VOLUME 47 · NUMBER 3 · September 2012

KJH

THE KOREAN JOURNAL OF HEMATOLOGY

CASE REPORT

# Thromboembolic events identified during diagnosis of germ cell tumors in 2 children

Hea-Lin Oh[1], Hae-Ryong Kang[1], Seok-Cheol Jeon[2], Young-Ho Lee[1]

*Departments of [1]Pediatrics, [2]Radiology, Hanyang University Medical Center, Seoul, Korea*

p-ISSN 1738-7949 / e-ISSN 2092-9129
http://dx.doi.org/10.5045/kjh.2012.47.3.233
**Korean J Hematol 2012;47:233-6.**

Received on February 20, 2012
Revised on June 11, 2012
Accepted on August 3, 2012

**Correspondence to**
Young-Ho Lee, M.D.
Department of Pediatrics, Hanyang University Medical Center, 222, Wangsimni-ro, Seongdong-gu, Seoul 133-792, Korea
Tel: +82-2-2290-8383
Fax: +82-2-2297-2380
E-mail: cord@hanyang.ac.kr

© 2012 Korean Society of Hematology

We describe 2 cases in which radiographic evidence of thromboembolic events was obtained during germ cell tumor diagnosis. There was no evidence of coagulation factor abnormalities or contributory procedures or drugs in either patient. We used anticoagulation therapy for thrombolysis in one patient, but in the other, the thromboembolism resolved spontaneously.

**Key Words** Thromboembolism, Germ cell tumor, Chemotherapy

## INTRODUCTION

Tumor-associated thromboembolisms have been widely reported. Their frequency varies with the type of cancer and is especially high in patients with malignant brain tumors; germ cell tumors; and adenocarcinomas of the ovary, pancreas, colon, stomach, lung, and prostate [1, 2]. In most cases, the thrombi are associated with surgery, central venous catheter insertion, or the use of chemotherapeutic agents such as cisplatin [3]. Sometimes, a thrombus develops because of tumor embolization, vascular compression by the tumor mass, or primary tumor metastasis [4-7]. We encountered 2 interesting cases of thromboembolic events that were not associated with chemotherapy, central venous catheter insertion, or underlying coagulation factor abnormalities in 2 girls with germ cell tumors.

## CASE REPORTS

### 1. Patient 1

A 12-year-old girl presented with a 3-week history of fever and myalgia and a 4-day history of a palpable neck mass. Blood pressure, heart rate, and respiratory rate were within normal ranges. Her weight was 40.15 kg (60th percentile); height, 157 cm (80th percentile); and body mass index (BMI), 16.29 kg/m$^2$. A non-painful, palpable firm mass, the size of an adult fist, was detected on her left lower abdomen. A small mass was also detected on the right side of her neck; it was superficial and movable, but not tender. Abdominal computed tomography (CT) indicated a large mass on the left ovary (10×8 cm), and neck Doppler ultrasonography revealed an expansile thrombus in the right internal jugular vein (IJV) (Fig. 1A). Laboratory tests were performed to evaluate the ovarian mass and thrombus. The coagulation profile results were as follows: prothrombin time (PT), 14.8 s; activated partial thromboplastin time (aPTT), 32 s; fibrinogen level, 1,150 mg/dL; level of fibrinogen degradation products, 5-20 μg/mL; D-dimer level, 2.5 mg/L; protein-C level, 113%; protein-S level, 82%; antithrombin III level, 66%; and lupus anticoagulant, positive. Levels of serum alpha fetoprotein (AFP), beta-human chorionic gonadotropin (β-HCG), and lactate dehydrogenase (LDH) were 770.3 ng/mL, <0.1 mIU, and 278 IU/L, respectively. The patient underwent left salpingo-oophorectomy, and pathological examination indicated an endodermal sinus tumor. The salpinx and appendix were normal, but the omentum

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

showed chronic inflammation with fibrosis and mesothelial hyperplasia. Because whole body positron emission tomography (PET)- CT and chest CT did not show evidence of distant metastasis, we started postoperative chemotherapy without management of the IJV thrombus and decided to observe the latter during serial follow-up visits, unless it caused any symptoms or became enlarged.

After 2 cycles of chemotherapy with bleomycin, etoposide, and cisplatin, the patient was discharged from hospital without any complications related to the thrombus. One month after the completion of chemotherapy, neck ultrasonography indicated that the size of thrombus in the IJV had decreased. Three months later, even without chemotherapy, the thrombus disappeared and the flow in the vein normalized (Fig. 1B). The patient has been followed-up for more than 3 years, without recurrence of the thrombus as well as the primary tumor.

