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Expression and Clinicopathological Significance of Hedgehog Signaling Pathway in Malignant Mesothelioma

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Abstract

Background: To investigate the expression of Hedgehog signalling pathway gene in malignant mesothelioma and benign mesothelioma reactive hyperplasia by immunohistochemistry, and to compare the diagnostic value of pleural and abdominal fluid samples in malignant mesothelioma.

Methods: In this study, 70 cases of chest and abdominal effusion specimens confirmed by surgical endoscopic biopsy in our hospital from January 2016 to December 2019 were selected, including 50 cases in the malignant mesothelioma group and 20 cases in the benign reactive mesothelioma group. Biopsy and effusion samples were examined by immunohistochemistry at the same time, and the protein expression of Smo and GLi1 genes in Hedgehog signalling pathway was compared to further analyze the application value in the diagnosis of thoracic and abdominal effusion samples of malignant mesothelioma.

Results: The positive rates of Smo and GLi1 in biopsy specimens were 94.00% and 90.00%, respectively. Their specificity was 85.71% and 77.27%, and their sensitivity was 95.92% and 93.75%. The positive rate of Smo was 90.00% and 88.00%, the specificity was 77.27% and 71.43%, and the sensitivity was 93.75% and 89.80%, respectively. It proved that the diagnostic results of chest and ascites specimens were consistent with those of biopsy specimens. After statistical analysis of clinic-pathological data, the prognosis of malignant mesothelioma was positively correlated with asbestos chemical exposure history ($P<0.05$), but had little correlation with sex, age, lesion site, proliferation index gene P53 expression Figure 1-12 and Table 1-4.

Conclusion: Therefore, the gene detection of thorax and ascites in Hedgehog signalling pathway can be used as a new method for diagnosis of malignant mesothelioma.

Key words: Malignant Mesothelioma; Hedgehog Signalling Pathway; Protein Expression; Thoraco-abdominal Effusion; Immunohistochemistry

Introduction

Malignant Mesothelioma (MM) is a highly aggressive tumor originating from serous mesothelioma cells [1], which is characterized by cryptic onset, high misdiagnosis rate and short survival period. In recent years, the number of people exposed to asbestos chemical materials is increasing [2-3]. At present, studies have proved that its incidence factors are closely related to occupational or asbestos contact, so there is a greater correlation with regional areas in China [4], and the prevalence rate of malignant mesothelioma is increasing year by year. According to previous reports, only about 12% of mesothelioma patients survive longer than 36 months [5-6], and the median survival time of malignant mesothelioma patients after diagnosis is only 12-15 months [7]. Although the survival time of patients can be prolonged by existing chemotherapy drugs, the 5-year survival rate of patients with intermediate and advanced mesothelioma is still less than 15% [8]. Early screening and accurate diagnosis are important means of prolonging the survival of patients with mesothelioma. Due to the current lack of conclusive cytological criteria, some pathologists are reluctant to issue a definitive diagnosis of mesothelioma. Currently use puncture biopsy specimen in the diagnosis of mesothelioma are common or cavity mirror, but with the specimen in the diagnosis of thoracic and abdominal cavity effusion is extremely difficult, the mesothelium cell in pleural effusion, gland cancer cells and skin between reactive hyperplasia cells are difficult to identify, and biopsy specimens of invasive examination, need through the cavity mirror surgery or fine needle biopsy can obtain [9], Therefore, in this paper, the diagnosis of malignant mesothelioma is considered to be performed on the patients with less traumatic thoracic and ascites specimens.

