Primary ovarian insufficiency associated with lenvatinib therapy in a patient with hepatocellular carcinoma: A case report

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Abstract. The therapeutic effects of molecular targeted drugs are, in some cases, more pronounced than those of conventional chemotherapy, and their introduction as a standard treatment is increasing. The present report describes a case of ovarian insufficiency in a young woman caused by tyrosine kinase inhibitor lenvatinib. The 25-year-old woman received lenvatinib (8 mg/day) for 98 days as preoperative chemotherapy for hepatocellular carcinoma. Blood testing the day before starting lenvatinib administration indicated 4.40 mIU/ml luteinizing hormone (LH), 5.2 mIU/ml follicle-stimulating hormone (FSH) and age-equivalent hormone values. Amenorrhea occurred after the start of administration, and 48 days later, the LH level was 41.8 mIU/ml and the FSH level was 44 mIU/ml, indicating a decrease in ovarian function. The patient underwent hepatectomy, and 49 days after the end of lenvatinib administration, the LH level had improved to 4.5 mIU/ml and the FSH level had improved to 2.5 mIU/ml. After the hepatectomy, the patient began to have regular menstrual cycles once again. Ovarian toxicity has not been recognized as a side effect of lenvatinib. However, the present report describes primary ovarian insufficiency considered to be caused by this drug. Potential damage to ovarian function may need to be considered when molecular targeted drugs with the same mechanism of action as lenvatinib are used in young women.

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Introduction

Chemotherapy is one of the treatment options for malignant tumors, and many of the recently developed molecular targeted drugs have been adopted as standard treatments, leading to an improved patient prognosis (1). The improvement in prognosis of adolescent and young adult female cancer patients aged 15 to 39 years has led to an increase in their desire to conceive and bear a child after cancer treatment (2).

Primary liver cancer is one of six major types of cancer and the third leading cause of cancer death (3). Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer. Patients with hepatitis C virus (HCV) develop chronic liver cirrhosis, with up to 20% of these patients developing cirrhosis and approximately 2% developing HCC (4). Up to 80% of the causes of HCC are due to HCV and hepatitis B virus (HBV) (5,6), HCC caused by HBV is common in younger patients in East Asia (7), but non-B and non-C HCC negative for these two viruses has been increasing in Japan in recent years. Alcoholic liver disease or non-alcoholic fatty liver disease is often the cause of these disorders, but in half of the cases, the cause remains unknown (8).

Surgery, drug therapy, and catheter ablation are performed for HCC, but the recurrence rate is high and the survival rate remains low (9). As evidence for neoadjuvant chemotherapy, there are reports of resectable cases in which the molecular targeted drug sorafenib has been used (10), and lenvatinib has shown non-inferiority to sorafenib for unresectable HCC in a phase 3 trial (11).

Lenvatinib exhibits antitumor effects by inhibiting the growth of vascular endothelial cells and the formation of vessel-like luminal structures (12). However, ovarian insufficiency is not a recognized complication of treatment with lenvatinib. We report a case of primary ovarian insufficiency during administration of lenvatinib for non-B, non-C HCC in a young woman.

Case report

A 25-year-old woman with epigastralgia visited her previous doctor, who diagnosed her as having a liver tumor. She underwent percutaneous liver biopsy resulting in a

pathological diagnosis of HCC. Computed tomography revealed a 103x98x100-mm tumor in the right lobe of the liver (Fig. 1). Her Child-Pugh classification was A. 99mTc-labelled diethylene triamine pentaacetate-galactosyl-human serum albumin scintigraphy was performed before surgery (13). The radioactivity of the liver regions of interest (ROI) divided by that of the liver-plus-heart ROI at 15 min (LHL15) was 0.969, and radioactivity of the heart ROI at 15 min divided by that at 3 min (HH15) was 0.753, thus revealing no reduction in hepatic blood flow due to the tumor. Inferior mediastinal lymphadenopathy was noted as an extrahepatic metastasis. She was ultimately diagnosed as having stage IVB HCC and was considered for lenvatinib treatment.

