Diagnosis of thymoma

S Suster

The diagnosis of thymic epithelial neoplasm has been a topic of controversy for many years. Reasons for this include the lack of predictive value associated with the morphology of these tumours and the multiplicity of classification schemes and terminologies proposed over the years. Recently, a new classification schema was introduced by the World Health Organization (WHO) in an attempt to standardise nomenclature and facilitate the diagnosis of primary thymic epithelial neoplasms. This schema, although not originally intended as a new histological classification, but rather as a means for translating equivalent terms from the various existing classifications, has represented a major step forward in this direction. However, problems still exist with the WHO schema, particularly with some of the criteria for the various histological subtypes as well as with issues of interobserver reproducibility. For this reason, we favour using a much more simplified approach to the morphological classification of thymic epithelial neoplasms. A personal approach to the morphological diagnosis of thymoma is described, with a brief explanation for the rationale for simplifying the existing diagnostic categories.

The morphological diagnosis of thymoma has traditionally posed difficulties for pathologists because of the great histological variability and intratumoral heterogeneity of these tumours. A cogent and easily reproducible morphological classification for these tumors has therefore been difficult to conceptualise. Many attempts were made in the past to devise a classification based on pure morphology (i.e., shape and proportion of the tumour cells), histogenesis and immunophenotype. Most of these approaches have proved cumbersome, difficult to reproduce in clinical practice and, in general, have failed to provide a sensible solution to the problem. Currently, the most widely used approach to the classification of thymic epithelial neoplasms is that proposed by the World Health Organization (WHO). We will first review the rationale and basis for this approach.

WHO CLASSIFICATION OF THYMOMA

The WHO classification of thymic epithelial neoplasms was first introduced in 1999. This schema was the result of extensive deliberation by an international panel of experts. The classification used a combination of letters and numbers to designate various common (and some uncommon) morphological appearances of thymoma. There was no anatomical, functional, histogenetic or other type of stated rationales underlying the schema, and the classification was essentially based on the shape of the neoplastic epithelial cells—that is, whether they adopted an oval or spindle shape (thymoma type A), a round or polygonal shape (type B) or a combination of the two (type AB). A fourth category, thymoma type C, was also introduced and defined as a tumour showing overt cytological features of malignancy, independent of the shape of the cells. The tumours in the type C group lacked any similarity to the other groups of thymoma and resembled instead a variety of carcinomas arising in other organs. Type B thymoma was further subclassified into three types (B1, B2 and B3) based on the proportional increase (in relation to the lymphocytes) and emergence of atypia of the neoplastic epithelial cells. A disclaimer was offered in the WHO monograph by the authors to the effect that this schema was not intended to replace any of the existing classifications, but rather to serve as a means for translating the different terms used by the already existing classifications, mainly the traditional classification of Bernatz et al and the histogenetic classification of Kirchner and Muller-Hermelink, into a common language. A revised version of the WHO classification was more recently published in 2004, which essentially retained the three basic morphotypes introduced in the original proposal (types A, B and AB), and excluded type C, segregating it into a separate category of thymic carcinoma. The updated version also introduced several unusual morphological types of thymoma that could not be easily placed into any of the other existing categories.

WHO type A thymoma is a tumour that is essentially characterised by a neoplastic population of oval to spindle cells devoid of any marked cytological atypia admixed in variable proportions with small (usually few) lymphocytes. This tumour essentially represents the counterpart of "spindle-cell thymoma" in the traditional classification proposed by Bernatz et al from the Mayo Clinic in 1961. Type AB thymoma is defined as a tumour in which foci having features of type A thymoma are admixed with foci showing features of type B thymoma. Type B1 thymoma is defined as a tumour that resembles the normal functional thymus and combines large expanses indistinguishable from the normal thymic cortex with areas resembling the thymic medulla. The neoplastic epithelial cells are scant and composed of oval cells with pale round nuclei and...
small nuclei, although it is also stated that in some cells they may be large and occasionally have conspicuous nuclei. This tumour is regarded as the equivalent of the lymphocyte-rich thymoma in the traditional classification. Type B2 thymoma is defined as a tumour in which the neoplastic thymic epithelial cells are increased in number and appear as scattered plump cells among a heavy population of lymphocytes. The epithelial cells are described as large, polygonal cells, with large vesicular nuclei and central prominent nucleoli. The tumour cells show a tendency to palisade around vessels and fibrous septa. Dilated perivascular spaces are commonly found. These tumours are regarded as the equivalent of mixed lymphoepithelial thymoma in the traditional classification. The main difference between types B1 and B2 seems to be the size of the epithelial cells, these being “larger and more numerous”, and with no areas of “medullary” differentiation in type B2 compared with type B1. Type B3 thymoma corresponds to tumours composed predominantly of epithelial cells having a round or polygonal shape and exhibiting negligible or mild atypia. Type C thymoma is defined as a tumour exhibiting clear-cut cytological atypia and a set of cytoarchitectural features no longer specific to the thymus, but rather analogous to those seen in carcinomas of other organs. They lack immature T lymphocytes; the lymphocytes present are usually mature T lymphocytes or B lymphocytes and are often admixed with plasma cells. Another designation for these tumours is thymic carcinoma. A variety of histological types are recognised, most having their counterpart in identical tumours arising from other organs, including keratinising squamous cell carcinoma, non-keratinising squamous cell carcinoma, lymphoepithelioma-like carcinoma, sarcomatoid carcinoma, clear-cell carcinoma, basaloid carcinoma, mucoepidermoid carcinoma, papillary carcinoma and undifferentiated carcinoma.