Hedgehog (Hh) signalling pathway is a research hotspot in recent years, which plays an important role in the process of embryonic development. Among them, Shh signalling pathway is a key component of Hh signalling family [10]. The Shh signalling pathway is composed of Shh, Patched (PTCH), Smoothened (Smo) and GLi1 genes [11]. Smo gene is a 7-fold transmembrane protein with zinc finger structure, which is a positive activator of Hh signaling pathway and belongs to G protein-coupled receptor of class F [12-13]. Smo receptor is responsible for maintaining the normal development of embryos. The abnormality of Smo protein is related to the occurrence of malignant mesothioma. When the upstream Ptc receptor of Hedgehog signalling pathway is activated, the inhibitory regulation of Smo by Ptc can be relieved, and the active Smo gene can cause the activation of downstream target genes. Mutation or abnormal expression of Smo gene is not only closely related to basal cell carcinoma, lung cancer and breast cancer [14], but also can lead to specific proliferation of mesothelioma and participate in the occurrence and development of malignant mesothelioma. GLi1 gene is a transcription activator and the only one that can directly activate Hh signalling pathway downstream transcription factors [15-16], which is considered as a reliable indicator of Shh signalling pathway activation. GLi1 gene enters the nucleus after activation and activates downstream genes such as Wnt and TGF-β1 [17]. In order to promote the formation of tumor blood vessels and cell invasion and metastasis. In

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addition to participating in angiogenesis of malignant tumours, Hedgehog-GLi signalling pathway can also activate and regulate the biological role of epithelial mesenchymal transformation in invasion and metastasis of malignant mesothelioma [18].

Materials and Methods

Data of clinical specimen data

Pathological specimens of all enrolled patients were collected, and questionnaires were issued at the same time to understand basic information and clinic-pathological data of patients. This study has been approved by the Ethics Committee of Cangzhou People's Hospital. After screening, 70 patients with serious disease treated in Cangzhou People's Hospital from January 2016 to December 2019 were selected, and their pathological diagnosis met the diagnostic criteria of clinical guidelines for diagnosis and treatment of malignant mesothelioma.

Inclusion criteria:

1. Age range: 18-80 years old.
2. Pathological type: patients with chest and peritoneal diseases with definite pathological diagnosis.
3. Informed consent of patients and their families was informed during follow-up.

Exclusion criteria:

1. Patients with incomplete pathological data and missing follow-up.
2. Patients without hereditary diseases in their family history of medical records.
3. Patients with contaminated specimens caused by improper operation in the experiment.

After screening, 50 patients with malignant mesothelioma and 20 patients with benign reactive mesotheliosis were included in the study.

Reagents and equipment

Smo is a rabbit monoclonal antibody (model AB124964) targeting amino acids from Abcam. Smo is cytoplasmic. Immunohistochemistry (paraffin embedded section) dilution concentration 1:1000-1:2500. GLi1 is a rabbit polyclonal antibody (model AB217326) from Abcam Company. It is localized in cytoplasm and diluted at 1:100 by immunohistochemistry (paraffin-embedded section).

Research methods

By immune histochemical method to detect the Smo XiongFuQiang effusion, GLi1 protein expression, the application of diagnostic test evaluation methods into the group of cases were retrospectively analyzed, would be in the case of into the exclusion standard diagnostic tests are carried out, the experiment accord with standard of excluding cases, using the double blind method will case to random numbers. A new round of diagnostic tests was conducted, and four pathologists with senior professional titles diagnosed the pathophysiology of each case. Then, immuno histochemical Smo and GLi1 tests were performed on all cases, and the sensitivity and specificity of the new combined diagnosis method were recorded to evaluate the efficacy of the diagnostic tests. The improved paraffin sectioning method of pleural effusion was as follows: repeated centrifugation was performed according to the size of the cell masses after centrifugation and precipitation. After the

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centrifugation of supernatant was discarded, appropriate amount of protein glycerol and 90% ethanol were dropped. After the centrifugation of supernatant again, cell masses were taken for conventional paraffin embedding and sectioning (3-4um) treatment.

Statistical method

SPSS 21.0 statistical software was used for statistical analysis. Spearman rank correlation analysis was used to test the correlation between Smo and GLi1 protein expression and clinicopathological features of mesothelioma, $\chi 2$ test was used to test the correlation between Smo and GLi1 protein expression and clinic-pathological features of mesothelioma. The counting data were expressed as percentage, and $P<0.05$ was considered as statistically significant.

