

Case Report

Paraneoplastic internal jugular vein thrombosis leading to diagnosis of bilateral ovarian ependymoma

Irappa Madabhavi*, Apurva Patel, Mukesh Choudhary and Asha Anand

Department of Medical and Pediatric Oncology, Gujarat Cancer Research Institute, Ahmedabad, Gujarat, India.

Accepted 22 November, 2013

Ovarian ependymomas are extremely rare tumors of the ovary with gliomatous differentiation toward ependymal cells that usually arises in the central nervous system. De novo thrombosis of the Internal Jugular Vein is also an extremely rare entity in patients with ovarian malignancy without any previous history of chemotherapy. We present the case of a 67 year old postmenopausal woman who presented to us a swelling in the right side of the neck for 2 months followed by intermittent subacute pelvic pain, lower abdominal distention and weight loss for 1 month. Her coagulation profile, blood chemistry, lipid profile, AFP, Beta-HCG and LDH were within normal limits. Neck Doppler ultrasonography revealed thrombus in the right internal jugular vein without any atherosclerotic plaque or calcification. CT scan of the thorax also showed right sided IJV thrombosis without any evidence of lung metastasis, mediastinal lymphadenopathy or any mass lesions compressing over IJV. CT scan of abdomen showed bilateral ovarian masses. Later patient was subjected to bilateral salpingo-oophorectomy for suspected ovarian cancer. Microscopic examination revealed a highly cellular tumor composed of small cells with hyper chromatic, round-to-oval nuclei and scanty cytoplasm with perivascular pseudo rosettes and ependymal rosettes. Diagnosis was confirmed by immunophenotype showing strong positivity to glial fibrillary acidic protein (GFAP). Postoperative adjuvant chemotherapy (including cisplatin, bleomycin and etoposide) was started along with anticoagulants. After 3 cycles of chemotherapy, CT abdomen was done which didn't show any abnormal feature. Neck Doppler revealed no thrombus in right internal jugular vein. Total 6 courses of chemotherapy were completed. Patient is under surveillance for 3 months. Ovarian cancer is usually epithelial origin in most of the geriatric patients. Thus the diagnosis of ovarian ependymoma is an unusual occurrence. Further IJVT was the first symptom that developed in this patient. After ruling out other common conditions for thrombosis in this age group, this seems to be a paraneoplastic presentation of ovarian malignancy that preceded the diagnosis of ependymoma by 2 months. An extensive review of literature, did not reveal many cases of ovarian ependymoma. To the best of our knowledge this is the first case report in the world literature, as "paraneoplastic internal jugular vein thrombosis leading to diagnosis of bilateral ovarian ependymoma".

Keywords: Ovarian ependymoma, paraneoplastic, IJV thrombosis, hypercoagulable states.

INTRODUCTION

Thrombosis of the upper limbs and neck are very rare as compared to lower extremities. Internal jugular vein thrombosis is a very serious event, which can lead to

pulmonary embolism and intracranial extension leading to intracranial thrombosis and cerebral edema. Patients usually presents with painful swelling in the neck but sometimes may also be asymptomatic¹.

The increased risk for venous thrombosis in cancer has been considered an epiphenomenon. Paraneoplastic syndromes are attributed to tumor secretion of functional

*Corresponding author E-mail: irappamadabhavi@gmail.com

peptides and hormones or immune cross-reactivity between tumor and normal host tissues. Venous thromboembolism (VTE) and particularly idiopathic VTE may be paraneoplastic phenomena. Thromboembolic events are a major cause of morbidity in cancer patients and may be harbingers of occult malignancy. Appropriate recognition of the syndrome is paramount because VTE often requires careful medical surveillance and management. Ovarian malignancy may be silent even when it presents with venous gangrene².

