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A case of premature onset of young cervical cancer with abnormal lipid metabolism and literature review

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Abstract: *Cervical cancer is the most common gynecological malignancy in developing countries. Scholars at home and abroad call cervical cancer younger than 35 years old as cervical cancer in young women (referred to as young cervical cancer). In recent years, with the promotion of cervical cancer screening, the incidence of young cervical cancer has gradually increased. This case reports a 17-year-old teenager with stage IV cervical squamous cell carcinoma with human papillomavirus type 16 and 18 positive and abnormal lipid metabolism. The onset is early, the clinical symptoms are typical, the disease progresses rapidly, and the prognosis is poor. Review the patient's family history, morbidity, sexual life history and related clinical examination indicators, and consult relevant literature to find factors related to the onset of cervical cancer, and summarize the characteristics of the case to improve clinicians' awareness and clinical diagnosis of the disease, And at the same time discuss whether the initial screening age for special populations should be treated specially.*

Keywords: *Young Women, Cervical Cancer, Human Papillomavirus Infections, Risk Factors, Abnormal Lipids Metabolism, Case Report*

1. Introduction

In recent years, cervical cancer (cervical cancer) has shown a younger trend in developing countries [1]. According to reports [2-3] 0.4% of cervical cancer cases occurred before the age of 25, and only 0.1% of cervical cancer cases occurred at before the age of 20. This case reports a 17-year-old teenager with stage IV cervical squamous cell carcinoma combined with human papillomavirus type 16 and 18 positive and abnormal lipid metabolism. The onset was early, the clinical symptoms were typical, the disease progressed rapidly, and the prognosis was poor.

2. Clinical Data

The patient, female, 17 years old, was admitted to our hospital on January 4, 2021 for "cervical malignant tumor was found for 1 week". Her previous menstruation was regular, and there was no abnormality in the past and family history. She has not been married and given birth. Height: 165cm, weight: 42.5kg.BMI: 15.61kg/m2. Gynecological examination: married and unborn type, there is a cauliflower-like vegetation about 5*6*4cm3 can be seen in the external cervix, which is brittle and easy to bleed when touched. The lower 1/3 of the vagina, the left side is heavy, and a nodular mass of about 3*4*2cm3 can be palpable on the front wall of the vagina. The mass infiltrates the left pelvic wall without tension; There is a gap between the uterus and the right side of the uterus. HPV16 and 18 were positive in the outside hospital. Gynecological ultrasound in our hospital: An uneven hypoechoic area of about 76*68mm can be seen in the cervix, and blood flow signals can be seen in the cervix. Pelvic MRI in the Figure 2: cervical hypertrophy and abnormal signal mass, multiple cystic and solid abnormal echoes on the back wall of the pelvis and bladder, consider metastasis. CTU urinary system imaging and three-dimensional reconstruction was performed after MDT: the middle part of the left ureter was partially wrapped and invaded. Cervical squamous cell carcinoma antigen (SCCA) was

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68.3ng/mL. The pathological section of cervical neoplasms in our hospital showed high-moderately differentiated squamous cell carcinoma of the cervix in the Figure 1. Diagnosis: High-moderately differentiated squamous cell carcinoma of the cervix, stage IV. After admission, the patient developed intermittent fever, up to 40.3℃. Blood routine, CRP and PCT were all significantly increased. Considering that fever is related to tumor tissue necrosis and shedding, secondary infection and tumor itself, anti-infection, cooling, correction of anemia, and hemostasis were given, Local radiotherapy and other symptomatic and supportive treatment, repeated blood cultures and cervical secretions were all normal. On January 13, the patient and his family refused further treatment and urged to leave from the hospital.

