Case Report About Extraperitoneal Metastasis of Cervical Adenocarcinoma In Situ

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Case report

Keywords: Adenocarcinoma in situ, CA125, Distant metastases,Monitor

Posted Date: October 11th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-956313/v1

Abstract

Background: adenocarcinoma in situ(AIS) cells are often misdiagnosed, and recognizing AIS in cervical cytology is challenging. Here, we present a case of extraperitoneal metastasis 5 years after a missed diagnosis of AIS.

Case presentation: We report a 49-year-old Chinese woman who presented with a retroperitoneal mass 5 years after cervical conization for AIS. The retroperitoneal mass was composed of glands lined by malignant mucinous epithelium; these tumors were metastases from her previous AIS which were misdiagonised cervical intraepithelial neoplasia(CIN) III in 2013. The patient is alive and well 2 years after resection of the tumors.

Conclusions: An experienced pathologist or multiple pathologists should take part in endocervical AIS diagnosis. We should follow these patients for over 15 years. When Cancer Antigen 125(CA125) or Carcinoembryonic antigen(CEA) levels are elevated, the occurrence of metastases should be strictly monitored.

Background

AIS was first described by Hepler in 1952 as a precancerous lesion of invasive cervical adenocarcinoma[1]. The incidence of cervical glandular lesions (AIS and invasive cervical cancer) of young women aged 20 to 34 has increased three-fold[2]. The pathological types of AIS include cervical tube type、intestinal type、clear cell type and endocrine type. Cervical type is the most common pathological type. Intestinal and endocrine types can coexist with cervical canal type and cervical canal type can be converted to other types. Mixed AIS has a worse prognosis. AIS cells are often misdiagnosed as normal endocervical cells、high-grade squamous intraepithelial lesion (HSIL) or squamous cell carcinoma(SCC). One of the main reasons is that thin-layer cytologic test(TCT) combined with Human papilloma virus(HPV) is not effective in detecting AIS [3]. Approximately 50% of AIS was found by biopsy or puncture for high-grade or invasive squamous lesions[4]. The false negative rate was as high as 3.8% - 11.7% which is easy to cause clinical missed diagnosis [5].Even if the combination with cytology、colposcopy、cervical multi-point biopsy and endocervical curettage pathology, atypical glandular cells were diagnosed in 3-4% AIS and 2% invasive cervical adenocarcinoma[6]. Recognizing AIS in cervical cytology is challenging. AIS is difficult to diagnose in early stage and may recur after 10 years. It is a serious threat to patients' lives. In order to help doctors to recognize and diagnose the disease and find the recurrent lesions as soon as possible,we presented a case of a missed diagnosis of AIS with an extraperitoneal metastasis 5 years after the initial misdiagnosis of CIN III.

Case Presentation

A 49-year-old Chinese woman presented with a chief complaint of “a mass on the left attachment area for 12 days was found by physical examination in Beijing Ditan Hospital affiliated Capital Medical

University” at 2018-6. Cervical biopsy pathology (2013-5): the cervix (3, 9, 10, 11, 12, 1 point) was CIN III and focal suspicious infiltration.Pelvic magnetic resonance imaging(MRI) (2013-6):1.The mass occupied the cervical neck; the pelvic floor showed slightly enlarged lymph nodes; 2. adenomyosis was considered; 3. a cervical nasal cyst and small cyst of the vaginal wall were observed. Paraffin pathology after cervical conization (2013-7): there was CIN grade III with gonads (1-6 points□10 points) and there was no lesion in margin,immunohistochemical results showed CD20 (+), CD3 (+), P16 (+), P53 (weak +). The follow up protocol after cervical cone:the patient was followed up every 3 months in 1 year, every 6 months in 2-5 years and once a year in ≥6 years. The follow-up included CA125□CEA□TCT□HPV detection, pelvic ultrasound or MRI and colposcopic multi-point biopsy (when TCT and HPV detection were abnormal).The results for TCT and HPV were both negative.The level of the tumor marker CA125 was >5111 U/mL (normal<35 U/mL) and Carcinoembryonic antige(CEA) was 222.9 ng/ml (normal<10 ng/ml)(Tables 1-3).Pelvic ultrasound (2018-6) revealed a left attachment block of approximately 54x50 mm. Pelvic MRI (2018-6): An oval-shaped abnormal signal was was approximately 53x30 mm.Pelvic examination revealed a fixed solid cystic mass approximately 50 mm in diameter in the left pelvic cavity (2018-6).

