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Photodynamic Therapy for Low-grade Cervical Intraepithelial Neoplasia (CIN1): A Case Report

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Abstract: As a drug-mechanical combination technology, photodynamic (PDT) can achieve accurate and targeted therapy for malignant tumors and benign diseases through the production of reactive oxygen species, oxygen free radicals or singlet oxygen by photosensitizers at specific wavelengths. Compared with traditional surgery, it has the advantages of selective killing, repeatable treatment, preserving target organ function and so on. The purpose of this study was to explore the clinical value of photodynamic therapy in cervical precancerous lesions by taking the patients with low-grade cervical intraepithelial neoplasia (CIN1) with high-risk human papillomavirus (HR-HPV) persistent infection diagnosed by "three-step diagnosis and treatment procedure" as an example. Using HiPorfin as a photosensitizer, photodynamic therapy was performed 48 hours after intravenous drip. Set laser wavelength 630nm, light dose density 137.58J/cm2, transmission efficiency 1.42, output power 2w. 3cm columnar optical fiber was placed around the 2cm in the cervical canal to cover all the lesions, and the irradiation time was 900s (600s in the cervical canal and 300s outside the cervical canal). The patients were given oxygen inhalation for 6 hours after operation, and the patients were observed for itching and other discomfort, and paid attention to avoid light. Photodynamic therapy was performed again in the same way on the second day. After two months of treatment, pathological biopsy showed chronic cervicitis, indicating that the disease had been effectively controlled. Theoretically, although the patient is not the absolute indication of photodynamic therapy (that is, meeting CIN Ⅱ or CIN Ⅲ, having fertility requirements and not undergoing surgery), this therapy can remove not only the superficial lesions inside and outside the cervix, but also the potential lesions not found under colposcopy. It can also block the persistent infection of HPV by inhibiting the expression of HPV18, E6 and E7mRNA in Hela cells. In combination with Baofukang suppository, it can block HPV infection. Increase the negative conversion rate of cervical HPV and reduce the probability of recurrence after CIN1 cure. For young female patients with persistent HR-HPV infection and fertility requirements, photodynamic therapy is an effective choice for clinical treatment of CIN1.

Keywords: Photodynamic; HiPorfin; Low-grade cervical intraepithelial neoplasia; High-risk human papillomavirus

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1 Introduction

Cervical cancer is one of the most common malignant tumors in gynecology, and it is the second biggest threat to women's health after breast cancer. Although it is a high incidence tumor, the course of disease is long (5-10 years) and the cause is clear (HR-HPV persistent infection). It can be screened for large area early cancer through the "three-step diagnosis and treatment procedure" to effectively control the risk of cancer[1]. Cervical intraepithelial neoplasia (CIN), as an early precancerous lesion, can be divided into

three grades according to the degree and extent of cervical epithelial atypical cell involvement: CIN3 is the early carcinogenic manifestation of CIN1-CIN2-CIN3. Although CIN1 is less likely to develop into cervical cancer, the natural history and the risk of progression of individual lesions are unpredictable[2]. The guidelines for the treatment of cervical lesions and colposcopy cooperation group in China clearly stipulate that patients with CIN1 and HPV positive should be given active treatment[3].

As a drug-mechanical combination technology, photodynamic (PDT) can achieve accurate and targeted therapy for malignant tumors and benign diseases through the production of reactive oxygen species, oxygen free radicals or singlet oxygen by photosensitizers at specific wavelengths[4]. Compared with the traditional surgery, it has the advantages of selective killing, repeatable treatment and retaining target organ function, especially for the removal of superficial lesions. The patient was a child-bearing age woman who had been diagnosed with CIN1. The lesion was confined to the cervical epithelium and the lesion thickness was 2-3 cm, which was in accordance with the effective depth of action (8cm) of photosensitizer HiPorfin at the optimal absorption wavelength of 630nm[5-6]. Therefore, this paper takes photodynamic therapy of CIN1 with high-risk HPV infection as an example to explore its value in clinical application.

2 One case

The patient, a 22-year-old married woman of childbearing age, was admitted to our hospital on October 26, 2019 due to "cervical lesion for 5 months". The patient was examined by electronic colposcopy in the first people's Hospital of Zhangjiagang City on May 9, 2019 (see Figure 1). The vinegar white epithelium and iodine are not stained, indicating HPV infection. The results of cervical biopsy (see Fig. 2) showed that: (cervical 1.5.7.11) mucosal chronic inflammation with focal glandular squamous metaplasia, in which (11 points) of small lesions showed low-grade intraepithelial neoplasia, (cervical canal scratch) showed chronic inflammation. On October 4, 2019, the results of HPV in Zhangjiagang first people's Hospital showed that hpv-52 was positive. Cervical DNA quantitative cytology showed that a small number of aneuploid cells. Specialty: vulva perineum married birth type; vagina smooth; a small amount of white secretion, no odor; cervix is often large, severe erosion, no blood contact; uterus bilateral adnexa area is not palpated. On October 26, 2019, blood cell analysis, urine analysis, electrocardiogram, chest X-ray, color Doppler ultrasound and liver and kidney function examination showed no obvious abnormality. The patient and his family members agreed to photodynamic therapy and signed informed consent.