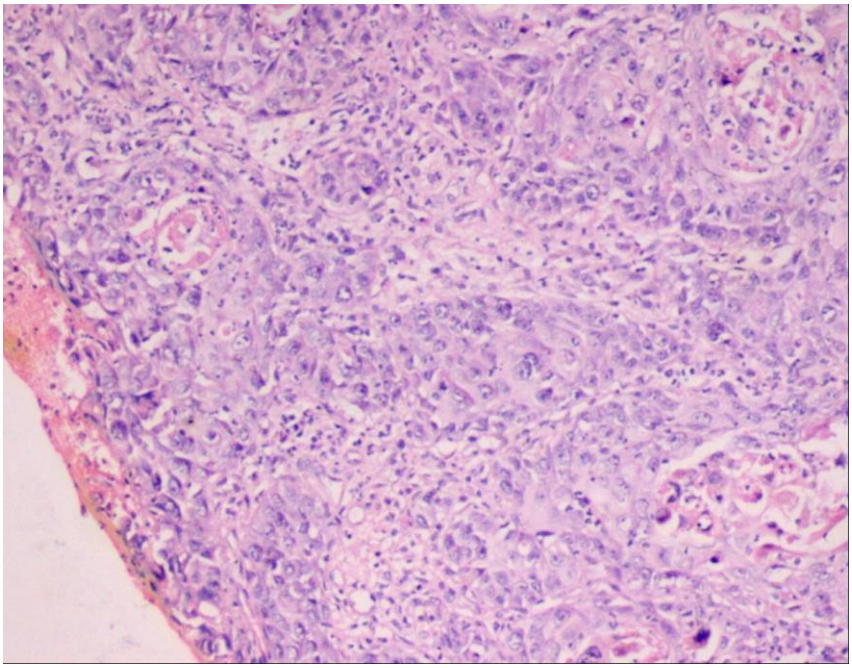

Figure 1 Pathological section.

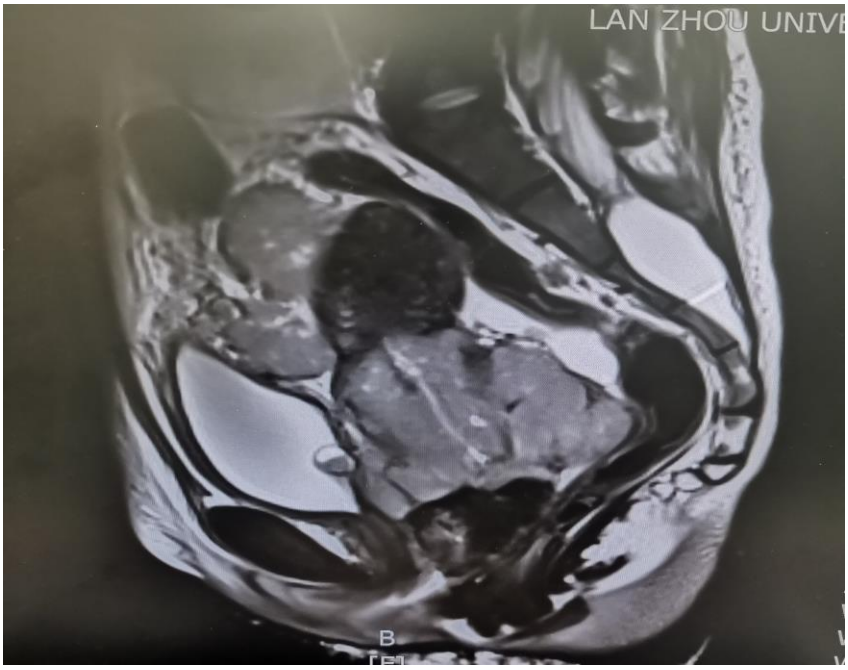

Figure 2 Pelvic MRI scan.

3. Discussion

Cervical cancer is the second most common female cancer in the world [4]. In 2013, the American