Ependymoma is a glioma with differentiation toward ependymal cells that usually arises in the central nervous system. The histologic picture will be similar to that of ependymomas of the central nervous system. The diagnosis of ovarian ependymoma is usually supported by positive staining of cytoplasmic processes for glial fibrillary acidic protein. Ovarian ependymoma is extremely rare, and the treatment strategies for this disease have not been established. They have a favorable prognosis; patients with advanced stage disease are reported alive and well after treatment with surgery and chemotherapy³. However, recent studies from several laboratories have linked more closely malignant transformation (oncogenesis), tumor angiogenesis and metastasis to the generation of clotting intermediates (e.g. tissue factor [TF], factor Xa and thrombin), clotting or platelet function inhibitors (e.g. COX-2) or fibrinolysis inhibitors (e.g. plasminogen activator inhibitor, type 1 [PAI-1])⁴.

CASE PRESENTATION

Sixty seven year old lady presented to us initially as an asymptomatic swelling in right side of neck for 2 months, which was insidious in onset and gradually progressive, followed by subacute pelvic pain, abdominal distension and weight loss for 1 month. Patient had no history of surgery, central venous catheter insertion, any chemotherapeutic drug intake, diabetes, hypertension or any ischemic disease in the past.

On examination her blood pressure, pulse rate and respiratory rate were within normal ranges. Her height, weight and body mass index were within normal range for her age. A small mass of size 2X2cm was palpable in her right side of the neck which was superficial, movable, non-tender and non-pulsatile. On abdominal examination 5X6 cm and 7X7 cm masses were palpable on both sides of the lower abdomen with ascites. Bilateral adnexal masses were felt on gynecological examination.

Her blood chemistry, lipid profile, ANA profile, AFP, Beta-HCG and LDH were within normal limits. Coagulation profile including homocysteine levels, prothrombin time, activated partial thromboplastin time, fibrinogen levels, fibrinogen degradation products, D-dimer, protein-C, protein-S and antithrombin III levels were within normal limits. In view of without any prior history suggestive of central venous catheter insertion or any history of

trauma/surgery or no symptoms suggestive of any local infection patient were subjected to upper limb venous Doppler.

Doppler ultrasonography revealed an expansile thrombus in the right internal jugular vein without any atherosclerotic plaque or calcification (Figure. 1). Computed Tomography (CT) image of the thorax also revealed right sided IJV thrombosis and there was no evidence of lung metastasis or mediastinal lymphadenopathy or any compressing mass lesions over IJV. CT scan of the abdomen showing predominantly cystic lesions with internal septations and solid component which was showing post contrast enhancement in bilateral adnexal regions of size 98X88X107 mm on right side and 110X52X94 mm on left side (Figure. 2).

Later patient was subjected to bilateral salpingo-oophorectomy for suspected ovarian cancer. Microscopic examination revealed a highly cellular tumor composed of small cells with hyperchromatic, round-to-oval nuclei and scanty cytoplasm. Perivascular pseudorosettes, ependymal rosettes, and extensive necrosis were observed (Figure. 3). Diagnosis was confirmed by immunophenotype showing strong positivity to glial fibrillary acidic protein.

Postoperative adjuvant chemotherapy was started with BEP regimen along with anticoagulants at an interval of 21 days, containing Bleomycin 30U IV on days 2, 9 and 16, Etoposide 100 mg/m² on days 1-5 and Cisplatin 20 mg/m² on days 1-5. After 3 cycles of chemotherapy, CT abdomen was done which didn't show any abnormality. Neck Doppler revealed no thrombus in right internal jugular vein. Total 6 courses of chemotherapy were completed. Patient is under surveillance for 3 months.

DISCUSSION

Paraneoplastic syndrome is a disease or symptom that is the consequence of the presence of cancer in the body but, unlike mass effect, is not due to the local presence of cancer cells and may precede the diagnosis of malignancy. Treatment is directed towards primary etiology and symptoms with or without immunosuppression. Some of the syndromes may not be reversible. Venous thromboembolism (VTE) and particularly idiopathic VTE may be paraneoplastic phenomena. Thromboembolic events are a major cause of morbidity in cancer patients and may be harbingers of occult malignancy. Thrombosis of the upper limbs and neck are very rare as compared to lower extremities. Internal jugular vein thrombosis is a very serious event, which can lead to pulmonary embolism and intracranial extension leading to intracranial thrombosis and cerebral edema. Patients usually presents with painful swelling in the neck but sometimes may also be asymptomatic¹.



