0.249$, $p = 0.207$, $p = 0.289$, $p = 0.105$, respectively).

	Successful ($n = 8$)	Unsuccessful ($n = 2$)
Maternal age	29.6 ± 3.8	35 ± 3
Gravidity	4 ± 1.65	4 ± 0
Parity	3.25 ± 1.47	3 ± 0
Prior C/S number	2.125 ± 0.78	3 ± 0
Gestational age [week]	5.87 ± 0.59	7.5 ± 2.5
Beta-hCG	36.999 ± 1368.9	42.389 ± 22.746
Data are presented as mean ± standard deviation. **hCG** – human chorionic gonadotropin.		

Tab. 3. Cesarean section ectopic pregnancies primarily treated only with systemic methotrexate

	Successful ($n = 5$)	Unsuccessful ($n = 1$)
Maternal age	31.8 ± 3.31	36
Gravidity	3.8 ± 2.71	5
Parity	1.6 ± 0.8	2
Prior C/S number	1.6 ± 0.8	2
Gestational age [week]	8 ± 1.89	6
Beta-hCG	39.9394 ± 33.64512	21.521
Data are presented as mean ± standard deviation. **hCG** – human chorionic gonadotropin.		

Tab. 4. Cesarean section ectopic pregnancies primarily treated only with laparoscopy

Treatment methods	Successful	Unsuccessful	Total
Systemic MTX only	8	2	10
L/S only	5	1	6
Others	32	7	39
Total	45	10	55
$p = 0.9$, * $p < 0.05$ was accepted to be statistically significant.			

Tab. 5. Comparison of MTX and L/S treatments by success rates

DISCUSSION

The present study had several limitations. First, this was a literature review of the available cases. The type of CSP was not reported in all cases. The cut-off value of serum beta-hCG might be different in different settings. CSP types were mentioned in only 9 patients out of 55 case reports. But in all type 2 patients ($n = 6$), an initial medical treatment was performed, followed by a conversion to surgery due to rising levels of beta-hCG.

CSP can easily be misdiagnosed in early pregnancy. In this situation, blind induced abortion may result in uncontrolled hemorrhage. Therefore, transvaginal ultrasonography is crucial in early pregnancy to rule out CSP. The ultrasonographic diagnostic criteria have been defined; a CSP is diagnosed when the uterine cavity and the cervical canal are empty, and the gestational sac is located in the anterior portion of the uterine isthmus[16].

In this study, ultrasonographic examination was used as a diagnostic tool in all cases. Jurkovic et al. reported that

72% of their CSP patients had undergone multiple (≥2) CS procedures. They reported that multiple CS procedures led to poor healing of the uterine incision, which was a high-risk factor for CSP[17]. In this study, the C-section number was mentioned in 50 out of 55 cases. In was not reported in 5 case reports. Out of 50 cases, 28 (56%) patients had undergone multiple (≥2) CS procedures.

When evaluating a pregnant patient with vaginal bleeding or abdominal pain, it is important to consider ectopic pregnancy, especially if the patient has a history of multiple previous cesarean sections. There are two types of cesarean scar ectopic pregnancy. It is important to determine this type during ultrasound examination. The first type can proceed to term with a viable fetus, with an increased risk of postpartum hemorrhage[18]. The second type carries the risk of rupture and hemorrhage during the first trimester. Management options for these CSP types have not been established[14]. There is no universal agreement on the optimal treatment modality for CSP. It is considered that MTX treatment is effective when serum Bhcg levels are lower than 5000 mIU/mL[12]. Seow et al. reported that up to 8 weeks of pregnancy with no fetal heart activity, a single i.m. dose of 50 mg/m^2 may be safe in CSP treatment[19]. Haimov-Kochman et al. reported 18 patients up to 8 weeks of pregnancy who were treated with MTX and 6 patients after 8 weeks who were treated with surgical treatment. In this study, the authors stated that systemic MTX administration is insufficient due to the poorer drug penetration in the fibrous tissue[20]. Sel et al. used a vacuum extraction under ultrasound guidance for CSP series[21]. In this study, selection criteria for vacuum extraction were: pregnancies <8 weeks gestation, beta-hCG level <10,000 mIU/mL, hemodynamically stable patients, no sign of uterine rupture. Patients who did not meet the criteria for vacuum extraction were treated with intramuscular MTX plus vacuum extraction technique if they were hemodynamically stable. The authors stated that the vacuum evacuation method is a feasible treatment for CSP. With the vacuum evacuation method, adjuvant use of an inflatable foley balloon catheter to treat or restrain massive blood loss has been reported[22,23]. In a study reported by Kim et al., MTX treatment alone as a first-line therapy showed a low success rate[24].

When to suspect CSP?

Sonography is the first-line diagnostic tool for cesarean scar pregnancy. CSP should be suspected based on the following criteria[25]: empty uterine cavity and closed empty cervical canal, placenta and/or gestational sac embedded in the cesarean section scar, thin (1–3 mm) or absent myometrial layer between the gestational sac and the bladder, the presence of embryonic/fetal pole and/or yolk sac with or without heart activity, the presence of a prominent and, at times, rich vascular pattern at or in the area of a cesarean section scar in the presence of a positive pregnancy test and a negative sliding organs sign.

Which treatment?

This study has some limitations. Sample size was the major limitation, which prevented us from claiming that any of the described techniques to be universally applicable to all patients with CSP. But as stated in the literature, the diagnosis should be followed by determination of the type of CSP. In the second type, we must be aware of the high risk of rupture if the pregnancy continues. Patients with this type should be appropriately informed. Although management options for these types of CSP have not been established, especially after 8 weeks gestation and with positive fetal cardiac activity, unstable hemodynamic state, serum beta-hCG of more than 5,000 mIU/mL, it should be kept in mind that medical treatment used as the first-line approach often needs additional surgical interventions. A combination of medical and operative treatment is considered to increase the success of treatment.

Surgical treatment modalities may be undertaken in hemodynamically unstable patients or when pharmacological treatment proves ineffective. Operative methods include laparotomy, laparoscopy, hysteroscopy, uterine artery embolization, high intensity focused ultrasound, obliteration of the feeding artery with fibrin sealant, hysteroscopy, and curettage with gestational sack suction. Combination of medical and operative treatment can increase the success of treatment.

In conclusion, based on the cases described in the literature, transvaginal sonography is an important tool in diagnosing CSP, especially patients with vaginal bleeding and abdominal pain. CSP is a product of cesarean section and is associated with multiple factors. Once it is diagnosed, early termination of pregnancy is extremely important to avoid serious complications. The knowledge of the CSP type is essential for the determination of the risk of rupture and hemorrhage. In the management of CSP, medical treatment (particularly not with MTX alone) is effective in most of the cases as first line treatment. However, surgical interventions and combination of medical and surgical treatments should be used in hemodynamically unstable patients or in the case of medical treatment failure.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

References

1. Larsen JV, Solomon MH: Pregnancy in a uterine scar sacculus – an unusual cause of postabortal haemorrhage. A case report. S Afr Med J 1978; 53: 142–143.
2. Ofili-Yebovi D, Ben-Nagi J, Sawyer E et al.: Deficient lower-segment Cesarean section scars: prevalence and risk factors. Ultrasound Obstet Gynecol 2008; 31: 72–77.
3. van der Voet LF, de Vaate B, Veersema S et al.: Long-term complications of caesarean section. The niche in the scar: a prospective cohort study on niche prevalence and its relation to abnormal uterine bleeding. BJOG 2014; 121: 236–244.
4. Martin JA, Hamilton BE, Osterman MJK et al.: Births: final data for 2013. Natl Vital Stat Rep 2015; 64: 1–65.
5. Dietz HP, Campbell S: Toward normal birth – but at what cost? Am J Obstet Gynecol 2016; 215: 439–444.
6. Timor-Tritsch IE, Monteagudo A: Unforeseen consequences of the increasing rate of cesarean deliveries: early placenta accreta and cesarean scar pregnancy. A review. Am J Obstet Gynecol 2012; 207: 14–29.
7. Birge Ö, Karaca C, Arslan D et al.: Medical management of cesarean scar pregnancy at advanced age: case report and literature review. Clin Exp Obstet Gynecol 2016; 43: 140–142.
8. Dibble EH, Lourenco AP: Imaging unusual pregnancy implantations: rare ectopic pregnancies and more. AJR Am J Roentgenol 2016; 207: 1380–1392.
9. Roberge S, Demers S, Berghella V et al.: Impact of single- vs double-layer closure on adverse outcomes and uterine scar defect: a systematic review and metaanalysis. Am J Obstet Gynecol 2014; 211: 453–460.
10. Rotas MA, Haberman S, Levgur M: Cesarean scar ectopic pregnancies: etiology, diagnosis, and management. Obstet Gynecol 2006; 107: 1373–1381.
11. Rajakumar C, Agarwal S, Khalil H et al.: Caesarean scar pregnancy. J Obstet Gynaecol Can 2015; 37: 199.
12. Vial Y, Petignat P, Hohlfeld P: Pregnancy in a cesarean scar. Ultrasound Obstet Gynecol 2000; 16: 592–593.
13. Godin PA, Bassil S, Donnez J: An ectopic pregnancy developing in a previous caesarian section scar. Fertil Steril 1997; 67: 398–400.
14. Glenn TL, Bembry J, Findley AD et al.: Cesarean scar ectopic pregnancy: current management strategies. Obstet Gynecol Surv 2018; 73: 293–302.
15. Uludag SZ, Kutuk MS, Ak M et al.: Comparison of systemic and local methotrexate treatments in cesarean scar pregnancies: time to change conventional treatment and follow-up protocols. Eur J Obstet Gynecol Reprod Biol 2016; 206: 131–135.
16. Ash A, Smith A, Maxwell D: Caesarean scar pregnancy. BJOG 2007; 114: 253–263.
17. Jurkovic D, Hillaby K, Woelfer B et al.: Cesarean scar pregnancy. Ultrasound Obstet Gynecol 2003; 21: 310.
18. Tamada S, Masuyama H, Maki J et al.: Successful pregnancy located in a uterine cesarean scar: a case report. Case Rep Womens Health 2017; 14: 8–10.
19. Seow KM, Cheng WC, Chuang J et al.: Methotrexate for cesarean scar pregnancy after in vitro fertilization and embryo transfer. A case report. J Reprod Med 2000; 45: 754–757.
20. Haimov-Kochman R, Sciaky-Tamir Y, Yanai N et al.: Conservative management of two ectopic pregnancies implanted in previous uterine scars. Ultrasound Obstet Gynecol 2002; 19: 616–619.
21. Sel G, Sucu S, Harma M et al.: Successful management of cesarean scar pregnancy with vacuum extraction under ultrasound guidance. Acute Med Surg 2018; 5: 358–361.
22. Armstrong V, Hansen WF, Van Voorhis BJ et al.: Detection of cesarean scars by transvaginal ultrasound. Obstet Gynecol 2003; 101: 61–65.
23. Timor-Tritsch IE, Cali G, Monteagudo A et al.: Foley balloon catheter to prevent or manage bleeding during treatment for cervical and Cesarean scar pregnancy. Ultrasound Obstet Gynecol 2015; 46: 118–123.
24. Kim SY, Yoon SR, Kim MJ et al.: Cesarean scar pregnancy; diagnosis and management between 2003 and 2015 in a single center. Taiwan J Obstet Gynecol 2018; 57: 688–691.
25. Timor-Tritsch IE, Monteagudo A, Santos R et al.: The diagnosis, treatment, and follow-up of cesarean scar pregnancy. Am J Obstet Gynecol 2012; 207: 44.e1–44.e13.

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Teresa Wolniewicz[1,2], Jakub Franke[2], Joanna Kacperczyk-Bartnik[3], Paweł Bartnik[3], Anna Wójcicka[4,5]

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The role of immunotherapy in cancer treatment

Rola immunoterapii w leczeniu chorób nowotworowych

[1] Students' Scientific Group Affiliated to the 2nd Department of Obstetrics and Gynecology, Medical University of Warsaw, Warsaw, Poland
[2] Students' Scientific Group Affiliated to Genomic Medicine, Medical University of Warsaw, Warsaw, Poland
[3] 2nd Department of Obstetrics and Gynecology, Medical University of Warsaw, Warsaw, Poland
[4] Genomic Medicine, Medical University of Warsaw, Warsaw, Poland
[5] Warsaw Genomics, Warsaw, Poland
Correspondence: Jakub Franke, Students' Scientific Group Affiliated to Genomic Medicine, Medical University of Warsaw, Banacha 1a, 02-097 Warsaw, Poland, tel.: +48 794 583 654, e-mail: jakub.franke@hotmail.com

Abstract

Cancer is a genetic disease with the growth of tumor cells initiated and promoted by mutations in a group of genes known as drivers. This is just the beginning of the process of cancerogenesis, characterized by cellular, genetic and epigenetic alterations as well as the loss of normal cellular regulatory processes. The revelation of complexity of mechanisms underlying the Cancer-Immunity Cycle has resulted in defining immunological and histological profiles responsible for suppressing or promoting anticancer immunity. It has been observed that such profile is determined not only by intrinsic tumor properties, patients' genetics, but also such extrinsic elements as gut microbiota, the presence of infection or exposure to sunlight. The balance between these factors, known as a cancer-immune set point, is a threshold that must be exceeded for a patient to respond to immunotherapy. Among various types of cancer immunotherapy, we can distinguish an adoptive T cell transfer, checkpoint blockade and neoantigen vaccines. The genuine features of human immune system, such as specific recognition and elimination of cancer cells, adaptation to an evolving tumor and immunological memory seem to be a perfect combination to create a powerful weapon for long-term cancer control. Nevertheless, the exact understanding of immunological mechanisms in both tumor growth and cancer elimination requires more thorough studies and may lead to enhancing the efficiency of a wide variety of immunotherapeutic anticancer approaches.

Keywords: immune system, immunotherapy, neoplasms

Streszczenie

Nowotwory należą do chorób genetycznych, wynikających z nadmiernego namnażania komórek zainicjowanego i promowanego przez różne mutacje. Jest to jedynie początek całego procesu kancerogenezy charakteryzującego się zmianami na etapie komórkowym, genetycznym i epigenetycznym, jak również upośledzeniem wielu funkcji regulatorowych. Złożoność mechanizmów odpowiedzialnych za interakcje między układem odpornościowym a procesem nowotworzenia przyczyniła się do zdefiniowania profili immunologicznych i histologicznych odpowiedzialnych za hamowanie lub zwiększanie odporności przeciwnowotworowej. Zaobserwowano liczne zależności ukształtowane przez cechy samego guza, jak również zależne od genetyki pacjenta, a także czynników zewnętrznych, np. składu flory bakteryjnej jelit, infekcji czy ekspozycji na promieniowanie słoneczne. Równowaga pomiędzy tymi czynnikami stanowi pewną bazę niezbędną do zrozumienia skuteczności odpowiedzi na immunoterapię nowotworów. Spośród licznych mechanizmów wykorzystywanych w terapii szczególną rolę odgrywają transfery limfocytów T, blokady punktów kontrolnych oraz szczepionki neoantygenowe. Dzięki specyficznym cechom ludzkiego układu odpornościowego, np. umiejętności rozpoznawania i eliminacji komórek nowotworowych, adaptacji podczas kancerogenezy czy pamięci immunologicznej, daje on wiele możliwości dla dalszego rozwoju terapii i nadzieję na długoterminową kontrolę nad chorobą.