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Cancer Society (ACS) reported that there are more than 4,000 died of Cervical Cancer (CC) in overtake 12,000 newly diagnosed cervical CC patients. The incidence of squamous cell carcinoma, which is sensitive to radiotherapy and has a good prognosis, is gradually decreasing, while the incidence of adenocarcinoma is increasing. In particular, the incidence of CC in young women is on the rise [5], the phenomenon is more obvious in developing countries. The incidence, etiology, clinical features and treatment of CC in young women are different from those of patients over 35 years old. Young cervical cancer is related to human papillomavirus (HPV) infection, multiple sexual partners, premature sex (<16 years), sexually transmitted diseases, malnutrition, oral contraceptives, etc. [6]. In China, the incidence of CC is second only to breast cancer, becoming the most serious disease threatening women's health. Since 2004, the Chinese government has been actively promoting and implementing CC screening programs, including the establishment of early intervention pilots and demonstration sites for CC patients. As of 2009, CC pilot projects have been established in many provinces and autonomous regions. Large-scale education and screening have significantly reduced the morbidity and mortality of CC in China. However, due to the huge population base, the limited level of economic development, the unbalanced allocation of medical resources and the low level of Chinese women's understanding of the disease, China still lags behind developed countries in preventing CC. It is worth noting that the incidence of CC in China is 6 times that of developed countries, and China's CC cases account for one third of the global cases. At the same time, the incidence of the disease in China is increasing at a rate of 2-3% per year, and about 100 Chinese women die of CC every day. Fortunately, if CC can be screened, detected, and treated early, the prognosis is good. According to a large number of surveys, less than 50% of women said they can accept the current price of CC screening. Women who have received CC screening have a higher recognition rate of CC and HPV than women who have not received CC screening. Therefore, the price of CC screening plays an important role in women's understanding of CC and HPV. The price of CC screening varies from hospital to hospital. This article hopes that developing countries and local governments and health departments can appropriately reduce the price of CC screening or add it and HPV vaccination in the scope of outpatient medical insurance, so that more people will have the opportunity to receive CC screening and HPV vaccination. At the same time, publicize relevant knowledge from all aspects to ensure that most people understand the screening and go to the hospital for regular check-ups. There is still a long way to go in developing countries to achieve full coverage of CC screening and HPV vaccination.

With the change of sexual attitudes, the phenomenon of premature intercourse for the first time and multiple sexual partners has become more and more common, which greatly increases the chance of contracting HPV. Adolescent girls (under the age of 20) have frequent sex lives, are more likely to have multiple sexual partners, and are more susceptible to HPV infection [7]. In addition, the immune function of the adolescent reproductive system is not yet fully developed, and the cervix is not yet fully mature. Premature sexual life exposes the cervix and causes HPV susceptibility. In particular, the transformation zone (TZ) is sensitive to inflammation, external carcinogens and carcinogens, and is more likely to evolve into precancerous lesions even cancer [8]. Studies have suggested that human semen may play a role in the development of cervical cancer. The component polyamines in semen can activate the expression of Epstein-Barr virus early antigens in raji cells. Semen has an effect on women's cervical epithelial cells and lymphocytes, which proves that semen supernatant is an inducer of heat shock protein and IL10 gene transcription, and an inhibitor of interferon 7 gene transcription. In addition, during sexual intercourse, semen enhances the expression of MMP-9 in cervical epithelial cells, and the enhancement of MMP-9 expression is closely related to cancer infiltration, thereby increasing the risk of cervical cancer. The age for initial screening for cervical cancer has always been a hot topic of discussion. The 2020 American Society for Colposcopy and Cervical Pathology guidelines recommend CC screening from 25 years old [9]. The recommended screening age for the two cancer screenings in China is 35 to 64 years old, and the WHO recommended screening age is 30-49 years. It takes about 5 to 10 years for cervical precancerous lesions to progress to cervical cancer. Combined with this 17-year-old patient with cervical cancer, we should pay attention to the early screening of adolescent HPV, which is of great significance to the early prevention and treatment of CIN and cervical cancer.

The patient's first sexual life was 14 years old (<16 years old) and had multiple sexual partners. His sexual partners were between 18 and 38 years old and had a history of taking oral contraceptives (OCs) multiple times. Many scholars have tried to analyze the relationship between OCs and CC, but the results are not consistent. At present, the more generally accepted conclusion is [10]: Long-term use of OCs in women infected with HPV will increase the risk of developing CC. In a 25-year cohort study of 46,000 women in the United Kingdom, the mortality rate of CC among OCs users increased significantly. Even after removing factors such as social class, recent use of OCs is also associated with

