Pediatric Ovarian Dysgerminoma Presenting With Hypercalcemia and Chronic Constipation: A Case Report

Mona Nourani, MD and Ricarchito B. Manera, MD*†*

Summary: Malignancy-associated hypercalcemia is a common finding among adult malignancies. However, the incidence of malignancy-induced hypercalcemia associated with germ cell tumor among pediatric patients is very rare. We describe a 9-year-old girl with an ovarian dysgerminoma presenting with chronic constipation and hypercalcemia. We review some of the causes of malignancy-associated hypercalcemia described in literature and treatment strategies. We also recommend considering oncological processes in the presence of hypercalcemia.

Key Words: dysgerminoma, hypercalcemia, chronic constipation

(*J Pediatr Hematol Oncol* 2013;35:e272–e273)

Malignancy-associated hypercalcemia is a common finding among 20% to 30% of adult patients with breast and lung cancer and multiple myeloma. The 3 most common mechanisms associated with hypercalcemia are: (1) local osteolytic hypercalcemia, most commonly observed in breast cancer, multiple myeloma, and lymphoma; (2) humoral hypercalcemia of malignancy (HHM) caused by systemic secretion of parathyroid hormone–related peptide (PTHrP) most commonly caused by squamous, renal, and ovarian cancer; and (3) secretion of active form of vitamin D, 1, 25-hydroxyvitamin D caused by lymphomas.[1] However, the incidence of malignancy-induced hypercalcemia among pediatric patients is very rare, mostly seen in patients with acute lymphoblastic leukemia at the time of initial diagnosis followed by solid tumors such as rhabdomyosarcoma, malignant rhabdoid tumor, and hepatoblastoma.[2] Among 2 studies on hypercalcemia-associated malignancy during the past decade which included 41 cases, acute lymphoblastic leukemia was the most common cancer associated with this electrolyte abnormality, and dysgerminoma was not included in either of the studies.[2,3]

CASE REPORT

A 9-year-old girl with past medical history of chronic constipation presented with a 6-month history of progressive abdominal distention, and 1-month history of early satiety and a 10 pound weight loss. She denied any abdominal pain, changes in mental status, nausea, vomiting, headache, fever, night sweats, or polyuria. She was admitted for gastrointestinal clean out. However, physical exam was notable for a palpable, firm well-delineated moveable central mass in the mid to lower abdomen.

Computed tomography scan of the abdomen revealed a 14.6×8.7 cm minimally heterogeneous vascular mass arising from the left ovary with moderate ascites. Initial blood work revealed calcium level of 14.5 mg/dL (normal, 8.6 to 10.5 mg/dL), ionized calcium 1.88 mmol/L (normal, 1.13 to 1.32 mmol/L), phosphorous 3.2 mg/dL (normal, 2.5 to 4.5 mg/dL), lactate dehydogenase (LDH) 2245 IU/L (normal, 150 to 345 IU/L). Parathyroid hormone (PTH) was low at 8 pg/mL (normal, 15 to 68 pg/mL), with PTHrP measured at <2.1 pmol/L and 25-hydroxyvitamin D (25-OH vitamin D) of 14 ng/mL (normal, 7 to 38 ng/mL). Tumor markers were notable for elevated β-human chorionic gonadotropin at 125 mIU/ML (normal, 0 to 5 mIU/ML), and mildly elevated CA-125 at 55 U/L (normal, 0 to 34 U/L). α-fetoprotein was normal at time of diagnosis. Placental-like alkaline phosphatase was not measured in our patient.

Hypercalcemia was corrected on hospital day 4 with aggressive intravenous (IV) hydration and 1 dose of furosemide before surgery. She underwent exploratory laparoscopy with excision of the tumor and left salpingo-oopherectomy on hospital day 4. There was no further rise in the calcium level postsurgery followed by an uneventful recovery.