Although the WHO classification has been greeted enthusiastically by many investigators, several shortcomings and problem areas have been noted that limit its application. The main problems associated with this classification seem to centre on the use of poorly researched or poorly defined terms with overlapping connotations. Problems associated with the use of this classification, in my opinion, limit the value and utility of the WHO schema for clinical practice.

SUSTER AND MORAN CLASSIFICATION OF THYMOMA

Owing to the various difficulties that we were experiencing with the existing thymoma classifications, in 1999 we presented a novel proposal for the histological classification of thymic epithelial neoplasms. This proposal essentially represented a simplified approach to the morphological classification of these tumours that separated thymic epithelial neoplasms into three broad categories based on their degrees of organotypical differentiation. In our proposal, the histological grading of these tumours was based on the premise that, as in other organs, primary thymic epithelial neoplasms form part of a continuous spectrum of lesions that range from well differentiated to moderately differentiated to poorly differentiated neoplasms. Well-differentiated tumours would correspond to tumours designated by convention as thymoma; poorly differentiated neoplasms are those conventionally designated as thymic carcinomas; and intermediate features of differentiation are designated as atypical thymoma (table 1).

The determination of the degree of differentiation for any given tumour in this system is established on the presence or absence of the characteristic organotypical features of differentiation of the normal thymus and on the degree of organotypical atypia of the proliferating epithelial cells. Thus, tumours displaying most or all of the organotypical features of thymic differentiation (such as lobulation, dual cell population with a mixture of thymic epithelial cells and immature T lymphocytes, perivascular spaces, areas of so-called medullary differentiation, and so on) and absence of organotypical features of thymic differentiation are classified as well-differentiated thymic epithelial neoplasms (ie, thymoma); tumours that retain some of the organotypical features of differentiation of the thymus, but which already display mild to moderate cytological atypia are classified as moderately differentiated thymic epithelial neoplasms (ie, atypical thymoma); and tumours characterised by total absence of the organotypical features of the thymus and showing overt cytological evidence of malignancy correspond to poorly differentiated thymic epithelial neoplasms (ie, thymic carcinoma). This classification is simple, easy to reproduce and does not depend on any purported histogenetic considerations or require the use of special stains or other specialised techniques. It can be easily applied on the basis of the examination of routinely stained slides by haematoxylin and eosin, and requires only familiarity with the organotypical features of differentiation for the different stages of maturation of the normal thymus, along with attention to the degree of organotypical atypia displayed by the neoplastic epithelial cells. Moreover, the division of these tumours based on degrees of differentiation (as is the norm for most other organs) provides a functional substrate for a rational classification of these tumours, as the various organotypical features of differentiation of the thymus closely parallel the functional status of the organ.

One of the problems for understanding the relationship between organotypical differentiation and the functional status of the organ in the past has been the failure to realise

