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Original Article

Clinicopathological features of type AB thymoma with liver metastases

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Abstract: Objective: We studied the clinicopathological features of type AB thymoma with liver metastases and explore the histological types, diagnosis and differential diagnosis, treatment and prognosis for this disease. Methods: Liver metastasis specimens were derived from one case of type AB thymoma 5 years after operation and were examined histologically using light microscopy and immunohistochemistry. A comprehensive analysis was performed on the patient's clinical manifestations, histopathology, immunohistochemistry features, differential diagnosis, treatment and prognosis in combination with a review of the relevant literature. Results: Metastases were detected 5 years after initial operation on a 49-year-old, female patient with type AB thymoma. The pathological diagnosis for the liver metastases was type AB thymoma. Immunohistochemistry staining showed CKpan (+), CD3 (+), CD2 (+), TdT (+), CD5 (+), P53 (+), Hep-1 (-), and Ki67-positive cells (25%). The expression level of galectin-3 was higher than in the mediastinal thymoma tissue identified 5 years prior. Conclusion: Liver metastases of type AB thymoma are extremely rare. This case indicated that type AB thymoma with low malignant potential might recur and develop distant metastases. Overexpression of p53, galectin-3 and Ki67 in type AB thymoma might coordinately manipulate the process of development, progression and malignant transformation of type AB thymomas.

Keywords: Type AB thymoma, liver, metastases, immunohistochemistry

Introduction

Thymoma is a tumor that arises from thymic epithelium or cells with thymic epithelial differentiation. The common form is type AB thymoma, which accounts for approximately 15-43% of thymomas. Type AB thymoma was previously considered to be a non-invasive tumor without recurrence and metastasis. Therefore, it is clinically considered to be benign. Here, we report a case of type AB thymoma with liver metastases occurring 5 years after operation, and we analyzed its histological typing, clinicopathological features, differential diagnosis, treatment and prognosis in combination with a review of the relevant literature. This study should improve our understanding of type AB thymoma.

Materials and methods

Clinical data

A 49-year-old female patient was admitted to our hospital on April 7, 2008 due to chest tightness and pain that lasted for more than 10 days. A computed tomography (CT) scan of her chest revealed a mass lesion in the left anterior mediastinum 8.0 × 9.0 cm in size with both high and low density areas and irregular calcification. The Tumor border was still clear, the left pulmonary artery was deformed due to compression and the left hilar structure was deformed. An enhanced scan indicated a heterogeneous heightened mass, and the diagnosis of a mediastinal tumor was made. No lesions were found in the liver, kidney, spleen or other

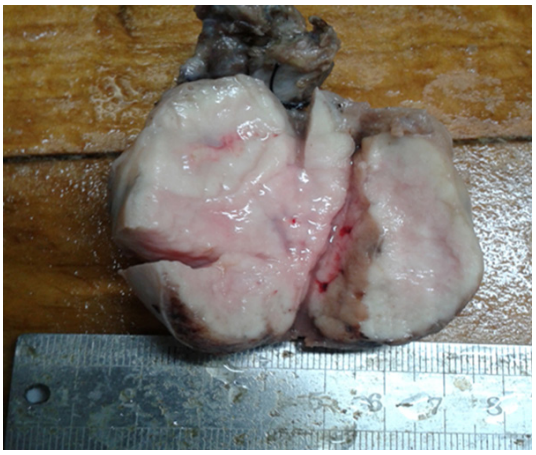

Figure 1. Liver metastasis of type AB thymoma. Thymomas demonstrate clear boundaries, nodular appearance, grey or grey-red color and soft consitency.

organs, as determined by an abdominal CT scan. Left thoracotomy and mediastinal tumor resection was performed on April 11, 2008. The postoperative pathological diagnosis was type AB thymoma. The patient presented with pain in her right quarter rib cage in January 2013, accompanied with anorexia and decreased food intake. Examination through abdominal CT scan and B-mode ultrasound revealed a mass in the right liver lobe 8.9 × 7.3 cm in size with a clear boundary. This was in line with the features of liver cancer. A blood test revealed that AFP and CEA levels were 1.42 ng/ml and 1.52 μg/ml, respectively, and HBsAg was absent. Surgery was performed under general anesthesia, and specimens were delivered to our department for pathological diagnosis on February 1, 2013.