Pathology report revealed that the left ovary was completely replaced by the tumor, measuring $18.2 \times 10.8 \times 8.7$ cm. The external surface of the ovary was shiny and lobulated, tan-yellow with multiple foci of hemorrhage (Fig. 2). The cut surface was solid, tan-white, and lobulated (Fig. 1). Histology was consistent with dysgerminoma with areas of necrosis. The tumor cells were positive for tyrosine protein kinase kit (c-kit) and vimentin. The ascitic fluid was positive for malignant cells. The tumor was staged as Ic according to International Federation of Gynecologist and Obstetricians, and stage III by Children's Oncology Group staging. According to National Comprehensive Cancer Network, patients with stage IB-III dysgerminoma, 3 courses of etoposide/carboplatin can be used to minimize toxicity. After resection, we decided to use the standard 3-drug regimen with cisplatin, etoposide, and

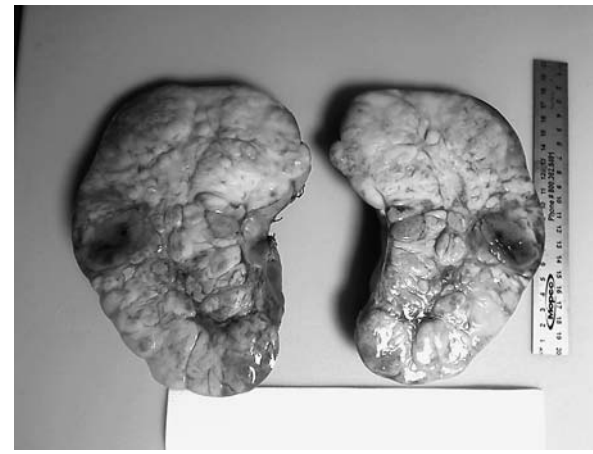

FIGURE 1. Cut surface of the ovary shows the lobulated tumor with hemorrhage.

Received for publication September 27, 2012; accepted April 16, 2013.
From the *Department of Pediatric Hematology/Oncology; and †Division of Pediatric Hematology/Oncology, Loyola University Health Center, Maywood, IL.
The authors declare no conflict of interest.
Reprints: Mona Nourani, MD, Division of Pediatric Hematology/Oncology, Loyola University Health Center, 2160 S. First Avenue, Maywood, IL 60153 (e-mail: monanourani@gmail.com).

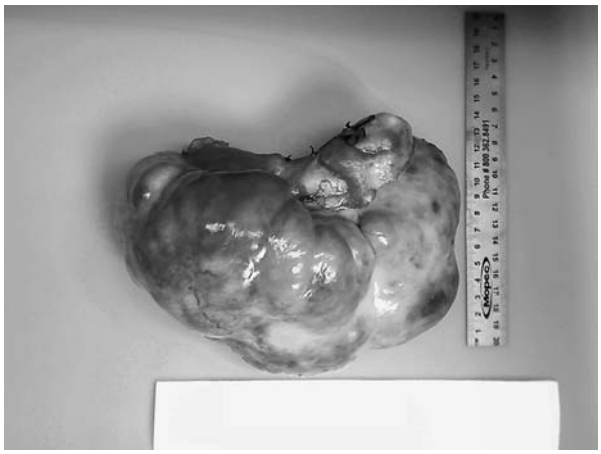

FIGURE 2. External surface of the ovary was lobulated.

bleomycin as a compressed therapy to be given over 3 days instead of 5 days. She received cisplatin 33.3 mg/m^2/dose IV on days 1, 2, and 3, etoposide 167 mg/m^2/dose IV on days 1, 2, and 3, and bleomycin 15 U/m^2/dose IV on day 1. These cycles were given every 21 days for total of 3 cycles. β-human chorionic gonadotropin was decreased significantly immediately after the surgery to 6 mIU/ML. CA-125 was normalized to 25 and serial measurement of LDH showed a decreasing pattern to 314 IU/L at 4 weeks after excision. She has remained free of disease 36 months after treatment.