Table 1
Tumor markers

Date(year)	2013	2014	2015	2016	2017	2018
CA125(U/ml)	16	24.1	33.9	84.4	111.4	>5111
CEA(ng/ml)	3.8	7.0	10.9	15.3	32.1	222.9

Table 2
HPV classification

date(year)	2013	2014	2015	2016	2017	2018
HPV16	Positive	negative	negative	negative	negative	negative
Other types HPV	negative	negative	negative	negative	negative	negative

Table 3
TCT:for details.

date(year)	2013	2014	2015	2016	2017	2018
TCT	HSIL	normal	normal	normal	normal	normal

Laparoscopic exploration was performed on 2018-6. The appearance of the whole uterus and double attachment was normal, and the left pelvic wall was slightly bulged. A swollen lymph node approximately 20*30*10 mm was below the left external iliac vein. Frozen pathology reported a “benign” result. A small 50*60*70 mm mass was found on the lower side of the left obturator nerve and was attached to the pelvic wall and the pelvic floor. Frozen pathology revealed a "serous cancer". The uterus□double adnexa□ appendix□omentum□the pelvic and para-aortic lymph nodes were removed (Fig. 1).Postoperative pathology was pelvic extraperitoneal mixed carcinoma caused by distant metastasis of cervical

AIS(Fig. 2-3). Two cycles of chemotherapy with the paclitaxel (200 mg) + carboplatin(550 mg) regimen were administered. Four cycles of pelvic radiotherapy(50.4 Gy/28 F) and intracavitary afterload radiation(5 Gy×2 F) were administered. Chemotherapy with a paclitaxel liposome(270 mg) and carboplatin(500 mg) regimen was administered again for two cycles. During radiotherapy, gastrointestinal reaction was grade 1; blood toxicity was grade 2; she had bilateral inguinal skin pigmentation and a small amount of dry peeling; all symptoms were relieved after symptomatic treatment. The follow up protocol after hysterectomy:the patient was followed up every 3 months in 2 years, every 6 months in 3-5 years and once a year in ≥6 years. The follow-up included CA125、CEA、exfoliative vaginal cytology、chest X-ray、the squamous cell carcinoma-associated antigen、pelvic MRI and colposcopic multi-point biopsy (when exfoliative vaginal cytology was abnormal).No abnormalities were found during clinical follow-up. On October, 2019, the squamous cell carcinoma-associated antigen was 0.6 ng/ml(normal<1.5 ng/ml), and the HPV16、HPV18 and other high-risk types have been negative up to now.

Discussion And Conclusions

The American society for colposcopy and clinical pathology recommended that biopsy should be performed under colposcopy when cytological screening results were atypical glandular cells (AGC)、HPV16 or 18 were positive,or colposcopy showed mild or translucent white acetate change in 2017[7]. In this case, the AIS patient was misdiagnosed with CIN III in 2013 after cervical conization. Because of the difficulty in obtaining cervical gland cells, it is very difficult to make AIS diagnosis if there are not enough cervical gland cells.Therefore, an experienced pathologist or multiple pathologists are required to jointly diagnose .

The treatment for AIS tends to be conservative and general cervical conization or loop electrosurgical excisional procedure(LEEP) is considered an effective treatment for women who want to maintain their fertility[8]. Sometimes even very small and superficial AIS cells may cause recurrence and follow-up is recommended for appearance for more than 10 years after surgery[9]. Although AIS was missed in the patient in 2013, the specimens after hysterectomy in 2018 did not show the presence of AIS primary lesions which indicated that AIS did not progress in the primary lesion of the cervix in the past 5 years. This proved that cervical conization at that time was also effective. Metastatic adenocarcinoma was found in the inguinal、pelvic and para-aortic lymph nodes 14 years after hysterectomy[10]. The patient was confirmed to have AIS only because of the discovery of pelvic metastases which indicated that the biological behavior of AIS was more active.More effective means were needed for follow-up monitoring. TCT combined with HPV can not effectively detect AIS and cervical adenocarcinoma. We suggest that colposcopy examination and pelvic ultrasound or contrast-enhanced MRI may be more conducive to the discovery of lesions outside the cervix.