Result

Interpretation standard

In Smo antibody, gastric cancer was the positive control, and the cytoplasm of malignant mesothelioma was brown-yellow. Reactive mesenchymal hyperplasia was negative. GLi1 antibody in colorectal cancer is a positive control, showing cytoplasmic positive, brownish yellow, malignant positive.

Experimental results of surgical biopsy specimens

The positive rate of Smo and GLi1 were 94.00% and 90.00%, the specificity was 85.71% and 77.27%, and the sensitivity was 95.92% and 93.75%, respectively. The positive rate was 93.33%.

The positive rate of Smo and GLi1 were 90.00% and 88.00%, the specificity was 77.27% and 71.43%, and the sensitivity was 93.75% and 89.80%, respectively. The positive rate of chest and ascites specimens was 91.33%. The diagnosis of malignant mesothelioma by thoracic and ascites specimens was compared with that by surgical biopsy specimens.

According to the statistical analysis of Smo and GLi1 protein expression and clinicopathological data, the development and prognosis of malignant mesothelioma were positively correlated with asbestos chemical exposure history ($P<0.05$), but had little correlation with sex, age, lesion site and the expression of P53 gene.

Through the specimen chest, ascites in the diagnosis of malignant mesothelioma and comparing surgical biopsy specimens of diagnosis, has the high consistency, chest, ascites specimens joint detection positive rate was 91.33%, the biopsy specimens of joint detection positive rate was 93.33%, the comprehensive analysis of the new joint diagnosis has high clinical application value, and has higher sensitivity and specific degree, The coincidence degree with gold standard fluorescence in situ hybridization FISH was also high.

Conclusion

Malignant mesothelioma is one of the most common fatal primary pleural neoplasms and is closely related to asbestos. Mesothelioma is difficult to distinguish from reactive mesothelioma (RMH), especially in cytology, with pleural mesothelioma having the highest incidence (81%) and the worst prognosis [19-

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21]. The media also occurs in other membranous structures, including peritoneum (9%), pericardium, and testicular sheath. WHO divides malignant mesothelioma into epithelioid (the most common), sarcomatoid and biphasic. The sensitivity of cytological diagnosis commonly used in clinic is only 30%-75% [22-23]. Since mesothelioma cells are difficult to distinguish from degenerative or proliferative mesenchymal cells, most patients with pleural and peritoneal effusion of malignant mesothelioma are already in advanced stage at the time of diagnosis. Fluorescence in situ hybridization combined with immunohistochemistry can easily identify these cells. Moreover, cytological sections have some disadvantages such as overlapping cell blocks, high false positive rate and easy deslice. The improved pleural effusion was centrifuged for paraffin embedding and sectioning, and the cells obtained were smooth and stained clearly [24]. The diagnosis results were accurate and easy to distinguish, which provided an important basis for the accurate cytological diagnosis of malignant mesothelioma. At present, the clear diagnosis of mesothelioma is mostly obtained by endoscopic surgery or puncture specimens, which are difficult to obtain and harmful to patients [25]. The pleural and abdominal fluid samples are easy to obtain, and do little harm to patients. After the extraction of pleural fluid, the clinical symptoms of patients can be alleviated [26], which has obvious advantages. Therefore, FISH detection of thoracic and ascites specimens is a relatively novel method, which has higher sensitivity, specificity and accuracy than clinical methods.

The pathogenesis of malignant mesothelioma is related to histone modification, chromatin remodelling and DNA methylation, including differentiation, development and tumorigenesis [27]. The Hh pathway regulates cell proliferation and differentiation during embryonic development. Smo - related signalling pathways include GPCR signalling and cancer signalling [28]. Smo is the positive activator of the signal pathway. Upstream Ptch1 is a 12-order transmembrane protein receptor, which mainly inhibits the activity of Smo in the pathway [29-30]. GLi1, as a direct promoter of downstream target gene transcription of Hh pathway, can express the functional status of Hh signalling pathway. Downstream transcription factors of Hh signalling pathway are composed of GLi1 family. Gli2 protein sequences contain transcriptional activation and inhibition domains, which can be positively or negatively regulated according to different conditions. GLi1 in pancreatic cancer is regulated by specific target genes such as P13K/AKT and TGF-β [31-32], and its siRNA transfection into normal pancreatic ductal epithelial cell line scan make hH-gli1 signalling pathway abnormally activate transcription of downstream genes and promote cell carcinogenesis. Some studies have also found that CDKN2A is positively correlated with HH-gli1 expression in cervical cancer [33-35], and GLi1 acts as a central hub for the interaction between signalling pathways and regulatory factors in the molecular mechanisms of tumor invasion and metastasis.