She was 155 cm tall, weighed 49 kg, and had a body mass index of 20.4 kg/m^2, HbA1C of 5.4%, and no diabetes. HBV and HCV antibody tests were negative. She had a thyroid-stimulating hormone level of 2.48 μU/ml, levels of free thyroid hormones 4 and 3 of 1.25 ng/dl and 2.91 pg/ml, respectively, and normal thyroid function tests. Diagnostic imaging of the pelvic area showed no abnormal findings such as tumors in her uterus or ovaries. She had no history of pregnancy, and her menstrual cycle was regular. Imaging studies revealed left pulmonary thrombosis and left common iliac vein thrombosis for which oral administration of rivaroxaban 15 mg/day was started.

A blood examination on the day before lenvatinib administration was started showed the following: luteinizing hormone (LH) 4.40 mIU/ml, follicle-stimulating hormone (FSH) 5.2 mIU/ml, estradiol (E2) 57.4 pg/ml, and age-equivalent hormone values. Oral administration of lenvatinib 8 mg/day was started as chemotherapy for the extrahepatic lesions. However, she became amenorrheic after the lenvatinib was started, and 48 days after the start of administration, LH was 41.8 mIU/ml, FSH was 44 mIU/ml, and E2 was 53.2 pg/ml, values indicating decreased ovarian function. Lenvatinib administration at 8 mg/day was continued for 98 days. Thirteen days after the end of lenvatinib administration, the hormone values were LH 33.5 mIU/ml, FSH 14.9 mIU/ml, and E2 474 pg/ml, indicating slight improvement. Menstruation then resumed (Fig. 2). Before oral administration of lenvatinib, tumor marker alpha-fetoprotein (AFP) was 10.4 ng/ml, and protein induced by vitamin K absence or antagonist-II (PIVKA-II), which reflects Des-gamma carboxyprothrombin, was 440 mAU/ml. PIVKA-II improved to 177 mAU/ml after administration of lenvatinib. After the hepatectomy, AFP decreased to 2.6 ng/ml and PIVKA-II was 38 mAU/ml.

The only adverse event (AE) other than amenorrhea was mild general fatigue at 3 months after administration, but no major lenvatinib-related AEs such as hand-foot skin reaction, hypertension, proteinuria, and diarrhea were observed. Her weight did not change by more than 5% during the observation period.

Imaging studies showed shrinkage of the liver tumor. An extended right hepatectomy, cholecystectomy, and dissection of liver perihilar lymph node #111 were then performed. The pathological findings showed a tumor macroscopically classified as a confluent multinodular type and histologically classified as HCC with an expansive pattern. The ratio of lymph node metastasis was 1/15. Thirty days later, the mediastinal lymph nodes were resected thoracoscopically, and no lymph node metastasis was observed. At the time of liver resection, her LH was 4.5 mIU/ml, FSH was 2.5 mIU/ml, and E2 was 235 pg/ml. Transvaginal ultrasound showed endometrial thickening, and she began to have regular menses. One year after receiving lenvatinib, she had a LH of 1.10 mIU/ml, FSH of 2.3 mIU/ml, and E2 of 159 pg/ml, and her menstrual cycles were regular. At 2 years after starting treatment, she had no metastasis or recurrence of liver cancer, and her menstruation remained regular without amenorrhea.

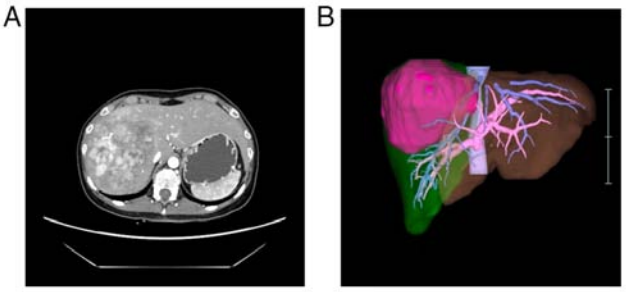

Figure 1. Computed tomography scanning images before surgery. (A) Large liver tumor in the right lobe. (B) Three-dimensional fusion image showing the relation between the hepatic tumor, veins and portal veins.

The patient consented to the publication of this case report, and ethical committee approval was not required.

Discussion

There have been no reports of primary ovarian insufficiency (POI) caused by lenvatinib. Our young female patient with liver cancer showed amenorrhea and high FSH levels during the administration of lenvatinib as preoperative chemotherapy for 3 months and then recovered to normal menstruation.