The tumor markers CA125 and CEA are of particular value in the follow-up of AIS and cervical adenocarcinoma, CA125 and CEA generally show an upward trend if the lesion progresses. In this patient, CA125 and CEA continued to increase for recent 2 years and metastatic lesions were found by ultrasound

and pelvic MRI 5 years after AIS was treated by cervical conization. Therefore,the occurrence of metastases should be strictly monitored in the clinical follow-up of AIS or cervical adenocarcinoma if CA125 or CEA is elevated.We should follow up these patients for over 15 years.

Although the side effects of radiotherapy made patient uncomfortable, she was satisfied with the whole treatment process.

Limitations

there was only one report, and the follow-up time was short.

Abbreviations

adenocarcinoma in situ(AIS);high-grade squamous intraepithelial lesion (HSIL) ;squamous cell carcinoma(SCC);cervical intraepithelial neoplasia(CIN);Cancer Antigen 125(CA125);Carcinoembryonic antige(CEA);thin-layer cytologic test(TCT),Human papilloma virus(HPV);magnetic resonance imaging(MRI);loop electrosurgical excisional procedure(LEEP)

Declarations

Ethics approval and consent to participate：All procedures performed in studies involving human participants were in accordance with the ethical standards of the Beijing Ditan Hospital Affliated Capital Medical University research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.Publish this information was obtained from study participants.

Consent for publication.: Consent for publication was obtained from all individual participants included in the study.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: they has no conflict of interest.

Funding: This study was funded by the Shen Zhen City Technology Creative Committee (No:JCYJ20190809104403566)which supported in the design of the study and collection，analysis， interpretation of data and writing the manuscript.

Authors' contributions: Lirong Han and Peng Wanganalyzed and interpreted the patient data regarding the disease. Kai Kang performed the surgery, and Aiwen Lewas a major contributor in writing the

manuscript. All authors read and approved the final manuscript.

Acknowledgments: Not applicable.

References

1. Codde 1:E,A Munro,Cjr Stewart K, Spilsbury,S Bowen J, Codde, et al.Risk of persistent or recurrent cervical neoplasia in patients with 'pure' adenocarcinoma-in-situ (AIS) or mixed AIS and high-grade cervical squamous neoplasia (cervical intra-epithelial neoplasia grades 2 and 3 (CIN 2/3)): a population-based study. BJOG.2018;125(1):74-9.
2. Katherine E, Tierney,Paul S, Lin,Charles Amezcua,Koji Matsuo,Wei Ye,Juan C, Felix, et al. Cervical conization of adenocarcinoma in situ: a predicting model of residual disease. Am J Obstet Gynecol. 2014;210:366.e1-5.
3. Aime Munro,Jim Codde,Katrina Spilsbury,Nerida. Steel,Colin JR, Stewart,Stuart G, Salfinger, et al. Risk of persistent and recurrent cervical neoplasia following incidentally detected adenocarcinoma in situ. Am J Obstet Gynecol. 2017; 216(3):272.e1-7.
4. Bryson P, Stulberg R, Shepherd L, McLelland K, Jeffrey J. Is electrosurgical loop excision with negative margins sufficient treatment for cervical ACIS? Gynecol Oncol. 2004;93(2):465–8.
5. Chengquan Zhao,Barbara A, Crothers Z, Laura Tabatabai,Zaibo Li, M, Ghofrani,Rhona J, Souers, et al.False- negative interpretation of adenocarcinoma in situ in the college of American pathologists gynecologic PAP education program.Arch. Pathol Lab. Med. 2017;141(5):666–70.
6. Deanna T. Fernanda Musa,Ritu Salani,Warner Huh,Edward Jimenez.Diagnosis and Management of Adenocarcinoma in Situ: A Society of Gynecologic Oncology Evidence-Based Review and Recommendations. Obstet Gynecol. 2020;135(4):869–78.
7. Michelle J, Khan,Claudia L, Werner,Teresa M, Darragh,Richard S, Guido,Cara Mathews A-B, Moscicki, et al. ASCCP colposcopy standards: role of colposcopy,benefits,potential harms,and terminology for colposcopic practice.J Low Genit Tract Dis. 2017.;21(4):223–9.
8. Massad,Mark LS, Einstein,Warner H, Huh,Hormuzd K, Katki,Walter A, Kinney,Mark K, Schiffman,et al. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. Obstet Gynecol. 2013;121(4):829–46.
9. Andrea Ciavattini,Luca Giannella,Giovanni Delli Carpini,Dimitrios Tsiroglou,Francesco Sopracordevole,Giuseppe Chiossi, et al. Adenocarcinoma in situ of the uterine cervix: Clinical practice guidelines from the Italian society of colposcopy and cervical pathology(SICPCV).European Journal of Obstetrics & Gynecology and Reproductive Biology. 2019 Sep;240:273-7.
10. Anthony B, Costales,Patricia J, Eifel,Michael T, Deavers,Michael. Frumovitz,Kathleen M Schmeler.Metastatic adenocarcinoma found in inguinal, pelvic and para-aortic lymph nodes 14 years following hysterectomy for adenocarcinoma in situ of the cervix. Gynecol Oncol Case Rep. 2012;2(3):97–9.

