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Cervical Squamous-Cell Carcinoma in a Case of Severe Beta Thalassemia/ Hemoglobin E Disease

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Abstract **Hematologic malignancies and liver cancers are slightly more common among thalassemia patients than the general population. Here we report a case of cervical cancer in a patient with beta thalassemia/ hemoglobin E disease. A 66-year-old Thai woman presented with spotted vaginal bleeding for two days. Her underlying condition was severe beta thalassemia/ hemoglobin E disease and she needed regular blood transfusions every 3-4 months. Physical examination revealed marked pallor, typical thalassemic facies, and hepatomegaly. Pelvic examination showed an ulcerative mass of 2-3 cm at the cervix, involving the entire fornix and right pelvic wall, with both sides showing inguinal lymphadenopathy. Blood tests showed hematocrit 17.5%, ferritin 3876.1 ng/ml, and negativity for HBV, HCV and HIV. The average hematocrit was 19.2±2.3% before transfusion. Microscopic pathology of the cervical mass found non-keratinizing squamous-cell carcinoma. She was clinically diagnosed with carcinoma of the cervix stage IIIB and underlying severe beta thalassemia/ Hb E disease, secondary hemosiderosis and mild transaminitis. After treatment by blood transfusion and chelating therapy, she was referred to the cancer center. Although an association between cervical cancer and severe thalassemia was not clearly established, the emergence of cancers in severe thalassemia cases should be kept under close surveillance because these patients survive longer with regular transfusion and chelation therapy.** *(Thai Cancer J 2019;39:1-5)*

Keywords: squamous cell carcinoma, cervix, beta thalassemia/ hemoglobin E disease

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มะเร็งปากมดลูกชนิดสะแควมัสในผู้ป่วยเบต้าธาลัสซีเมียฮีโมโกลบินอีชนิดรุนแรง

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บทคัดย่อ มะเร็งโลหิตและมะเร็งตับเป็นโรคมะเร็งที่พบในผู้ป่วยธาลัสซีเมียบ่อยกว่าคนทั่วไปเล็กน้อย แต่ในบทความนี้เป็นรายงานผู้ป่วยมะเร็งปากมดลูกที่พบในผู้ป่วยโรคเบต้าธาลัสซีเมีย/ ฮีโมโกลบิน อี ผู้ป่วยหญิงไทย อายุ 66 ปี มีเลือดออกทางช่องคลอดเล็กน้อยมานาน 2 วัน ประวัติเดิมเป็นโรคเบต้าธาลัสซีเมียฮีโมโกลบินอีชนิดรุนแรง ต้องให้เลือดประจำทุก 3-4 เดือน ตรวจร่างกายพบว่า ซีดมาก รูปหน้า และศีรษะเปลี่ยนเป็นแบบธาลัสซีเมียชัดเจน ตับโต ผลตรวจภายในพบก้อนเนื้อมีแผลที่ปากมดลูกขนาด 2-3 ซม.คลุมซอกทั้งหมดรอบปากมดลูกและผนังช่องคลอดด้านขวา และต่อมน้ำเหลืองที่ขาหนีบโตทั้งสองด้าน ผลตรวจเลือดพบฮีมาโตคริต 17.5%, ferritin 3876.1 นาโนกรัม/มล, และตรวจไม่พบเชื้อ HBV, HCV และ HIV ก่อนให้เลือดค่าฮีมาโตคริตเฉลี่ย 19.2$\pm$2.3% ผลตรวจชิ้นเนื้อเป็นมะเร็งชนิด non-keratinizing squamous cell ผลการวินิจฉัยทางคลินิกพบว่าเป็นมะเร็งปากมดลูกชนิด สะแควมัสเซลล์ ระยะที่ IIIB ในผู้ป่วยโรคเบต้าธาลัสซีเมีย/ ฮีโมโกลบินอีชนิดรุนแรง มีภาวะเหล็กสะสมเกินชนิดทุติยภูมิ และตับอักเสบเล็กน้อย หลังจากให้เลือดและยาขับเหล็กแล้ว ได้ส่งตัวไปรับการรักษาต่อที่ศูนย์มะเร็ง โดยสรุปรายงานนี้เป็นการพบมะเร็งปากมดลูกในผู้ป่วยโรคเบต้าธาลัสซีเมีย/ ฮีโมโกลบินอีชนิดรุนแรง สูงวัย แม้ว่าความสัมพันธ์ระหว่างมะเร็งปากมดลูกกับธาลัสซีเมียชนิดรุนแรง จะไม่สามารถสรุปได้โดยง่ายก็ตาม การอุบัติของโรคมะเร็งชนิดต่าง ๆ ก็ควรจะมีการเฝ้าระวังมากขึ้นในผู้ป่วยธาลัสซีเมียชนิดรุนแรง เนื่องจากผู้ป่วยมีอายุขัยยาวนานขึ้นจากการให้เลือดประจำและยาขับเหล็ก *(วารสารโรคมะเร็ง 2562;39:1-5)*

คำสำคัญ: มะเร็งชนิดเซลล์สะแควมัส ปากมดลูก โรคเบต้าธาลัสซีเมีย/ ฮีโมโกลบินอี

Introduction

Thalassemia is a genetic disease which is mainly characterized by microcytic anemia, varied degrees from asymptomatic to regularly transfusion-dependent. In severe cases, its major complication is the secondary hemosiderosis which is the major cause of death among thalassemia patients[1]. Other common cause of death may include an infectious disease particularly in case of the postsplenectomy[2].

