Iliac vein thrombectomy in a metastatic ovarian cancer patient: a case report and literature review

Fanchun Yang
Shanghai Tenth People's Hospital
Jie Liu
Shanghai Tenth People's Hospital
Ning Luo
Shanghai Tenth People's Hospital
Hui ci Jiang
Shanghai Tenth People's Hospital
Jing Guo
Shanghai Tenth People's Hospital
Zhongping Cheng (mdcheng18@263.net)
Shanghai Tenth People's Hospital

Case report

Keywords: Venous thromboembolism, thrombectomy, metastatic ovarian neoplasms, circulating tumor cells, multiple disciplinary teamwork

Posted Date: November 12th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-103099/v1

Abstract

Background

Circulating tumor cells (CTCs) is a major prognostic factor in both primary and metastatic tumor and associated with thrombosis,which may resulted in the formation of Venous thromboembolism (VTE) and the incidence of some adverse events. For the VTE, we can use anticoagulant treatment and Inferior vena cava filter (IVCF) to reduce the risk of pulmonary embolism (PE). However, For large vessels thrombus, These methods can't solve the problem. So, innovative therapies can quickly and effectively alleviate symptoms and remove tumor thrombus, reducing the possibility of tumor hematogenous dissemination. External iliac venous thrombosis from metastatic ovarian cancer has rarely been reported, especially involving the mechanism that CTCs may lead to the formation of VTE. And little has been reported about the therapy of iliac vein thrombectomy to remove embolus. Here, we present a case of external iliac venous thrombosis and review relevant literature to provide a better recognition of this disease and relevant mechanism.

Case presentation

The present case report describes a 60-year-old woman with the external iliac vein thrombosis. She received anticoagulant treatment and we inserted an IVCF to reduce the risk of PE. But it can't alleviate symptoms and remove tumor thrombus. Finally, we incised external iliac vein to remove the embolus by open operation with the help of multiple disciplinary teamwork(MDT). The IVCF was retrieved on postoperative day nine. And the patient was discharged home on postoperative day twelve. She has good recovery after operation and has no recurrence.

Conclusions

The current report demonstrated that Preoperative IVCF insertion and iliac vein thrombectomy combined with MDT in the treatment of this metastatic cancer patient with deep venous thrombosis(DVT) is effective. And CTCs may involve in the formation of DVT of cancer patients, Exploring the mechanism of VTE that is associated with CTCs is vital important. In addition, Using innovative therapies such as iliac vein thrombectomy to remove embolus is also significant.

Background

Trousseau described the clinical association between malignant tumor and venous thromboembolism (VTE) for the first time in 1865[1]. Women suffered from ovarian cancer are at a higher risk of VTE because a large pelvic tumor and massive ascites may compress intrapelvic veins. Up to 20% of women with ovarian cancer suffer from VTE[2]. Patients with colorectalcarcinoma, pancreatic neuroendocrine tumor or hepatocellular carcinoma may also suffer from VTE[3]. Studies found that ovarian cancer patients closely associate with intravascular thrombosis and the rate of its intravascular tumor thrombus is more than the VTE rate. What's more, study found that residual tumor increased the risk of thrombosis

by more than 3-fold. However, the rate of intravascular tumor thrombus rate of other cancer is relatively low[4].With metastasis, the risk of thrombosis may be even higher[5, 6]. High D-dimer levels are associated with a higher DVT risk, too[6]. Circulating tumor cells (CTCs), deriving from both primary and metastatic tumors, are believed to be involved in poor prognosis and metastasis[7, 8]. CTCs could be involved in coagulation activation and eventually prompt numerous tumor types, e.g., breast cancer, pancreatic cancer, endometroid ovarian carcinoma to form the embolus, increasing the risk of VTE. CTCs are also a risk factor for VTE in metastatic cancers[9] However, CTCs' contribution to thrombosis in patients with metastatic ovarian cancer is rarely known.

We report a case of a 60-year-old patient with metastatic ovarian cancer presenting preoperatively with iliac venous thrombosis and our experience of external iliac vein thrombectomy intraoperatively.

Case Presentation

A 60-year-old Han-Chinese woman presented to Shanghai Tenth People's Hospital, Tongji University in March 5, 2018 with complaints of swelling and distending feeling in right leg. the circumference of the right thigh was 58 cm compared with 48 cm on the left thigh (Figure. 1). Diagnosedwith abdominal tuberculosis 5 years ago, she received anti-tuberculosis chemotherapy and was cured. In addition, she had a history of bladder malignant tumor and underwent bladder tumor resection in October 2017. The patient claimed no other risk factors for thrombosis.