Słowa kluczowe: układ odpornościowy, immunoterapia, nowotwory

INTRODUCTION

Cancer is a genetic disease, with the growth of tumor cells initiated and promoted by mutations in a group of genes known as drivers. This is just the beginning of a process of cancerogenesis, characterized by cellular, genetic and epigenetic alterations as well as the loss of normal cellular regulatory processes[1]. Mutanome – the set of all mutations – gradually increases, leading to the heterogeneity of tumor cells and the synthesis of novel proteins and peptide sequences (neoantigens)[2]. Their mutated epitopes (neoepitopes) are then processed and presented by the major histocompatibility complex (MHC) molecules, exposing the tumor cells to the risk of recognition by the immune system. Such immune recognition, undeniably defective in cancer patients, has become a muse for scientists all over the world, committed to pursuing a cure for cancer. Immunotherapy is, in fact, a type of treatment that exploits one's immunological system in order to cure a disease, including cancer. For many decades, the possible role of the immune system in cancer treatment remained unappreciated[3] not only due to the lack of appropriate analytic techniques, but also because of the undoubtedly disabled function of the host immunological response against the tumor. However, it was revealed already in 1950s that mice with syngeneic carcinogen-induced tumors are resistant to redeveloping tumor with the same cancer cells due to the development of adaptive tumor immunity[4]. In 1970s, it was proved that tumor-derived T cell clones recognize human tumor cell lines and correlate with adaptive immunity[5]. Yet, only in the 1980s, a detailed conformation of tumor neoantigens was revealed with the help of the newly introduced cloning techniques[6]. The studies classified the molecules into the tumor-associated antigens (TAAs) and tumor-specific antigens (TSAs). TAAs are either overexpressed in cancer tissues and arise from the tissue differentiation (e.g. HER2) or preferentially expressed by cancer cells, but not normal tissues (except for fetal or immune-privileged tissues – e.g. MAGE, NY-ESO-1, TPBG). TAAs are subject to some degree of central tolerance and lack complete specificity to the tumor. TSAs, on the contrary, arise as an effect of somatic gene mutations in cancer cells. As such, the resulting antigens are tumor specific and highly immunogenic, as they are not subject to the central tolerance[7]. Therefore, TSAs seemed an alluring target for immunotherapy, but the background for elaboration of new techniques was lacking. Thanks to recent advances in next-generation sequencing (NGS) technique, clear detection of all mutations occurring in cancer, allowing for identification of TSA sequences, has become feasible, on the basis of comparison of the DNA structure in non-mutated and cancer cells.

THE CANCER-IMMUNITY CYCLE

In the recent years, the pace of progress in cancer immunotherapy has increased. In 2012, scientists discovered that immune response in cancer is a series of carefully regulated events that may be optimally addressed not separately, but as a group[8]. This series was named a Cancer-Immunity Cycle and each of its steps was thoroughly examined, with a special focus on the stimulatory and inhibitory signals. It resulted in much broader understanding of the whole process, starting from the release of neoantigens and their recognition by dendritic cells, through activation of T cells and their infiltration of the tumor, up to the recognition and killing of cancer cells. This allowed a cancer immune response to be approached from a significantly wider perspective and, therefore, presented an innovative and immense spectrum for potential therapies. Next year showed that the defective immune protection in cancer patients results from inhibiting T cell responses by negative regulators in lymphoid organs (checkpoints) and in the tumor bed (immunostat function)[9]. Finally, one of the most crucial observations was that the Cancer-Immunity Cycle is aberrant in oncological patients. With all this knowledge, scientists concluded that immunotherapy may be an effective therapeutic option in a wide range of cancers, and exploiting the proper immunological anticancer response shall be a starting point of this approach. Therefore, the main goal in tailoring cancer-specific therapy is to revive the Cancer-Immunity Cycle, i.e. initiate the immunological response and allow for its undisturbed continuation by influencing various regulatory mechanisms, leading to effective killing of cancer cells[4]. However, the approach based on increasing the immunological activity poses a threat in the form of autoimmune inflammatory responses, which cannot be ignored[10].

The revelation of the complexity of mechanisms underlying the Cancer-Immunity Cycle has resulted in defining immunological and histological profiles of patients, responsible for suppressing or promoting anticancer immunity. Interestingly, it has been shown that such a profile is determined not only by intrinsic tumor properties (e.g. its' genetic composition) and patients' genetics (possible alterations in inflammatory signaling cascade), but also such extrinsic elements as gut microbiota, the presence of infection or exposure to sunlight. The balance between these factors, known as a cancer-immune set point, is a threshold that must be exceeded for a patient to respond to immunotherapy[3].

CANCER IMMUNOTHERAPY MECHANISMS

Among various types of cancer immunotherapy, we can distinguish an adoptive T cell transfer, checkpoint blockade and neoantigen vaccines.

Adoptive T cell transfer (ACT) is a new area of transfusion medicine involving the use of patient's own lymphocytes to mediate antitumor, antiviral or anti-inflammatory effects. The genetically modified autologous lymphocytes are reinfused into the patient and allow for achieving a substantial clinical benefit in otherwise treatment-refractory cancers. Three forms of ACT are being developed for cancer

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therapy: tumor-infiltrating lymphocytes (TILs), T cell receptor (TCR) T cells and chimeric antigen receptors (CAR) T cells[11].

TILs lead to durable clinical responses in patients with metastatic melanoma and other cancers[12–14]. TCR therapies were tested in patients with metastatic melanoma, with the use of TCRs recognizing shared tumor associated antigens such as HLA-A2, MART-1 and NY-ESO-1. The improved avidity and, therefore, improved immunological response rate was inextricably linked to greater off-tumor toxicity, caused by addressing the same antigen in normal melanocytes localized in the skin, eye and cochlea[15]. Although it seems that in shared antigenic targets such on-target, off-tumor toxicity is unavoidable and increases with the avidity, although some studies disagree with this conclusion[16] and suggest that developing therapies with TCRs recognizing tumor-specific neoantigens may be associated with milder safety. The CAR T cells therapy appears to be the most outstanding and developed among ACT therapies. The patient's T cells are transfected with a construct encoding an antibody against the tumor surface antigen, fused to the T cell signaling domains[17]. The procedure avoids the need for immunization and may even overcome the mechanisms of immune suppression by overwhelming the system through infusion of large quantities of modified T cells, promoting self-propagation of the Cancer Immunity Cycle. The method has recently been approved by the U.S. Food and Drug Administration (FDA) for treatment of refractory pre-B cell acute lymphoblastic leukemia and diffuse large B cell lymphoma on the basis of impressive clinical trials' results. Although the first clinical trials with the first-generation CAR T cells were unsatisfying, the second-generation, targeting CD19 and encoding for an additional costimulatory domains, proved to be an effective approach. CD19 is an antigen expressed solely on the surface of B cell lineage cells, indispensable for B cell advancement and with high expression levels in B cell – related malignancies. Interestingly, however, multiple myeloma, which is accompanied with low levels of CD19, is associated with a good response to the CD19 CAR T cell therapy. The possible use of the CAR T cells therapy was also investigated in solid tumors, but the results weren't favorable.

For all that, the question is whether this approach might be applied effectively in malignancies other than hematologic, whether the adverse consequences can be managed or eliminated and, eventually, whether large numbers of monospecific T cells won't face resistance due to antigenic drift[4]. This requires further studies.

The next type of immunotherapy is an immune checkpoint blockade (ICB). Its design and use are based on a hypothesis that immunological activity and response against cancer cells might be tuned down with negative immune regulation. Molecules taking part in such regulation are referred to as immune checkpoint inhibitors. There are many known particles transducing negative signaling, among which CTLA-4 and PD-1 gained the most attention. CTLA-4 is presented on a T cell surface after initial activation with two costimulatory signals in lymph nodes, and allows for competing with the CD28 molecule for the B7 ligands. The competition not only weakens the positive signaling of CD28, and lymphocyte activation, but also leads to the transduction of inhibitory regulation when the ligand is bound. Another possible step of inhibition takes place in a tumor microenvironment, where cancer cells present PD-L1 – a ligand for PD-1. PD-1 molecule is a negative receptor, which is presented by the T cells after recognition of a specific antigen by the TCR region. Therefore, blockade of CTLA-4 or PD-1 helps to avoid the suppression of antitumor response and overcome the adaptive immune resistance. There are a few monoclonal antibodies developed or currently tested in clinical trials. Ipilimumab, the first anti-CTLA-4 antibody was engineered in 2000 and in 2011 received the FDA approval for the treatment of melanoma. Other antibodies, used in the clinical practice include nivolumab (anti-PD-1), pembrolizumab (anti-PD-1), avelumab (anti-PD-L1) or atezolizumab (anti-PD-L1). The most common indications include melanoma, non-small cell lung cancer or urothelial cancer, but the therapy seems promising in many cancer types, therefore numerous clinical trials are currently on-going.

Ipilimumab treatment significantly improves survival among patients with metastatic melanoma, traditionally considered as a fatal diagnosis, thus, puts a lot of hope in this new generation of cancer treatments. After 8 years since the first FDA approval, more data on the efficiency of checkpoint blockade therapies has been gathered. In malignancies, such as the Hodgkin's lymphoma, Merkel cell carcinoma or cancers with high mutation burden, checkpoint blockade allows for achieving the objective response rate (ORR) of 53% to 90%. However, in other diseases this therapy fails to lead to such high response rates: in renal cell carcinoma, gastroesophageal cancers or non-small cell lung cancer (NSCLC) the ORR ranges from 15% to 25%[18]. On the other hand, the frequency of rapid tumor shrinkage from single-agent anti-PD-L1/PD-1 antibodies ranges from 10% to 40%, depending on the disease type. One of the possible ideas to improve response rates is to combine PD-1/PD-L1, CTLA-4 blockade together or with different anticancer agents. Both approaches seem to have a mechanistic background as they have different targets. The combination of ipilimumab and nivolumab in metastatic melanoma resulted in ORR >50%, whereas single agent nivolumab treatment ORR was 35–40%[18,19]. However, when using multidrug treatment schemes, the problem of serious adverse effects is emerging. In cases of combined checkpoint blockade treatment, the risk of immune-related adverse effects might be up to 60%[18,20].

The response rates of checkpoint blockade might also be reduced by patient specific factors, such as a preexisting low antitumor T cell response, scarce infiltration of the tumor microenvironment or its immunogenicity. Checkpoint blockade is believed to result in longer responses,

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which remain significantly more durable when compared with other therapies. Nonetheless, there are cases of relapse due to resistance acquired as a result of impaired IFN-gamma signaling or defective antigen presentation[21]. About 40–60% and, in some malignancies, even higher percentage of patients will not benefit from ICB. This shows the need for identification of precise biomarkers, allowing for prediction of response. Such predictors would allow for using ICB only in selected patients, as the therapy has adverse effects, is expensive and, most importantly, there might be other treatment schemes more beneficial for patients who will not respond to immune checkpoint blockade. Both the human immune system and cancer cells are in a constant process of changing and adapting, which hinders the efforts of identifying relevant biomarkers. PD-L1 expressed on tumor cells is the most commonly analyzed biomarker for predicting the treatment response. Depending on cancer, high PD-L1 expression may be a positive or negative predictor. Even in malignancies, in which overexpression correlates with better response, not all of the patients with high levels of PD-L1 are going to respond to the therapy, as well as patients without expression of PD-L1 are able to achieve a significant response with ICB[20,22].

TUMOR ENVIRONMENT

Chen and Mellman[3,8] distinguished three phenotypes of tumor environment: the inflamed tumor (characterized by tumor infiltration by CD8+ T cells), the immune excluded tumor (the CD8+ T cells are present on the margin of the tumor, but do not penetrate the tumor efficiently), and the immune desert tumor (in which CD8+ cells are absent). A study showed that patients with immune-active microenvironment are more likely to achieve a better outcome[23]. However, it is worth noting that the immunity of tumor microenvironment is variable and chemotherapy treatment may induce higher activation of the immune system in the tumor[24].

Also, data from cancer DNA sequencing may be a significant biomarker as the mutational burden is known to correlate with better response rates in ICB therapy. Moreover, defects in the mismatch repair genes have been shown to be a positive marker of response to pembrolizumab in hereditary non-polyposis colorectal cancer (HNPCC) cases[22,25]. On the other hand, there are known cases of resistance to ICB due to mutations in JAK, JAK2 or beta-2-microglobulin[21].

T-CELL-MEDIATED RESPONSE

The importance of a T-cell-mediated response in cancer treatment led the scientists to attempt to create a vaccine, which would work similarly to the vaccines used for the prevention of contagious diseases. Recent advances in NGS and bioinformatics allowed for efficient mapping of the cancer mutanome and for choosing the most suitable targets for the vaccines. Choosing a few mutations as targets gives a chance to address the problem of antigenic escape. With positive results of mouse tests, there were 3 first human trials, conducted recently in melanoma patients. All three trials took different approach and created vaccines in distinct forms.

The first trial consisted of 3 patients with a resected stage III melanoma. The vaccine was prepared based on the dendritic cells. Prior to vaccination, patients were given ipilimumab. It proved neoantigen vaccine to be safe and able to promote neoantigen-specific T cell reaction[26]. The second trial was conducted in 6 patients with at least stage IIIB melanoma, who underwent surgery with curative intent. Each patient received 5 priming and 2 boosting doses of long peptide vaccine. After the median follow-up period of 25 months, 4 patients staged IIIB were free of any recurrences and 2 patients with lung metastases showed radiographic recurrences. After additional 4 doses of pembrolizumab, both patients achieved complete response. For comparison, complete response rate in disseminated melanoma was reported to be 6.1% for pembrolizumab and 1.4% for ipilimumab[27]. The last trial was conducted in 13 patients with at least stage III melanoma. The patients were given a vaccine consisting of a synthetic RNA, encoding the 10 targeted neoantigens. The study showed that 8 non-metastatic patients had no signs of recurrence during the follow-up period of 12 to 23 months. In 5 patients with metastatic disease, the vaccine enhanced the response to standard treatment. The study faced a significant problem, which has to be addressed in further trials - an escape mechanism of tumor cells, which occurred in one patient. It relied on the β2-microglobulin deficiency, leading to the lack of response to the vaccine and subsequent death of the patient[28].

Though the results obtained so far are promising, many questions remain to be answered, including the aspects of the most efficient vaccine formulation, which determines the way of administration of the vaccine to the patient. Other aspects include creating more efficient algorithms for choosing the best mutations to target, managing cross reactivity with wild-type antigens, achieving higher rates of immunization against chosen neoantigens or prevention of antigenic escape among the tumor lines. Based on the treatment response rates achieved by patients with metastatic diseases, it appears that combining neoantigen vaccines with checkpoint blockade might be an efficient treatment approach in more advanced cases. Such combination would allow for priming of new T cells and avoiding the negative regulation of inhibitory checkpoints[5].