On October 27, 2019, the patient was intradermal injected with 0.01mg/ml hematoporphyrin injection (HiPorfin) 0.1 ml. After 15min observation, there was no local allergic reaction such as swelling and induration. After the skin test was negative, the patients were intravenous drip with HiPorfin (150mg of HiPorfin + 250 ml of 0.9% normal saline) and finished within 1 hour. Keep the patient away from light, during which the patient's skin does not itch, erythema and other discomfort. First photodynamic therapy was performed on October 29, 2019: a 3cm columnar optical fiber was placed in the cervical tube about 2cm to cover the lesion completely. The transmission efficiency was 1.42, the output power was set to be 2W, the irradiation time was 900s (600s in the cervical canal and 300s outside the cervical canal), and the optical dose density was 137.58J/cm2.After the operation, oxygen inhalation was given for 6 hours. The patient's skin did not itch and other discomfort, and continued to avoid light. The second photodynamic therapy was performed on October 30, 2019.After two times of photodynamic therapy, the patient's perineum and other parts had no discomfort, and the electronic colposcopy (see Figure 3) was significantly improved. He was discharged on November 2, 2019.

Two months after photodynamic therapy, the patient will return to the hospital on January 7, 2020. The results showed that HPV typing was negative; cytological examination showed no abnormality; colposcopy (see Figure 4) showed a small amount of vinegar white epithelium. After the pathological biopsy, the results showed that chronic cervicitis.

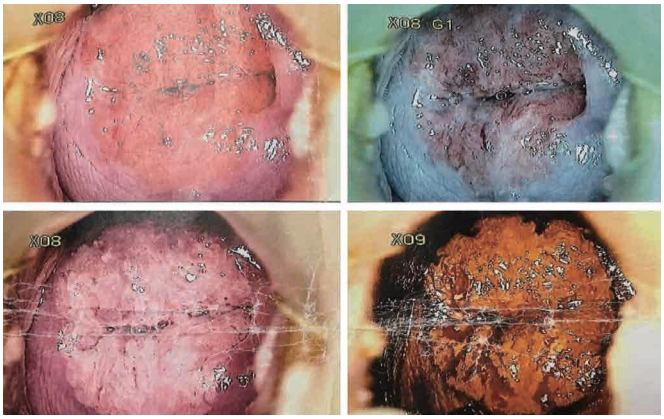

Figure 1. Electronic colposcopy in outside hospital before operation: HPV infection (52 positive)

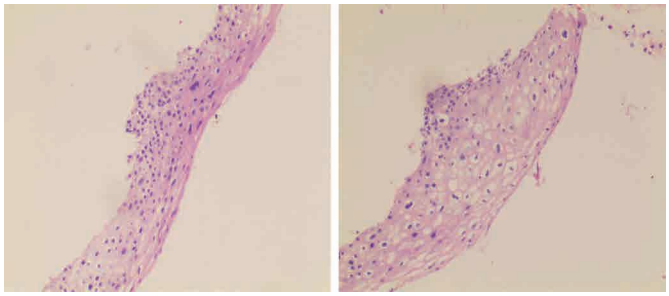

Figure 2. Preoperative out-of-hospital cervical biopsy: (11 points) small lesions, low-grade intraepithelial neoplasia; (cervical canal curettage) showed chronic inflammation.

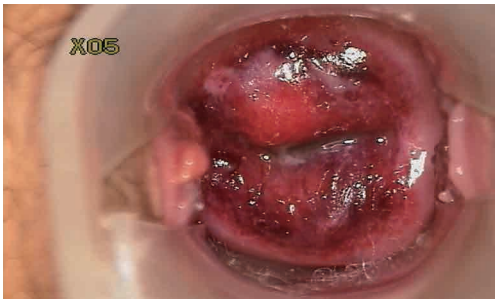

Figure 3. Electronic colposcopy before discharge: Eschar removal of local lesions after photodynamic therapy