The CEA, CA125 and CA19-9 tumor markers were measured and found to be elevated. What's more, platelets were found to be elevated and especially the level of D-dimer was found to be significantly elevated. Magnetic resonance imaging (MRI) showed a tumor mass of 67 × 77 × 85 mm occupying the right adnexal region, and an oval shaped lesion measuring approximately 4.0 cm in diameter seen next to the right common iliac artery above the mass with multiple swollen lymph nodes on both sides of the pelvic wall, suggesting possible metastatic malignant tumor (Figure. 2A and B). Urinary system ultrasonography showed right hydronephrosis with slightly dilated upper ureter. Doppler ultrasound of the lower extremities revealed bilateral lower extremity arteriosclerosis with plaque formation in the right lower limb, as well as retarded deep venous blood flow in bilateral lower extremities.However, Digital subtraction angiography (DSA) indicated a mild filling defect in the right external iliac vein(Figure. 3)

Then the IVCF was inserted via left femoral vein to reduce the risk of pulmonary embolism (PE)(Figure. 4). A double-J tube was inserted in the right ureter by cystoscopy to relieve hydronephrosis. At the same time, the patient received anticoagulant treatment of a 4000-unit bolus of intravenous heparin.

On March 13, the patient underwent laparoscopic exploration. A mass was seen in the right iliac vessel area with about 6 cm in diameter, and the right ovary was enlarged. Considering severe peritoneal adhesion, open operation was selected. After resecting the mass and the right adnexa, the distal segment of right external iliac vein was clipped temporarily by a bulldog clamp. Then the blood vessel was cut open with the length of 3 cm and the embolus was removed with gallbladder stone forceps. The vessel was suturedwith 3 − 0 Prolene and the bulldog clamp was taken off. The size of the embolus was about

3 × 0.5 × 0.5 cm. There was an enlarged lymph node near the spot where right common iliac artery originates from abdominal aorta and we resected it (Figure. 5).

Pathological examination revealed that the mass in the right iliac vessel area was malignant tumor surrounded by lymphocytes, and the paraaortic lymph node and the right adnexal region were also considered as carcinoma. Besides, there were malignant cells in the thrombus from right external iliac vein.

4000 AXa IU of Low-molecular-weight heparinssodium injection (Clexane) was applied from 24 hours postoperatively, and was replaced with oral anticoagulant drugs at discharge.On postoperative day two, The patient can walk normally, and swelling and pain in the right lower extremity were relieved, and the circumference of the right thigh decreased to 52 cm (Figure. 1) .The IVCF was retrieved on postoperative day nine. And the patient was discharged home on postoperative day twelve.

Discussion And Conclusions

VTE is a highly prevalent and potentially fatal disease, which can develop into the incidence of PE, causing higher mortality[10]. It is estimated that the annual incidence of VTE in patients with cancer is 0.5% compared to 0.1% in the general population. Active cancers account for 20% of the overall incidence of VTE and cancer-associated thrombosis (CAT) has worse survival among VTE patients, which is the second most prevalent cause of death from cancer, second only to cancer itself[10].In addtion, some therapeutic agents which targets tumor angiogenesis have been reported to be associated with venous and arterial thrombosis or tumor thrombus formation. For example,VEGF Inhibitors like the bevacizumab has been proven that increase the risk of arterial thrombosis. while the risk of VTE is uncertain. EGFR inhibitors like cetuximab and panitumumab have been tied to a signifificant increase in VTE[11]. Further research found that tumor cells can stimulate clotting and thrombosis in multiple approaches, which involves tissue factor (TF), platelets, tumor derived microparticles, CTCs, etc. In metastatic cancer, CTCs are particularly associated with tissue factor, platelets, and tumor derived microparticles in thrombosis[8]. Tissue factor (TF) is a transmembrane glycoprotein and primary initiator of blood coagulation. Circulating TF is mainly present as microparticles that are highly procoagulant, which contribute to venous thrombosis in cancer patients[12]. Phillips et al found that TF-positive CTCs and microparticles from primary tumors may serve as a trigger for cancer-associated thrombosis[13]. And TF can result in enhanced migration and upregulation of VEGF. In addition, TFs are overexpressed on cancer stem cells and on CTCs. It has been demonstrated that EGFR driven EMT in human carcinoma cells results in increased TF expression on these cells with high metastatic phenotype, finally promoting the thrombosis[9]. Platelets can protect tumor cells in circulation from immune response, contributing to metastasis. In addition, platelets can directly interact with tumor and enhance its growth, migration, and colonization through platelet-derived lysophosphatidic acid (LPA) and transforming growth factor β signaling pathway[14]. Mego et al found that CTC-positive patients had a significantly higher level of plasma D-dimer than CTC-negative patients. Plasma D-dimer and CTCs may play a part in coagulation cascade activation in early metastasis[15].