POLYTHERAPY

Even though immunotherapy has been introduced into treatment schemes of a few cancers, there are still numerous malignancies, in which monotherapy with immunotherapeutic agent fails to achieve high response rates. In such situations, polytherapy, whether with chemotherapeutic

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or other immunotherapeutic drug, seems to be a possible solution[29,30], primarily in order to prevent the immune escape. Therefore, complementary therapies that reverse the immune suppression in the tumor microenvironment may play a key role in unleashing the full potential of a neoantigens-based cancer vaccine. For example, several studies have suggested the possible additive or synergistic effects between a cancer vaccine and checkpoint blockade[30]. Furthermore, mouse models showed that the dual blockade of both CTLA-4 and PD-1 pathways resulted in an additive response, allowing for more effective T cell activation, further augmented with a vaccine[30], which provides the scientific basis for clinical trials. Targeting other inhibitory receptors is actively tested in preclinical and clinical studies. Undeniably, however, higher response rates with multidrug schemes carry the risk of more serious adverse events[18,20].

CONCLUSIONS

The genuine features of the human immune system, such as specific recognition and elimination of cancer cells, adaptation to an evolving tumor and immunological memory seem to be a perfect combination to create a powerful weapon for long-term cancer control. Nevertheless, the exact understanding of immunological mechanisms in both tumor growth and cancer elimination requires more thorough studies and may lead to an enhanced efficiency of a wide variety of immunotherapeutic anticancer approaches.

Conflict of interest

Authors declare no conflicts of interest.

References

1. Tian T, Olson S, Whitacre JM et al.: The origins of cancer robustness and evolvability. Integr Biol (Camb) 2011; 3: 17–30.
2. Castle JC, Kreiter S, Diekmann J et al.: Exploiting the mutanome for tumor vaccination. Cancer Res 2012; 72: 1081–1091.
3. Chen DS, Mellman I: Elements of cancer immunity and the cancer-immune set point. Nature 2017; 541: 321–330.
4. Foley EJ: Antigenic properties of methylcholanthrene-induced tumors in mice of the strain of origin. Cancer Res 1953; 13: 835–837.
5. Sahin U, Türeci Ö: Personalized vaccines for cancer immunotherapy. Science 2018; 359: 1355–1360.
6. van der Bruggen P, Traversari C, Chomez P et al.: A gene encoding an antigen recognized by cytolytic T lymphocytes on a human melanoma. Science 1991; 254: 1643–1647.
7. Hu Z, Ott PA, Wu CJ: Towards personalized, tumour-specific, therapeutic vaccines for cancer. Nat Rev Immunol 2018; 18: 168–182.
8. Chen DS, Irving BA, Hodi FS: Molecular pathways: next-generation immunotherapy–inhibiting programmed death-ligand 1 and programmed death-1. Clin Cancer Res 2012; 18: 6580–6587.
9. Mullard A: New checkpoint inhibitors ride the immunotherapy tsunami. Nat Rev Drug Discov 2013; 12: 489–492.
10. Chen DS, Mellman I: Oncology meets immunology: the Cancer-Immunity Cycle. Immunity 2013; 39: 1–10.
11. June CH, O'Connor RS, Kawalekar OU et al.: CAR T cell immunotherapy for human cancer. Science 2018; 359: 1361–1365.
12. Stevanović S, Draper LM, Langhan MM et al.: Complete regression of metastatic cervical cancer after treatment with human papillomavirus-targeted tumor-infiltrating T cells. J Clin Oncol 2015; 33: 1543–1550.
13. Tran E, Robbins PF, Lu YC et al.: T-cell transfer therapy targeting mutant KRAS in cancer. N Engl J Med 2016; 375: 2255–2262.
14. Rosenberg SA, Yang JC, Sherry RM et al.: Durable complete responses in heavily pretreated patients with metastatic melanoma using T-cell transfer immunotherapy. Clin Cancer Res 2011; 17: 4550–4557.
15. Johnson LA, Morgan RA, Dudley ME et al.: Gene therapy with human and mouse T-cell receptors mediates cancer regression and targets normal tissues expressing cognate antigen. Blood 2009; 114: 535–546.
16. Rapoport AP, Stadtmauer EA, Binder-Scholl GK et al.: NY-ESO-1-specific TCR-engineered T cells mediate sustained antigen-specific antitumor effects in myeloma. Nat Med 2015; 21: 914–921.
17. Kochenderfer JN, Rosenberg SA: Treating B-cell cancer with T cells expressing anti-CD19 chimeric antigen receptors. Nat Rev Clin Oncol 2013; 10: 267–276.
18. Ribas A, Wolchok JD: Cancer immunotherapy using checkpoint blockade. Science 2018; 359: 1350–1355.
19. Wolchok JD, Kluger H, Callahan MK et al.: Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med 2013; 369: 122–133.
20. Postow MA, Callahan MK, Wolchok JD: Immune checkpoint blockade in cancer therapy. J Clin Oncol 2015; 33: 1974–1982.
21. Zaretsky JM, Garcia-Diaz A, Shin DS et al.: Mutations associated with acquired resistance to PD-1 blockade in melanoma. N Engl J Med 2016; 375: 819–829.
22. Maleki Vareki S, Garrigós C, Duran I: Biomarkers of response to PD-1/PD-L1 inhibition. Crit Rev Oncol Hematol 2017; 116: 116–124.
23. Ji RR, Chasalow SD, Wang L et al.: An immune-active tumor microenvironment favors clinical response to ipilimumab. Cancer Immunol Immunother 2012; 61: 1019–1031.
24. Katsuya Y, Horinouchi H, Asao T et al.: Expression of programmed death 1 (PD-1) and its ligand (PD-L1) in thymic epithelial tumors: impact on treatment efficacy and alteration in expression after chemotherapy. Lung Cancer 2016; 99: 4–10.
25. Le DT, Uram JN, Wang H et al.: PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015; 372: 2509–2520.
26. Carreno BM, Magrini V, Becker-Hapak M et al.: Cancer immunotherapy. A dendritic cell vaccine increases the breadth and diversity of melanoma neoantigen-specific T cells. Science 2015; 348: 803–808.
27. Ott PA, Hu Z, Keskin DB et al.: An immunogenic personal neoantigen vaccine for patients with melanoma. Nature 2017; 547: 217–221.
28. Sahin U, Derhovanessian E, Miller M et al.: Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer. Nature 2017; 547: 222–226.
29. Moynihan KD, Opel CF, Szeto GL et al.: Eradication of large established tumors in mice by combination immunotherapy that engages innate and adaptive immune responses. Nat Med 2016; 22: 1402–1410.
30. Ali OA, Lewin SA, Dranoff G et al.: Vaccines combined with immune checkpoint antibodies promote cytotoxic T-cell activity and tumor eradication. Cancer Immunol Res 2016; 4: 95–100.

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Aleksandra Szczęsna[1], Joanna Kacperczyk-Bartnik[2], Paweł Bartnik[2], Agnieszka Dobrowolska-Redo[2], Ewa Romejko-Wolniewicz[2]

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A patient with breast implants – possible complications and oncological vigilance

Pacjentka z implantami piersi – możliwe komplikacje i czujność onkologiczna

[1] Students' Scientific Group Affiliated to the 2nd Department of Obstetrics and Gynecology, Medical University of Warsaw, Warsaw, Poland
[2] 2nd Department of Obstetrics and Gynecology, Medical University of Warsaw, Warsaw, Poland
Correspondence: Joanna Kacperczyk-Bartnik, Karowa 2, 00-315 Warsaw, Poland, tel.: +48 22 59 66 421, e-mail: asiakacperczyk@gmail.com

Abstract

Background: In the light of a growing interest in breast augmentation with implant devices, physicians should be aware of medium and long-term complications after such procedures. Moreover, an increased risk of breast cancer with higher mortality in the group of implant recipients is observed, which requires an implementation of accurate screening. **Summary:** A special approach must be considered when managing a patient with breast implants due to the possibility to encounter unexpected difficulties during the diagnostic process. Certain complications of breast augmentation require urgent diagnosis followed by adequate treatment, often including surgical management. On the other hand, a patient may report worrying symptoms which mimic those related to breast implants. Plastic surgery patients should be counseled on multiple health aspects prior to the surgery, with emphasis on the oncological risk. Regular breast check-ups are necessary among women with breast implants since proper exposition of breast tissue may be problematic. **Key messages:** Proper oncological vigilance is needed as adequate imaging of augmented breasts might be compromised. A decreased survival of breast cancer patients with breast implants compared with non-augmented women is observed. A holistic approach towards the patient with breast implants helps to mitigate the risk of overlooking important symptoms.

Keywords: breast implants, breast neoplasms, mammaplasty, postoperative complications

Streszczenie

Wstęp: W związku z coraz większym zainteresowaniem zabiegami powiększania piersi personel medyczny powinien posiadać wiedzę na temat możliwości wystąpienia komplikacji po tego typu operacjach. Ze względu na obserwowaną większą śmiertelność związaną z rakiem piersi wśród pacjentek z implantami piersi jest to grupa wymagająca szczególnej uwagi podczas badań przesiewowych. **Rozwinięcie:** Badania przesiewowe w kierunku raka piersi powinny być odpowiednio dostosowane do pacjentek z implantami z uwagi na możliwe trudności w wyborze metody obrazowania piersi. Dodatkowe utrudnienia w procesie diagnostycznym mogą wynikać z niektórych komplikacji zabiegu powiększania piersi. Kluczową rolę odgrywają edukacja pacjentek na temat konieczności wykonywania regularnych badań obrazowych oraz samobadania piersi, jak również informowanie przed samą operacją o możliwych odległych skutkach zabiegu, z ryzykiem onkologicznym włącznie. **Podsumowanie:** Odpowiednia czujność onkologiczna u pacjentek z implantami piersi jest konieczna ze względu na możliwe utrudnienia w obrazowaniu i konieczność dostosowania postępowania diagnostycznego.

Słowa kluczowe: implanty piersi, mammoplastyka, nowotwory piersi, powikłania pooperacyjne

INTRODUCTION

Breast cancer (BC) is the most prevalent female cancer worldwide[1]. A 41% increase in breast implants augmentation was observed during the period of 2000–2017, as reported by the American Society of Plastic Surgeons and the Plastic Surgery Foundation[2]. Surgical outcomes contribute to women's increase in self-esteem and confidence as the majority of women are satisfied with the effects[3]. However, cosmetic aspects are not the only reason for implantation. Breast augmentation is commonly indicated in reconstruction after mastectomy and correction of congenital breast malformations. During the postoperative follow-up period, patients should be given precise information about the prophylaxis of BC, including both diagnostic imaging and breast self-examination[4]. These women should be aware of the possible neoplastic transformation and get acquainted with the methods of early detection of BC.

POSTOPERATIVE COMPLICATIONS

According to reports, complications of breast augmentation with devices are diagnosed in 1–4.6% of patients after the surgery, and those accumulate with time after the procedure[5,6]. The most serious complications include local sequelae. The severity of some of these complications may require surgical treatment or other medical procedures. Complications of breast implant augmentation are as follows (according to frequency of occurrence): implant rupture, capsular contracture, reoperation, implant removal, pain, changes in nipple and breast sensation, infection, scarring, asymmetry, wrinkling, implant displacement/migration, implant palpability/visibility, breastfeeding complications, hematoma/seroma, implant extrusion, necrosis, delayed wound healing, breast tissue atrophy/chest wall deformity, calcium deposits, and lymphadenopathy[7]. Implant rupture may arise in a silent or prominent manner at physical examination. It may lead to pouring out of the device, which may afterwards remain in the scar tissue capsule or relocate outside of the capsule. To exclude an asymptomatic implant rupture, it is recommended to follow-up the patients with magnetic resonance imaging (MRI) 3 years after the implantation, and then every 2 years, but the procedure is not mandatory or customary[8,9]. Unintended intraoperative damage by a sharp surgical instrument is a common cause of implant shell rupture. Moreover, it may be associated with a history of experiencing blunt force trauma or mammography[8]. Explantation with capsule removal followed by a reimplantation is required if silicone leakage, implant rupture or capsular contraction are at least suspected.

BREAST IMPLANT-ASSOCIATED ANAPLASTIC LARGE CELL LYMPHOMA

The texturization of an implant is meant to diminish the risk of its displacement due to a more pronounced inflammatory reaction and following the development of scar tissue adjacent to the device. This was introduced to reduce the incidence of capsule contractures and additionally to protect the anatomically shaped implant from displacement by developing a scar tissue. Unfortunately, it has been noticed that breast augmentation with the use of implants may promote the development of local anaplastic large cell lymphoma (ALCL). In 2008, a possible association between breast implants and ALCL development within the scar tissue was reported[10]. The incidence of this rare peripheral T-cell lymphoma among breast implant owners varies depending on a study from 1 case per 30,000 women with implants to 1 case per 4,000 women per year[11]. Nevertheless, breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) has a more promising curative prognosis compared to systemic ALCL due to its indolent course of the disease. According to data from November 2018, 17 cases of death were reported among 656 patients diagnosed with BIA-ALCL[12]. The cases of BIA-ALCL were diagnosed from 3.5 to 11.6 years after the implantation of anatomical, textured devices[13]. A 47% increase in the disease diagnosis was observed since the beginning of 2017, which suggests a higher awareness among professionals dealing with patients with breast implants[12]. The precise cause of BIA-ALCL development is unknown, although a few hypotheses have been presented, including texturization of implant surface, genetic factors, immune response, and microbiome biofilm[11].

BREAST CANCER

In a meta-analysis comparing the outcome of women with a history of augmentation mammoplasty with implants for cosmetic purposes and a control group of women who were diagnosed with BC, an association between antecedent breast augmentation and higher risk of BC specific mortality with overall hazard ratio of 1.38 (95% confidence interval, CI; 1.08–1.75) was noticed[14]. Similar hazard ratio was not observed in further studies, according to the literature. Contrary to these findings, the BC specific mortality ratio based on a large population of 40,451 women with or without breast implants showed no significant difference between these groups, with hazard ratio of 1.06 (95% CI; 0.65–1.76)[15]. The adverse effect on the survival is assumed to be a result of an inadequate imaging by mammography due to either radio-opacity or the development of capsular contracture that can overshadow the neoplasm[14]. The compression of the breast parenchyma may facilitate physical examination in search of any tumor mass and is suggested to be advantageous in the case of subglandular implants. It is widely believed that an implant might act as background for a thorough palpation of any tumor mass. A study by Cho et al. suggested no link between more advanced BC stage in women who had undergone breast augmentation; however, subglandular placement of implants was correlated with diagnosis at a more advanced stage of disease than with subpectoral ones[16]. Implant location has

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no actual impact on BC stage or lymphovascular invasion, but the only difference observed was tumor size. Subglandular breast implant was associated with a higher incidence of tumor size between 2 and 5 cm in diameter[17].