Lenvatinib is an oral inhibitor of multiple receptor tyrosine kinases that suppresses stem cell factor (SCF)-producing tumors via vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), SCF, inhibition of tyrosine-protein kinase (KIT), and VEGF signaling. Lenvatinib inhibits the kinases VEGF receptor (VEGFR) 1-3, fibroblast growth factor receptor (FGFR) 1-4, platelet-derived growth factor receptor (PDGFR), rearranged during transfection (RET), and KIT (14,15) (Fig. 3). An *in vitro* study also reported that it suppresses FGFR and PDGFR signaling (16).

Lenvatinib was found to inhibit kinase-insert domain-containing receptor and KIT kinases more strongly than did imatinib (12). The antiangiogenic activity of lenvatinib in an in vivo experiment was similar to that of lenvatinib 10 mg/kg and sorafenib 100 mg/kg in an experiment using human pancreatic cancer VEGF121 (17).

The effect of lenvatinib on malignant tumors has been reported in HCC (8), thyroid carcinoma (18), and advanced endometrial carcinoma (19). Currently, treatment of advanced HCC with lenvatinib significantly prolongs overall survival compared to sorafenib, and lenvatinib has become one of the first-line treatment drugs (11).

Typical AEs of lenvatinib include hand-foot skin reaction, general fatigue, appetite loss, hypertension, diarrhea, and proteinuria, among others. However, our patient experienced only amenorrhea and mild general fatigue (20-23). The toxicities of