In this case, preoperative tests indicated elevated platelet and D-dimer levels, which is accord with mechanisms mentioned above. Considering the mechanism of CAT, the pathological examination, and the monism principle, we speculate this patient suffered metastasis after bladder tumor resection. The positive lymph nodes are likely to result from lymphatic metastasis. As for the origin of malignant cells in the thrombus, one scenario was that extranodal extension involving adjacent vascular wall and malignant cells entered circulation. The other scenarios were that the patient had hematogenous metastasis of primary bladder tumor. CTCs expressing TF promoted thrombosis by activating platelets and releasing micro particles, which explains the existence of malignant cells in the embolus.

Given the elevated risk of thrombosis in cancer patients, anticoagulation therapy is essential in preoperative management and anticoagulant therapy remains standard care protocol in patients with acute venous thromboembolism[16].And clinical guidelines recommend low-molecular-weight heparin (LMWH) as preferred anticoagulant for treatment in the first 6 months in patients with proximal deep venous thrombosis(DVT) or PE and prevention of recurrent VTE in patients with advanced or metastatic cancer. If DVT exists before surgery, anticoagulation therapy might be ineffective or contraindicated or the proximal DVT, then IVCF insertion can be considered[15]. IVCF has been proven effective in preventing DVT and PE, as well as improving prognosis[17, 18]. Nevertheless, filter penetration and fracture as well as the risk of DVT after IVCF insertion has raised concern[18, 19]. As a preventive strategy, IVCF insertion cannot remove the thrombus directly. In this case, the patient missed the time window of thrombolytic therapy. The large emboli containing malignant cells in external iliac vein may not be resolved by conventional anticoagulation. With IVCF inserted to inhibit thrombus dissemination and PE, we performed right external iliac vein thrombectomy after mass resection to relieve the patient’s symptoms in time. Postoperative pathology confirmed a cancer thrombus. External iliac vein incision and thrombectomy is relatively risky, but it can quickly and effectively alleviate symptoms and remove tumor thrombus, reducing the possibility of tumor hematogenous dissemination. In this case, the benefit of thrombectomy outweighed risks. It was reported that thrombectomy was effective to treat acute iliofemoral DVT and had advantages on reducing the length of hospital stay and major bleeding events[20].

Another characteristic of this case is the cooperation among gynecologists, radiologists, urologists, and pathologists, which highlights the role of MDT and makes it possible to obtain unique and innovative treatments for complex conditions. MDT is viewed as an additive where collaboration with other disciplines provides a new perspective to solving the problem and can create methodological innovations, knowledge, approaches, or paradigms [21].

In conclusion, Preoperative IVCF insertion and iliac vein thrombectomy combined with MDT in the treatment of this metastatic cancer patient with DVT is effective. Given involvement of CTCs in DVT, when treating DVT patients with malignant tumor history, we should alert to the possibility of tumor metastasis, and the thrombus should be handled appropriately in case of PE. In the future, we should further research the mechanism of thrombosis caused by CTCs, so that we can better prevent the formation of VTE.

Abbreviations

CTCs Circulating tumor cells

VTE Venous thromboembolism

IVCF Inferior vena cava filter

PE pulmonary embolism

MDT multiple disciplinary teamwork

DVT deep venous thrombosis

CAT cancer-associated thrombosis

TF tissue factor

LPA lysophosphatidic acid

LMWH low-molecular-weight heparin

Declarations

Availability of data and materials

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

Acknowledgements

Not applicable.

Funding

No specific funding was obtained for this stydy.