DIAGNOSTIC DILEMMAS

Oncological vigilance should be increased when taking care of patients with breast implants as a higher rate of malignancy detection error during screening examinations is observed among these women[18]. Silicone and other augmentation materials can attenuate the intensity of X-ray beam or produce an opaque appearance in mammography, which may lead to a malignant mass being overlooked[18]. Moreover, complications, such as capsular contracture, bear a risk of mimicking a BC, resulting in a high number of false positive results. Standard mammographic view seems to be inadequate to evaluate malignant lesions; however, as suggested by Eklund et al., the method of displacing the implant back may allow for an assessment of more of the breast tissue[19,20]. Still, there is a risk of obscuring the posterior part of glandular tissue. A study in a small group of patients with augmented breasts underlined the decreased sensitivity of both standard screening examination, as well as modified one with implant displacement[20]. Additionally, parenchymal perturbations caused by surgical procedures might create scars in the breast tissue and alter the architecture of parenchyma. This can lead to an increased number of false positive results and reduced visualization sensitivity by up to 10%[21].

An extrinsic compression of breast tissue by a subglandular implant may contribute to atrophy of the breast parenchyma, impaired lactation, sensory and vascular impairment, chest wall deformities, and aesthetic changes, including implant rippling, bottoming-out deformity, and loss of upper pole projection[22].

MRI plays a vital role both in the screening and diagnosis of implant complications due to a distinguishable resonance frequency of silicone. This feature allows an assessment of a silent implant rupture, either intra- or extracapsular one. MRI stands out from other imaging methods due to its accuracy corresponding with a higher sensitivity in BC confirmation[23]. Even though MRI seems to be the most promising BC screening method, sufficient evidence is still missing. The process of lesion diagnosis should include a comparison with a previous imaging examination prior to breast surgery[24]. Women at a high risk of developing BC may benefit from adding MRI to mammographic screening[25]. A follow-up screening among asymptomatic women after breast augmentation should involve an annual ultrasound (US) of the breast and axillary lymph nodes, and MRI every five years[26].

Any palpable mass accessible in physical examination in women with breast implant should be assessed using both US and MRI, followed by a biopsy of the palpable mass to obtain a precise diagnosis[24]. Higher sensitivity of MRI is an undeniable advantage in doubtful lesions; however, it implies the need for further lesion evaluation and increased rates of false positive findings[27]. US may detect masses which are occult in mammography and palpation. According to Kolb et al., who studied a group of women with dense breasts only, the sensitivity for BC screening with mammography alone was lower compared to mammography with ultrasound[28]. Sonography is recommended for women aged 40–75 years with dense breasts with average risk of BC[29]. In the case of high breast density, US should be considered as a supplementary examination to screening mammography[30].

CONCLUSION

An adequate approach towards patient counseling prior to cosmetic breast augmentation with implants should be introduced to thoroughly inform the recipient about possible short- and long-term complications. Proper evaluation of symptoms reported by the recipient should involve diagnostic exclusion of BC and BIA-ALCL. Although oncological screening of augmented breasts might be problematic, appropriate imaging modalities should help establish the most reliable differential diagnosis.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

References

1. International Agency for Research on Cancer. Global Cancer Observatory. Available from: https://gco.iarc.fr/ [cited: 24 April 2020].
2. American Society of Plastic Surgeons: 2017 Plastic Surgery Statistics Report. Available from: https://www.plasticsurgery.org/documents/News/Statistics/2017/plastic-surgery-statistics-full-report-2017.pdf [cited: 24 April 2020].
3. Kalaaji A, Bjertness CB, Nordahl C et al.: Survey of breast implant patients: characteristics, depression rate, and quality of life. Aesthet Surg J 2013; 33: 252–257.
4. Green LA, Karow JA, Toman JE et al.: Review of breast augmentation and reconstruction for the radiologist with emphasis on MRI. Clin Imaging 2018; 47: 101–117.
5. Araco A, Gravante G, Araco F et al.: A retrospective analysis of 3,000 primary aesthetic breast augmentations: postoperative complications and associated factors. Aesthetic Plast Surg 2007; 31: 532–539.
6. Alderman AK, Collins ED, Streu R et al.: Benchmarking outcomes in plastic surgery: national complication rates for abdominoplasty and breast augmentation. Plast Reconstr Surg 2009; 124: 2127–2133.
7. Young VL, Watson ME: Breast implant research: where we have been, where we are, where we need to go. Clin Plast Surg 2001; 28: 451–483.
8. Hölmich LR, Vejborg IM, Conrad C et al.: Untreated silicone breast implant rupture. Plast Reconstr Surg 2004; 114: 204–214; discussion 215–216.

9. U.S. Food and Drug Administration: Breast Implants. Available from: https://www.fda.gov/medical-devices/implants-and-prosthetics/breast-implants [cited: 24 April 2020].
10. de Jong D, Vasmel WLE, de Boer JP et al.: Anaplastic large-cell lymphoma in women with breast implants. JAMA 2008; 300: 2030–2035.
11. Leberfinger AN, Behar BJ, Williams NC et al.: Breast implant-associated anaplastic large cell lymphoma: a systematic review. JAMA Surg 2017; 152: 1161–1168.
12. Collett DJ, Rakhorst H, Lennox P et al.: Current risk estimate of breast implant-associated anaplastic large cell lymphoma in textured breast implants. Plast Reconstr Surg 2019; 143 (3S A Review of Breast Implant-Associated Anaplastic Large Cell Lymphoma): 30S–40S.
13. McGuire P, Reisman NR, Murphy DK: Risk factor analysis for capsular contracture, malposition, and late seroma in subjects receiving Natrelle 410 form-stable silicone breast implants. Plast Reconstr Surg 2017; 139: 1–9.
14. Lavigne E, Holowaty EJ, Pan SY et al.: Breast cancer detection and survival among women with cosmetic breast implants: systematic review and meta-analysis of observational studies. BMJ 2013; 346: f2399.
15. Xie L, Brisson J, Holowaty EJ et al.: The influence of cosmetic breast augmentation on the stage distribution and prognosis of women subsequently diagnosed with breast cancer. Int J Cancer 2010; 126: 2182–2190.
16. Cho EH, Shammas RL, Phillips BT et al.: Breast cancer after augmentation: oncologic and reconstructive considerations among women undergoing mastectomy. Plast Reconstr Surg 2017; 139: 1240e–1249e.
17. Azzi AJ, Gornitsky J, Viezel-Mathieu A et al.: The impact of implant location on breast cancer characteristics in previously augmented patients: a systematic literature analysis. J Cancer Prev 2018; 23: 93–98.
18. Ekpo EU, Alakhras M, Brennan P: Errors in mammography cannot be solved through technology alone. Asian Pac J Cancer Prev 2018; 19: 291–301.
19. Eklund GW, Busby RC, Miller SH et al.: Improved imaging of the augmented breast. AJR Am J Roentgenol 1988; 151: 469–473.
20. Fajardo LL, Harvey JA, McAleese KA et al.: Breast cancer diagnosis in women with subglandular silicone gel-filled augmentation implants. Radiology 1995; 194: 859–862.
21. van Breest Smallenburg V, Duijm LEM, Voogd AC et al.: Lower sensitivity of screening mammography after previous benign breast surgery. Int J Cancer 2012; 130: 122–128.
22. Roxo ACW, Nahas FX, Bazi F et al.: Evaluation of the effects of silicone implants on the breast parenchyma. Aesthet Surg J 2015; 35: 929–935.
23. Shah M, Tanna N, Margolies L: Magnetic resonance imaging of breast implants. Top Magn Reson Imaging 2014; 23: 345–353.
24. Orel SG, Schnall MD: MR imaging of the breast for the detection, diagnosis, and staging of breast cancer. Radiology 2001; 220: 13–30.
25. Warner E, Messersmith H, Causer P et al.: Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer. Ann Intern Med 2008; 148: 671–679.
26. Maijers MC, Niessen FB, Veldhuizen JFH et al.: Magnetic resonance imaging screening results compared with explantation results in Poly Implant Prothèse silicone breast implants, recalled from the European market in 2010. Plast Reconstr Surg 2014; 133: 114e–120e.
27. Spick C, Szolar DHM, Preidler KW et al.: 3 Tesla breast MR imaging as a problem-solving tool: diagnostic performance and incidental lesions. PLoS One 2018; 13: e0190287.
28. Kolb TM, Lichy J, Newhouse JH: Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27,825 patient evaluations. Radiology 2002; 225: 165–175.
29. Evans A, Trimboli RM, Athanasiou A et al.; European Society of Breast Imaging (EUSOBI), with language review by Europa Donna–The European Breast Cancer Coalition: Breast ultrasound: recommendations for information to women and referring physicians by the European Society of Breast Imaging. Insights Imaging 2018; 9: 449–461.
30. Warrier S, Tapia G, Goltsman D et al.: An update in breast cancer screening and management. Womens Health (Lond) 2016; 12: 229–239.

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Shailesh Puntambekar, Kshitij Manerikar, Mihir Chitale, Arjun Goel, Deep Bhadra, Ravindra Sathe, Mangesh Panse

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Laparoscopic nerve-sparing radical trachelectomy: retrospective study of four patients

Laparoskopowa radykalna trachelektomia oszczędzająca nerwy: retrospektywna analiza czterech pacjentek

Department of Surgical and Gynaecological Oncology, Galaxy Care Laparoscopy Institute, Opposite Garware College, 25-A, Ayurvedic Rasashala Premises, Karve Road, Pune, Maharashtra – 411004, India
Correspondence: Dr. Shailesh Puntambekar, Department of Surgical and Gynaecological Oncology, Galaxy Care Laparoscopy Institute, Opposite Garware College, 25-A, Ayurvedic Rasashala Premises, Karve Road, Pune, Maharashtra – 411004, India, tel.: +91-9822023706, e-mail: shase63@gmail.com

Abstract

Introduction: Cervical cancer is the third most common cancer in females worldwide. The standard proposed treatment for early-stage carcinoma cervix (IA1–IB1) is radical hysterectomy. Patients desirous of fertility can undergo laparoscopic radical trachelectomy. The aim of this study is to present a series of 4 patients with early-stage cervical cancer who underwent total laparoscopic nerve-sparing radical trachelectomy and laparoscopic pelvic lymphadenectomy. We describe our surgical technique, and compare our results for surgical, oncological and reproductive outcomes with other available studies. **Materials and methods:** A retrospective review study of 4 patients with early-stage cervical cancer who underwent total laparoscopic nerve-sparing radical trachelectomy and laparoscopic pelvic lymphadenectomy in the Galaxy Care Laparoscopy Institute, India between 2016 and 2018. **Results:** Four cases of laparoscopic nerve-sparing radical trachelectomy performed in young patients with stages ranging from IA2 to IB1 invasive squamous cell carcinoma of the cervix. The operative time was 100–150 minutes. The intraoperative and postoperative periods were uneventful. The histopathology report was confirmatory with free margins, and pelvic lymph nodes did not show any tumor metastasis. At routine follow-up, all patients started menstruating, and the bowel-bladder function was normal. All patients had satisfying sexual history in the postoperative period, without any complaints of vaginal dryness or difficulty in coitus. A total of 3 patients attempted conceiving, and 2 succeeded. No recurrence has been seen to date. **Conclusion:** Laparoscopic nerve-sparing trachelectomy in young females desiring fertility is a preferred technique in early-stage cervical cancer. Nerve-sparing techniques specifically enable the prevention of urinary dysfunction, and anorectal and sexual problems postoperatively.

Keywords: laparoscopic, nerve-sparing, trachelectomy, cervical cancer

Streszczenie

Wstęp: Rak szyjki macicy jest trzecim pod względem częstości zachorowań nowotworem u kobiet na świecie. Standardowo stosowaną metodą leczenia tego nowotworu we wczesnym stadium (IA1–IB1) jest radykalna histerektomia. U pacjentek, które chcą zachować płodność, można stosować laparoskopową radykalną trachelektomię. Celem pracy jest przedstawienie serii czterech pacjentek z rakiem szyjki macicy we wczesnym stadium, u których wykonano laparoskopową radykalną trachelektomię oszczędzającą nerwy oraz laparoskopową limfadenektomię miednicy. W pracy opisujemy stosowaną przez nas technikę operacyjną i porównujemy uzyskane wyniki chirurgiczne, onkologiczne i reprodukcyjne z badaniami dostępnymi w literaturze. **Materiały i metody:** Przeprowadzono retrospektywne badanie przeglądowe obejmujące cztery pacjentki z rakiem szyjki macicy we wczesnym stadium, u których w latach 2016–2018 w Galaxy Care Laparoscopy Institute (Indie) wykonano laparoskopową radykalną trachelektomię oszczędzającą nerwy i laparoskopową limfadenektomię miednicy. **Wyniki:** Cztery przypadki laparoskopowej radykalnej trachelektomii oszczędzającej nerwy u młodych pacjentek z inwazyjnym rakiem płaskonabłonkowym szyjki macicy w stadium od IA2 do IB1. Czas zabiegu wyniósł 100–150 minut. Okres śród- oraz pooperacyjny przebiegł bez powikłań. W badaniu histopatologicznym potwierdzono rozpoznanie wraz z marginesami wolnymi. Nie odnotowano zmian przerzutowych do węzłów chłonnych miednicy. Przy rutynowej kontroli stwierdzono, że u wszystkich pacjentek wystąpiła menstruacja; nie zgłaszano upośledzenia czynności jelit ani pęcherza moczowego. Wywiad dotyczący życia seksualnego pacjentek w okresie pooperacyjnym nie wykazał dolegliwości związanych z suchością pochwy ani trudności w odbyciu stosunku seksualnego. Trzy pacjentki podjęły próbę zajścia w ciążę, z czego u dwóch kobiet próba ta zakończyła się powodzeniem. Do czasu opracowania publikacji u żadnej pacjentki nie odnotowano nawrotu choroby. **Wnioski:** Laparoskopowa trachelektomia

oszczędzająca nerwy jest preferowaną metodą chirurgiczną u młodych pacjentek z rakiem szyjki macicy we wczesnym stadium, które chcą zachować płodność. Techniki chirurgiczne oszczędzające nerwy zapobiegają pooperacyjnemu upośledzeniu czynności układu moczowego, nieprawidłowościom odbytniczo-odbytowym i problemom w sferze seksualnej.

Słowa kluczowe: laparoskopowa, oszczędzająca nerwy, trachelektomia, rak szyjki macicy

INTRODUCTION

Cervical cancer is the third most common cancer in females worldwide, and approximately 85% of these cases and deaths occur in developing countries[1]. The standard proposed treatment for early-stage carcinoma cervix (IA1–IB1) was radical hysterectomy[2]. Dargent et al. in 1994 first described vaginal radical trachelectomy (VRT)[3], whereas open abdominal radical trachelectomy (ART) was introduced by Smith et al. later[4]. Both VRT and ART were fertility-sparing trachelectomy techniques which changed the overall approach for early cervical cancer surgeries.

Patients desirous of fertility can undergo radical trachelectomy either by abdominal, vaginal or laparoscopic route[2]. Laparoscopic radical trachelectomy (LRT) is now emerging as the new mode of management in minimal invasive cancer surgery.