Methods

The specimens were fixed in 10% neutral formalin and subsequently went through conventional dehydration, paraffin embedding, slicing, H&E staining and examination under a light microscope. Immunohistochemical staining was performed with the EnVison two-step method according to the manufacturer's protocol. CKpan, CD3, CD2, CD5, Hep-1, TdT, P53, Galectin-3 and Ki67 antibodies were obtained from the Beijing Zhongshan Golden Bridge Company. Chromogenic detection was completed with DAB. Positive and negative controls were used in each staining procedure. Brown particulate staining in the cytoplasm or nucleus of tumor cells was considered a positive reaction.

Results

Gross features

The size of the surgically removed liver tissue was 11.0 × 10.0 × 8.0 cm. In cross section, the mass was 9.5 × 9.0 × 7.0 cm in size. This mass had a clear boundary, was grey-white in color, was solid and leaf-shaped, and was adjacent to the surrounding liver capsule (**Figure 1**).

Microscopic characteristics

In histological examination under low magnification, dispersed nodules and lymphocyte-rich and poor regions were observed. The lymphocyte-rich region was primarily composed of small polygonal cells with small, round or oval nuclei; weak staining; and inconspicuous nucleoli. In contrast, the lymphocyte-poor region was composed of spindled fibroblast-like cells in sheets or cords distributed among the lymphocytes. These cells possessed weak nuclear staining with inconspicuous nucleoli (**Figure 2A-C**).

Immunohistochemical features

Immunohistochemistry staining showed that the cells were CKpan (+) (**Figure 3A**), CD20 (+) (**Figure 3B**), CD5 (+) (**Figure 3C**) and Hep-1 (-). Immunohistochemical staining of the present liver metastases showed p53 expression (**Figure 3D**), strong galectin-3 staining (**Figure 3E**), and positive Ki67 staining for 25% of the cells (**Figure 3F**). We then reviewed sections of the mediastinal thymoma obtained 5 years ago from the same patient that were processed with conventional H&E and immunohistochemical staining. Immunohistochemical staining showed the absence of p53 (**Figure 4A**) and weak galectin-3 staining (**Figure 4B**). In addition, 10% of the cells stained positive for Ki67 (**Figure 4C**). Both the original and metastasized tumors exhibited identical histological morphologic features and other biological markers assessed by immunohistochemical staining. In the final pathological diagnosis, the patient had type AB thymoma in the right posterior lobe of her liver and the tumor was adjacent to the liver capsule and the cutting edge.

Discussion

Thymoma is the most common solid, primary mediastinal tumor, accounting for 20% of medi-

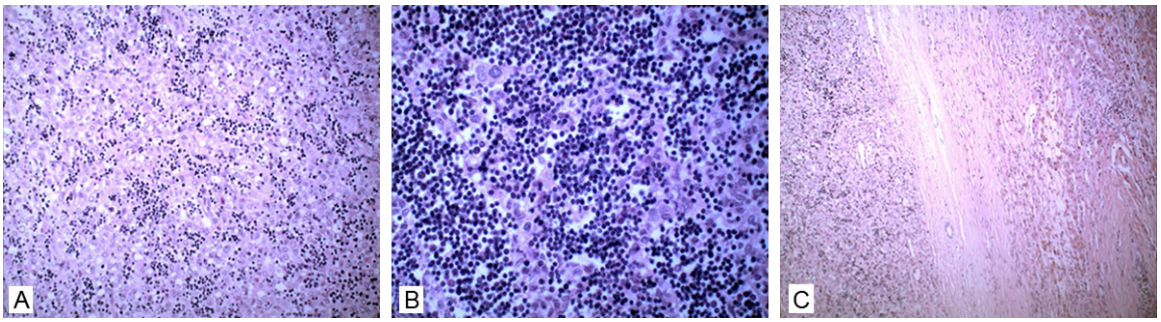

Figure 2. Histology of type AB thymoma. A. Mixed with lymphocyte-component B and less lymphocyte-component A (H&E, × 200). B. Type A component is composed primarily of fibroblast-like spindle cells, while type B component is primarily composed of small polygonal cells and diffuse lymphocytes (H&E, × 200). C. There are distinct boundaries between tumor and normal liver tissues. Tumor tissue is on the left and liver tissue is on the right (H&E, × 100).