Figures

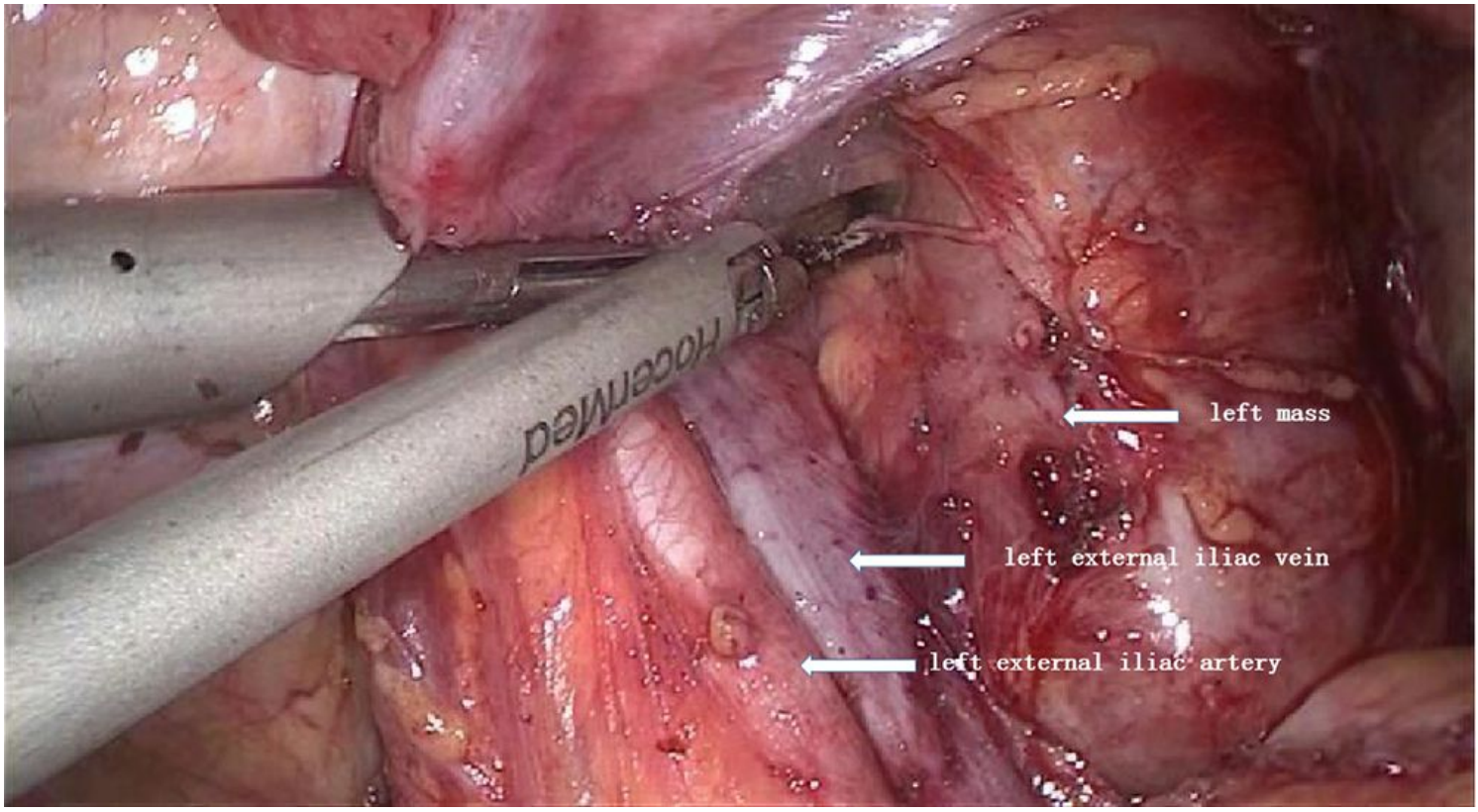

Figure 1

Laparoscopic exploration showed a teratoma like appearance 50*60*70 mm mass on the lower side of the left obturator nerve,it was near the left external iliac vein and artery

