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Original article

Clinical and pathological characteristic of metastatic malignant mesothelioma initially diagnosed by lymph node biopsy

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ABSTRACT

Background: It is a great challenge for pathologists to initially diagnose metastatic malignant mesothelioma (MM) by the lymph node biopsy without any history of primary MM. Because the onset of MM is hidden and the metastatic MM in lymph node is relatively uncommon. Besides, morphologic and immuohistochemistry features of MM are similar to other tumors.
Methods: In order to improve the initial diagnostic accuracy of metastatic MM from LN biopsy and to reduce or avoid the possibility of missed diagnosis or misdiagnosis, we had collected the clinical and pathological data of the metastatic MM cases in our department, and summarized the characteristics of morphological, immunohistochemical and fluorescence in situ hybridization (FISH) results.
Results: Seven patients (4 males and 3 females) with 21–73 year-old had been included in our study. Six cases showed serous cavity effusion, serosal thickening and systemic multiple lymph node enlargement. The "moderate, nice" tumor cells were arranged in variable patterns. Mitosis was hardly to be found and necrosis was absent. Four immunohistochemical staining panels and FISH detection had been used for diagnosis and differential diagnosis of MM. All cases expressed broad-spectrum epithelial markers and at least 2 mesothelial-cell-origin markers. None were positive for specific-tissue-origin markers, and all cases were diagnosed of malignancy according to immunohistochemical markers and detection of *pl6* gene deletion.
Conclusion: It is necessary for us to keep our awareness of metastatic MM in lymph node. Correct diagnosis of MM metastasis by lymph node biopsy were based on detailed understanding of the clinical manifestation and the image data, careful observation of morphologic characteristics, and properly using immunohistochemical markers or FISH detection if necessary for diagnosis and differential diagnosis.

1. Background

Malignant mesothelioma (MM) is a rare and aggressive tumor with poor prognosis [1]. MM mainly occurs in the pleura and peritoneum, and a minority of MM may involve the pericardium or tunica vaginalis testis [2]. In clinic, the metastasis of MM into lymph nodes (LN) is relatively uncommon, while lymph node enlargement as the initial manifestation of MM is rarer [3,4]. Besides, morphologic and immunohistochemistry features of MM are similar to carcinoma and other tumors. So it is very difficult and challenging to make the correct diagnosis of metastatic MM from LN biopsy before the diagnosis of the MM in the primary location. In this study, we summarized the clinical, morphological, immunophenotypic and molecular pathological characteristics of metastatic MM and proposed some diagnostic approaches, to improve the initial diagnostic accuracy of metastatic MM from LN biopsy, even without MM history, and to reduce or avoid the possibility of missed diagnosis or misdiagnosis.

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Table 1
Characteristics of Clinical Pathology for Our group.

Case	Age	Sex	AEH	Site of biopsy	Possible original site	MLNE	Clinical Symptoms or signs	PSS in lung	Course (/months)	Treatment	Follow-up
1	26	F	N	supraclavicular	pericardium	Y	polyserositis	Y	13	ST	6 months Death
2	61	M	Y	supraclavicular	NM	Y	N	Y	1	ST	4 months Death
3	45	M	Y	axillary	pleural	Y	polyserositis	Y	16	ST	6 months Death
4	55	F	N	supraclavicular	peritoneal	Y	polyserositis	Y	6	ST	6 months Death
5	50	M	N	cervical	pleural	Y	Pleural effusion	Y	12	chemotherapy	5 years
6	21	M	N	mediastinal	pericardium	Y	polyserositis	N	12	chemotherapy	10 months
7	73	F	N	axillary	pleural	N	polyserositis	Y	12	chemotherapy	10 months

AEH: asbestos exposure history; MLNE: multiple lymph node enlargement; PSS: sporadic patchy shadow; ST: symptomatic supportive anti-inflammation therapy; Y: yes; N: no; NM: Not mentioned.

2. Materials and methods

2.1. Pathology and light microscopy

Thirty-one cases of metastatic tumors diagnosed from lymph nodes biopsy between January 2009 and April 2015 without any primary tumor history were selected. By reviewing clinical data, observation of pathological sections, and performance of immunohistochemistry (IHC) staining and fluorescence in-situ hybridization (FISH), 7 cases of metastatic MM which were initially diagnosed by lymph node biopsy were included in our study.

The clinical data included age, gender, clinical symptoms/signs, laboratory data, imaging examination, treatment and prognosis.