The aim of this study is to present a series of 4 patients with early-stage cervical cancer who underwent total laparoscopic nerve-sparing radical trachelectomy (TLNSRT) and laparoscopic pelvic lymph node dissection (LPLND) at our institute. We describe our surgical technique of TLNSRT, and compare our results for surgical, oncological and reproductive outcomes with other available studies.

MATERIALS AND METHODS

A retrospective review study of 4 patients with early-stage cervical cancer who underwent TLNSRT and LPLND was carried out in the Galaxy Care Laparoscopy Institute, Pune, Maharashtra, India between 1st January 2016 and 31st December 2018. All 4 surgeries were performed by same surgical team headed by Dr. Shailesh Puntambekar.

The demographic details of all patients were recorded as per protocol. All patients underwent necessary investigations for confirmation of diagnosis of cervical cancer including PAP smear, colposcopy and biopsy, and magnetic resonance imaging (MRI) of the pelvis.

The inclusion criteria were: (1) patient desirous of fertility, (2) tumor size less than 2 cm in the largest diameter, (3) International Federation of Gynecology and Obstetrics (FIGO) stages IA1 to IB1, (4) absence of distant metastasis on MRI, (5) absence of unfavorable histologic types (small-cell carcinoma, neuroendocrine tumors, sarcoma), (6) no suspicion of pelvic lymph node involvement and no deep stromal invasion (>10 mm). Patients not meeting the above criteria were excluded from the study.

All patients were informed about their malignancy, and all the available modalities of treatment were explained in detail to them including the chances of future pregnancy. Informed and written consent were obtained from all patients prior to surgery.

Surgical technique of TLNSRT

The patient was placed in the modified Lloyd-Davies position at 30–45 degree tilt. A total of 5 ports were used: a 10 mm camera port at the umbilicus and a 10 mm working port at the right McBurney's point, a 5 mm port in the para-rectus position in the mid-clavicular line. Mirror image ports were placed on the left side. The surgeon operated from the right side, and the assistant was on the left side. The uterus was hitched at the level of fundus to the anterior abdominal wall using Vicryl No. 1 sutures (Fig. 1).

The dissection started with cutting the round ligament on the right side with the help of harmonic shears and extending the cut downwards towards the utero-vesical fold. Traction was given to the uterus by the assistant surgeon by pulling the uterus cranially holding the opposite ovarian ligament. The bladder was pushed down after dissecting

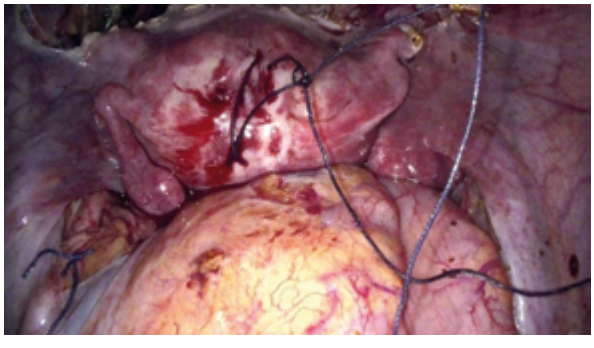

Fig. 1. Hitching of the uterus to the anterior abdominal wall

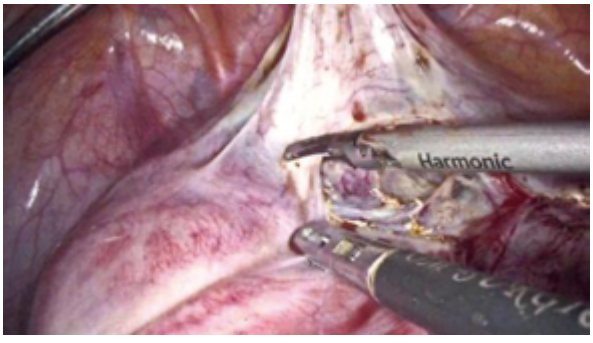

Fig. 2. Dissecting the uterovesical fold starting from the right-sided round ligament

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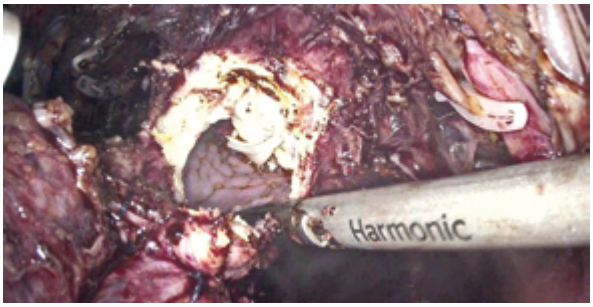

Fig. 3. Colpotomy after stitching the vagina below the level of the external os

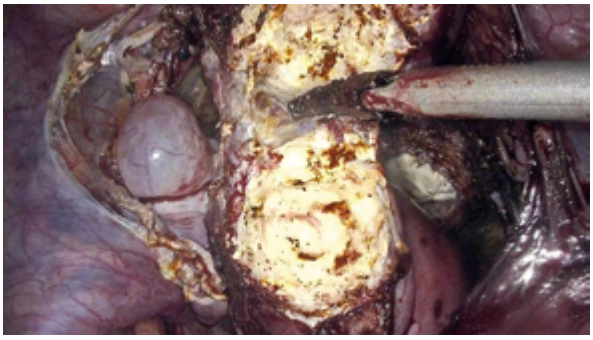

Fig. 4. Proximal part of the cervix cut with the help of harmonic shears

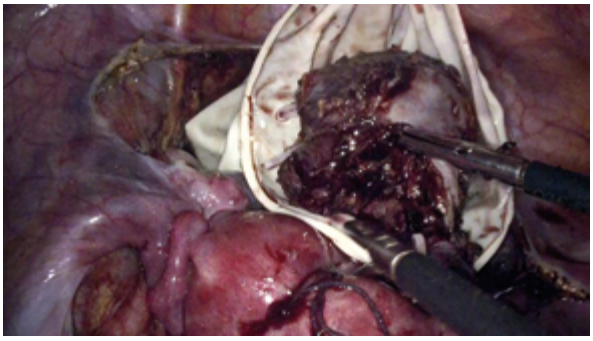

Fig. 5. Specimen inserted into the endo-bag and exteriorized through the vault

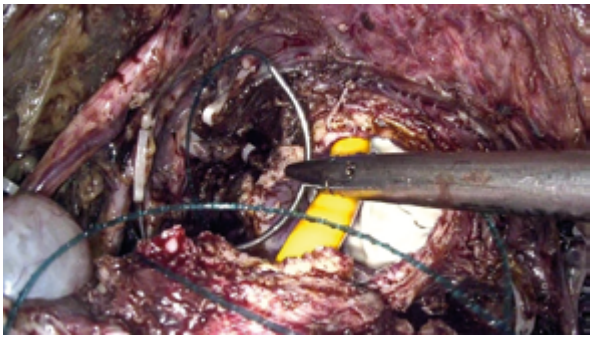

Fig. 6. Isthmus of the uterus sutured with the vaginal vault

the uterovesical fold. The dissection was carried out until the opposite round ligament was reached (Fig. 2).

A posterior 'U' cut was started from the right side. The peritoneum medial to the infundibulopelvic ligament (IP ligament) was lifted, and the ureter was visualized at the level of the sacral promontory. The fold of the peritoneum was cut medial to the ureter (Okabayashi's space), and dissection was carried out until reaching the pouch of Douglas (POD), keeping the ureter laterally. The inferior hypogastric nerve and its branches to the rectum, cervix and urinary bladder were dissected in this space and preserved. A similar procedure was done on the opposite side using harmonic shears. With cranial traction to the rectum, the peritoneum was opened in the POD, and the posterior vaginal wall was further dissected from the rectum.

The left ureter was then retracted medially, and the dissection was carried out parallel and lateral to the ureter to open the lateral pararectal space (Latzko's space) with the help of harmonic shears. The internal iliac artery forms the lateral boundary of this space. Further dissection along the ureter anteriorly identified the uterine artery, as it is the only structure which crosses this space from lateral to medial. The uterine artery was traced to its origin from the anterior division of the internal iliac artery and cauterized, clipped and cut. The uterine vein passing from below the ureter was also cauterized, clipped and cut medial to the inferior hypogastric nerve and its branches. The uterosacral and cardinal ligaments were cut with harmonics preserving the hypogastric nerves supplying the bladder and uterus.

Ureteric tunnel dissection was done with the aid of Maryland forceps which helped to visualize the ureter as far as the uretrovesical junction. Similar steps were repeated on the right side, and the bladder was pushed further down.

A purse string suture with Vicryl No. 1 was taken below the level of the external os to prevent the spillage of contents in the abdominal cavity as well as in the vagina while exteriorizing the specimen. A cut was made posteriorly at the origin of the uterosacral ligament, and colpotomy was done. The incision extended circumferentially, and the uterus with the cervix was separated from vagina with the help of harmonic shears (Figs. 3, 4).

The peritoneum was cut at the bifurcation of the left common iliac artery, and the dissection was carried out medial to the external iliac vessels with the help of suction cannula. All the fibrofatty tissue present along the external iliac vessels medially was removed until the obturator nerve and iliac bone were reached. A similar procedure was done on the right side (Figs. 5, 6).

A thorough normal saline wash was given, and the bladder and rectum were checked for any serosal or mucosal tears. After confirmation of no bladder and rectum injury, the isthmus of the uterus was sutured with the vaginal vault using barbed sutures in a continuous manner with no 14 Foley catheter inside the endometrial cavity. The round ligament cut ends were re-sutured, and the anterior uterovesical fold of the peritoneum was closed. Cervical cerclage was not done, as it might cause irritation of the anastomotic site. No intraoperative complications were seen (Fig. 7).

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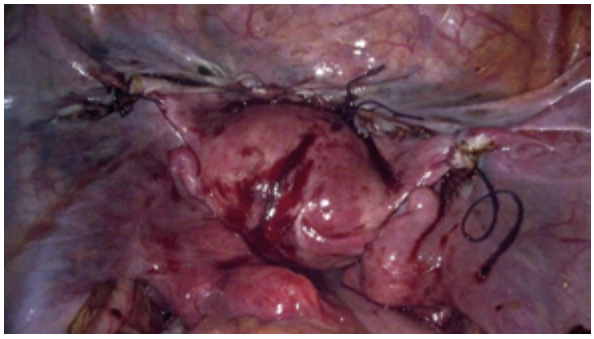

Fig. 7. Bilateral round ligaments and uterovesical folds closed back

The surgical approach for laparoscopic pelvic lymphadenectomy (LPL) was as per standard treatment for any cervical cancer, and the nerve-sparing intent did not require any specific different techniques.

The total operative time and blood loss were noted after each surgery. The Foley catheter was removed from the uterus on postoperative day 1, and the urinary Foley catheter was removed on postoperative day 2 in view of the nerve-sparing surgery. The patients were asked to maintain abstinence from sexual activity for 4 weeks.

The patients were followed up on postoperative day 7, and the post-void residual urine and bowel functions were

Parameter	Case 1	Case 2	Case 3	Case 4
Age [years]	24	32	29	31
Gravidity, parity, abortion history	G2P0A2	G1P1A0	G0P0A0	G2P2A0
PAP smear and human papilloma virus (HPV testing, if done – high-risk type – 16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59)	Atypical squamous cells. 16 and 51 positive	Atypical squamous cells. 16, 18, 35 positive	Atypical squamous cells. 33, 34, 35, 39 positive	Atypical squamous cells. HPV testing not done
Colposcopic biopsy	Squamous cell carcinoma (SCC)	SCC	SCC	SCC
Per vaginal examination	Cervix: no gross lesion. Parametrium and upper vagina: free from tumor	Cervix: thickened wall. Parametrium and upper vagina: free from tumor	Cervix: palpable lesion? Parametrium and upper vagina: free from tumor	Cervix: no gross lesion. Parametrium and upper vagina: free from tumor
MRI	Thickening of anterior lip of cervix with no adjacent structure involvement	Thickening of anterior and posterior lip of cervix with no adjacent structure involvement	Visible growth of 1.7 × 1.1 cm on anterior cervical wall without any deep infiltration or adjacent structure involvement	Diffuse thickening of anterior lip of cervix without any obvious visualized growth or lesion
FIGO staging	IA2	1B1	1B1	1A2
Histopathological report (HPR)	SCC. Margins: free of tumor. Residual tumor: nil. Pelvic lymph nodes: no metastasis	SCC. Margins: free of tumor. Residual tumor: nil. Pelvic lymph nodes: no metastasis	SCC. Margins: free of tumor. Residual tumor: nil. Pelvic lymph nodes: no metastasis	SCC. Margins: free of tumor. Residual tumor: nil. Pelvic lymph nodes: no metastasis
Mean numbers of pelvic lymph nodal yield	24	22	31	19
Average intraoperative blood loss [mL]	70	90	100	60
Operative time [minutes]	120	110	160	90
Postoperative hospital stay [days]	3	4	6	3
Duration of postoperative catheterization [DPC in days]	2	2	2	2
Post-void residual volume on day 7 [mL]	10	15	25	20
Urinary complaints	Incontinence: none. Retention: none. Dysuria: none. Urgency: none	Incontinence: none. Retention: none. Dysuria: none. Urgency: none	Incontinence: none. Retention: none. Dysuria: none. Urgency: none	Incontinence: none. Retention: none. Dysuria: none. Urgency: none
Anorectal complaints	Constipation: none. Diarrhea: none. Fecal incontinence: none	Constipation: none. Diarrhea: none. Fecal incontinence: none	Constipation: none. Diarrhea: none. Fecal incontinence: none	Constipation: none. Diarrhea: none. Fecal incontinence: none
Vaginal dryness and difficulty in coitus	None	None	None	None
Dyspareunia	None	None	None	None
Sexual satisfaction (NONE, POOR, AVERAGE, GOOD)	GOOD	GOOD	AVERAGE	GOOD
Menstrual cycle after surgery [month]	1st	1st	2nd	1st
Pregnancies post operation to date	1	Nil (not conceived)	1	None
Recurrence for 2 years	None	None	None	None

Tab. 1. Results of all four patients

Parameters of comparison	Lee et al.[12]	Bafghi et al.[10]	Park et al.[11]	Rendón et al.[2]	Martin and Torrent[9]	Kim et al.[13]	Puntambekar et al.
Number of patients	2	6	4	1	9	27	4
Mean age [years]	32	30	29.5	31	NA	29	29
Stage of disease	IBI – 2	IAII – 2 IBI – 4	IAII – 1 IBI – 3	IBI	IAII – 2 IB1 – 7	IBI – 26 IIA – 1	IAII – 2 IBI – 2
Histological type	SCC	SCC – 5 Other – 1	SCC	Adenocarcinoma	SCC – 6 Adenocarcinoma – 3	SCC – 20 Adenocarcinoma – 6 Others – 1	SCC
Lymphovascular space invasion (LVSI)	NA	1	NA	0	NA	0	0
Mean number of lymph nodes	35	18	NA	10	NA	25.7	24
Average blood loss [mL]	650	NA	185	100	NA	332	80
Mean operative time [minutes]	352.5	201	250	340	270	290	120
Transfusions	NA	NA	0	0	NA	6	None
Mean hospital stay [days]	12.5	4.5	6	2	NA	9	4
Miscarriages post surgery	NA	1	0	0	NA	2	0
Pregnancies post surgery	NA	2	0	0	2	3	2
Recurrence rate	0	1	1	0	1	1	0

Tab. 2. Available literature studies and their data for comparison

evaluated. All the patients were followed up at months 1, 3 and 6, and years 1 and 2. They were asked in detail about any complaints of urinary incontinence, urinary retention, dysuria, urgency, anorectal dysfunctions such as constipation, diarrhea, and fecal incontinence. Furthermore, detailed history of reduced libido, vaginal dryness, difficulty in coitus, dyspareunia, and a decrease in orgasm was reported. Sexual satisfaction was marked by patients themselves on a scale of NONE, POOR, AVERAGE, GOOD.