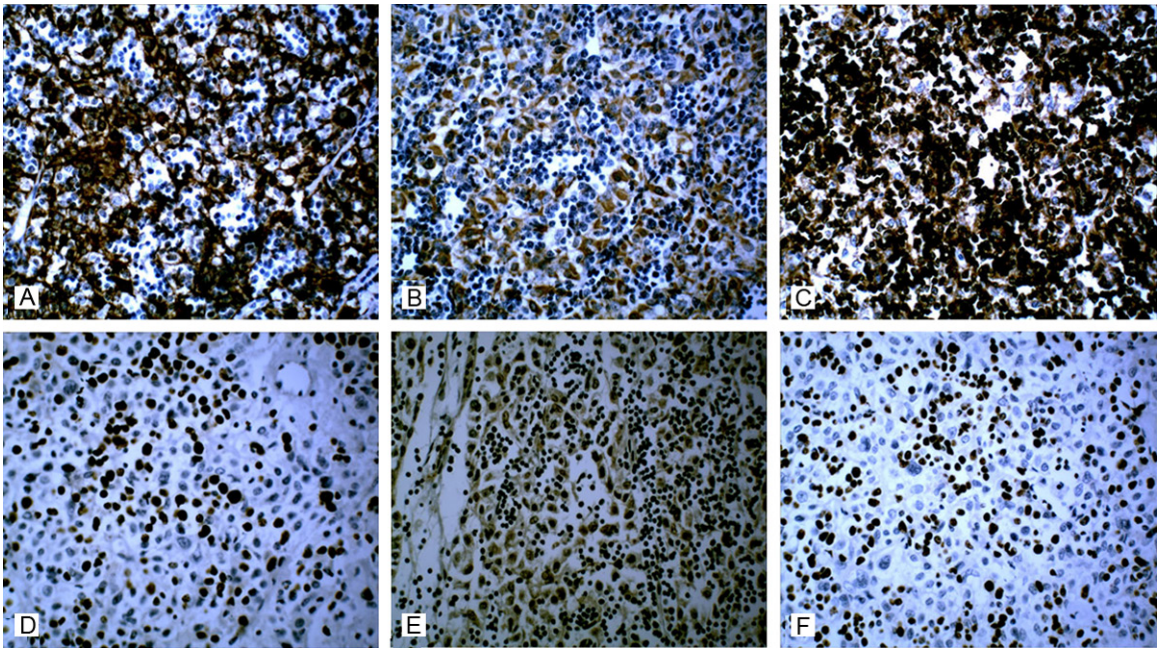

Figure 3. Immunohistochemical staining of type AB thymoma. A. Strong positive staining of CKpan in tumor cells. B. Type A and B tumor cells with positive CD20. C. CD5 positive medullary differentiated lymphocyte clusters. D. p53 positive tumor cells. E. Galectin-3 positive tumor cells. F. Ki67 index was 25%.

astinal neoplasms. Ninety percent of thymoma occurs in the anterior superior mediastinum, and a smaller portion occur in the neck and posterior mediastinum or other locations [1]. Thymoma typically results in the compression of surrounding tissue, causing chest pain, chest tightness, coughing, and general malaise, among other symptoms. Chest CT scans indicate a mediastinal mass. Benign thymomas grow more slowly, and possess more regular shapes. They are entirely encapsulated and generally do not produce lymphogenic and hematogenic metastases. Malignant thymoma is typically characterized by an irregular shape and uneven density that tends to invade surrounding tissue and metastasize. Approximately 10-15% of thymomas are associated with myasthenia gravis [2]. Other clinically relevant lesions include acquired hypogammaglobulinemia, pure red-cell aplasia, systemic lupus erythematosus, rheumatoid arthritis, scleroderma and polymyositis [3]. In addition to pain in the right quarter rib cage, our patient experienced loss of appetite and reduced food intake, but there were no indications of myasthenia gravis or other relevant diseases.