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the occurrence of CC. It can be seen that there seems to be a certain relationship between OCs and the occurrence of CC. Under normal circumstances, Langerhans cells (LCS) only appear in the lower 1/2 layer of the cervical squamous epithelium. In the tissues of HPV infection and cervical intraepithelial neoplasia (CIN), the distribution and number of Langerhans cells have changed. In addition, Compared with patients who did not take OCs, the number of Langerhans cells in the cervical TZ of patients taking OCs decreased, and the decrease of cervical Langerhans cells can weaken the body's specific immune response ability against foreign antigens, leading to local cervical acquired immunodeficiency. The decrease of cervical Langerhans cells and local immunodeficiency make the potentially malignant cells further develop into cervical cancer when the body's immune response is absent or low. Therefore, long-term use of OCs may be the cause of tumor, and it may also have a priming effect in the early stage of tumor formation. However, does OCs really increase the chance of developing CC? The chance of HPV infection is related to contraceptive methods. Tool contraception does not increase the risk of CC, and women who use OCs for contraception often no longer use tools for contraception at the same time. This increases its exposure to HPV. Therefore, it is not so much that OCs increase the chance of CC. It is more that OCs change the way of sexual life, and increase the chance of women being infected with HPV, thereby increasing the risk of CC. Fortunately, this risk can still be minimized through prevention. It is recommended that people who use OCs for contraception should undergo CC screening at least once a year, especially those who have used OCs for more than 5 years.

It is currently believed that persistent HPV infection is an essential factor for CC, and HPV infection is one of the most common sexually transmitted diseases (STD) in the world. At present, there are many researches about infecting HPV on women, but not enough attention has been paid to men who are infected with HPV and thus infect his sexual partner through sexual behavior. Studies have found [11]: Males aged 20-40 have the highest chance of being infected with HPV. Males who infect HPV when they are young will still carry and will still be infected with new HPV types when they are older, thereby increasing the risk of HPV-related diseases and persistent infecting their sexual partners. In contrast to women, men who are infected with HPV usually have no clinical symptoms. Male foreskin is a repository of high-risk human papillomavirus (HR-HPV). Excessively long foreskin or phimosis of sexual partners is an independent risk factor for HPV infection in women. It promotes HPV reproduction and at the same time can make the virus spread through sex intercourse. HR-HPV infection causes inflammation persists continually, resulting in the release of reactive oxygen species and free radicals, causing cell damage, inhibiting cell antitumor activity, and promoting tumor development and leading to cancer eventually. Therefore, the promotion of male HPV screening or circumcision can help prevent the occurrence of CC in women.

The patient denied family history of CC and did not undergo genetic testing. The occurrence and development of CC are the result of the comprehensive accumulation of multi-factors, multi-events, and multi-gene effects. Certain gene mutations, activation of proto-oncogenes and tumor metastasis genes, inactivation of tumor suppressor genes and tumor metastasis suppressor genes, and a series of abnormal signal transduction caused by changes are the molecules biological basis for the occurrence and development of CC. By Sequencing of HPV16 genes in cervical lesions tissue found that HPV16 type E6 and E7 gene mutations are correlated with the progression of cervical lesions [12]; C-MYC genes are often amplified and overexpressed in CC and are closely associated with the occurrence and development of CC [13]. Studies have shown that the expression level of the proto-oncogene C-MYC protein in CC tissue is higher than that in normal cervical tissue, and the positive rate is higher in lately clinical stage and poorly differentiated CC, and its expression is increasing with the progress of CC. Then promoting the malignant biological behavior of CC, suggesting that the expression of the protein plays a vital role in the malignant biological phenotype of CC. Studies have shown [14] that the expression of PTEN gene in CC is related to the histological grade, clinical stage, depth of invasion, and lymph node metastasis of CC, and has nothing to do with age and tumor size. CC metastasis is related to PTEN gene suppression. Research on genetic susceptibility factors of CC has also achieved certain results. The most mature is the human leukocyte antigen (HLA) gene family, which has a certain relationship with the occurrence of invasive CC. At present, transforming growth factor β family genes, p53 gene codon 72 polymorphism, tumor necrosis factor (TNF) gene, and other immune-related gene sites have gradually been confirmed to be associated with CC susceptibility.