The histopathology reports of all patients with margin status, residual tumor and pelvic lymph node yield were noted carefully. Menstrual cycle details, pregnancy status and miscarriages, if any, with recurrence rates were meticulously noted. All data was compiled in a database using Microsoft Excel.

RESULTS

The detailed findings of all 4 patients are listed in Tab. 1.

DISCUSSION

Cervical cancer is one of the leading causes of cancer-related deaths in the female population worldwide[1]. Latest diagnostic modalities and better screening programs for cervical cancer have led to early detection of cancer mainly in young females. The treatment for early cervical cancer i.e. FIGO stages IA1 to IB2, is mainly radical surgery with or without subsequent radiotherapy, depending on presence or absence of adjunctive risk factors (lymphovascular invasion, grading).

Radical surgery often does not spare fertility, leading to psychosexual dysfunction and poor quality of life[5,6]. An increase in the number of younger patients with cervical cancer desirous of future pregnancy has recently led to a revision in the radical surgical approaches, so that fertility can be preserved without compromising the oncological principles.

There are ample studies advocating vaginal radical trachelectomy as well as open abdominal radical trachelectomy, but very few regarding laparoscopic fertility-preserving nerve-sparing radical trachelectomy. Cibula et al. in 2005 first reported the case of laparoscopic radical trachelectomy and considered it an alternative technique which can be practiced if one has an adequate knowledge of laparoscopic surgery[7]. According to Rendón et al., only 44 cases of laparoscopic abdominal radical trachelectomy had been reported until 2012 in the available literature[2], whereas Vieira et al. in 2015 in their retrospective study noted that there were only 42 patients who underwent minimally invasive surgery (laparoscopic or robotic) for early cancer cervix[8].

We had a total of 4 patients in our study, similarly to other studies in their series[2,9–12]. The largest series published to date is that by Kim et al., consisting of a total of 27 patients who underwent laparoscopic trachelectomy[13]. The mean patient age in our study was 29 years (range: 24–31), and the result was consistent with other available studies (Tab. 2).

All the available literature studies like ours were strict with respect to the inclusion criteria, and hence all the patients had early-stage cervical cancer (FIGO IA1–IB1). All patients in our series were diagnosed with squamous cell carcinoma (SCC), whereas Martin and Torrent in their study of 9 patients had 3 patients with adenocarcinoma[9].

Lymphovascular space invasion was noted in 1 out of 10 patients in the study by Bafghi et al., necessitating referral for radiation and chemotherapy[10], however, other studies like ours did not encounter this.

There was a vast difference in operative time across different available literature studies. Our mean operative time was 120 min, with a range of 90 to 160 min. Bafghi et al. had a mean surgery time of 201 min[10], and other studies had their mean operative times of 352.5 min, 340 min, and 270 min, respectively[2,9,12] (Tab. 2). Comparing to other available studies with ART or VRT, the duration of surgery was significantly longer in laparoscopy. Kucukmetin et al. mention that the median operative time was longer with the laparoscopic approach compared to the laparotomic approach (320 vs. 192.5 minutes)[14]. Vieira et al. observed that the median surgical time for minimal invasive surgery (MIS) including laparoscopic or robotic modalities was 272 min (range: 130–441 min) compared with 270 min (range: 150–373 min) for open surgery[8]. However, our operative time was shorter than in any available studies. Although the duration of surgery is not a criterion of comparison, we need to emphasize that the operative time vastly depends on the experience and expertise in laparoscopic surgery.

The introduction of the laparoscopic approach has significantly decreased intraoperative complications as well as postoperative morbidity. We did not encounter any intraoperative or postoperative complications in our patients, similarly to some other studies[10,11,13]. The latest study by Vieira et al. found that intraoperative complications such as bladder injury, fallopian tube injury and vascular injury were seen in 3% of cases in MIS including both laparoscopic and robotic surgeries. Also, they also found that there was not much difference in the rate of postoperative complications in MIS vs. open surgery (30 vs. 31%)[8] (Tab. 2).

Blood loss during surgery was significantly less in cases of LRT than ART or VRT[1,6–8]. In our series of 4 patients, an average intraoperative blood loss was only 80 mL, which was far less than in any other published studies where the blood loss volume was 650, 332, and 185 mL[11–13]. Six out of 27 patients in the study by Kim et al. needed intraoperative blood transfusion[13] (Tab. 2).

Lee et al. in their series of 2 patients noted that the mean postoperative hospital stay was 12.5 days[12], whereas two other studies reported that the mean hospital stay was 9 and 6 days, respectively[11,13]. Our 4 patients had an average hospital stay of 4 days (range: 3–6 days). Saadi et al. in their study of 4 patients had a mean length of hospital stay of 33 hours (range: 24–36 hours)[6]. It was the only available study who had a shorter mean hospital stay than ours. Mean number of pelvic lymph node yield was 24 (range: 19–31) in our study. Kim et al. in his 27 patients had 25.7 lymph nodes[13], whereas Lee et al. in their 2 patients observed that the mean number of lymph nodes was as high as 35[12]. However, one study noted that the median lymph node count was higher in open surgery compared to MIS (22 vs. 17)[8] (Tab. 2).

Urinary and/or anorectal complaints and sexual dysfunction post radical trachelectomy is closely related to autonomic dysregulations after surgical disruptions[15–18]. Nerve-sparing radical trachelectomy, which deals with the preservation of sympathetic nerves in the hypogastric nerve and parasympathetic nerves in the pelvic splanchnic nerve with vesical branches of the pelvic plexus, reduces the chances of autonomic dysfunction[19]. Conventional radical trachelectomy (CRT) may increase the days of postoperative catheterization (DPC) and urinary incontinence and frequency[16,17]. We removed the Foley catheter on postoperative day 2 in all 4 cases, and none of our patients had any complaints of incontinence, frequency or dysuria. We confirmed bladder function on postoperative day 7, and at subsequent follow-ups by investigating post-void residual volume which was insignificant in all patients. Kim et al. in their meta-analyses of 2,253 patients from January 2000 to February 2014 concluded that autonomic nerve preservation in nerve-sparing radical trachelectomy (NSRT) had significant impact on urinary function, and observed that DPC was shorter, and urinary incontinence and frequency were less common in NSRT[15].

Barnes et al. mentioned that injury to the pelvic autonomic nerves in CRT might cause internal sphincter dysregulation and decreased rectal sensation[20]. We found no anorectal complaints such as constipation, diarrhea or fecal incontinence in our patients until the last follow-up. We observed that in our patients bowel function returned to normalcy on postoperative day 2. A meta-analysis hypothesized that NSRT might reduce the incidence of functional defecation disorders such as constipation, like in our study[15].

One of the major advantages of TLNSRT is preserving sexual function in young females. Currently, there are no relevant studies comparing CRT and TLNSRT in terms of sexual dysfunction outcomes. We in our 4 cases carefully compiled the data on the patients' sexual functionality in the post-surgery period. All our patients were allowed coitus 4 weeks after surgery. In our series, none of the patients had any complaints of vaginal dryness or difficulty in lubrication during the coitus. We found no dyspareunia or inability to achieve an orgasm. Three out of 4 patients rated their post-surgical sexual activity as GOOD, and it was comparable to their sexual function prior to surgery.

Available literature data suggests that autonomic nerves damage during CRT may change the neurogenic control of the blood vessels of the vaginal wall, disturbing the vaginal blood flow during sexual arousal and lubrication, and leading to poor sexual activity[21,22]. Kim et al. in their large analysis concluded that only autonomic nerve preservation might not be associated with an improvement in sexual functions, and the authors believe that post-surgery vaginal shortness, tissue fibrosis, radiotherapy, ovarian function status, and psychological factors might also be linked to the sexual function outcome[15].

Preserving fertility is the major goal of LRT. We carefully monitored all our patients during the postoperative follow-up period, and noticed that 3 out of 4 patients had their regular menstruation in the first postoperative month, and the remaining patient had her menstrual cycle in the second postoperative month. Three out of 4 patients in our series

attempted to conceive, and 2 succeeded. We did not find any miscarriages post-surgery in our series. In a series of 27 patients studied by Kim et al., a total of 6 patients attempted to conceive, and 3 were able to get pregnant[13]. Out of these 3 patients, 2 patients had a miscarriage. Ebisawa et al. in their retrospective study of 56 patients found that 25 women attempted to conceive, and 13 succeeded, for a total of 21 pregnancies[23]. Five patients had first trimester miscarriages, 2 patients – second trimester miscarriages, and 13 – live births. There are also some case series in which patients could not conceive to date[2,11] (Tab. 2).

A retrospective review of 4 institutions where patients underwent radical trachelectomy for early-stage cervical cancer found that there was only one recurrence in a patient who underwent ART and none in LRT[8]. We did not find recurrence in our 4 patients during 2 years of follow-up, like in some other studies[2,12]. Kim et al. in their series of 27 patients found recurrence in only 1 patient[13], similarly to a few other studies[9–11] (Tab. 2).

CONCLUSION

We found that laparoscopic radical trachelectomy was the best available technique for early-stage cervical cancer in women desirous of children. Nerve-sparing techniques specifically enable the prevention of urinary dysfunction, anorectal problems and sexual problems postoperatively. Laparoscopic radical trachelectomy is minimally invasive in nature, with a shorter recovery time.

We conclude that laparoscopic nerve-sparing radical trachelectomy is a novel approach to minimally invasive gynecologic cancer surgery, and a major breakthrough in the field of reproductive medicine (if performed by trained surgeons), with excellent perioperative outcomes. Further such studies will definitely contribute to building consensus about these findings.

Conflict of interest

No conflict of interest with respect to any financial or commercial entities. No conflict of interest amongst authors regarding the subject matter in the manuscript or submission.

References

1. Gizzo S, Ancona E, Saccardi C et al.: Radical trachelectomy: the first step of fertility preservation in young women with cervical cancer (Review). Oncol Rep 2013; 30: 2545–2554.
2. Rendón GJ, Ramirez PT, Frumovitz M et al.: Laparoscopic radical trachelectomy. JSLS 2012; 16: 503–507.
3. Dargent D, Brun JL, Roy M et al.: La trachelectomie elargie (TE), une alternative a l'hysterectomie radical dans le traitment des cancers infiltrants developpes sur la face externe du col uterin. J Obstet Gynecol 1994; 2: 285–292.
4. Smith JL, Boyle DC, Corless DJ et al.: Abdominal radical trachelectomy: a new surgical technique for the conservative management of cervical carcinoma. Br J Obstet Gynaecol 1997; 104: 1196–1200.
5. Rob L, Skapa P, Robova H: Fertility-sparing surgery in patients with cervical cancer. Lancet Oncol 2011; 12: 192–200.
6. Saadi JM, Perrotta M, Orti R et al.: Laparoscopic radical trachelectomy: technique, feasibility, and outcomes. JSLS 2015; 19: e2013.00248.
7. Cibula D, Ungár L, Pálfalvi L et al.: Laparoscopic abdominal radical trachelectomy. Gynecol Oncol 2005; 97: 707–709.
8. Vieira MA, Rendón GJ, Munsell M et al.: Radical trachelectomy in early-stage cervical cancer: a comparison of laparotomy and minimally invasive surgery. Gynecol Oncol 2015; 138: 585–589.
9. Martin A, Torrent A: Laparoscopic nerve-sparing radical trachelectomy: surgical technique and outcome. J Minim Invasive Gynecol 2010; 17: 37–41.
10. Bafghi A, Castaigne D, Pomel C: Radical trachelectomy: from the laparoscopic approach to the vaginal route. J Gynecol Obstet Biol Reprod (Paris) 2006; 35: 696–701.
11. Park NY, Chong GO, Cho YL et al.: Total laparoscopic nerve-sparing radical trachelectomy. J Laparoendosc Adv Surg Tech A 2009; 19: 53–58.
12. Lee CL, Huang KG, Wang CJ et al.: Laparoscopic radical trachelectomy for stage Ib1 cervical cancer. J Am Assoc Gynecol Laparosc 2003; 10: 111–115.
13. Kim JH, Park JY, Kim DY et al.: Fertility-sparing laparoscopic radical trachelectomy for young women with early stage cervical cancer. BJOG 2010; 117: 340–347.
14. Kucukmetin A, Biliatis I, Ratnavelu N et al.: Laparoscopic radical trachelectomy is an alternative to laparotomy with improved perioperative outcomes in patients with early-stage cervical cancer. Int J Gynecol Cancer 2014; 24: 135–140.
15. Kim HS, Kim K, Ryoo SB et al.: Conventional versus nerve-sparing radical surgery for cervical cancer: a meta-analysis. J Gynecol Oncol 2015; 26: 100–110.
16. Querleu D, Narducci F, Poulard V et al.: Modified radical vaginal hysterectomy with or without laparoscopic nerve-sparing dissection: a comparative study. Gynecol Oncol 2002; 85: 154–158.
17. Todo Y, Kuwabara M, Watari H et al.: Urodynamic study on post-surgical bladder function in cervical cancer treated with systematic nerve-sparing radical hysterectomy. Int J Gynecol Cancer 2006; 16: 369–375.
18. Raspagliesi F, Ditto A, Hanozet F et al.: Nerve-sparing radical hysterectomy in cervical cancer: evolution of concepts. Gynecol Oncol 2007; 107 (Suppl 1): S119–S121.
19. Rob L, Halaska M, Robova H: Nerve-sparing and individually tailored surgery for cervical cancer. Lancet Oncol 2010; 11: 292–301.
20. Barnes W, Waggoner S, Delgado G et al.: Manometric characterization of rectal dysfunction following radical hysterectomy. Gynecol Oncol 1991; 42: 116–119.
21. Pieterse QD, Ter Kuile MM, Deruiter MC et al.: Vaginal blood flow after radical hysterectomy with and without nerve sparing. A preliminary report. Int J Gynecol Cancer 2008; 18: 576–583.
22. Maas CP, ter Kuile MM, Laan E et al.: Objective assessment of sexual arousal in women with a history of hysterectomy. BJOG 2004; 111: 456–462.
23. Ebisawa K, Takano M, Fukuda M et al.: Obstetric outcomes of patients undergoing total laparoscopic radical trachelectomy for early stage cervical cancer. Gynecol Oncol 2013; 131: 83–86.