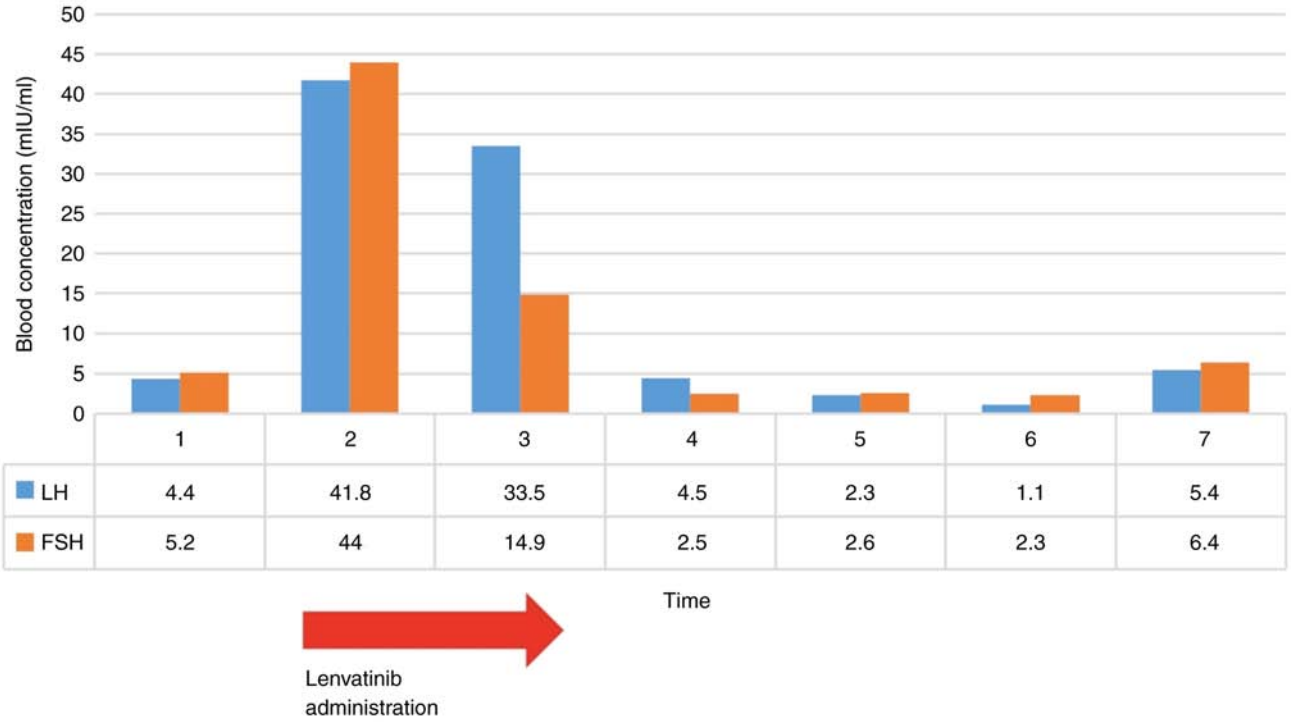

Figure 2. Changes in LH and FSH levels over the administration period of lenvatinib. Blood sampling times are indicated by the numbers 1-7: 1, 2 days before administration of lenvatinib; 2, 48 days after starting lenvatinib administration; 3, 111 days after starting lenvatinib administration and 13 days after ending lenvatinib administration; 4, 147 days after starting lenvatinib administration and 49 days after ending it; 5, 257 days after starting lenvatinib administration and 159 days after ending it; 6, 380 days after starting lenvatinib administration and 282 days after ending it; and 7, 482 days after starting lenvatinib administration and 384 days after ending it. FSH, follicle-stimulating hormone; LH, luteinizing hormone.

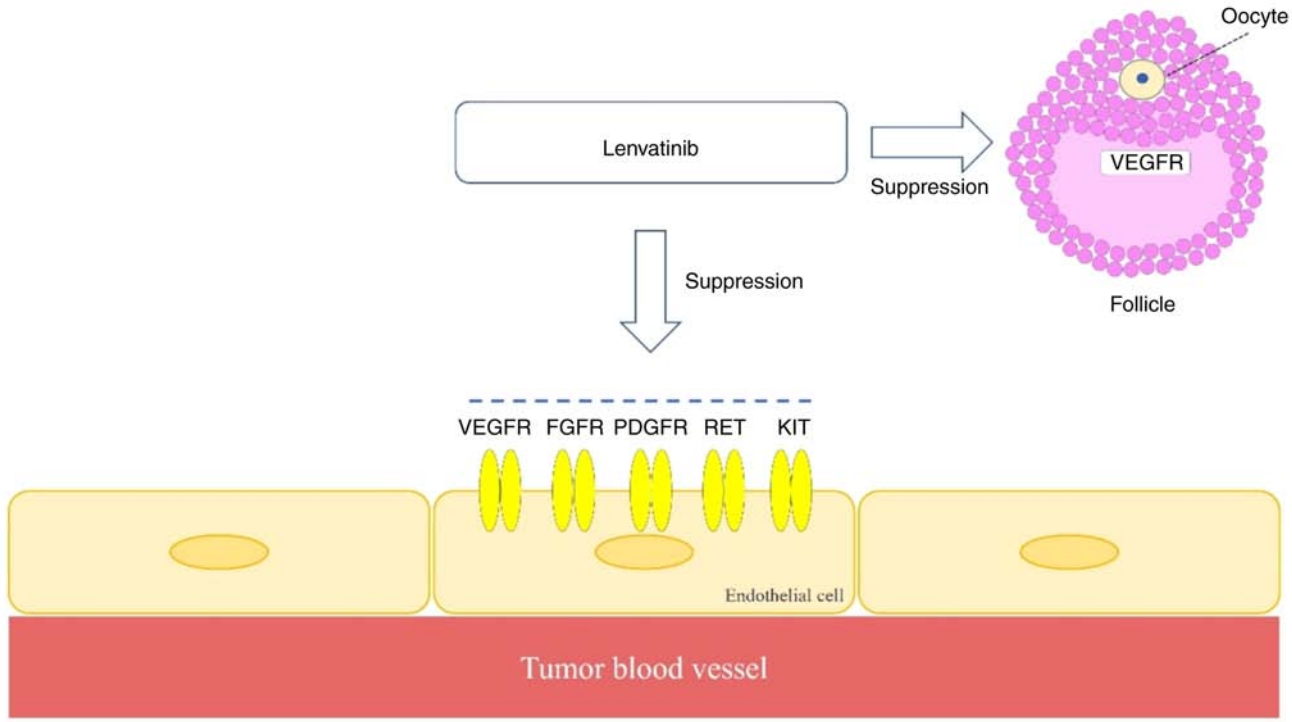

Figure 3. Numerous types of tyrosine kinase receptor expressed on the surface of endothelial cells on tumor blood vessels are suppressed by lenvatinib. VEGFR is expressed in follicles and suppressed by lenvatinib. FGFR, fibroblast growth factor receptor; PDGFR, platelet-derived growth factor receptor; RET, rearranged during transfection; KIT, tyrosine-protein kinase; VEGFR, vascular endothelial growth factor receptor.

lenvatinib are hypertension and proteinuria, which are likely to occur with drugs that target the VEGF pathway (24). Bevacizumab, sorafenib, and sunitinib, which also act on the VEGF pathway, have similar mechanisms of hypertension risk (25-27).