Figure 1. Doppler ultrasonography shows a thrombus in the right internal jugular vein.



Figure 2. CT scan of the abdomen showing predominantly cystic lesions with internal septations and solid component which was showing post contrast enhancement in bilateral adnexal regions of size 98X88X107 mm on right side and 110X52X94 mm on left side.

A hypercoagulable or prothrombotic state of malignancy occurs due to the ability of tumor cells to activate the coagulation system. Prothrombotic factors in cancer include the ability of tumor cells to produce and secrete procoagulant (Tissue Factor, Cancer Procoagulant and Factor V receptor) /fibrinolytic substances (Plasminogen Activator, Plasminogen Activator Inhibitor-1, 2) and inflammatory cytokines (IL-1b, TNF-a, VEGF) and the physical interaction between tumor cell and blood

(monocytes, platelets, neutrophils) or vascular cells. Other mechanisms include nonspecific factors such as the generation of acute phase reactants, abnormal protein metabolism, and hemodynamic compromise (i.e., stasis). In addition, anticancer therapy (i.e., surgery/chemotherapy/hormone therapy) may significantly increase the risk of thrombo-embolic events by similar mechanisms, e.g., procoagulant release, endothelial damage, or stimulation of tissue factor

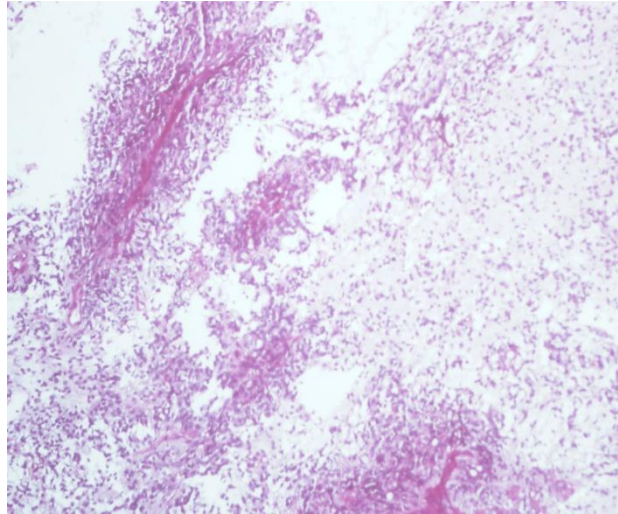


Figure 3. Histological section of ovary: Highly cellular tumor composed of small cells with hyper chromatic, round-to-oval nuclei and scanty cytoplasm. Perivascular pseudo rosettes, ependymal rosettes, and extensive necrosis.

production by host cells⁵. Sometimes thrombosis may be attributed to excessive production of erythropoietin by the kidney secondary to a pressure effect on the ureter by an ovarian tumor.

Cancer alone was associated with a 4.1-fold risk of thrombosis, whereas chemotherapy increased the risk 6.5-fold⁶. The increased risk for venous thrombosis in cancer has been considered an epiphenomenon. Ten percent of women with advanced ovarian cancer receiving chemotherapy are associated with venous thrombosis⁷. Tumour cells can directly activate the clotting through two procoagulants: tissue factor (TF) and cancer procoagulant (CP) (Molnar et al, 2007)⁸.

Ependymomas are a rare type of glioma. Ependymomas usually arise in the central nervous system, but they can also occur rarely in various extra axial locations. They develop from the ependymal cells, which line the ventricles (fluid-filled spaces in the brain), and from the central canal of the spinal cord. They can be found in any part of the brain or spine. In children, they are more commonly found in the cerebellum.