<table>
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<tr>
<th>Tumour type</th>
<th>Grading</th>
<th>Histological criteria</th>
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<tr>
<td>Thymoma</td>
<td>Well differentiated</td>
<td>Preservation of organotypical features of thymic differentiation; no cytological evidence of atypia</td>
</tr>
<tr>
<td>Atypical thymoma</td>
<td>Moderately differentiated</td>
<td>Partial preservation of organotypical features of differentiation; mild to moderate cytological atypia</td>
</tr>
<tr>
<td>Thymic carcinoma</td>
<td>Poorly differentiated</td>
<td>Loss of organotypical features of differentiation; presence of overt cytological evidence of malignancy</td>
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that the thymus is unique among human organs in that its
"normal" morphotype can vary considerably depending on
the age of the patient and the stage of maturation of the
organ.15 Unlike most other organs in the human body, the
thymus reaches its functional maturity during childhood and
adolescence and undergoes a process of loss of functional
activity and progressive involution thereafter. This results in
an organ whose "normal" histological appearance can vary
widely depending on the age of the patient (fig 1A,B). Recent
studies by Hale16 have mapped this process and shown that
with loss of functional maturity, the lymphocytic component
of the thymus is progressively replaced by fat and, although
the thymus retains its normal size and shape even with
advancing age, the residual thymic elements become atrophic
and reduced to microscopic remnants. The epithelial cell
component also undergoes a process of involution and with
loss of functional activity, the cells lose their round shape and
become smaller, with oval to spindle nuclei and scant
cytoplasm.15 16 Well-differentiated thymic epithelial neo-
plasms (ie, thymoma) therefore can show a wide spectrum
of morphological appearances that can vary depending on
whether the neoplastic cells are attempting to recapitulate
the normal, mature thymus of infancy and adolescence or
whether they resemble the normal involuted thymus of the
adult.13–15 Most tumours that recapitulate the normal thymus
of infants and adolescents are characterised by well-devel-
oped lobules, with a predominance of small immature
T lymphocytes and few intermingled neoplastic thymic
epithelial cells (fig 2). The lobules are usually separated by
fibrous bands of variable thickness that are often angulated.
Dilated perivascular spaces are commonly present in these
tumours. Focal areas of medullary differentiation charac-
terised by pale foci containing a smaller number of lympho-
cyes than the surrounding tissue can also be seen. The
proportion of small lymphocytes to epithelial cells can vary
widely among tumours and within different areas of the same
tumour. The epithelial cells are round, with large vesicular
nuclei and single small eosinophilic nucleoli, and are
surrounded by abundant cytoplasm with indistinct cell
borders. The cells usually do not show any marked cytological
atypia and are devoid of mitotic activity. Mitoses can often be
observed in the more immature lymphoid cell elements. These
tumours are the equivalent of the lymphocyte-rich thymoma
and mixed (lymphoepithelial) thymoma of the traditional

Figure 1 (A) Normal, mature thymus
of childhood. (B) Normal thymus in a
57-year-old man. Note the massive
involution of the thymus with extensive
replacement by fat and thin strands of
flattened, atrophic, spindle thymic
epithelial cells.

Figure 2 Thymoma showing features that recapitulate the mature,
functionally active thymus of childhood and adolescence, with
predominance of immature T lymphocytes admixed with scattered large,
round thymic epithelial cells.

Figure 3 Thymoma showing features that recapitulate the atrophic or
involuting, non-functional thymus of the adult. Sheets of bland-appearing
spindled epithelial cells with occasional small T lymphocytes can be
observed.
Atypical thymoma, characterised by partial preservation of the organotypical features of the thymus (perivascular spaces and dual cell population), but showing paucity of lymphocytes and sheets of large polygonal epithelial cells with nuclear atypia and dense chromatin pattern.

Tumours recapitulating the features of the normal involuted thymus of the adult are characterised by a solid proliferation of oval to spindle cells, with small elongated nuclei showing a dense chromatin pattern with occasional small, inconspicuous nucleoli and scant rim of cytoplasm (fig 3). The cells often adopt a fascicular growth pattern, but may grow as sheets admixed with variable numbers of small lymphocytes, or they can adopt a variety of unusual growth patterns, such as the creation of rosette-like structures, storiform pattern, hemangiopericytic pattern, micronodular pattern, trabecular (adenoid) pattern and others.3 The epithelial tumour cells are completely devoid of cytological atypia or mitotic activity. These tumours are usually characterised by a paucity of lymphocytes, although some cases can show a considerable number of T lymphocytes admixed with the epithelial cells. These tumours correspond to the spindle cell type of thymoma in the traditional classification4 and to the medullary type of thymoma in the Kirchner and Muller-Hermelink classification, and are also the equivalent of type A thymoma in the WHO schema.1 Patients showing admixtures of spindle cell areas with round cells and lymphocyte-rich areas are often encountered and correspond to the mixed category in the Kirchner and Muller-Hermelink classification1 and to the type AB thymoma in the WHO schema.1

Atypical thymoma, characterised by absence of the organotypical features of the thymus, with overt cytological evidence of malignancy.

