CEA, MIB1 index, and BAC component ratio were significantly associated with prognosis. Cases stained strongly with anti-CEA antibody showed a significantly less favorable outcome than CEA-negative cases (p=0.02). Cases with a MIB1 index of 10% or more showed a less favorable outcome than cases with a MIB1 index of less than 10%. Cases in which the BAC component accounted for 50% or more of the tumor showed a better outcome than cases in which the BAC component accounted for less than 50% (p<0.01). However, none of the other factors were related to outcome. Although numerous prognostic factors of lung adenocarcinoma have been reported, this study found that only three factors, i.e. the two immunohistochemical factors, CEA and MIB1 index, and the histological factor, the ratio of the BAC component in the largest cut surface of the tumor, were significantly associated with the prognosis of small-sized adenocarcinoma of the lung.

In order to achieve desirable and evidence-based selective diagnosis of small-sized adenocarcinomas that are treatable by reduction surgery, a more extensive study to search for convenient prognostic factors should be performed. One trial to find new prognostic factors for small-sized adenocarcinomas, especially replacement-type adenocarcinoma, has already been done using two representative cases that were subjected to polymerase chain reaction-based cDNA suppression subtractive hybridization (SSH) (2). One case was LBAC (type A), which shows an extremely favorable prognosis, and the other was LBAC with foci of fibroblastic proliferation (type C), which was considered to be an invasive adenocarcinoma. Differential screening using virtual reverse northern hybridization and quantitative real-time reverse transcription-polymerase chain reaction (qRT-PCR) showed that five genes (TncRNA, OCIAD2, ANXA2, TMED4 and LGALS4) were expressed at significantly higher levels in invasive adenocarcinoma with a BAC component (type C) than in LBAC (type A). After in situ hybridization and qRT-PCR analyses, the OCIAD2 gene showed significantly higher expression in the tumor cells of invasive adenocarcinoma than in LBAC. The OCIAD2 gene was originally identified by Strausberg et al. in 2002 because of its sequential similarity to ovarian carcinoma immunoreactive antigen 1 through the National Institutes of Health Mammalian Gene Collection Project. OCIAD2 and OCIAD1 constitute the OCIA domain family. OCIAD1 was identified by Luo et al. in 2001 by immunoscreening of an ovarian carcinoma cDNA expression library with ascites from ovarian cancer patients. The function of OCIAD2 has not yet been elucidated, but the protein may be immunosensitive as an antigen and, like OCIAD1, could be a cancer-specific protein. Using in situ hybridization, the expression of OCIAD2 was examined in 56 replacement-type adenocarcinomas resected at Tsukuba University Hospital (Ibaraki, Japan). The patients with OCIAD2 expression showed a better clinical outcome than those without OCIAD2 expression, and OCIAD2 expression showed an inverse correlation with lymphatic invasion, blood vessel invasion and lymph node metastasis. These results suggest that OCIAD2 begins to be expressed during progression from in situ to invasive carcinoma, and is associated with a favorable prognosis of invasive adenocarcinoma with a BAC component (type C).

References


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Session E13: Insights into Thymic Epithelial Tumor

E13-01 Insights into Thymic Epithelial Tumor, Tue, Sept 4, 16:00 – 17:30

Insights into thymic epithelial tumor: pathology

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The histopathological classification of thymic epithelial tumours has for a long time been controversial. The great morphologic variability, their rareness, and the lack of consistent follow-up data were arguments to attribute only minor value to the histopathological descriptive classification and to rely on the clinical appearance at surgery almost exclusively for deciding further therapy of prognosis. A major problem for the introduction of a new and biology-oriented classification was the general believe that in spite great morphological variability, prognosis would be almost the same and recurrences or metastases could not be predicted. Therefore, as a pragmatic approach, the usual categories of malignancy, namely benign tumours, low grade malignant and high grade malignant tumours in the thymus where classified at surgery: encapsulated, non-invasive tumours as benign thymoma, those with minimal atypia (whatever this is) as malignant thymoma type 1, and those with marked atypia thymic carcinoma and increasing invasive and metastatic potential (6). Coming from a completely different approach, namely from the investigation of the complicated epithelial and lymphoepithelial structure of the thymus a “histogenetic” classification has been proposed, comparing the organization of epithelial cells and their lymphocyte content to the normal thymic structure in 5 histopathologically defined categories of thymoma, as medullary thymoma, mixed thymoma, predominantly cortical thymoma, cortical thymoma, and well differentiated thymic carcinoma - and the group of thymic carcinomas not presenting organotypic features (5,7). The tumour types and their definitions were accepted as basis of the WHO classification (1999), but as no agreement could be reached for the naming, the types were designed with letters A, B, and C (Table 1).