Author contributions

Fanchun Yang and Jie Liu drafted the manuscript. Ning Luo, Hui-ci Jiang, Jing Guo, Zhong-ping Cheng revised and edited the manuscript multiple times. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Shanghai Tenth People's Hospital(Shanghai, China).The patients next of kin provided written informed consent and had complete clinical data.

Consent for publication

The patients next of kin provided consent for publication.

Competing interest

The authors declare that they have no competing interests.

References

1. Trousseau A Phlegmasia alba dolens. In. Lectures on Clinical Medicine Delivered at the Hotel Dieu, Paris,5th edn.London. New Sydenham Society.1872; p.281-295.
2. Abu Saadeh F, Norris L, O'Toole S, Gleeson N. Venous thromboembolism in ovarian cancer: incidence, risk factors and impact on survival. Eur J Obstet Gynecol Reprod Biol. 2013;170(1):214-218.
3. Yedururi S, Kang H, Cox VL, Chawla S, Le O, Loyer EM, Marcal L. Tumor thrombus in the venous drainage pathways of primary, recurrent and metastatic disease on routine oncologic imaging studies: beyond hepatocellular and renal cell carcinomas. Br J Radiol .2019;92(1098):20180478.
4. Tateo S, Mereu L, Salamano S, Klersy C, Barone M, Spyropoulos AC, Piovella F. Ovarian cancer and venous thromboembolic risk. Gynecol Oncol.2005; 99: 119- 125.
5. Corley AM, Sullivan MJ, Friedman SE, O'Rourke DJ, Palac RT, Gemignani AS. Relation of Venous Thromboembolism Risk to Ischemic Stroke Risk in Hospitalized Patients with Cancer. Am J Cardiol .2019;123(4):679-683.
6. Beinse G, Berger F, Cottu P, Dujaric ME, Kriegel I, Guilhaume MN, Diéras V, Cabel L, Pierga JY. Circulating tumor cell count and thrombosis in metastatic breast cancer. J ThrombHaemost.2017;15(10):1981-1988.
7. Micalizzi DS, Maheswaran S, Haber DA. A conduit to metastasis: circulating tumor cell biology. Genes Dev.2017; 31(18):1827-1840.
8. Poudineh M ,Sargent EH, Pantel K, Kelley SO. Profiling circulating tumour cells and other biomarkers of invasive cancers. Nat Biomed Eng.2018; 2(2):72-84.
9. Bystricky B, Reuben JM, Mego M. Circulating tumor cells and coagulation-Minireview. Crit Rev OncolHematol 114:33-42, 2017.
10. Fernandes CJ, Morinaga LTK, AlvesJL, Castro MA, Calderaro D, Jardim CVP, Souza R. Cancer-associated thrombosis: the when, how and why. EurRespir Rev.2019; 28(151):180119.
11. Debbie Jiang MD, Alfred Ian Lee MD. Thrombotic Risk from Chemotherapy and Other Cancer Therapies.Cancer Treat. Res.2019; 179:87-101.
12. Kasthuri RS, Taubman MB, Mackman N. Role of tissue factor in cancer. J ClinOncol.2009; 27(29):4834-8.

13. Phillips KG, Lee AM, TormoenGW, Rigg RA, Kolatkar A, Luttgen M, Bethel K, Bazhenova L, Kuhn P, Newton P and McCarty OJ. The thrombotic potential of circulating tumor microemboli: computational modeling of circulating tumor cell-induced coagulation. Am J Physiol Cell Physiol.2015; 308(3):C229-36.
14. Franco AT, Corken A, Ware J. Platelets at the interface of thrombosis, inflammation, and cancer. Blood.2015; 126(5):582-8.
15. Mego M, Karaba M, Minarik G, Benca J, Sedlácková T, Tothova L, Vlkova B, Cierna Z, Janega P, Luha J, et al. Relationship between circulating tumor cells, blood coagulation, and urokinase-plasminogen-activator system in early breast cancer patients. Breast J.2015; 21(2):155-60.
16. Lee AYY. Overview of VTE treatment in cancer according to clinical guidelines. Thromb Res.2018; 164:S162-S167.
17. Gul MH, Htun ZM, Rigdon J, Rivera-Lebron B, Perez VJ. Clinical outcomes of inferior vena cava filter in complicated pulmonary embolism. PulmCirc.2019; 9(4): 2045894019882636.
18. Decousus H, Leizorovicz A, Parent F, Page Y, Tardy B, Girard P, Laporte S, Faivre R, Charbonnier B, Barral FG, et al. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. Prevention du Risqued'EmboliePulmonaire par Interruption Cave Study Group. N Engl J Med.1998; 338(7):409-15.
19. Ayad MT, Gillespie DL. Long-term complications of inferior vena cava filters. J VascSurg Venous Lymphat Disord.2019; 7(1):139-144.
20. Rodríguez LE, Aboukheir-Aboukheir A, Figueroa-Vicente R, Soler-Bernardini H, Bolanos-Avila G, Torruella-Bartolomei LJ, Comerota AJ, Martinez-Trabal JL. Hybrid operative thrombectomy is noninferior to percutaneous techniques for the treatment of acute iliofemoral deep venous thrombosis. J VascSurg Venous LymphatDisord.2017; 5(2): 177-184.
21. Weaver TE. Enhancing multiple disciplinary teamwork. Nurs Outlook. 2008;56(3):108-114.