In this study, it was found that Smo and GLi1 had high specificity in the diagnosis of mesothelioma by puncture biopsy, with positive rate, specificity and sensitivity all greater than 91%, thus having

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ssthe value of standardized detection. Chest, ascites specimens tested positive rate, degree of sensitivity, specific test results consistency index and biopsy specimens is higher, but because the cells contained in the chest, ascites, less atypia of exfoliated cells is poorer, different time extraction effusion cells require, including whether extraction fluid position accuracy will affect the diagnostic accuracy with chest, ascites specimens [36], Therefore, the diagnostic accuracy will be slightly lower. Therefore, the combination of Smo and GLi1 protein expression method can make the detection results more reliable, and chest and ascites specimens are more superior than needle biopsy, which is non-invasive, easy to operate, easy to obtain clinical materials, and patients feel less pain. Studies have shown that Smo and GLi1 have a positive rate of more than 85% in the diagnosis of mesothelioma in thorax, ascites or biopsy. Differences in immuno histochemical conditions, such as antibody cloning or fixation used and/or staining procedures, may be contributing factors to the observed differences. Another possibility is that the gene's protein expression may not last forever; it plays an important role in cell proliferation and its expression is strictly regulated. Hyper methylation of the promoter region is also the mechanism of reduced gene expression in some tumours. It is observed from the comparison Figure 1-12 and Table 1-4. That the diagnostic method of the new gene indicators has high sensitivity and specificity and the greatest diagnostic value, which is expected to be applied in the future clinic-pathological diagnosis.

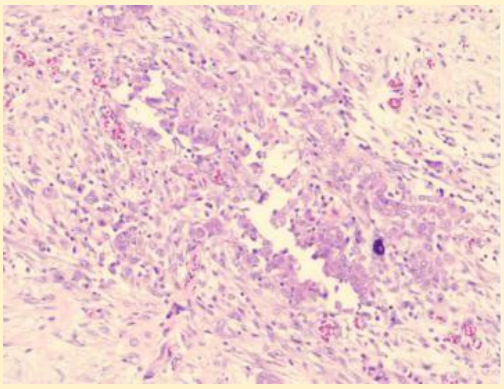

Figure 1: shows HE staining of malignant mesothelioma biopsy specimen.

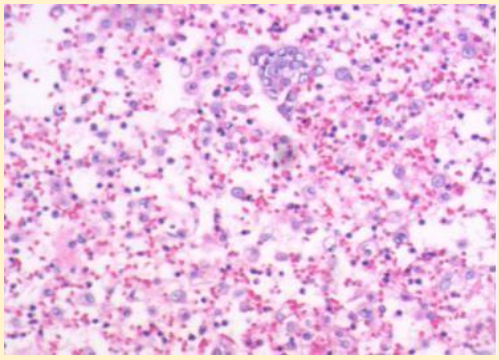

Figure 2: shows HE staining of a biopsy specimen with benign mesenchymal hyperplasia(X200).

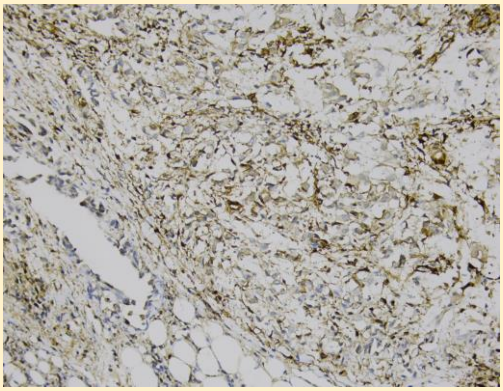

Figure 3: shows positive expression of Smo in mesothelioma biopsy specimens,

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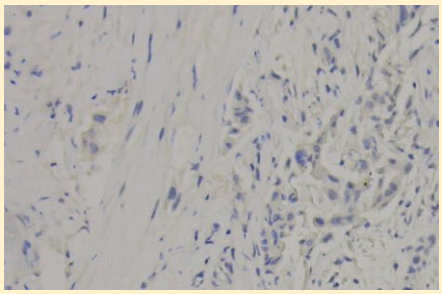