## 2. Patient 2

A 14-year-old girl presented with a 1-month history of polydipsia and hypersomnia. She had also experienced blurred vision for several days. Her weight was 55.15 kg (75th percentile); height, 153 cm (25th percentile); and BMI, 22.57 kg/m². Brain magnetic resonance imaging revealed a solid mass in the suprasellar cistern and hypothalamus. Osteoplastic cranioplasty and subtotal tumor resection were performed. Pathological findings of the resected specimen were compatible with a germinoma. The patient had been taking synthroid, desmin, and hydrocortisone for panhypopituitarism, and a metastatic work-up was performed after surgery. There proved to be no evidence of metastasis, but chest CT and a PET-CT scan revealed an acute thromboembolism with inflammatory changes and ground glass opacity on the right lower lobe (Fig. 2A). The coagulation profile results were as follows: PT, 11.9 s; aPTT, 33 s; D-dimer level, 0.12 mg/L; and protein S level, 55%. Protein C, antithrombin III, and lupus anticoagulant were not examined. The serum AFP

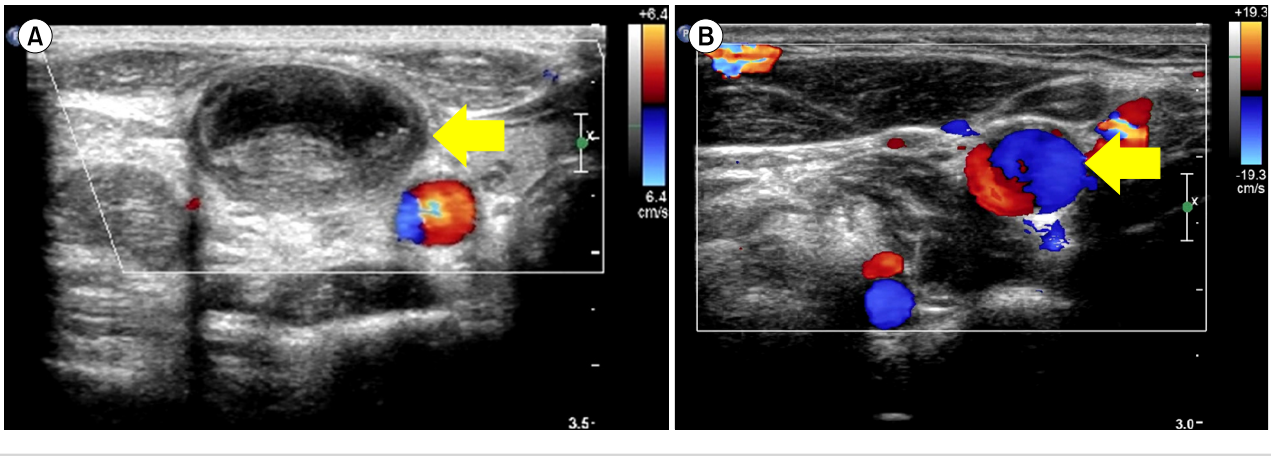


**Fig. 1.** Initial neck Doppler ultrasonography revealing an expansile thrombus in the right jugular vein (**A**, arrow). Three months after the completion of chemotherapy, the thrombus disappeared and the flow in the vein normalized (**B**, arrow).