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Eftekhar Hassan Al-Ojaimi[1], Janan Nabeel Alajaimi[2]

A rare case of perineal endometriosis in an episiotomy scar

Rzadki przypadek endometriozy umiejscowionej w bliźnie po nacięciu krocza

[1] Department of Obstetrics and Gynaecology, Al Zahra Hospital, Dubai, United Arab Emirates
[2] Royal College of Surgeons in Ireland – Medical University of Bahrain, Kingdom of Bahrain
Correspondence: Dr. Eftekhar Hassan Al-Ojaimi, P.O. Box. 37320, Dubai, United Arab Emirates, tel.: 0097156 6608555, fax: 009714 3481255, e-mail: eojaimi@gmail.com

Abstract

Introduction: Episiotomy scar endometriosis is an extremely rare entity and often causes diagnostic uncertainty. **Case report:** We report a case of perineal swelling and cyclical pain following obstetric delivery with episiotomy. Magnetic resonance imaging revealed possible episiotomy scar endometriosis confined to the perineum. Wide surgical excision was performed and the histopathological report confirmed the diagnosis. No recurrence was noted after the surgery. **Conclusion:** Episiotomy scar endometriosis should be considered whenever a woman with previous episiotomy presents with cyclical pain or a nodule in the perineum. Magnetic resonance imaging can assist with the diagnosis and wide excision remains the best treatment option for this condition.

Keywords: episiotomy, perineal endometriosis, scar endometriosis

Streszczenie

Wstęp: Endometrioza umiejscowiona w bliźnie po nacięciu krocza (episiotomii) jest niezwykle rzadką jednostką chorobową i częstą przyczyną wątpliwości diagnostycznych. **Opis przypadku:** W pracy przedstawiono przypadek obrzęku w okolicy krocza z towarzyszącym cyklicznym bólem u pacjentki po porodzie siłami natury, podczas którego wykonano nacięcie krocza. Na podstawie badania metodą rezonansu magnetycznego wysunięto podejrzenie ogniska endometriozy umiejscowionej w bliźnie po episiotomii i ograniczonej do okolicy krocza. Wykonano szerokie wycięcie chirurgiczne zmiany. Wynik badania histopatologicznego potwierdził rozpoznanie. Po przeprowadzonym zabiegu nie odnotowano nawrotu choroby. **Wnioski:** Rozpoznanie endometriozy w bliźnie po episiotomii należy brać pod uwagę w każdym przypadku pacjentki z nacięciem krocza w wywiadzie, u której występują cykliczne dolegliwości bólowe lub guzowata zmiana w obrębie krocza. Pomocne w diagnostyce może okazać się badanie metodą rezonansu magnetycznego, natomiast najlepszą opcją leczenia pozostaje szerokie wycięcie chirurgiczne zmiany.

Słowa kluczowe: endometrioza, nacięcie krocza (episiotomia), endometrioza krocza, endometrioza umiejscowiona w bliźnie

INTRODUCTION

Endometriosis is defined as the presence of functional endometrial tissue and stroma outside the uterine cavity. It is one of the most common gynecological disorders, seen in 10–25% of women in reproductive age group[1]. The etiology and pathogenesis of endometriosis remains controversial. Several theories about the pathogenesis of endometriosis have generally been attributed to direct implantation, lymphatic dissemination, coelomic metaplasia, or hematogenous spread. Other factors, such as immunological, familial and genetic factors, may also be involved in the pathogenesis of this disease.

Endometriosis is commonly observed in the pelvic organs, especially the ovaries, fallopian tubes, pelvic peritoneum, uterine ligaments and pouch of Douglas. Extra-pelvic localization of endometrial tissue is rather uncommon, accounting for approximately 12% of all cases[2]. The most common extra-pelvic type is surgical scar endometriosis[3], which is more frequently seen in scars after cesarean sections, and rarely in episiotomy and other obstetrical, gynecologic and non-gynecologic surgeries. Episiotomy scar endometriosis is extremely rare, occurring in only 0.00007% of births[4]. As episiotomy is frequently performed at the time of vaginal delivery, one should know about this rare entity, its etiopathogenesis, various diagnostic measures and management options. Herein, we report a case of episiotomy scar endometriosis successfully treated with wide surgical excision with excellent results.

CASE REPORT

A 36-year-old multiparous woman presented with pain and swelling in perineal region for three years. She was initially evaluated by a general surgeon and diagnosed with a perineal abscess. An incision and drainage were performed, and

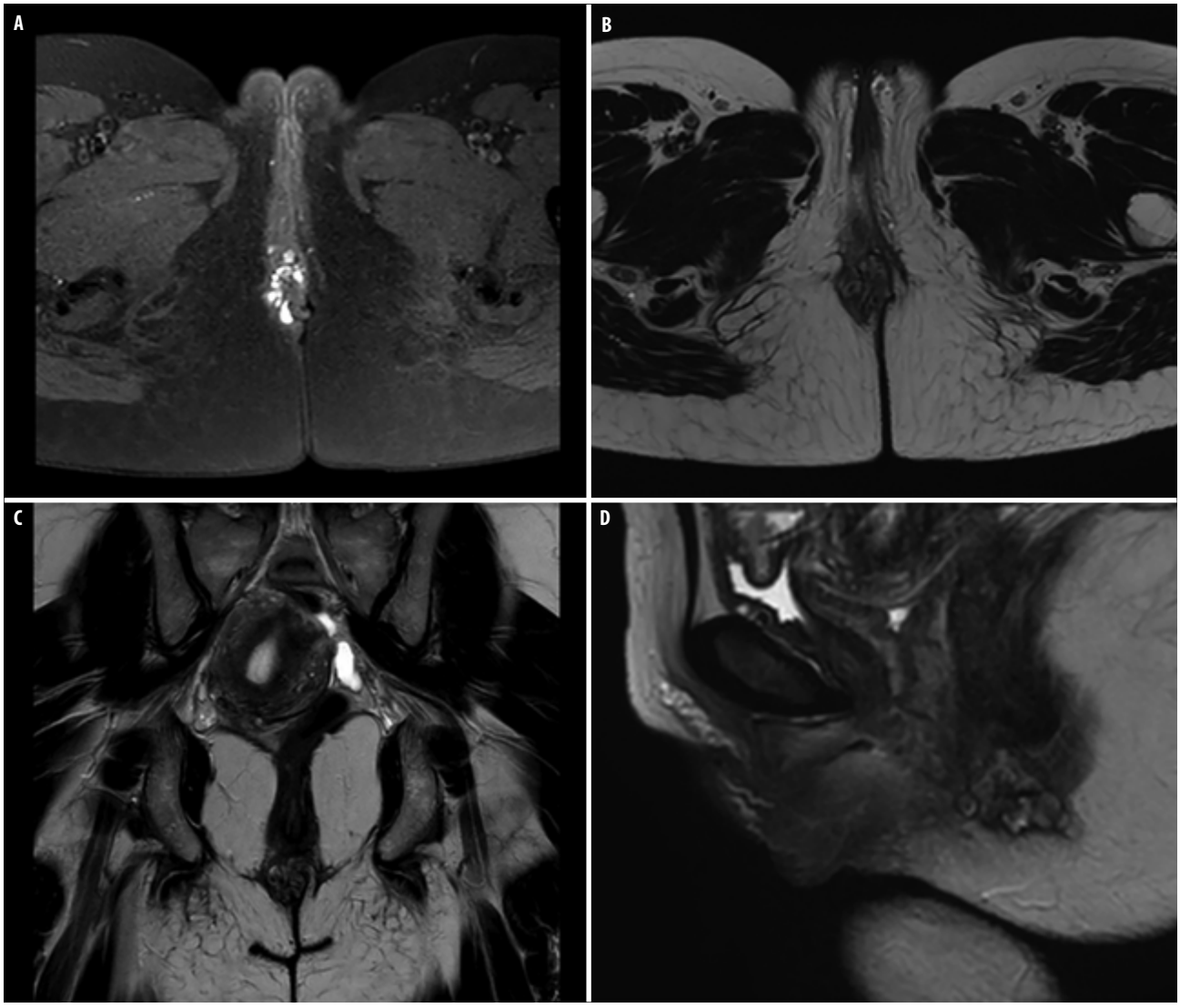

*Fig. 1. Pelvic MRI shows right perineal lesion. (**A**) Axial T1-weighted image, (**B**) axial T2-weighted image, (**C**) coronal T2-weighted image, (**D**) sagittal T2-weighted image*

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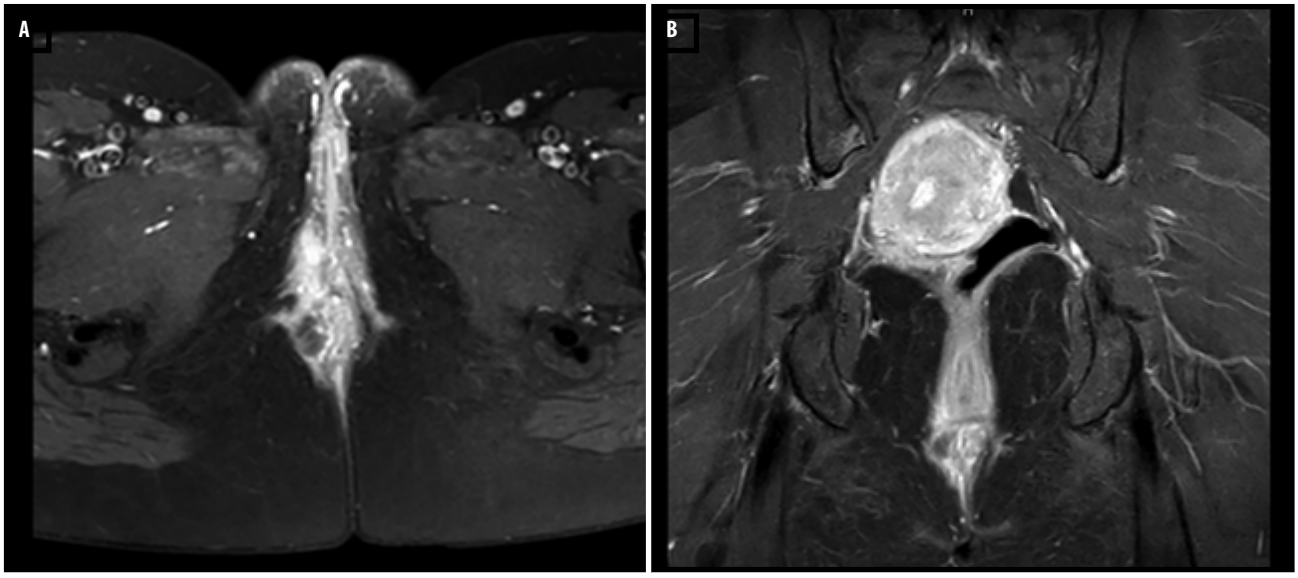

*Fig. 2. Pelvic MRI after injecting IV contrast shows enhancement of the lesion with a linear sinus tract in the right perineal region. (**A**) Axial view, (**B**) coronal view*

blood with dirty material was evacuated. The postoperative period was uncomplicated and the patient experienced no pain. However, five months later a clinical relapse occurred when she completely abandoned oral contraceptives. The pain was progressive and cyclical, correlated with her menstrual cycle and appeared several days before its onset. She had 3 previous vaginal deliveries with a right medio-lateral episiotomy performed each time. Her last parturition was 10 years ago. A year after the last delivery, the patient felt a small swelling at the episiotomy site, and 6 years later,

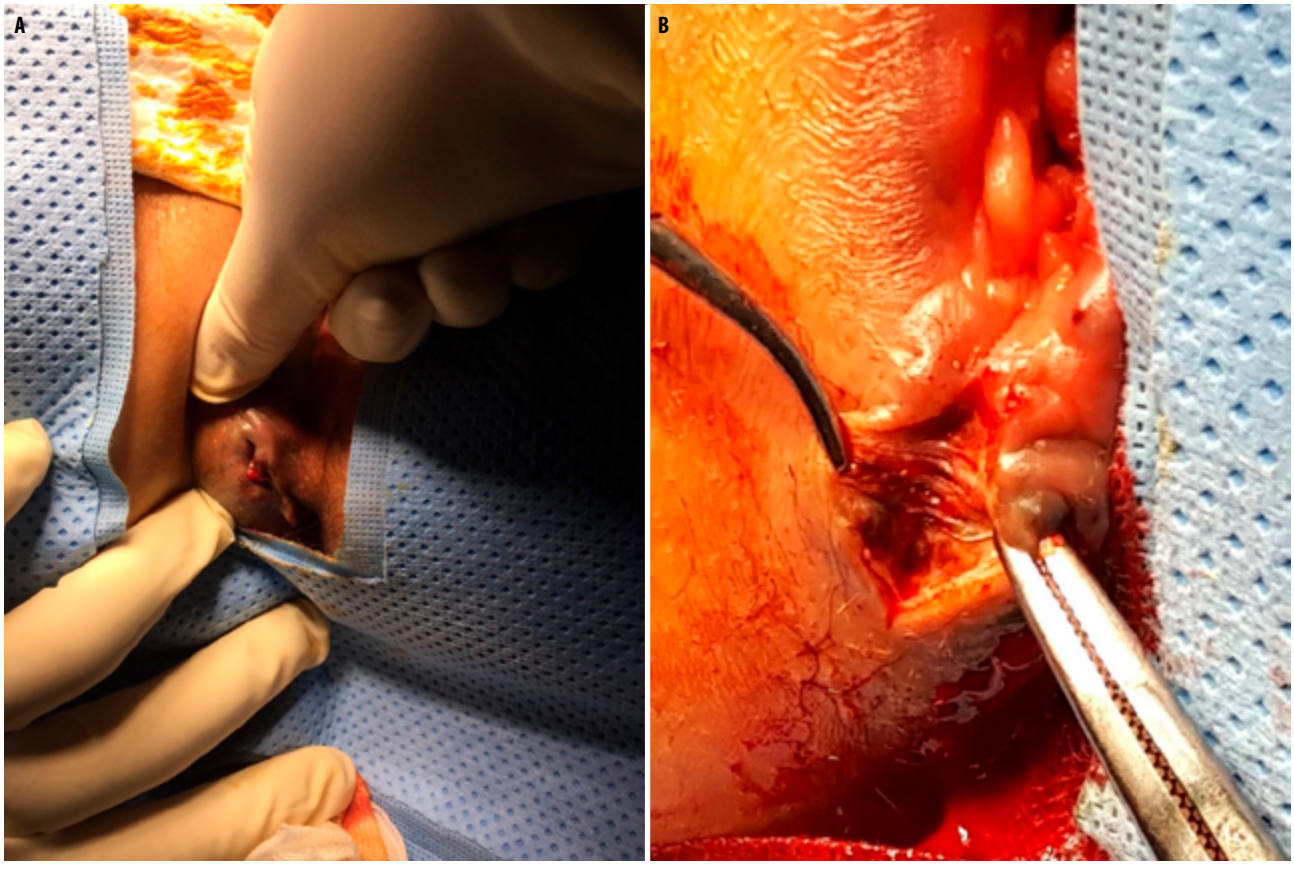

*Fig. 3. Perineal mass with the (**A**) sinus opening discharging blood, (**B**) brownish endometriotic-like deposit*