Figures

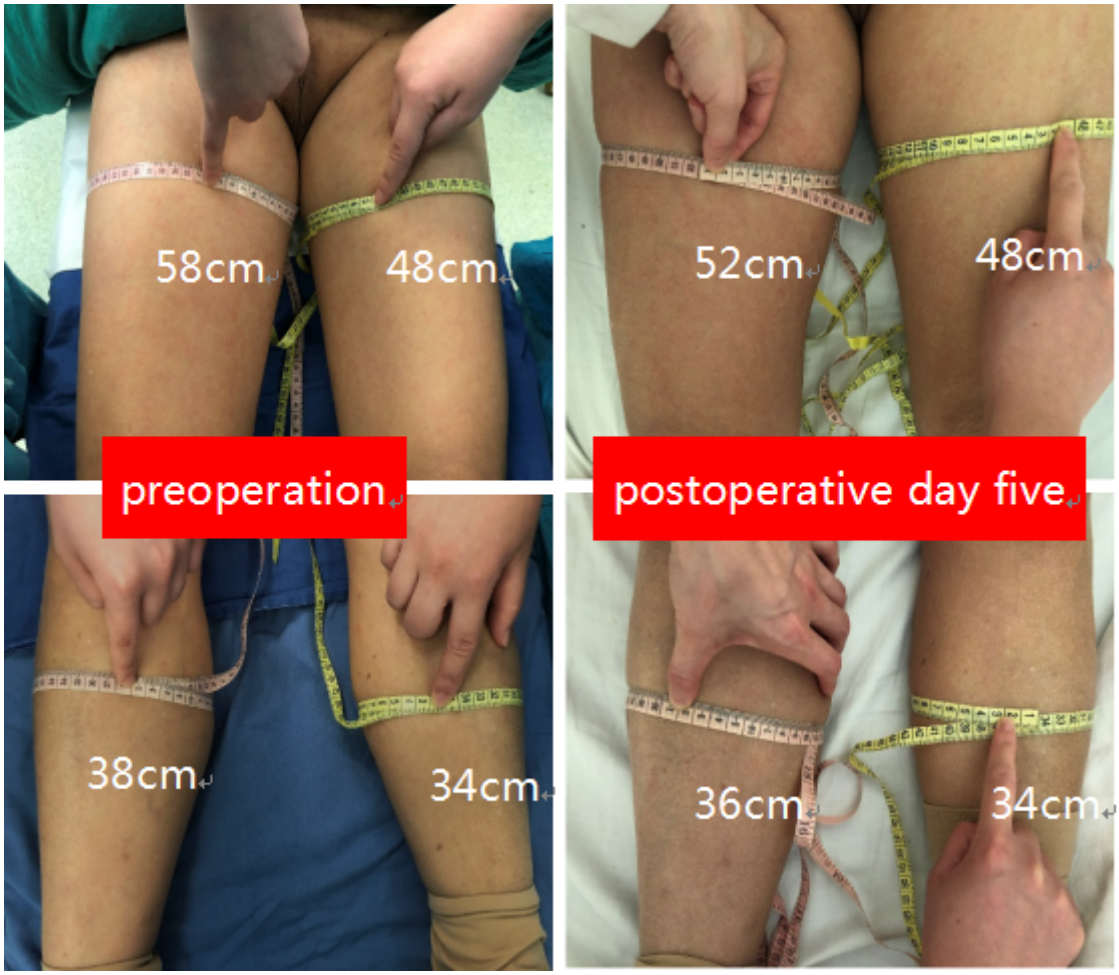

Figure 1

Girth measurements of both lower extremities. (preoperation) circumference of bilateral thigh: 58 cm on the right, compared with 48cm on the left. Circumference of bilateral crus: 38 cm on the right, compared with 34 cm on the left curs.(postoperative day five) circumferenceof bilateral thigh: 52 cm on the right, compared with 48cm on the left. Circumference of bilateral crus: 36 cm on the right, compared with 34 cm on the left curs.