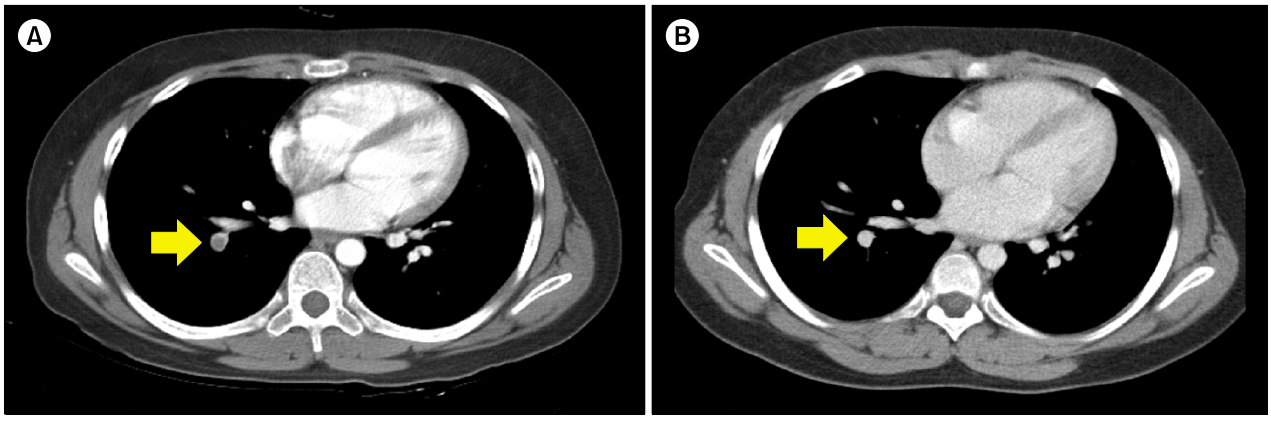


**Fig. 2.** Chest computed tomography showing a pulmonary thromboembolism in the main, lateral, and posterior basal segmental pulmonary artery on the right lower lobe (**A**, arrow). The thromboembolism resolved after 2 weeks of heparin and warfarin therapy (**B**, arrow).

level was 1.6 ng/mL, the β-HCG level was <0.1 mIU, and the LDH level was 220 IU/L. Hormonal levels, including luteinizing hormone, follicular stimulating hormone, progesterone, and estradiol, were within the normal ranges.

Before postoperative chemotherapy, we started oral heparin (2 mg/day) and subcutaneous warfarin (5,000 IU/day) on a 2-week schedule. After 7 days, PT (international normalized ratio, INR) had risen to 2.06; therefore, administered warfarin only for the remaining 7 days. PT and aPTT remained within the normal range for the next 7 days, at the end of which, a chest CT scan showed that the pulmonary thromboembolism had disappeared (Fig. 2B). Thereafter, a central venous catheter was inserted and we started chemotherapy for a pure germinoma, with carboplatin, etoposide, and cyclophosphamide, followed by cranial radiotherapy. The patient has been well for 1 year, without recurrence of the thrombus as well as the primary tumor.

## DISCUSSION

In children, thromboembolism is characteristically seen in combination with serious underlying medical disorders and the incidence is very low. Studies report that the incidence of venous thromboembolism is 8.6-57:100,000 and that of pulmonary thromboembolism is 0.007-0.53:100,000 in hospitalized children, whereas the incidence of venous thromboembolism in all children in the community is estimated to be 0.14-0.9:100,000 [8]. The incidence of thromboembolism in children is increasing. This is due to a combination of heightened awareness regarding thromboembolism in the pediatric population; increased utilization of vascular access devices in intensive care units; and increased use of indwelling catheters for intravenous antibiotics, parenteral nutrition, and chemotherapy [9].

The most common causes of thromboembolism in children with cancer are the effect of the tumor mass and tumor-associated operations or procedures. The incidence of thromboembolism is significantly lower in children than in adults [4-8]. Tumor-associated thrombi are also commonly associated with cisplatin-based chemotherapy. Cisplatin is thought to initiate degenerative processes in vessel walls and also to alter the balance between thrombosis and the dissolution of blood clots, eventually causing occlusive vascular disease [3]. The incidence of germ cell tumor-associated thromboembolism is not known and there are only scattered reports of such cases [10]. Thromboembolisms in germ cell tumors could be associated with elevated serum β-HCG levels [11], obesity, and high serum LDH levels [12, 13]. These are the reasons for frequent venous thromboembolisms in gliomas, which are usually accompanied by elevated serum β-HCG levels [14]. Coagulation abnormalities such as protein C and S deficiency or antithrombin deficiency, thrombocythemia, elevated homocysteine levels, and abnormal lipid profile with obesity could also cause thromboembolism in children.

In this study, both patients had normal BMIs and no coagulation abnormalities. Neither patient had received cisplatin-based chemotherapy. In fact, the thromboembolisms were detected prior to chemotherapy. One of the patients had a high AFP level, but β-HCG levels, which are related to tumor-associated thromboembolisms, were within the normal range in both patients. A further point of interest is that the thromboembolisms in our patients did not seem to be associated with surgery or any kind of procedure. Although one of the patients (patient 2) underwent osteoclastic cranioplasty prior to detection of the pulmonary embolism, thromboembolisms due to brain surgery are rarely reported and they tend to occur near the operation site [4-8].