Ovarian ependymomas are extremely rare tumors of the ovary with gliomatous differentiation toward ependymal cells that usually arises in the central nervous system. Ependymomas usually develop from neuroectodermal organs. Pure ovarian ependymoma is an extremely rare tumor, and the treatment strategies for this disease have not been established. Differential diagnosis included mainly endometrioid and small cell carcinoma of the ovary. The histologic feature that most facilitated the diagnosis of ovarian ependymoma is the prominence of rosettes and perivascular pseudorosettes. With positive immunohistochemical staining for GFAP, this cellular pattern is quite characteristic of an ependymoma.⁹

Although rare, primary ovarian ependymoma must be kept in mind in the differential diagnosis of ovarian tumors, especially in young women. Administration of etoposide-based chemotherapy along with cytoreductive surgery is a potential standard treatment for advanced ovarian ependymoma¹⁰. If strong tumoral expression of estrogen and progesterone receptors, an aromatase inhibitor can be initiated¹¹.

CONCLUSION

Ovarian cancer is usually epithelial origin in elderly patients. Thus the diagnosis of ovarian ependymoma is an unusual occurrence. Further IJVT was the first symptom that developed in this patient. After ruling out other common conditions for thrombosis in this age group, this seems to be a Paraneoplastic presentation of ovarian malignancy that preceded the diagnosis of ependymoma by 2 months. An extensive review of literature did not reveal many cases of ovarian ependymoma. To the best of our knowledge this is the first case report in the world literature with association between Internal Jugular Vein Thrombosis and bilateral ovarian ependymoma.

Learning points

Knowledge of tumor thrombosis and paraneoplastic hypercoagulability is very important. Histopathologic diagnosis and treatment of ovarian ependymoma are challenging. Surgery and Etoposide based chemotherapy are mainstay of treatment.

Conflicts of interest: The authors declare no conflicts of interests.

Acknowledgements: None.

REFERENCES

- 1.Boedeker CC, et al. Etiology and therapy of the internal jugular vein thrombosis. . *Laryngorhinootologie*. 2004 Nov;83(11):743-9.
- 2.Adamson AS, Littlewood TJ, Poston GJ, Hows JM, Wolfe JN. Malignancy presenting as peripheral venous gangrene. *J R Soc Med* 1988;81:609-10
- 3.Victoria Garcia-Barriola, et al. Ovarian Ependymoma. A Case Report. *Pathology- Research and Practice*.Volume 196, Issue 8, 2000, Pages 595-599.
- 4.Rickles FR. Mechanisms of cancer-induced thrombosis in cancer. *Pathophysiol Haemost Thromb*. 2006;35(1-2):103-10.
- 5.Graham J Caine, Paul S Stonelake, Gregory YH Lip and Sean T Kehoe. The hypercoagulable state of malignancy: Pathogenesis and current debate. *Neoplasia*. Nov 2002; 4(6): 465–473.
- 6.Heit JA, Silverstein MD, Mohr DN, et al. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. *Arch Intern Med*. 2000; 160: 809–815.
- 7.von Tempelhoff GF, Dietrich M, Niemann F, et al. Blood coagulation and thrombosis in patients with ovarian malignancy. *Thromb Haemost*. 1997; 77:456–461.
- 8.Molnar S, Guglielmo H, Lavarda M, Rizzi ML, Jarchum G (2007) Procoagulant factors in patients with cancer. *Hematology* 12, 555-559.
- 9.Velasco ME, Dahl D, Roessmann U, et al: Immunohistochemical local-ization of glial fibrillary acidic protein in human glial neoplasms. *Cancer* 45: 484.494. 1980.
- 10.Takano T et al: Primary ependymoma of the ovary: a case report and literature review.*Int J Gynecol Cancer*. 2005 Nov-Dec;15(6):1138-41.
- 11.Deval B et al: Treatment of ovarian anaplastic ependymoma by an aromatase inhibitor.*Obstet Gynecol*. 2014 Feb;123(2 Pt 2 Suppl 2):488-91.