Figure 4: shows negative expression of Smo in benign reactive mesothelioma biopsy specimens (X200).

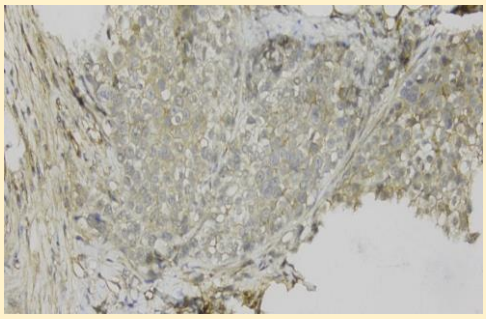

Figure 5: shows positive expression of GLi1 in mesothelioma biopsy specimens.

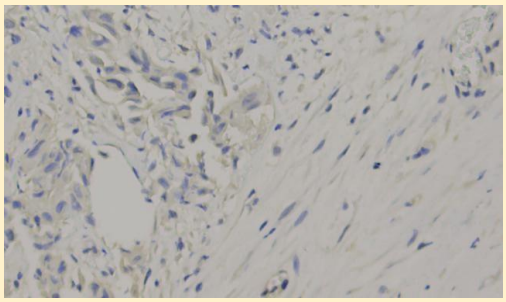

Figure 6: shows negative expression of GLi1 in benign reactive mesothelioma biopsy specimens (X200).

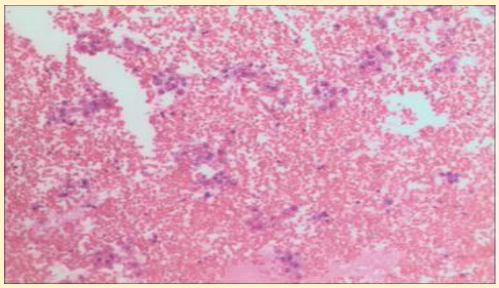

Figure 7: shows HE staining of pleural and peritoneal effusion of malignant mesothelioma,

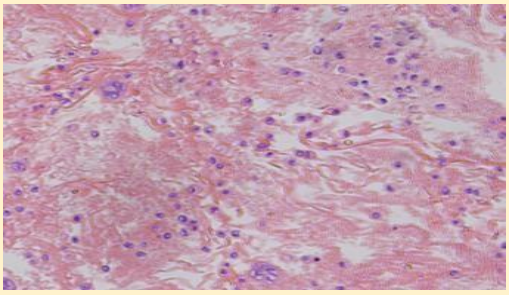

Figure 8: shows HE staining of pleural and peritoneal effusion samples with reactive mesenchymal hyperplasia(X200).

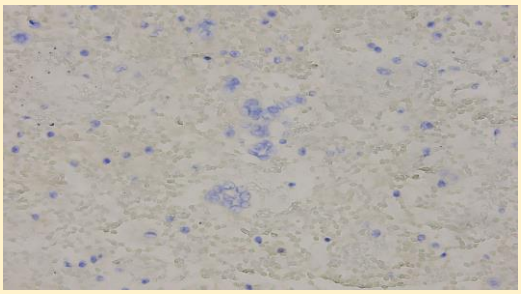

Figure 9: shows positive expression of Smo in mesothelioma effusions.

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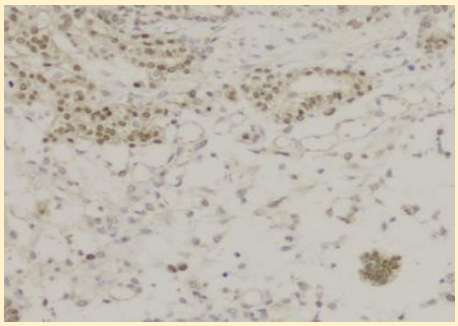

Figure10: shows negative expression of Smo in benign reactive mesothelioma effusions (X200).