The initial and standard pharmacological approach for patients with thromboembolisms is intravenous administration of unfractionated heparin (UFH) followed by long-term administration of warfarin. Warfarin should be initiated at 0.2 mg/kg/dose with dose adjustments based on INR. UFH may be continuously infused intravenously or may be administered subcutaneously for documented thromboembolism. UFH requires laboratory monitoring and has major side effects such as bleeding complications, immune thrombocytopenia, and osteoporosis. Continuous infusion of heparin is necessary to achieve a therapeutic range of aPTT. Typically, targeted aPTTs are 1.5 to 3 times of baseline values. It would be measured every 4 h until 2 consecutive aPTTs are within the goal range, and thereafter, every 24 h [9]. Anticoagulation may be required for 3-6 months, and longer treatment is indicated in patients with ongoing thrombotic disease. Recently, UFH has been replaced by subcutaneously administered low molecular-weight heparin, which is as effective as UFH but safer and can be administered in fixed, weight-adjusted doses. If anticoagulation therapy is not effective, thrombolysis with recombinant tissue plasminogen activator is recommended [15]. The thromboembolism resolved spontaneously in one of our patients. In the other, we administered heparin and warfarin combination therapy for 7 days, and thereafter, only warfarin for the remaining 7 days because of the increased PT (INR). In principle, this treatment was insufficient for the pulmonary thromboembolism, but the patient's chest CT improved and she has had no symptoms of thromboembolism since then.

Herein, we describe 2 cases of thromboembolisms found in association with pediatric germ cell tumors, which differ from many other cases in that there was no evidence of underlying coagulation abnormalities or contributory procedures or drugs.

## REFERENCES

1. Thodiyil PA, Kakkar AK. Variation in relative risk of venous thromboembolism in different cancers. Thromb Haemost 2002;87:1076-7.
2. Piketty AC, Fléchon A, Laplanche A, et al. The risk of thromboembolic events is increased in patients with germ-cell tumours and can be predicted by serum lactate dehydrogenase and body

surface area. Br J Cancer 2005;93:909-14.
3. Jafri M, Protheroe A. Cisplatin-associated thrombosis. Anticancer Drugs 2008;19:927-9.
4. Mitomi M, Kimura K, Iguchi Y, et al. A case of stroke due to tumor emboli associated with metastatic cardiac liposarcoma. Intern Med 2011;50:1489-91.
5. Stergiopoulos K, Vasu S, Bilfinger T, Poon M. Embolic stroke in a patient with metastatic renal cell cancer. Hellenic J Cardiol 2011;52:256-8.
6. Abdel-Razeq HN, Mansour AH, Ismael YM. Incidental pulmonary embolism in cancer patients: clinical characteristics and outcome-a comprehensive cancer center experience. Vasc Health Risk Manag 2011;7:153-8.
7. Natsuaki M, Numaguchi K, Tada H, Nakashima Y, Okabe M, Yamamoto Y. Recurrence of pulmonary embolism in young man with retroperitoneal tumor despite insertion of temporary IVC filter. Circ J 2009;73:1756-8.
8. Dijk FN, Curtin J, Lord D, Fitzgerald DA. Pulmonary embolism in children. Paediatr Respir Rev 2012;13:112-22.
9. Oschman A, Kuhn RJ. Venous thromboembolism in the pediatric population. Orthopedics 2010;33:180-4.
10. Latorre González G, López de Silanes de Miguel C, Escribano Gascón AB. Cerebral venous thrombosis in a chemotherapy patient with dysgerminoma. An Pediatr (Barc) 2008;69:485-6.
11. Cyriac S, Sagar TG, Mahajan V. Choriocarcinoma with arterial and venous thrombosis. Neurol India 2009;57:505-7.
12. Zhou W, Ding SF. Concurrent pheochromocytoma, ventricular tachycardia, left ventricular thrombus, and systemic embolization. Intern Med 2009;48:1015-9.
13. Owen RJ. Embolization of musculoskeletal bone tumors. Semin Intervent Radiol 2010;27:111-23.
14. Simanek R, Vormittag R, Hassler M, et al. Venous thromboembolism and survival in patients with high-grade glioma. Neuro Oncol 2007;9:89-95.
15. Moheimani F, Jackson DE. Venous thromboembolism: classification, risk factors, diagnosis, and management. ISRN Hematol 2011;2011:124610.