Expression of mismatch repair gene proteins in endometrial complex hyperplasia

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Abstract: Objective To observe the expression of mismatch repair gene proteins in endometrial complex hyperplasia. Methods A total of 50 pathological tumor specimens from patients with endometrial complex hyperplasia were collected. Immunohistochemical detection was performed on the pathological tissues. Clinical information was obtained from medical records for analysis. Results Among the 50 patients with endometrial complex hyperplasia, 27 cases (54%) showed deletion of at least one mismatch repair gene expression, 18 cases (36%) showed deletion of two or more mismatch repair gene expressions, and 3 cases (6%) showed negative expression of all four mismatch repair genes. Conclusion More comprehensive genetic testing should be performed for patients with endometrial complex hyperplasia, so as to provide an effective means for the prevention of endometrial carcinoma.

Keywords: Endometrial Complex Hyperplasia; Mismatch Repair; Gene Expression

Endometrial carcinoma is the second most common gynecological malignant tumor. In the United States, there are 50,000 new cases of endometrial carcinoma and 8,000 deaths from the disease each year, which seriously threatens women's health[1]. Endometrial carcinoma usually develops from endometrial hyperplasia, and abnormally elevated estrogen plays a catalytic role in this process. For example, the incidence of endometrial carcinoma is higher in people with obesity, ovulation cessation and excessive exogenous estrogen intake[2]. The risk of developing endometrial carcinoma in female patients with endometrial complex hyperplasia is 28%, which is 14 times higher than that in patients without endometrial complex hyperplasia[3]. Early detection of endometrial complex hyperplasia and appropriate treatment are of great value for the prevention of endometrial carcinoma. It is reported that about 5% of endometrial carcinoma cases are caused by genetic changes[4]. Among them, Lynch syndrome is an autosomal dominant genetic disorder caused by mutations in mismatch repair (MMR) genes, including mutL homolog 1 (MLH1), mutS homolog 2 (MSH2), mutS homolog 6 (MSH6) and PMS2[5–6], which can lead to 2%–3% of endometrial carcinoma cases[7]. These MMR gene mutations are inherited in an autosomal dominant manner. MMR gene mutations result in abnormal DNA replication and microsatellite instability. More than 75% of endometrial tumor patients with Lynch syndrome have microsatellite instability[8]. This study intends to explore the expression of MLH1, MSH2, MSH6 and PMS2 in patients with endometrial complex hyperplasia by immunohistochemistry, and to investigate the genetic risk in the occurrence and development of endometrial complex hyperplasia.

1. Materials and methods

1.1. Clinical data

A total of 50 pathological tumor specimens diagnosed as endometrial complex hyperplasia by surgical biopsy in Chengde Maternal and Child Health Hospital from January 2014 to January 2016 were selected. The average age of the patients was 49 years old, with an average body mass index (BMI) of 24.2 kg/m². Fifteen cases (30%) had a BMI >25 kg/m². Twenty-eight cases (56%) were premenopausal, and 5 cases were nulliparous.

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1.2. Immunohistochemical detection

Immunohistochemistry was used to detect the expressions of mismatch repair gene proteins MLH1, MSH2, MSH6 and PMS2 in the pathological tumor specimens. The streptavidin-biotin method was adopted for immunohistochemical staining. Tissue sections were dewaxed with xylene and rehydrated, then incubated with 0.3% hydrogen peroxide solution in methanol for 30 minutes. The tissue sections were rehydrated with graded ethanol and rinsed with phosphate-buffered saline (PBS). After tissue fixation, the sections were incubated with monoclonal antibodies in PBS containing 1% bovine serum albumin at a dilution ratio of 1:200 at 4℃. Subsequently, the specimens were rinsed with PBS and incubated with secondary antibodies at room temperature for 30 minutes. DAB staining and hematoxylin counterstaining were conducted, followed by observation under an optical microscope.

1.3. Evaluation and analysis

The staining results were interpreted by two pathological experts. The criteria for evaluating staining intensity[9] were as follows: Score 0: no staining of cells; Score 1: minimal staining of cell nuclei, cell membranes and cytoplasm compared with the intercellular matrix; Score 2: obvious brown staining of cell nuclei, cell membranes and cytoplasm; Score 3: dark brown staining of cell nuclei, cell membranes and cytoplasm with blurred morphology.

2. Results

2.1. Expression of mismatch repair gene proteins

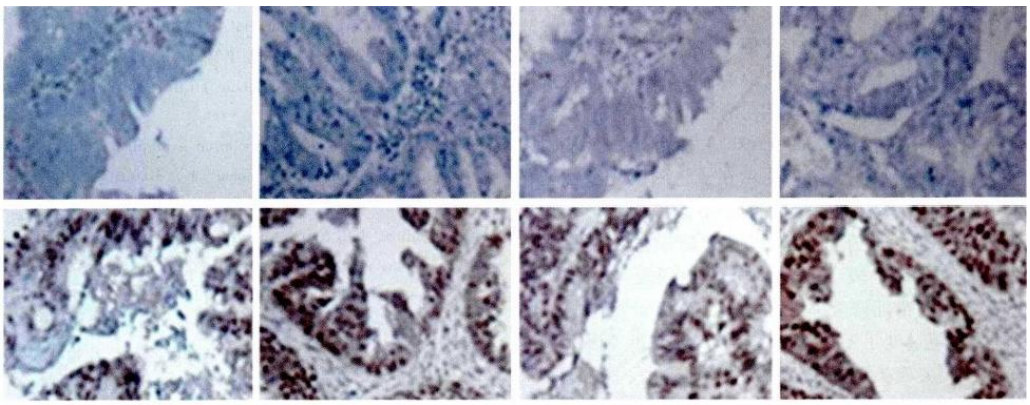
Positive results of mismatch repair gene proteins MLH1, MSH2, MSH6 and PMS2 showed partial brown staining in the cytoplasm, while brown staining was occasionally observed in negative results (see Figure 1).