VEGF has several isoforms: VEGF145 is expressed in carcinoma cells, whereas VEGF121 and 165 are expressed in the ovary (28). Follicle development requires angiogenesis, for which the action of VEGF is important (29,30). When VEGF Trap was administered to macaques during the early luteal phase in in vivo experiments on the corpus luteum, attenuation of E2 and elevation of LH and FSH occurred. These findings suggested that VEGF plays an important role in ovarian function and fertility (31). The anti-angiogenic drug bevacizumab is thought to affect the process of ovulation by this mechanism (32). In the present patient, it is most likely that the inhibitory effect of lenvatinib on VEGF impaired follicle angiogenesis, inhibited follicle development, and caused temporary ovarian insufficiency (Fig. 2).

The definition of POI is ovarian insufficiency in women under 40 years of age that causes infertility (33), the criterion of which is a FSH ≥40 mIU/ml with amenorrhea (34). According to a prospective cohort study by Coulam *et al* (35), premature ovarian failure was reported to occur in 0.1% of women by age 30 years and in 1% by age 40 years, and it increased with age. The present patient met the criterion of FSH ≥40 associated with amenorrhea during lenvatinib administration, and ovarian insufficiency could be diagnosed. There have been no reports of ovarian insufficiency due to administration of the Xa inhibitor rivaroxaban, which was taken during the same period (36). Antiphospholipid antibody syndrome has been reported to decrease ovarian reserve in blood coagulation disorders. In our patient, although lower extremity venous thrombosis was observed before starting lenvatinib, her menstrual cycle was normal, and no elevation of FSH was observed. While it can be difficult to accurately evaluate the impact of blood coagulation abnormalities associated with tumor growth on ovarian function, the timing of the administration of lenvatinib and the onset of amenorrhea coincided, suggesting that the trigger for amenorrhea was the administration of lenvatinib (37-39).

There are few reports of ovarian insufficiency caused by molecular targeted drugs. An 18-year-old female patient with breast angiosarcoma was reported to have POI due to the effects of pazopanib (40), which is also an inhibitor of multiple receptor tyrosine kinase. Pazopanib also inhibits VEGFR, PDGFR, and c-Kit (41). c-Kit and PDGFR are thought to be involved in primary follicle formation (42), but three regimens (doxorubicin, ifosfamide, and gemcitabine, among others) were administered in this case, and there was a delay before the administration of pazopanib.

Ifosfamide-containing regimens have also been reported to cause ovarian insufficiency (43) that may result in some ovarian damage. Multitargeted tyrosine kinase inhibitors that impair VEGFR include sorafenib and sunitinib, and these drugs may also have side effects that impair ovarian function (26,27). The administration of pazopanib, sorafenib, and sunitinib doses in in vivo rat experiments did not cause a meaningful change in the number of ovarian follicles (44).

In conclusion, a young woman with HCC experienced transient ovarian hypofunction as a possible side effect of lenvatinib use. Although this side effect has not been reported so far, to our knowledge, when treating such patients, it may be necessary to consider the risk of POI caused by molecular targeted drugs that impair the VEGF pathway.

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Availability of data and materials

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

Authors' contributions

YA, YI, NS, MO, KI, AK, TT, HK and MW made substantial contributions to the conception and design of the study, acquired data and revised the manuscript critically for important intellectual content. YA, YI and MO analyzed and interpreted the data. YA and HK drafted the manuscript. KI made the pathological diagnosis. YA and YI confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Written informed consent for participation in this study was obtained from the patient using our institutional consent form. All identifying information has been removed or anonymized to ensure confidentiality. Approval from our institutional ethical committee was not required.

Patient consent for publication

Written informed consent for publication was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

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