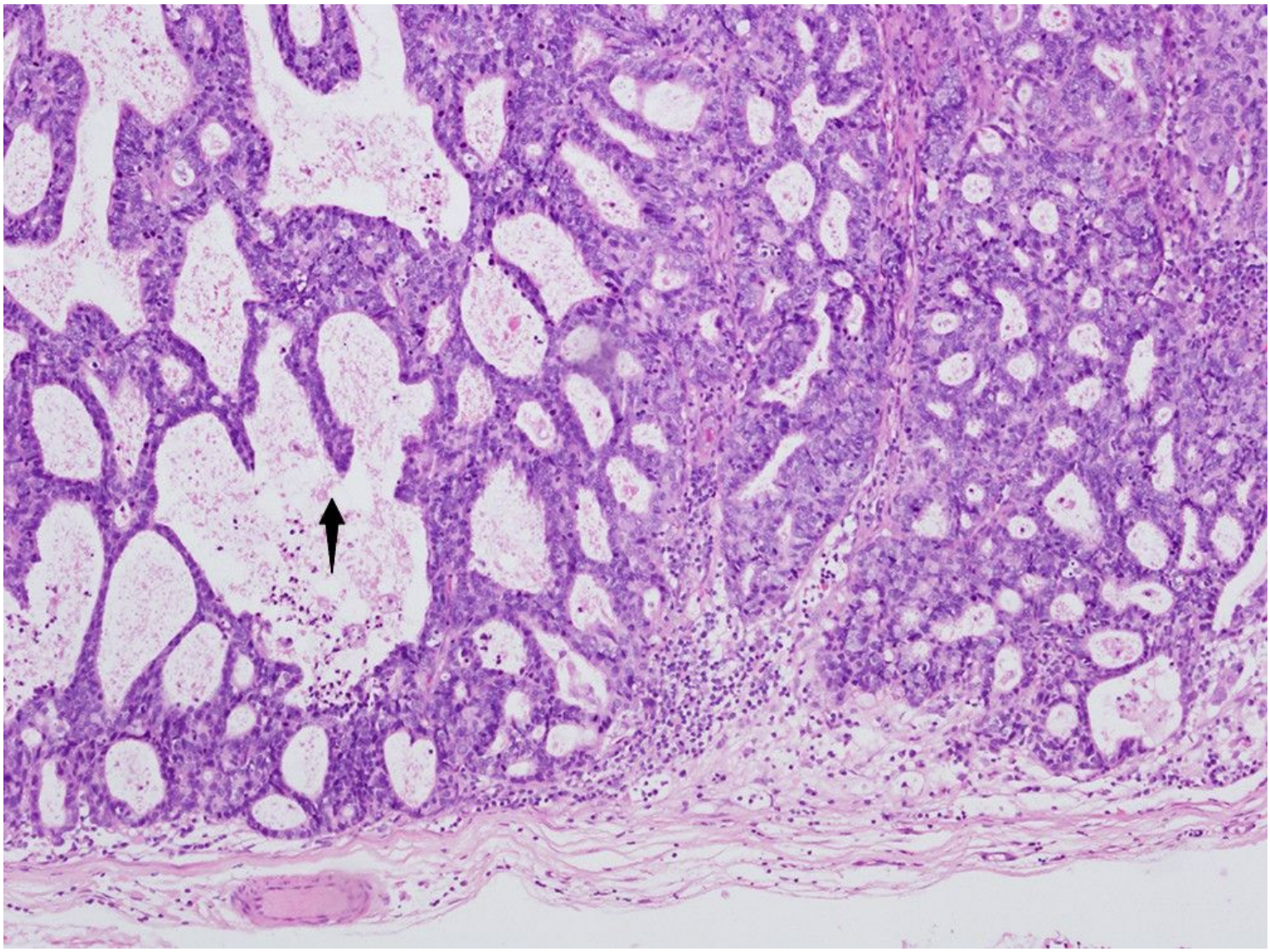

Figure 2

The left mass was lymph nodes metastatic adenocarcinoma which had complex cribriform or labyrinthine structure .The arrow was cribriform.