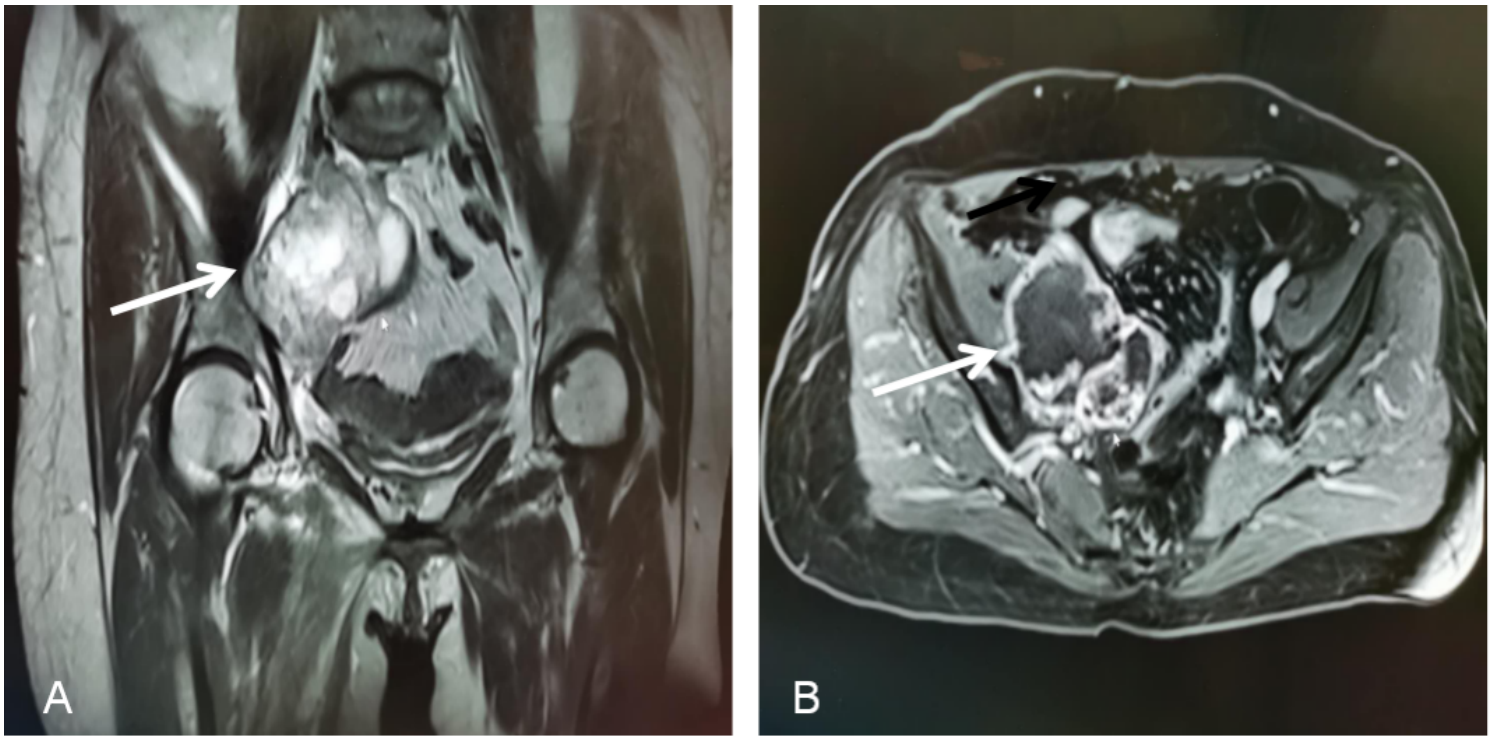

Figure 2

Magnetic resonance imaging (MRI) (a)- Arrowhead indicates a tumor mass of 67 × 77 × 85 mm occupying the right adnexal region (b)-Arrowhead indicates an oval shaped lesion whose diameter is about 4.0 cm that was seen next to the right common iliac artery.