The 2021 Chinese Resident Dietary Guidelines Scientific Research Report pointed out that the body mass index (BMI) under 18.5kg/m2 is underweight, the patient’s BMI is 15.61kg/m2, this index indicates she is underweight and malnutrition. Retrospect her medical history, her patients had divorced since her childhood, she had worked outside for a long time and had an extremely irregular diet, and seldom consumed high-quality protein, fruits and vegetables. Studies have shown [15]: The risk of HR-HPV in low-weight or malnutritious patients to cause CC is more than 2 times comparing to the

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normal-weight patients. Studies at home and abroad have shown that increasing the intake of fresh vegetables, fruits, and high-fiber foods can effectively prevent CC; And lacking of vitamin A, C, E, folic acid, etc. is very likely to be a potential risk factor for CC. Epidemiology has confirmed that folic acid deficiency is closely related to the occurrence and development of DNA hypomethylation and CC. Some foreign scholars conducted a 2-year follow-up study and concluded that folic acid deficiency can be accompanied by high-risk HPV infection, eventually leading to CC or cervical precancerous lesions. In particular, women with HPV-16 infection and folic acid deficiency are more likely to develop CC, suggesting that it can reduce the chance of women suffering from CC by effectively supplement folic acid.

After she was in hospital, related indicators of the digestive system indicate she has abnormal lipid metabolism and severe non-alcoholic fatty liver (NAFL). The current research on lipids mainly focuses on its relationship with digestive system tumors and metabolic diseases. There is little research on its relationship with gynecologic tumors. A research [16] found that elevated cholesterol levels can enhance the recognition of tumor antigens by cytotoxic T lymphocytes and play a role in killing tumor cells. The patient's cholesterol levels was significantly reduced, so her immune system's ability to kill tumor cells was reduced. Because young women have faster metabolism, the growth of cervical malignant tumors will consume a large amount of cholesterol to synthesize more tumor cell membranes. High density lipoprotein cholesterol (HDL-C) maintains the normal cholesterol balance in cells and is related to cell surface receptors. Above it also can combine and selectively promotes cholesterol efflux within the cell. This shows that young CC often has different degrees of dyslipidemia, mainly manifested by lower levels of total cholesterol and high-density lipoprotein cholesterol [17]. Studies have shown [18]: serum leptin (Leptin, LP) levels are elevated in patients with NAFL. Suganami [19] found that: LP can not only directly promote tumor cell growth, proliferation, immune response, migration and angiogenesis, but also indirectly induce the production of fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF). It can also participate in tumor invasion and metastasis through HIF and other pathways. FGF and VEGF have a synergistic angiogenesis effect, which provides rich nutrition for the division, proliferation and distant metastasis of cancer cells. In a pilot study by Nie Ming [20], LP and VEGF were measured in CC and healthy women. The results showed that LP and VEGF are low in healthy conditions, and both are elevated when CC occurs. Therefore, the division and proliferation of cancer cells in the early stage of canceration needs to be obtained through capillaries, and constantly induces the formation of new blood vessels, and the permeability of new blood vessels is relatively high, which will provide more sufficient nutritions for cancer cells. The significant increase in LP secretion will stimulate the production of VEGF and form more new blood vessels. Therefore, the growth, proliferation and distant metastasis of CC cells are strongly dependent on blood vessel.

The occurrence of CC is a complex process involving multiple factors and genes. In order to reduce the occurrence of CC, we must vigorously implement the tertiary prevention of CC. The primary prevention of CC includes preventing HPV infection, such as sexual guidance and HPV vaccination, the use of condoms is particularly important for young people. The basis of the secondary prevention of CC is the early detection of precancerous lesions or tumors through cervical cytology screening and/or HPV testing for people at high risk of DNA. The use of these 2 tests is advocated by some international organizations. Although there is a clear CC screening policy in China, we still do not have a clear HPV vaccine and vaccination policy. Data and evidence on knowledge and understanding of HPV infection, CC and HPV vaccines are still unclear. However, among adolescents and young adults, the best way to prevent is to get vaccinated rather than screened.

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