2.2. Immunohistochemistry

All specimens were fixed in 10% formalin, embedded with routine paraffin, cut into continuous 4 um sections, and stained with hematoxylin-eosin (HE). IHC tests were conducted in an EnVision two-step way, with DAB coloration and hematoxylin contrast coloration. Four panels of antibodies were included as following: (1) Broad-spectrum epithelial cell origin markers: PCK, CK7; (2) Specific-tissue-origin markers: CEA, BerEP4, TTF1, NapsinA, CK20, CDX2, P63; (3) Mesothelial-cell-origin markers: CR, HBME1, CK5/6, WT-1, D2-40; (4) Benign or malignant mesothelial cell markers: Glut-1, Desmin, P16 (See Table 5).

2.3. Fluorescence in situ hybridization

After paraffin sections were deparaffinized, dehydrated in ethanol and air-dried, dual-color FISH analysis was performed using a Spectrum Green-labeled chromosome 17 centromeric probe and a Spectrum Orange-labeled, locus-specific p16 probe (Abbott). As previously suggested, a FISH result was considered positive if at least one of the following criteria was met [38–40]: (1) 10% of mesothelial cells with increased copy number of at least one signal of at least one chromosome, and/or (2) at least 15% of mesothelial cells with heterozygous or homozygous deletion of 9p21. A rare tetraploid pattern in, 10% of mesothelial cells (four signals of each probe within one nucleus) was defined as FISH negative. Inflammatory cells served as internal control and had two 9p21 signals per FISH probe. Homozygous deletion was defined as lack of both 9p21 signals. Heterozygous deletion was assumed when only one 9p21 signal was present, or when the number of 9p21 signals did not exceed half the number of the centromeric signals [38].

3. Results

3.1. Clinical manifestation

Four males (57%) and 3 females (43%) patients were included in our study. The range of age were 21–73 years old (mean 47.3 years old; median 50 years old). Six cases (86%) were form superficial enlargement lymph node (3 cases from supraclavicular lymph node, 2 from axillary lymph node and 1 from cervical lymph node), and one was from deep-seated lymph node (anterior mediastinal lymph node). Lymph node biopsies were performed in 5 patients and core needle biopsy in the other 2 cases. The clinical symptoms were diversified. Six cases showed serous cavity effusion, serosal thickening, systemic lymph node enlargement, and with different degrees of cough, expectoration, chest pain and fever. Two cases had contacted with asbestos. Computed tomography (CT) indicated most of patient had dropsy of serous cavity, serosal thickening and massive soft-tissue shadow (located in pericardium, pleura and peritoneum), peripheral lymph node enlargement, and sporadic patchy shadow (PSS) in the lung. What caught our attention is that all cases were misdiagnosed as lymphoma, metastatic tumor or tuberculosis by clinicians according to the clinical and image data (Tables 1 and 3).

3.2. Morphology features

There were two infiltrative patterns (Table 2): one was sinus infiltration (3 cases). The nodal architecture was preserved, the subcapsular and medullary sinuses were remarkably distended filled with a large number of tumor cells (Fig. 1A–C). The other pattern was diffuse infiltration (2 cases). Architecture of the lymph node had been destroyed by neoplasm cells (Fig. 1D–F). In both infiltrative patterns, the tumor cells were arranged in solid, nest-like, papillary and glandular pattern. Relative uniform medium-size epithelioid and polygonal-shape neoplasm cell had abundant cytoplasm, round nuclei with middle small nucleoli and fine nuclear chromatin, which were called “moderate, nice” cellular atypia. Mitosis was hardly to be found and necrosis was absent.

3.3. Immunohistochemistry

Immunohistochemistry results (Table 2 and 4; Fig. 2) showed (1) All of the infiltrative tumor cells expressed broad-spectrum epithelial markers PCK and CK7. (2) Specific-tissue-origin markers were negative in all cases. Besides, only 1 case partially positive for P63 and 3 cases locally weak-positive for BerEp4 (Fig. 2 right in F). (3) The infiltrative tumor cells of all patients expressed at least 2 mesothelial markers (5 cases were positive more than 3 mesothelial markers). The positive rates of CR, HBME-1, WT-1, D2-40, and CK5/6 were 71%, 71%, 71%, 57% and 57% separately. (4) All cases were diagnosed of malignancy according to three immunohistochemical markers which were used to indentify benign and