Figure 3

Digital subtraction angiography (DSA) a mild filling defect in the right external iliac vein(Arrowhead indicates the mild filling defect)

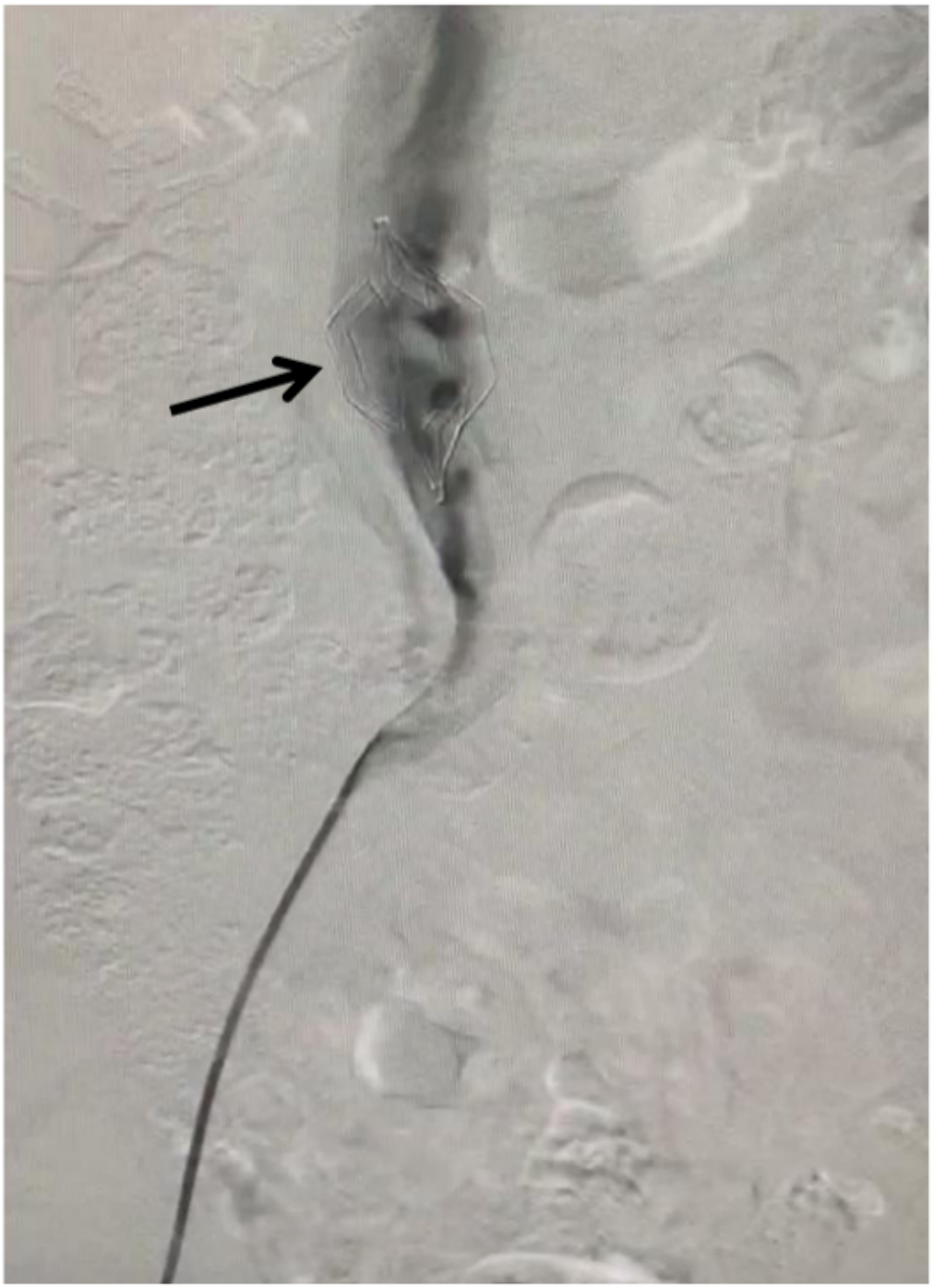

Figure 4

IVCF insertion. The arrowhead indicates location of the IVCF.