Malignancy has not been rarely found in beta thalassemia major and beta thalassemia intermedia particularly hematologic malignancy, either leukemia or lymphoma[3], viz., adjusted hazard ratio of hematologic malignancy is 5.32 (95 % CI=2.18 to 13.0), whereas that of abdominal malignancy is 1.96 (95 % CI=1.22 to 3.15), which are more common than those of the comparison cohort. Furthermore, the patients who receive transfusion have more prevalence of cancer than the one who do not receive transfusion[4].

Besides hematologic and abdominal malignancies, hepatocellular carcinoma and papillary carcinoma of the thyroid gland are more commonly found in thalassemia possibly due to hemosiderosis, hepatitis B and C infections from multiple transfusions[5-7]. Moreover, few cases of renal cell carcinoma, breast carcinoma, meningeal cancer were occasionally mentioned as case reports[7]. So far the carcinoma of the

cervix has not been mentioned in severe beta thalassemia/ hemoglobin E disease patient.

Case Report

A 66-year-old Thai woman was admitted with spotted vaginal bleeding for two days. She was formerly known to harbor severe beta thalassemia / hemoglobin E disease since she got the first pregnancy at 20 years of age. She needed regular blood transfusions every 3-4 months since then. Her hematocrit usually fluctuated between 14.8 and 21.3 %, mean 19.2$\pm$2.3 % before any transfusions. The physical examination revealed the temperature of 36.8 degree Celsius, pulse rate 78/min, typical thalassemic facies, marked pallor with mild jaundice, and hepatomegaly with 3 fingerbreadths.

The current blood tests included: Hb 5.6 g%, Hct 17.5 %, WBC 7730/mm^3, platelet 226,000/mm^3, MCV 50.4 fl, MCH 16.1 pg, MCHC 32.0 g%, RDW 23.8 %, hypochromia 3+, few macrocytes, polychromasia 1+, anisocytosis 2+, microcytes 2+, ferritin 3876.1 ng/ml, serum iron 191 mcg/dl (normal 50-170), TIBC 232 mcg/dl (normal 259-388), transferrin saturation 82 % (normal 20-50), Hb analysis using the capillary zone electrophoresis method: Hb A2 8.8 %, Hb F 15.9 %, Hb E 75.3 %, direct and indirect anti-globulin tests-negative.

FBS 111 mg%, Hb A1c 5.0 %, creatinine 0.53 mg%, eGFR 99.2 ml/min, albumin 3.7 g%, globulin 4.9 g%, AST 53 U/L, ALT 51 U/L, alkaline phosphatase 92 U/L, direct bilirubin 0.7 mg%, indirect bilirubin 2.0 mg%, coagulation tests: PT INR 1.43, aPTT 27.3 sec, alpha fetoprotein 5.23 ng/ml (normal 1.09-8.04), HBV, HCV, and HIV antigen / antibody-all negative.

The pelvic examination: an ulcerative cervical mass 2-3 cm involving the entire fornix and the right pelvic wall. Multiple inguinal lymphadenopathies about 1 cm were palpable at both sides. The rectal examination and the proctoscopy revealed no rectal shelf. The microscopic pathology of the cervix showed non-keratinizing squamous cell carcinoma.

The chest film showed no pulmonary infiltration, mild cardiomegaly. The ultrasonography of the whole abdomen revealed mild hepatomegaly with diffuse increase parenchymal echo, mild splenomegaly, multiple small gall stones, a thin walled cyst without septation or nodule 4x3 cm at left adnexa, no omental mass, no hydronephrosis.

She was clinically diagnosed as having carcinoma of the cervix stage IIIB and underlying severe beta thalassemia / hemoglobin E disease, secondary hemosiderosis, left ovarian cyst and mild transaminitis. After treatment by blood transfusion and chelation therapy, she was referred to the cancer center for specific management of the

cervical cancer.

Discussion

The definite diagnosis of carcinoma of the cervix in our patient was based on the microscopic finding of the cervical mass biopsy. It could be clearly distinguished from other differential diagnoses of the cervical mass including the polyp, leiomyoma and cervical endometriosis[8].

Most authorities do not believe the association between malignancies and severe thalassemia. However, the life expectancy of severe thalassemia patients appears longer after the era of regular transfusion and chelating therapy[9], malignancies are seemingly more frequently found because the older people grow, the cancer incidence rates will continue to increase[10].

For non-hematologic malignancy, hepatocellular carcinoma is found slightly more prevalent in patients with thalassemia both major and intermedia due to many risks which are specific for thalassemia including hepatotropic viruses, hemosiderosis, and longer life span of the postmenopausal women[6]. The serum ferritin in our case fell into the range of moderate hemosiderosis, 2000-4000 ng/ml[1]. This can provide the risk of hepatocellular carcinoma among thalassemia intermedia patients even though they do not have hepatitis B or C infection[11].

One important pathogenesis of the cervical cancer is the human papilloma virus (HPV) infection; it has been found in most cases with cervical carcinoma[12], but it was not studied in our patient or other cases with thalassemia major. On the contrary, human parvovirus B19 that has been frequently reported in thalassemia major since childhood is found complicating only one patient with the cervical cancer but it has never been found contributing to the emergence of the cervical cancer[13-16]. In further studies, HPV in severe thalassemia should be clarified.

Conclusion

A 66-year-old Thai woman with severe beta thalassemia/ hemoglobin E disease was diagnosed as having carcinoma of the cervix. Although the cervical cancer has never been mentioned in severe thalassemia, the emergence of any new kind of malignancy should be kept under close surveillance because these patients survive longer with regular transfusion and chelation therapy.

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