DISCUSSION

Ovarian germ cell tumors are very rare in childhood, representing approximately 1.5% of childhood malignancy, and the time of diagnosis is commonly made when the tumor is large and causing symptoms such as acute abdominal pain, nausea, vomiting, palpable mass, and abdominal distention.[4] The ovarian tumor cell lines arise from 3 cell lines: stromal elements of the urogenital ridge, the germinal epithelium covering the urogenital ridge and the yolk sac. While in adult women, the vast majority are derived from epithelial line, in children, germ cells are the most common cells for ovarian neoplasms.[4] Because of the rapid growth of these tumors, patients often present with abdominal enlargement which was also manifested in our case. These tumors can contain giant cells that produce placental-like alkaline phosphatase, LDH, and 3% to 5% produce β-hCG. Therefore, serial measurements of these markers are useful for monitoring the disease.[5,6] A retrospective review of patients with median age of 9.5 years over 10 years showed an excellent prognosis after tumor resection with 5-year relapse-free survival and overall survival of 93.4% and 98.3%, respectively.[6] Although dysgerminoma is the most common malignant ovarian tumor in adolescents with 80% occurring in the first 2 decades of life, it is very infrequently described with hypercalcemia, and chronic constipation has not yet been reported.[7] The causes of hypercalcemia can be classified as either local osteolytic hypercalcemia by osteoclastic metastasis to the areas surrounding the malignant cells within the marrow space, HHM due to tumor secretion of PTHrP by effecting the renal calcium handling and bone resorption similar to PTH, or by secreting active form of vitamin D, 1,25-dihydroxyvitamn D causing hypercalcemia by combination of enhanced osteoclastic bone resorption and enhanced intestinal absorption of calcium.[1,8]

Although HHM is a common paraneoplastic disorder occurring because of increase in tumor secretion of PTHrP, in other rare cases more uniquely related to dysgerminomas, increased circulating levels of the active form of vitamin D, 1,25 dihydroxyvitamin D3 (1,25(OH)2D3) has been reported. In 1 investigation, it was shown that the inflammatory mechanism associated with dysgerminomas is the underlying cause of increased activity of 1 alpha hydroxylase, catalyzing the synthesis of the active of vitamin D 1,25 (OH)2D3.[8] However, in our case, the low levels of PTH and normal PTHrP indicated a nonparathyroid mechanism for her hypercalcemia, and interestingly her vitamin D levels were also normal. In a previously reported similar case report describing a 16-year-old female with hypercalcemia and dysgerminoma, the normal levels of active form of vitamin D may have been related to its measurement 18 hours after removal of tumor.[2] However, in our case, the levels were drawn before the tumor removal, which leads to the conclusion that vitamin D was not responsible for hypercalcemia. There was also no osteolytic metastasis of the tumor.[7] Therefore, the cause of hypercalcemia remains unclear.

The treatment of hypercalcemia in cancer patients is initiated by parenteral volume expansion to correct the dehydration caused by nephrogenic diabetes insipidus induced by hypercalcemia and decreased oral hydration from anorexia and nausea. Loop diuretics may also be added to increase calcium excretion once adequate hydration has occurred. Ultimately if hypercalcemia is related to tumor secreting substance, the removal of the tumor is necessary to treat the condition.[1,7] Although hypercalcemia is an uncommon manifestation of tumor, from review of literature and our case report, we recommend including oncological processes in evaluation of pediatric patients presenting with hypercalcemia.

REFERENCES

1. Stewart A. Hypercalcemia associated with cancer. *N Engl J Med*. 2005;352:373–379.
2. McKay C, Furman WL. Hypercalcemia complicating childhood malignancies. *Cancer*. 1993;72:256–260.
3. Kerdudo C, Aerts I, Fattet S, et al. Hypercalcemia and childhood cancer: a 7-year experience. *J Pediatr Hematol Oncol*. 2005;27:23–27.
4. Chu SM, Ming YC, Chow HC, et al. Ovarian tumors in the pediatric age group: 37 cases treated over an 8 year period. *Chang Gung Med J*. 2010;33:156–156.
5. Levato F, Martinello R, Campobasso C, et al. LDH and LDH isoenzymes in ovarian dysgerminoma. *Eur J Gynaecol Oncol*. 1995;16:212–215. Review.
6. Yang C, Wang S, Li CC, et al. Ovarian germ cell tumors in children: a 20 year retrospective study in a single institution. *Eur J Gyn Oncol*. 2011;32:289–292.
7. Matthew R, Otis C, Philippa S, et al. Brief report, severe malignancy associated hypercalcemia in dysgerminoma. *Pediatr Blood Cancer*. 2006;47:621–623.
8. Hibi M, Hara F, Tomishige H, et al. Case report 1,25-dihydroxyvitamin D-mediated hypercalcemia in ovarian dysgerminoma. *Pediatr Hematol Oncol*. 2008;25:73–78.