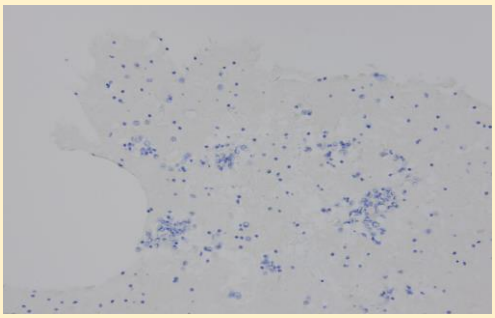

Figure 11: shows GLi1 positive expression in mesothelioma effusions.

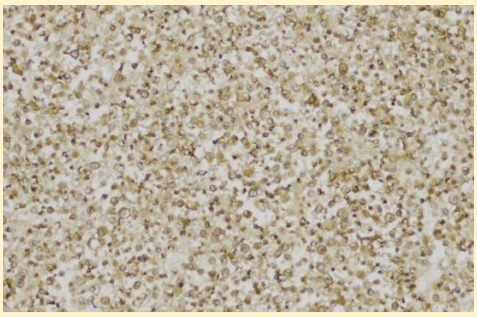

Figure 12: shows GLi1 negative expression in benign reactive mesothelioma effusions (X200).

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Detection method	Malignant mesothelioma - +~+++	Reactive mesothelial hyperplasia - +~+++	Positive rate %	Specific degrees %	sensitivity %
Smo	3 47	18 2	94	85.71	95.92
GLi1	5 45	17 3	90	77.27	93.75

Table 1: The pathological and morphologic results of the biopsy specimen were combined with the immunohistochemical Smo and GLi1 diagnosis results.

Detection method	Malignant mesothelioma - +~+++	Reactive mesothelial hyperplasia - +~+++	Positive rate %	Specific degrees %	sensitivity %
Smo	5 45	17 3	90	77.27	93.75
GLi1	6 44	15 5	88	71.43	89.8

Table 2: The pathological and morphologic results of the fluid specimens were combined with the immunohistochemical Smo and GLi1 diagnosis results.

Clinicopathological features	The specimen				
	n	-	+	PR(%)	P
Gender					
male	22	2	20	90.91	0.639
female	28	3	25	89.29	
Age（year）					
<60	12	4	8	66.67	0.816
<60	38	1	37	97.37	
Chemical exposure history of asbestos					
Yes	26	1	25	96.15	<0.01
No	24	4	20	83.33	
Pathological changes					
pleural	17	2	15	88.24	
peritoneal	25	2	23	92	0.98
Others (greater omentum, ovary, appendix, etc.)	8	1	7	87.5	
P53					
negative	11	3	8	72.73	0.356
positive	39	2	37	94.87	

Table 3: Correlation of Smo expression with clinicopathological data of patients with malignant mesothelioma.

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Clinicopathological	The specimen			
	n	-	+	PR(%) P
Gender male	22	2	20	90.91
female	28	4	24	85.71

Table 4: Correlation of GLi1 expression with clinic-pathological data of patients with malignant mesothelioma.

In conclusion, immuno histochemical detection of Hedgehog signalling pathway genes in pleural and peritoneal fluid samples was used to diagnose malignant mesothelioma. Compared with the surgical biopsy specimens, chest, abdominal cavity effusion specimens are more likely to get is easy to operate, so for small trauma patients, in the future is expected to be used in the pathological diagnosis, clinical work for the early detection, early diagnosis of malignant mesothelioma provide effective screening method, and the Hedgehog signalling pathway genes can also become the new targets for gene therapy in the future.

Availability of data and material

We used pathological specimens from the Pathology Department of Cangzhou People's Hospital for the experiment, which had been approved by the Ethics Committee and signed by the pan-informed consent.

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