Table 2 Comparison of World Health Organization schema and the Suster and Moran histological classification of thymoma

<table>
<thead>
<tr>
<th>WHO</th>
<th>Suster and Moran</th>
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<tr>
<td>Type A</td>
<td>Thymoma</td>
</tr>
<tr>
<td>Type A8</td>
<td>Thymoma</td>
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<tr>
<td>Type B1</td>
<td>Thymoma</td>
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<tr>
<td>Type B2</td>
<td>Thymoma</td>
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<tr>
<td>Type B3</td>
<td>Atypical thymoma</td>
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WHO, World Health Organization.

can be encountered. The cells can sometimes show clear cytoplasm and often show a tendency to palisade around vessels or perivascular spaces. The tumours also show at least some of the organotypical features of the thymus, such as lobulation, prominent dilated perivascular spaces and an admixture of epithelial cells with small lymphocytes. These tumours are more often invasive than other types of thymoma, with a tendency for earlier recurrences. Atypical thymoma can also be composed of spindle to oval cells rather than round or polygonal cells. In such instances, the spindle cells will show increased nuclear size, with prominent nucleoli and occasional mitotic figures.

Poorly differentiated thymic epithelial neoplasms (ie, thymic carcinoma) are characterised by loss of the organotypical features of differentiation of the thymus and the presence of marked or overt cytological features of malignancy (fig 5). These tumours are the equivalent of thymoma type C in the original proposal of the WHO classification2 and they essentially resemble carcinomas similar to those arising in other epithelial organs.17 Thymic carcinoma represents a diagnosis of exclusion. Currently, as no reliable specific markers are available that can help us determine the primary nature of these tumours, definitive diagnosis depends on the demonstration of the absence of a primary tumour elsewhere by thorough clinical and imaging studies or at the time of autopsy.18 19 A large variety of histological variants have been described, including keratinising squamous cell carcinoma, non-keratinising, poorly differentiated (lymphoepitheliom-like) squamous cell carcinoma, mucoepidermoid carcinoma, clear cell carcinoma, basaloid carcinoma, spindle cell (sarcomatoid) carcinoma, anaplastic carcinoma, neuroendocrine carcinoma and others.17 19 The main problem associated with
their diagnosis lies in making a determination as to whether they are primary or metastatic. Although our proposal was initially severely criticised, this approach has been recently validated in studies carried out (ie, electron microscopy, cytogenetics, flow cytometry and so on). Support my diagnosis or the results of any relevant immunohistochemical stains that will be needed by the clinician or oncologist for proper management. The spindle cell variant of thymoma can occasionally be confused for a variety of mesenchymal spindle cell tumours, including solitary fibrous tumour and synovial sarcoma, as well as for a neuroendocrine neoplasm when the tumour is predominantly composed of rosette-like or trabecular structures. The absence of appreciable cytological atypia and identification of some of the organotypical features of thymic differentiation will help separate these tumours from other conditions. Additionally, strong and diffuse positivity for cytokeratin and negative results for other differentiation markers can help arrive at the correct diagnosis. Other immunohistochemical markers that can be helpful for the diagnosis of thymoma under certain circumstances include CD1a, CD3, TdT and CD99, all of which mark immature T lymphocytes whose presence is a constant feature (in varying proportions) of well-differentiated thymic epithelial neoplasms. Surgical pathology report Once a diagnosis of thymoma has been established, the surgical pathology report should include three essential components: the main-line diagnosis; a comment; and the synoptic report (fig 6). In the line diagnosis, I simply indicate whether the tumour corresponds to a thymoma or an atypical thymoma, followed by whether the tumour is encapsulated or invasive. In the comment section (or note), I usually provide a short description of the morphology and indicate the salient histological features of the tumour, usually accompanied by a categorisation into one of the histological types in the traditional classification (if possible), and with an indication of its equivalence in the current WHO schema (if possible). I mention that in the note if the tumour cannot be fitted into any of the current WHO types or if precise categorisation is not possible. In this section, I also provide the results of any relevant immunohistochemical stains that support my diagnosis or the results of any other ancillary studies carried out (ie, electron microscopy, cytogenetics, flow cytometry and so on). In recent years, both the College of American Pathologists (CAP) and the Association of Directors of Anatomic and Surgical Pathology in the USA have proposed the use of diagnostic checklists or “templates” that summarise, under a separate heading, all of the relevant information on a case that will be needed by the clinician or oncologist for proper staging of the disease and for the planning of patient management. Thus, the most salient features of the tumour required for clinical staging and management are also listed in the section under synoptic report (fig 6, bottom half).
also recommend becoming familiarised with the protocol for the examination of specimens from patients with thymic epithelial tumours published by the Cancer Committee of the CAP.21 The CAP developed these protocols as an educational tool to assist pathologists in providing clinically useful and relevant information when reporting results of surgical specimen examinations. The type of information necessary for producing a complete and accurate reporting of thymic epithelial neoplasms, including clinical information, macroscopic examination and microscopic evaluation, is detailed in the CAP guidelines.21