Histogenetic classification WHO classification Biology

Mixed thymoma A Benign
Predominantly cortical thymoma B1 Borderline
Cortical thymoma B2
Well differentiated thymic carcinoma, malignant, organotypic, usually no extra thoracic metastases
Well differentiated thymoma B3
Thymic carcinomas C Malignant, low grade high grade related to subtypes

This classification was discussed and updated in the new series of the WHO classification of tumours pathology and genetics and basically confirmed (WHO 2004, 8).

Histopathological classification of thymic epithelial tumours

The term thymoma is used for organotypic thymic epithelial tumours, characterized by similarities to the structural organization of the normal thymus. The histopathological typing is highly predictive for the risk of invasiveness, recurrence, and metastases, and for the need of adjuvant treatment after surgery.
Thymic carcinoma do not or only minimally show organotypic features and are classified and grades as morphologically identical malignant epithelial tumours in other organ systems.

The following table summarizes the main clinical and biological features of the different subtypes of thymoma.

<table>
<thead>
<tr>
<th>Type</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>A</td>
<td>160</td>
</tr>
<tr>
<td>AB</td>
<td>80</td>
</tr>
<tr>
<td>B1</td>
<td>60</td>
</tr>
<tr>
<td>B2</td>
<td>40</td>
</tr>
<tr>
<td>B3</td>
<td>20</td>
</tr>
<tr>
<td>TSCC</td>
<td>55</td>
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</tbody>
</table>

Fig. 1 Frequency of histological thymoma subtypes at the Institute of Pathology, Würzburg

Fig. 2 Age and sex distribution of thymoma patients

Fig. 3 Tumour Stage of histological thymoma subtypes

Type A and type AB thymomas are almost in very case encapsulated tumours found in stage 1 or 2 (with invasion of capsule but not cross invasion of mediastinal fat of pleura). They are found in a slightly older age group than the group of cortical type thymomas type B1, B2, and B3. The overall sex distribution is almost equal for male and female patients, type AB and B1 showing a slight dominance of female patients. Type B1, B2, and B3 show increasing invasive potential where type B1 may be regarded still as benign/borderline, but type B2 and B3 show high invasive and metastatic potential at surgery.

All types of thymoma may be associated with myasthenia gravis. The association is significantly higher in type B1, B2, and B3.

Genetic features of different thymoma subtypes

Whereas type A and AB show no or only minimal genetic imbalances at comparative genomic hybridization, type B2 and B3 as well as thymic carcinomas show very high frequencies of genetic imbalances, which is correlated their malignant behaviour. The pattern of genetic imbalances is highly characteristic for these tumours and allows the conclusion of a genetic relationship of type B and B3 thymoma and thymic carcinoma. The most frequent aberrations are found on chromosome 6, where homozygous deletions are found even in type A on chromosome 6p (involving the MHC locus), loss of heterozygocity and monosomy 6 involving 6p and 6q of the most frequent genetic changes in thymomas. Loss of heterozygocity or uniparental disomy of 6p implies a hemizygous MHC expression and therefore may be related to the increase of autoimmune paraneoplastic diseases (2,3,4,10,11,12).

Type B3 thymomas are more heterogeneous. The distribution of genetic imbalances hint to two different transformation pathways:

1. 6q23.3-25.3 associated oncogenic transformation and
2. a transformation pathway with loss of APC, RB, and p53 loci.

These findings have recently been confirmed and extended by gene expression profiling studies in thymoma, showing that all five subtypes of thymoma can be definitely distinguished by unique genetic signatures involving different pathways of oncogenic pathways of transformation.

Clinicopathological correlation

A large retrospective analysis of tumour stage at surgery using the Masaoka staging system, the WHO histotype of thymoma, and the surgical resectability (R0, R1) define independent predictive parameters. In this large retrospectively analysed cohort of 267 thymic tumours, WHO histotype A, AB, and B1 tumours do not show tumour-related death, but even B2 and B3 tumours, if complete surgical resection is possible or performed, the probability of recurrence is low, implying that adjuvant treatment by chemotherapy or radiation can be restricted to...
thymoma types B2, B3, and, of course, thymic carcinoma. In the case of thymoma (B2, B3), there is good retrospective evidence that local irradiation definitely reduces the rate of recurrences by 20%.

In conclusion, WHO type A, AB, and B1 thymoma types do not need adjuvant treatment, if surgical resection is complete. WHO type B2 and B3, as well as combined tumours and thymic carcinoma profit from adjuvant treatment which should at least be directed to local recurrences (local irradiation) or imply adjuvant chemotherapy (1,10). No prospective clinical studies are available.