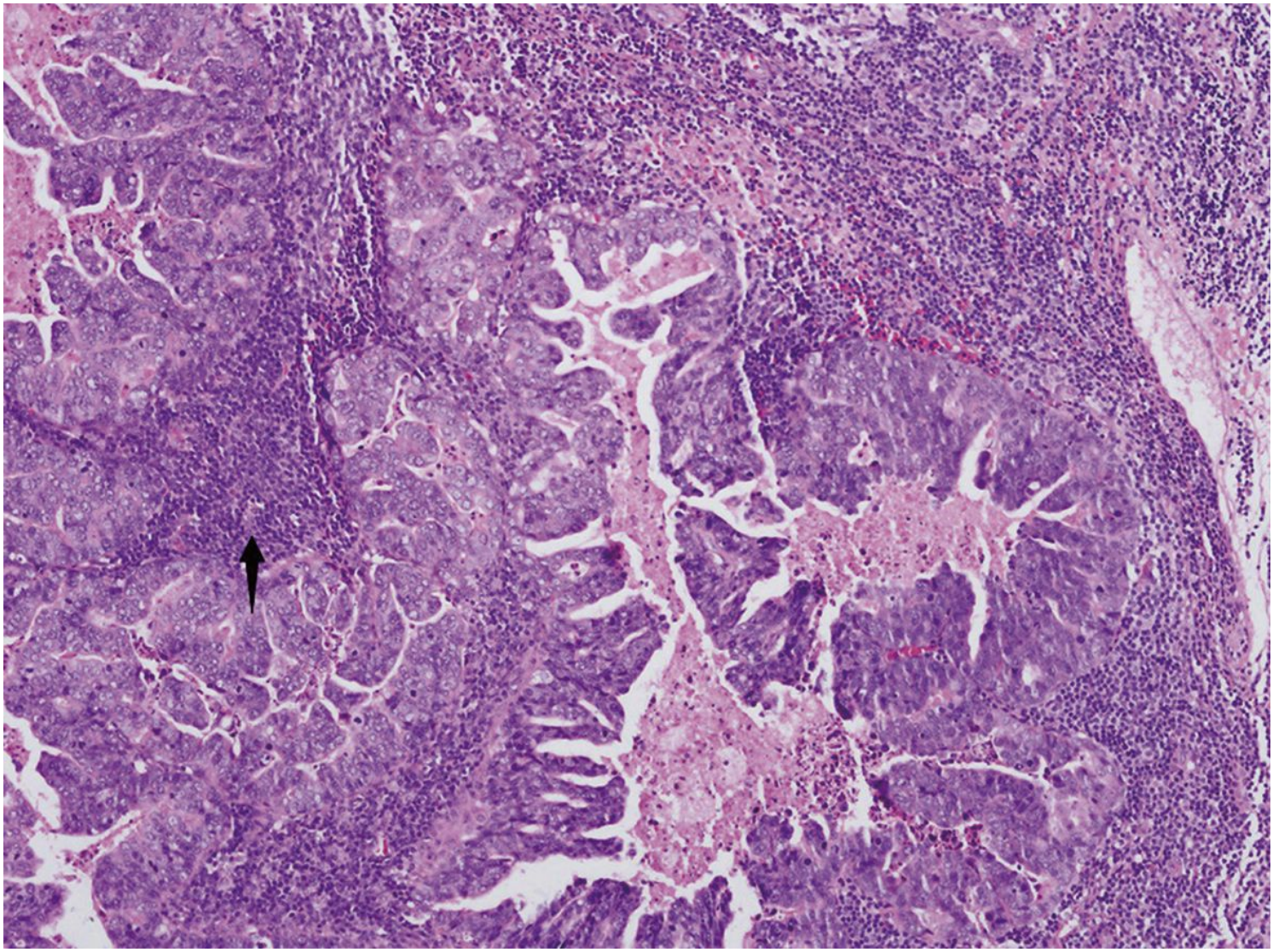

Figure 3

The center necrosis and peripheral lymphocytes infiltration were seen in the poorly differentiated solid tumor area.The arrow was lymphocyte infiltration.