2.2. Immunohistochemical results of mismatch repair gene proteins

Twenty-seven cases showed deletion of at least one protein expression, 18 cases had deletion of two or more protein expressions, and 3 cases were negative for all four protein expressions (see Table 1).

Figure 1 Expression of mismatch repair gene proteins MLH1, MSH2, MSH6 and PMS2 in endometrial complex hyperplasia (DAB staining and hematoxylin counterstaining ×200)

The upper image shows negative expression, and the lower image shows positive expression



3. Discussion

According to the latest statistics, there are 12,000 new cancer cases and 7,500 cancer-related deaths in China every day[10]. Relevant domestic studies have found that in cities such as Beijing and Shanghai, endometrial carcinoma has surpassed cervical cancer to become the most common gynecological malignant tumor in terms of incidence rate. Screening, risk assessment, early diagnosis and appropriate treatment of endometrial carcinoma in female population are effective ways to reduce the mortality rate of endometrial carcinoma and alleviate the economic burden. Endometrial hyperplasia is a common

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gynecological disease, including simple hyperplasia, atypical hyperplasia and complex hyperplasia. Among them, atypical hyperplasia and complex hyperplasia are considered as precancerous lesions of endometrial carcinoma. Studies have shown that 25% of endometrial complex hyperplasia cases will progress to endometrial carcinoma[12]. Therefore, attention should be paid to the early detection, diagnosis and treatment of endometrial complex hyperplasia.

It is reported that about 5% of endometrial carcinoma cases are caused by genetic changes[13]. Lynch syndrome is an autosomal dominant genetic disease caused by MMR gene mutations. Mismatch repair genes play an important role in maintaining genetic stability. Among them, MLH1, MSH2, MSH6 and PMS2 are mainly involved in the recognition of mismatched bases and DNA strands. DNA defects or mismatched bases can be caused by physical and chemical damage as well as polymerase errors. In the normal replication process of DNA, the helical structure is maintained by hydrogen bond complementarity between bases. MLH1, MSH2, MSH6 and PMS2 mainly identify and repair mismatched bases during DNA replication, so as to maintain the stability of heredity in the body[14]. Mismatch repair is a post-replication repair mechanism of cells. Abnormalities of mismatch repair genes are also associated with tumorigenesis. Defects in mismatch repair function caused by MMR gene abnormalities can lead to genetic instability, manifested as replication errors, which is one of the main reasons for individual differences in tumors[15]. Endometrial carcinoma is the most common extraintestinal cancer in female patients with Lynch syndrome[16]. Abnormal mutations in MLH1, MSH2, MSH6 and PMS2 genes may promote the occurrence and development of endometrial carcinoma. Mutations in mismatch repair genes can affect the expression of corresponding proteins. Detecting the protein expression of mismatch repair genes in endometrial complex hyperplasia tissues is beneficial to the evaluation of the disease condition and the prevention of endometrial carcinoma. Immunohistochemical detection is a simple and low-cost method for protein detection. Detecting the genetic risk of endometrial complex hyperplasia by immunohistochemistry is of great significance for the prevention and early diagnosis of tumors[17].

The results of this study showed that among 50 patients with endometrial complex hyperplasia, 27 cases (54%) had deletion of at least one mismatch repair gene protein expression, 18 cases (36%) had deletion of two or more mismatch repair gene protein expressions, and 3 cases (6%) were negative for all four mismatch repair gene protein expressions. The results suggest that there is also a high frequency of mismatch repair gene protein expression deletion in endometrial complex hyperplasia. Prophylactic hysterectomy is an effective means to prevent malignant tumors of the uterus and ovaries[18]. Appropriate mismatch repair gene testing for patients with endometrial complex hyperplasia is beneficial to the prevention of endometrial carcinoma and avoids the risk of excessive surgery. However, further research is needed to investigate the progression risk of patients without mutations and those with different mutation types.

In conclusion, this study confirms that there is a high probability of mismatch repair gene protein expression deletion and gene mutation in the endometrium of patients with endometrial complex hyperplasia. Mismatch repair genes are associated with the occurrence of Lynch syndrome and endometrial carcinoma. Therefore, to further determine the clinical significance of mismatch repair gene protein expression deletion and gene mutation in endometrial complex hyperplasia, gene detection and long-term follow-up studies on larger samples are needed, so as to provide effective means for the prevention of endometrial carcinoma.

4. References

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