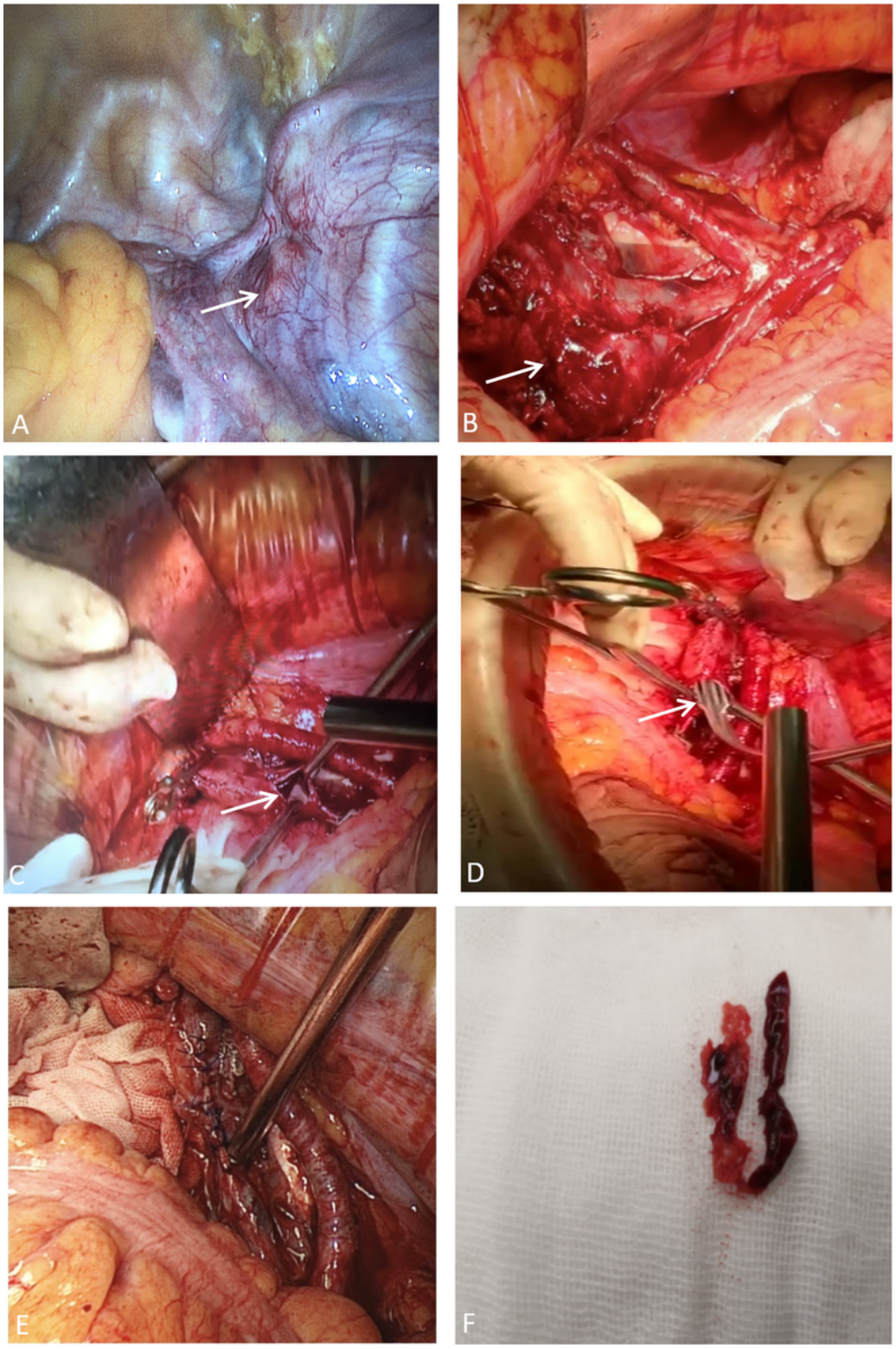

Figure 5

Incising right external iliac vein to remove the embolus. (a b)- Arrowhead indicates an oval shaped lesion that was seen next to the right common iliac artery.(c d)-The blood vessel was cut open and the embolus was removed with gallbladder stone forceps(Arrowhead).Arrowheads indicatethe incision site. (e)- The vessel was sutured with 3-0 Prolene and the bulldog clamp was taken off.(f)-The embolus from external iliac vein.