Staging of thymoma

Staging of thymoma continues to be a controversial issue. Clinical staging of thymoma was first introduced by Berg et al22 and later modified by Wilkins and Castleman.23 The most popular staging system for thymoma was published in 1981 by Masaoka et al24 and this is the one that has been most widely used in most of the published studies on thymoma. A modification of the Masaoka staging scheme has been more recently introduced by Koga et al,25 in which the four original categories (ie, stages I, II, III and IV) have been retained. However, the authors noted that the survival curves for their tumours between stages I and II as well as for the tumours between stages III and IV did not differ markedly. They therefore concluded that the staging of thymoma could be simplified into two groups: non-invasive for stages I and II (ie, tumours that are still confined to the anterior mediastinum, without invasion of neighbouring organs) and invasive for stages III and IV (ie, tumours showing invasion of adjacent organs and metastases). I use the non-invasive and invasive scheme25 in my synoptic report, and also include

Figure 6 Example of a surgical pathology report for thymoma (no actual patient). The top half contains the line diagnosis and a supplementary explanatory comment; the bottom half lists the synoptic report.
Take-home messages

- A simplified three-tiered histologic classification (thymoma, atypical thymoma and thymic carcinoma; or low-, intermediate and high-grade tumours) is favoured over more complex histologic classifications for the reporting of thymic epithelial neoplasms.
- The equivalent type in the current WHO schema is appended in a comment (whenever possible) to facilitate comparison with other classification schemes.
- Staging is a more important predictive parameter for prognosis than histology.
- The simplified modification of the Masaoka clinical staging scheme proposed by Koga et al is recommended, which categorises these tumours into non-invasive (confined to the mediastinum) and invasive (with infiltration of adjacent structures).
- Use of a synopsis report to summarise the salient clinical information is recommended.

It implicitly in my line diagnosis, where I always indicate whether the tumour is invasive or non-invasive. I prefer to designate stage II, however, as “minimally invasive”, to distinguish it from stage III, which is widely invasive, because the two are associated with dramatically different prognoses. A somewhat similar, simplified system has been proposed recently by Bedini et al, which stages the tumours into three tiers: locally restricted disease, locally advanced disease and systemic disease.

No universally accepted staging scheme for thymic carcinoma exists yet, and these tumours are not included in the latest edition of the Cancer Staging Manual of the American Joint Committee on Cancer. In the largest series published on thymic carcinoma, the authors applied the original Masaoka staging scheme for the staging of tumours in their patients. Until additional information becomes available or a consensus is developed, it is probably best to use the modified Masaoka staging of thymoma for these tumours in the same way that it is applied for thymomas.

SUMMARY

Although much emphasis in recent years has been placed on the histological classification of thymoma, the bulk of the evidence continues to point to clinical staging as the most important parameter for prognostication, particularly for well-differentiated thymic epithelial neoplasms. For this reason, I believe the most relevant information for the clinician in the main-line diagnosis of the pathology report should be whether the tumour is well, moderately or poorly differentiated, and whether the tumour is invasive or non-invasive. Assigning a tumour to any particular WHO subtype is, in my opinion, of secondary importance, particularly for types A, AB, B1 and B2. All of these tumours essentially represent examples of well-differentiated neoplasms that retain most of the organotypical features of differentiation of the thymus and are devoid of marked cytological atypia. The status of capsular integrity in such cases will be a more accurate predictor of their biological potential and future behaviour than the histology. The specific WHO subtype in this context, although of academic interest for the pathologist, is of secondary importance to the clinician and may actually contribute to create confusion when provided in the line diagnosis. The simplified approach to the reporting of thymic epithelial neoplasms offered here provides all of the pertinent information for our clinical colleagues, including the WHO subtype (when applicable) in the comment section, with minimal chance for error and confusion. Owing to its simplicity and the reduced potential for confusion, this is the format that I favour and use in my clinical practice for the reporting of thymoma.

Competing interests: None declared.

REFERENCES