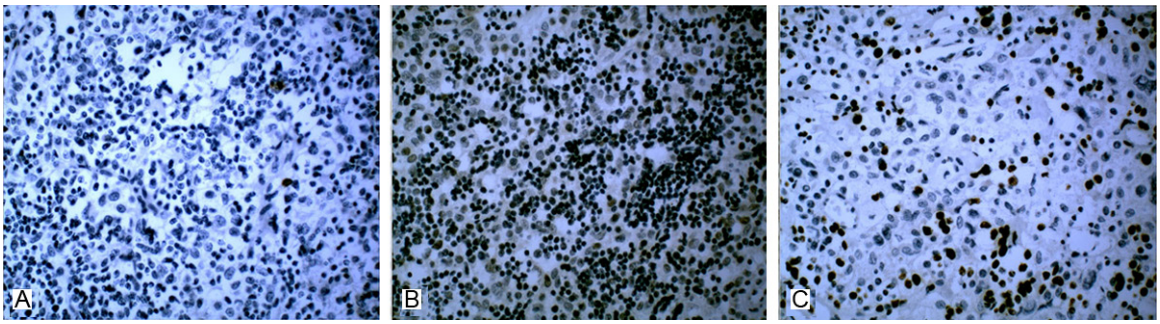

Figure 4. Immunohistochemical staining of primary type AB mediastinal thymoma. A. Negative p53 staining in tumor cells. B. Tumor cells with weak Galectin-3 staining. C. Ki67 index was 10%.

Most thymomas are lobulated and encapsulated, and larger tumors may have cystic lesions. There are a series of histological features. Benign tumors usually have evident fibrous capsules composed of thymic epithelial cells with neoplastic proliferation and different numbers of non-neoplastic T lymphocytes. Thymic epithelial tumor cells are of two types. These cells can appear oval or spindle-shaped with non-dense chromatin and occasionally observable nucleoli. Otherwise, they are rounded or epithelioid cells with eosinophilic cytoplasm and large, clear and round eosinophilic nucleoli. Upon histological classification, the specific diagnosis may remain controversial. Traditionally, thymomas have been classified into one of three subclasses: the epithelial cell type, the lymphatic cell type or a hybrid type of intraepithelial lymphocytes. The widely accepted current classification method proposed by the World Health Organization (WHO) (Travis, 2004) indicates that there are three forms, namely type A, type AB, type B1-3 and thymic carcinoma. The invasive potential increases along with the pathological type from A to B3, although some type AB thymomas exhibit capsular invasion or the formation of adhesions to surrounding structures. Even so, they are still considered to be benign tumors. These tumors rarely develop distant metastases [4]. In this reported case, the mediastinal tumor occurred 5 years prior, and liver metastases were large in size. The capsule remained intact however, and there were no signs of invasion. Based on histopathological examination and the results of immunohistochemical staining, this tumor complied with the characterization of type AB thymoma.

Galectin-3 is a ribonucleoprotein involved in cell growth, differentiation, apoptosis and tumor formation that also plays a prominent role in tumorigenesis. p53 is the most significant tumor suppressor gene discovered so far, and several genetic mutations in p53 have been described in a variety of human tumors. These mutations contribute to tumorigenesis, tumor progression and poor prognosis. If mutations are present in the p53 gene, the result is dysregulation of apoptosis, uncontrolled cell proliferation and oncogenesis. In this case, immunohistochemical staining of liver metastasis 5 years after the removal of mediastinal thymoma showed significantly more positive staining of mutant p53, galectin-3 and Ki67 compared with staining of the primary mediastinal thymoma 5 years prior. These results suggested that along with the expression of mutant p53, galectin-3 and a higher Ki67 proliferation index, type AB thymoma exhibited enhanced invasive and distant metastasis capabilities. Overexpression of mutant p53, galectin-3 and Ki67 might coordinately regulate the development, progression and malignant transformation of thymomas. The characterization of these three biological markers will improve early diagnosis, estimation of malignant potential and invasiveness and general prognosis of thymomas. This case further suggested that type AB thymoma is not always a benign tumor, and, in turn, postoperative radiotherapy and chemotherapy should be considered based on the patient's condition, especially for larger tumors. This might be clinically significant for the prevention of recurrence and metastasis of this form of thymoma.