Pathogenesis of thymoma-associated autoimmune phenomena

Thymomas are associated to a large variety of autoimmune phenomena where myasthenia gravis is the most frequent and classical paraneoplastic autoimmune disease. A detailed functional analysis of thymoma associated with myasthenia gravis reveals that these tumours produce and export autoreactive CD4+ T cells into the periphery (while thymomas not associated to myasthenia gravis do not). A major effect related to the generation of autoimmune disease may be attributed to the finding that within these tumours the production of adequate numbers of regulatory T cells (CD4+, CD25+) is significantly decreased (10,11).

Further pathogenetic findings related to thymomas associated myasthenia gravis shows that polymorphisms in the co-stimulatory receptor CTLR4 with high expression is found in patients with thymoma (2). Furthermore, the already cited hemizygous expression of MHC molecules is definitely a factors increasing the overall probability of autoimmune diseases in these patients. The findings imply that tumour-associated intratumourous defects of T cell differentiation are the reason for these autoimmune diseases and that different pathogenetic pathways may play a role.

Differential diagnosis of thymic carcinoma

Mediastinal involvement by carcinoma may be derived from different primary sites. The differential diagnosis of squamous cell carcinoma of thymus vs. lung is the most challenging problem. Some topographic and structural features favour a thymic origin:

If the squamous cell carcinoma is adjacent to thymoma or combined with thymoma type B3, a thymic origin is very likely. Prominent perivascular spaces in the tumour and the overall lobular architecture also suggests thymic squamous cell carcinoma (TSCC). Furthermore, immunohistochemical findings may help: thymic squamous cell carcinomas often express CD5 and CD70, and may contain myoid cells (similar to the normal thymus). The value and sensitivity of CD5 expression in the most frequent subtype (SCC) is about 60%, but the specificity in squamous cell carcinoma is almost absolute. Another highly sensitive and specific marker is the expression of the c-kit tyrosin kinase receptor (CD117). Expression is found in squamous cell carcinoma of the thymus in 90% whereas it is seen in pulmonary squamous cell carcinoma only in 5% (8). Further differences reside on genetic characterization. A typical loss of the long arm of chromosome 16 (16q-) or the combination of 16q- with deletions on chromosome 6 or amplification of chromosome 18 are highly predictive for a primary thymic tumour in comparison to lung or squamous cell carcinoma of the upper respiratory track.

Conclusion

The diagnosis of thymoma and thymic carcinoma is now in a stage where an agreed histopathological classification is accepted. The rules of this classification have to be learnt but are highly reproducible in all published series. This classification will help to elaborate therapeutic protocols for prospective clinical studies. The variability of clinical presentation and behaviour still requires several clinicopathologic correlations. Modern techniques of immunostechemistry, molecular techniques and gene expression will improve the diagnosis and open new horizons for an individualized therapy.

References
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E13-02 Insights into Thymic Epithelial Tumor, Tue, Sept 4, 16:00 – 17:30

Insights into Thymic Epithelial Tumor: Imaging Findings

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Thymic epithelial tumors (TET) are uncommon, with a broad spectrum of biologic and morphologic features. Of several proposed classifications, WHO histologic classification reflects both the clinical and the functional features of TET and thus contributes to the clinical assessment and treatment of patients with these tumors (1, 2). Recently, several reports described specific CT, MR imaging, and FDG-PET features of TET that reflect the WHO histologic subtypes (3-7). In this section, we discuss imaging features of TET correlated with histologic subtypes.

Computed Tomography (CT)

Because of embryonic background and anatomic location, TET can occur adjacent to the junction of the great vessels and the pericardium; less commonly, in the cardiophrenic angles or adjacent cardiac borders; and, rarely in the neck or other mediastinal compartments (8). CT has a much higher sensitivity for detecting TET than conventional radiography, and also allows evaluation of (a) invasion of the surrounding mediastinal fat, vascular structures, and adjacent lung; and (b) the presence of pleural and extrapleural seeding. On CT scans, TET usually appear as homogeneous, oval, rounded or lobulated soft-tissue masses in the anterior mediastinum (8). In cases of invasive thymoma or thymic carcinoma, invasion of the mediastinal fat or adjacent structures as well as pleural seeding may be seen.

Tomiyama et al (3) assessed the CT features of various subtypes of TET and reported that smooth contours and a round shape are most suggestive of type A tumors, irregular contours are most suggestive of type C tumors, and calcification is suggestive of type B tumors. Jeong et al (5) reviewed the CT findings correlated with simplified WHO classification of TET (low-risk thymomas (type A, AB, and B1); high-risk thymomas (type B2 and B3); thymic carcinomas (type C)) and prognosis. CT findings that are more common in high-risk thymomas and thymic carcinomas include lobulated contour, mediastinal fat invasion, and great vessel invasion. Findings associated with significantly more frequent recurrence and metastasis include lobulated or irregular contour, oval shape, mediastinal fat invasion or great vessel invasion, and pleural seeding.