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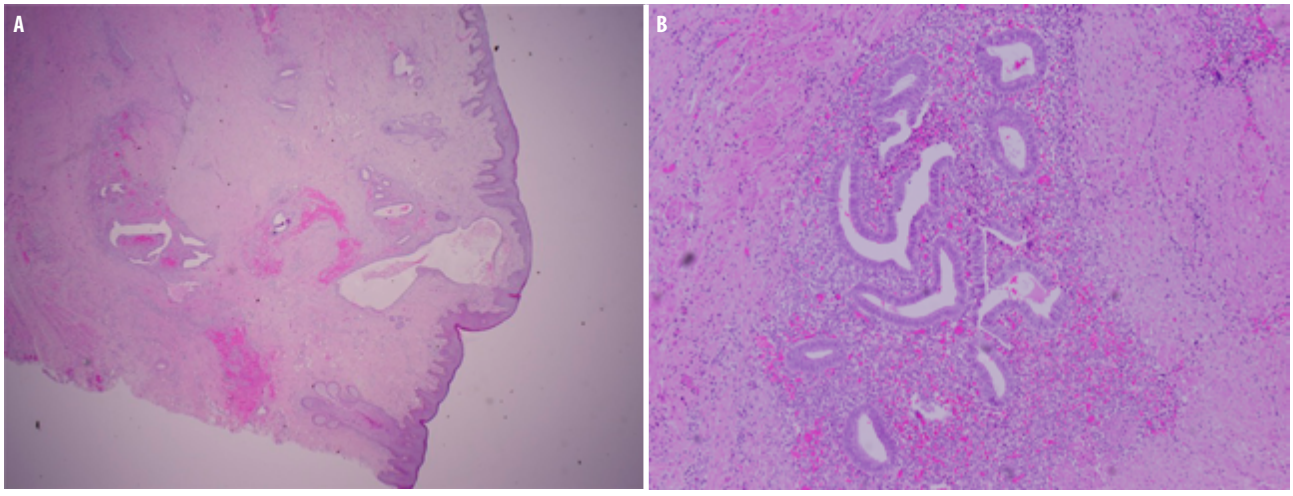

*Fig. 4. Endometrial glandular epithelium and stroma in the perineal region (**A**) in the subcutaneous tissue, (**B**) in the perineal tissue*

when oral contraceptive pills were changed, she observed slight growth of the swelling, which became larger and more painful during menses. The swelling was also reported to have sporadic drainage that ranged from dark red to brown. Her menarche was at the age of 13 years. Her menstrual cycles were regular; the flow was normal but accompanied by pain in the abdomen as well as the perineal region. She described the pain as severe, preventing her from sitting, sexual intercourse and ordinary daily activities. There was no personal or family history of endometriosis.

On examination her vitals were normal and systemic examination revealed no abnormality. On local examination, a sinus opening was seen externally at the site of episiotomy scar, and did not seem to be communicating with the vagina or anal orifice. Episiotomy scar site felt indurated and was tender on touch, hindering us from proper examination. A professional diagnosis of possible episiotomy scar endometriosis with fistula-in-ano was made.

Magnetic resonance imaging (MRI) was requested to assess the deeper extension of the lesion and to exclude involvement of the anal sphincter complex. MRI showed a 1.5 × 1.3 × 1.3 cm right perineal hemorrhagic fluid collection just below the level of the anal orifice in the midst of the scar tissue with blood lined sinus tract extending to the right buttock cutaneous opening and also multiple hemorrhagic foci seen around the perineal body to the right of the midline, probably related to the episiotomy scar (Fig. 1A–D and Fig. 2A, B). There was no definitive evidence of anal canal fistula or anovaginal communication. External and internal sphincter muscles appeared normal. Pelvic organs, such as uterus, both ovaries, rectum and urinary bladder, were unremarkable. The overall picture suggested episiotomy scar endometriosis confined to the perineum without disturbing the anal sphincter complex. The findings and impression were discussed with the patient, and the need for examination under anesthesia with excision of the endometriotic tissue was explained.

The procedure was performed under spinal anesthesia. Intraoperative findings revealed a firm mass about 4 × 4 cm in the perineal region, at the site of episiotomy scar. The mass was extending from the posterior fourchette up to 1 cm lateral to the right side of the external anal sphincter. A sinus opening was seen over the mass, discharging old blood (Fig. 3A). Probe examination was attempted and found that the sinus was very superficial, and no fistulous tract seen. Per speculum and vaginal examinations were normal. Anal sphincter and rectal mucosa were found to be uninvolved on per rectal examination. After identification of the limits of the mass, incision was made in the skin overlying it at the level of prior episiotomy scar lateral to the sinus opening. The mass was deep and adherent to the surrounding tissue, separated by sharp dissection. During dissection, brownish endometriotic-like deposit was seen in the mass tissue (Fig. 3B). Wide local excision of the mass with 1 cm margin of surrounding normal tissue was done to prevent recurrence. The mass with the overlying skin and the sinus opening were excised completely and sent for histopathology. Reconstruction of the perineum was done in layers. Histopathological examination revealed endometrial glandular epithelium and stroma confirming the diagnosis of scar endometriosis, and no evidence of atypia or malignancy was seen (Fig. 4A, B). The postoperative recovery was uneventful, and on receiving the histopathological report, the patient was given injection Zoladex (goserelin) 3.6 mg intramuscular to prevent recurrence. At the sixth week's postoperative visit, the wound was primarily healed with no residual pain. Sexual activity was resumed without any discomfort. Eight months later, the patient remains asymptomatic with painless subsequent menstruation and no signs or symptoms of recurrence.

DISCUSSION

Although pelvic intraperitoneal surfaces are the most common sites of endometriotic disease, perineal endometriosis is a relatively uncommon condition, accounting for 0.31% of women with endometriosis treated surgically at Peking

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Union Medical College[5]. Perineal trauma, such as perineal tearing or episiotomy scars, appear to be more commonly affected especially if the episiotomy is associated with a vaginal delivery and subsequent uterine curettage[6]. The etiology of perineal scar endometriosis can be explained by the theory of transplantation; however, the incidence of endometriosis is small compared to the spillage of endometrial cells into surgical incisions that probably occurs quite frequently during obstetrical or gynecologic surgery. This implies that women with endometriosis have additional factors, such as genetic, immunological or biochemical factors that contribute to the survival of endometrial fragments against the body defences, which then attach to surfaces, and consequently invade and modify normal tissue in order to form an endometriotic lesion[7]. Many factors, such as receptor-binding cancer antigen expressed on SiSo cells (RCAS1), metallothionein (MT), and DNA fragmentation factor-45 (DFF45), have been proposed to play an important role in the pathogenesis of endometriosis[8–10]. The ability of endometrial cells to regulate cytotoxic activity (RCAS1 expression) and high protection against DNA damage or apoptosis (MT expression) with associated changes in the immune cells appears to be essential for pathological characteristics of endometriosis[8]. The expression of RCAS1 and MT by the endometrium may support the survival of ectopic endometrial cells in scar endometriosis[9]. DFF45 also appears to play an important role in the apoptotic process, and a decreased level of DFF45 found in endometriotic lesions might be a part of an apoptosis resistance mechanism contributing to the progression of the disease[10]. All these studies indicated that these factors are significantly involved in the pathogenesis of endometriosis; however, it is still unclear if these factors are responsible for endometriosis development, and more research is needed to reach a better understanding of this condition.
Symptoms and/or signs of endometriosis usually appear shortly after ectopic endometrial cell implantation, with some cases having a prolonged latent period of up to 20 years after implantation[4,11,12]. In our patient, symptom onset was ten years after last childbirth with episiotomy. Although the patient first noticed the swelling one year after her last delivery, she presented to the clinic only when she could no longer cope with the pain. Her past oral contraceptive usage with its temporary suppression effect on the symptoms may explain the delay of consultation and treatment. The diagnosis of perineal scar endometriomas can be made by detailed history and thorough pelvic and perineal examination. Usually, a classical triad of cyclic pain, perineal mass and previous episiotomy or tear during vaginal delivery is sufficient to clinch the diagnosis in perineal scar endometriosis. Although this triad was met in our patient, the diagnosis of a perineal abscess was initially suspected by the general surgeon. The rarity of perineal endometriosis and the limited knowledge of the disease cause difficulty in diagnosing this condition, especially among specialists who do not normally treat these cases and may not have included perineal endometriosis in the differential diagnosis of perineal masses.
Various imaging modalities have been used to establish differential diagnosis of this entity. Ultrasonography can reveal the size and character of the masses, depth of invasion and surrounding structures. However, the sonographic features are non-specific, which are usually hypoechoic or heterogeneous nodules, sometimes hyperechoic, with external outlines often fuzzy and irregular, having a variable shape and size depending on the timing of menstrual cycle or current medical treatment[4,13]. Endoanal or endorectal sonography has been recommended particularly for assessing anal sphincter involvement[13]. Computed tomography (CT) scan is rarely advised as it lacks resolution and has radiation hazards[4]. MRI is currently considered the best imaging modality to evaluate the extension of endometriotic lesions and its relation to the nearby structures. Pelvic MRI shows greater sensitivity (90–92%) and specificity (91–98%) for diagnosing endometriomas compared to CT and ultrasound[12]. It is particularly useful for identification of small lesions and differentiation from other integument tumor-like lesions, such as lipoma or an abscess. The use of fine needle aspiration is controversial, although some authors assert that the use of this technique provides a pathological diagnosis before surgery, others suggest that it might increase the risk of a new implant in the puncture site[4]. CA-125 is a glycoprotein antigen expressed in the endometrium. Women with endometriosis often have serum CA-125 greater than 35 IU/mL. However, its levels can also be elevated in normal women at the time of ovulation, menstruation, pregnancy and following peritoneal irritation by infection or surgery[14]. Therefore, serum CA-125 is not an ideal marker for the diagnosis of endometriosis, but could be helpful in monitoring treatment outcomes and recurrence.
Wide excision of the endometriotic tissue with 1 cm margin of the surrounding normal tissue on all sides is the treatment of choice for perineal endometriosis[15]. This procedure, which usually cures the patient, was performed in our case. Therefore, a thorough preoperative evaluation to define the limits of the lesion is important to ensure its complete removal. It has also an advantage of providing a sample for biopsy to confirm the diagnosis and exclude malignancy, though rare[4]. Incomplete excision predisposes the patient to recurrence of the disease as shown in the described case, when the initial diagnosis was considered as perineal abscess and only an incision and drainage was done, and the patient presented again five months later with the same problem. The option of medical treatment alone does not appear to be effective. Although symptomatic relief might be achieved with hormonal suppression, most patients have a recurrence of symptoms after treatment discontinuation. Medical therapy might be a preoperative option in cases with a large endometriomas or coexisting with pelvic endometriosis[5,11], and a postoperative option to prevent recurrence. The drugs most commonly

used are oral contraceptives, danazol, progesterone and gonadotropin releasing hormone agonists. In our patient, a single dose of 3.6 mg Zoladex postoperatively was helpful. There is a question as to whether perineal endometriosis cases are preventable. There are no consistent data in the literature to support any preventive measure. Hypotheses have been suggested, such as washing the episiotomy wound with normal saline before suturing, avoiding manual uterine exploration and postpartum curettage; however, further studies are needed to support these actions.

In conclusion, although perineal scar endometriosis is a rare condition, it should be suspected whenever a woman in reproductive age group with previous history of episiotomy presents with perineal pain or a nodule coinciding with her menstrual cycle. MRI is the preferred imaging modality to reinforce the diagnosis and assess the deeper extension of the lesion. Wide surgical excision remains the best treatment option for perineal endometriosis, and follow-up is essential as recurrence is not uncommon. Luckily, in our patient, a good recovery with a favorable outcome was achieved and no evidence of recurrence was noted in the eight months of follow-up.

Conflict of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1. Ruiz de Gauna B, Rodriguez D, Cabré S et al.: A case of endometriosis in episiotomy scar with anal sphincter involvement. Int J Clin Med 2011; 2: 624–626.
2. Ling CM, Lefebvre G: Extrapelvic endometriosis: a case report and review of the literature. J Soc Obstet Gynaecol Can 2000; 22: 97–100.
3. Douglas C, Rotimi O: Extragenital endometriosis – a clinicopathological review of a Glasgow hospital experience with case illustrations. J Obstet Gynaecol 2004; 24: 804–808.
4. Vellido-Cotelo R, Muñoz-González JL, Oliver-Pérez MR et al.: Endometriosis node in gynaecologic scars: a study of 17 patients and the diagnostic considerations in clinical experience in tertiary care center. BMC Womens Health 2015; 15: 13.
5. Zhu L, Lang J, Wang H et al.: Presentation and management of perineal endometriosis. Int J Gynaecol Obstet 2009; 105: 230–232.
6. Paull T, Tedeschi LG: Perineal endometriosis at the site of episiotomy scar. Obstet Gynecol 1972; 40: 28–34.
7. Ahn SH, Monsanto SP, Miller C et al.: Pathophysiology and immune dysfunction in endometriosis. Biomed Res Int 2015; 2015: 795976.
8. Wicherek L, Popiela TJ, Galazka K et al.: Metallothionein and RCAS1 expression in comparison to immunological cells activity in endometriosis, endometrial adenocarcinoma and endometrium according to menstrual cycle changes. Gynecol Oncol 2005; 99: 622–630.
9. Wicherek L, Dutsch-Wicherek M, Galazka K et al.: Comparison of RCAS1 and metallothionein expression and the presence and activity of immune cells in human ovarian and abdominal wall endometriomas. Reprod Biol Endocrinol 2006; 4: 41.
10. Banas T, Skotniczny K, Basta A: DFF45 expression in ovarian endometriomas. Eur J Obstet Gynecol Reprod Biol 2009; 146: 87–91.
11. Wasfie T, Gomez E, Seon S et al.: Abdominal wall endometrioma after cesarean section: a preventable complication. Int Surg 2002; 87: 175–177.
12. Kinkel K, Frei KA, Balleyguier C et al.: Diagnosis of endometriosis with imaging: a review. Eur Radiol 2006; 16: 285–298.
13. McCormick JT, Read TE, Akbari RP et al.: Occult perineal endometrioma diagnosed by endoanal ultrasound and treated by excision: a report of 3 cases. J Reprod Med 2007; 52: 733–736.
14. Bischof P: What do we know about the origin of CA 125? Eur J Obstet Gynecol Reprod Biol 1993; 49: 93–98.
15. Kaplanoglu M, Kaplanoğlu DK, Dincer Ata C et al.: Obstetric scar endometriosis: retrospective study on 19 cases and review of the literature. Int Sch Res Notices 2014; 2014: 417042.