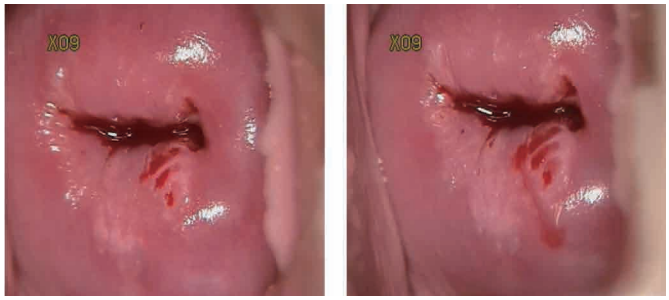

Figure 4. Electronic colposcopy 2 months after operation: a small range of vinegar white epithelium-suggesting that HPV infection may still exist

3 Discussion

The patient is a woman of childbearing age who has been diagnosed with CIN1. In clinical diagnosis and treatment, there are three kinds of treatment methods for CIN: surgical treatment (cold knife conization, Lipp knife conization), drug therapy and physical therapy (microwave, laser, freezing, photodynamic, etc[7]). Cervical conization is the first choice for clinical treatment of CIN Ⅱ and CIN Ⅲ, with high cure rate and low missed diagnosis rate. However, for young women who still have fertility requirements, cervical conization will affect cervical function and lead to adverse pregnancy outcomes; secondly, such surgery can only remove the visible damage tissue, but can not clear the potential lesions[8]. For patients with HR-HPV infection, the virus continues to exist and the recurrence rate of CIN is high.In terms of drug treatment, the national comprehensive cancer network (NCCN) recommended in the clinical practice guidelines for cervical cancer published in 2018 that cisplatin monotherapy or cisplatin combined with fluorouracil is the first choice for concurrent chemoradiotherapy in the treatment of cervical cancer[9]. However, the traditional chemotherapy drugs currently used in the treatment of cervical cancer have poor specificity and high drug resistance, and the side effects of targeted drugs are obvious. This seriously affects the compliance of patients. Laser therapy is a kind of traumatic physical therapy, its high radiation intensity will cause damage to normal human tissues[10]; the vagina will have burning sensation, after healing, local tissue will become hard and scar formation; the unborn will have difficulty in dilating the uterine orifice during childbirth, so cesarean section is necessary. Photodynamic technology as a combination of medicine and equipment, combined with photosensitizer, therapeutic light source and oxygen, can achieve the precise killing of pathological tissue. Although its penetration depth is limited, and adverse reactions such as photoallergy, immunosuppression, and inflammatory infection may occur during the treatment process, compared with the above-mentioned traditional treatment methods, it can not only clear the lesions inside and outside the cervix, but also clear the potential lesions not found under colposcopy, which greatly reduces the recurrence rate; at the same time, it has the advantages of selective killing, repeatable treatment and protection of target organ function[11]. It is the best choice for this patient in clinical treatment.

In the treatment of HPV. Many studies have

shown that the overexpression of E6/E7 protein caused by the integration of HPV virus DNA into the host genome is the key to cell carcinogenesis[12]. Therefore, in order to eradicate the disease, the patient in this case needs to inhibit the persistent infection of HPV. Compared with other traditional therapies, photodynamic therapy can inhibit the expression of HPV18, E6 and E7mRNA in Hela cells[12]. Chinese patent medicine Baofukang suppository can significantly reduce the expression of cervical HPVE6/E7 gene fragment mRNA, which has the potential to treat cervical HPV infection at the cellular and molecular level. Therefore, the combination of photodynamic and Baofukang suppositories can double block HPV infection and improve the negative conversion rate of cervical HPV[13]. In the treatment of CIN1. Although the patient is not an absolute indication of photodynamic therapy (i.e. CINII or CINIII, fertility requirements, no surgery)[14], but this time we used HiPorfin as photosensitizer, setting laser wavelength 630nm and light dose density 137.58 J/cm2 is effective in the treatment of CIN1 with high-risk HPV persistent infection, which is worthy of clinical promotion. In the three-step diagnosis and treatment procedure after operation, based on the results of HPV typing and cervical biopsy, the small area of vinegar white epithelium shown by colposcopy in this patient was caused by cervical inflammation. In the selection of photosensitizer. Although the first generation photosensitizer- HiPorfin used by the patient in this case is slightly weaker than ALA, which is the second generation photosensitizer widely used in clinic, in terms of light protection time and tissue selection[15]. Due to the intravenous drip, it has the advantages of rapid onset and constant blood drug concentration required for sustained curative effect.

The curative effect of this case is remarkable after photodynamic therapy, and it has reached the cure level. However, due to the possibility of recurrence, it is necessary for medical staff to make regular follow-up and emphasize the importance of regular follow-up of patients to prevent the transformation of the disease[16].At the same time, advocate a healthy lifestyle, carry out sexual knowledge and mental health education, actively promote HPV vaccination for women of school age, in order to effectively prevent the occurrence and development of cancer[17].

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