It is necessary to differentiate primary type AB mediastinal thymoma from lymphoma, thymic hyperplasia, germ cell tumors, and thymic neuroendocrine tumors. Lymphocyte-rich mediastinal thymomas are difficult to distinguish from

large cell lymphoma, lymphoblastic lymphoma, Burkitt lymphoma and Hodgkin's lymphoma. Lymphoblastic lymphoma is most common in children and adolescents, and there are immature cells in the peripheral blood. Tumor cells are TDT (+) with immunohistochemical staining, and there are no CK (+) thymic epithelial cells. Burkitt lymphoma primarily develops in children or in patients with AIDS, both of which may present histologically with a "starry sky" phenomenon. There is no epithelial component in Burkitt's lymphoma. Additionally, in Burkitt's lymphoma, immunohistochemical staining demonstrates the absence of CK-positive cells, and almost 100% of the cells express Ki-67. Hodgkin's lymphoma occurs mostly in young women and children, mainly leading to local compression symptoms including difficulty breathing, coughing and chest pain. Microscopically, Hodgkin's showed nodules separated by fibrous tissue, in a manner similar to thymoma. However, fibrous and tumor components are more distinct in thymoma. Lymphoma contains characteristic diagnostic R-S and pit cells. Immunohistochemical staining shows cells that are CD15 (+) and CD30 (+). However, atypical epithelial cells are CK (+) in thymoma. This feature can be used to identify these two types of tumors. Germ cell tumors primarily occur in men, with almost all mediastinal germ cell tumors occurring in or near the thymus, i.e., the anterior mediastinum. Histologically, there are large round cells with translucent cytoplasm and some visible fiber trabecular spacing. Immunohistochemical staining often indicates that cells are negative for LCA and CK. All of these features are characteristic and allow germ cell tumors to be differentiated from thymoma easily. Thymic hyperplasia is more common in children with histopathologically determined lobular structure characteristic of a normal thymus. There is a normal distribution of lymphocytes and epithelial cells, and this disease also retains differentiated thymic cortex and medulla. The thymoma often lacks differentiation of cortex and medulla. Even if there are some cortex and medulla-like regions, their arrangement is not normal and there are no normal lobulated structures.

Type AB thymoma metastasized to the liver must be differentiated from primary liver cancer and other metastatic malignancies. The main histological types of primary liver cancers include hepatocellular carcinoma, cholangiocarcinoma or mixed hepatocellular carcinoma and cholangiocarcinoma. Other common metastatic cancers are mostly neuroendocrine carcinoma or adenocarcinoma from the gastrointestinal tract. Primary or metastatic cancers histologically showed epithelial structure and obvious nest structure with little lymphocyte infiltration. Immunohistochemical staining was CK-pan, CK19, Hep-1, and CK20 positive and TDT, CD3, and CD5 negative. These are good markers for the identification of these two tumors.

Currently, the mainstay of treatment for thymoma is surgical excision. According to the type and stage of the thymoma, different adjuvant radiotherapies or chemotherapies may be employed. Kundel et al. [5] suggested that postoperative radiotherapy for invasive thymoma can improve survival. The recurrence rates for patients with and without postoperative adjuvant radiotherapy were 25 and 57%, respectively. Prognosis was closely linked with the staging of thymoma [6]. The Masaoka clinical staging method was most commonly used in the staging of thymoma and was also the most important parameter affecting the prognosis [7]. The stages of the Masaoka method include clinical stage I with an intact capsule with no capsular invasion, stage II with an invasion of the capsule, stage III with an invasion of adjacent organs, stage IV A with dissemination into the pleural cavity, and stage IV B with lymphogeneous or hematogeneous metastasis. According to previous reports, the postoperative 5- and 10-year survival rates for patients with Masaoka clinical stage I thymoma were 100% and 95%, respectively. For stage II, the 5 and 10-year survival rates were 91% and 81%, respectively, and the 5 and 10-year survival rates were 74% and 46%, respectively, for stage III [8]. The postoperative 5-year survival rate for patient with stage IV was low, at less than 25% [9]. Radiotherapy for patients with stage II and III thymoma could reduce the recurrence rate and prolong survival. For patients with advanced thymoma for which operation may be challenging, radiation therapy could shrink tumors such that patients could be operated upon. The effect of chemotherapy for patients with thymoma is not well defined. Effective chemotherapy drugs for thymoma treatment include cisplatin, ifosfamide, doxorubicin, cyclophosphamide and the glucocorti-

coids. Most studies have demonstrated that, for metastatic, recurrent or advanced thymoma, the treatment efficiency of chemotherapy combined with platinum-based agents is as high as 75% [10]. Currently, there are few studies about the treatment of patients with distant metastasis, and reoperation or radiotherapy was performed on these patients [11, 12]. In this case, the type AB thymoma liver metastases were surgically removed, and the patient did not receive postoperative chemotherapy. The patient is currently living in good condition and is being closely followed.

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Disclosure of conflict of interest

None.

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