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REVIEW ARTICLE

Classification, histopathology and molecular pathology of thymic epithelial tumors: a review

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Summary

Thymic epithelial tumors represent 0.2-1.5% among all malignant neoplasms. They are slow-growing tumors with an overall recurrence rate around 10% and 90% of them are located in the anterior mediastinum. In this review we focused on the classification, histopathology, molecular pathology and prognosis of thymic epithelial tumors, mainly thymoma and thymic carcinoma.

Key words: *thymomas, thymic carcinoma, classification, histopathology, immunohistochemistry, molecular pathology*

Introduction

Thymus is a lymphoepithelial organ located in the upper anterior mediastinum extending into the neck close to the lower segments of the thyroid gland. Thymus derives from both ectoderm and endoderm of the 3rd and 4th pharyngeal pouches which interact with the associated mesenchyme contributing to its development [1,2]. However, there is evidence suggesting that the diverse thymic epithelial lineages all develop from a common thymic stem cell of endodermal origin [3]. Thymus is completely differentiated by the 17th week, grows until puberty and then involutes [2].

Thymus histologic architecture includes two distinct compartments: an outer called cortex and an inner called medulla. Both cortex and medulla are composed by a network of reticular fibers, epithelial and lymphoid cells. The thymic epitheliocytes are distinguished in type 1 (subcapsular and perivascular), types 2-4 (cortex) and types 5-6 (medulla). The lymphoid cells, known as thymocytes, are mostly of T-lymphocyte lineage and located in the cortex. The medulla contains few lymphoid cells and the Hassall's corpuscles formed by types 4 and 6 epitheliocytes [4].

Thymus has complex functions mainly of selecting precursors T-lymphocytes arriving from the bone marrow and differentiate them into mature T-lymphocytes, thus preventing autoimmunity. Additionally, the thymus functions as an endocrine organ by producing thymosins, thymopoietin, thymopentin, thymulin and thymic humoral factor-γ2 (THF-γ2) [5,6].

A wide variety of tumors can be derived from the epithelium and the lymphoid component of thymus including thymomas, thymic carcinomas, neuroendocrine carcinomas, lymphoproliferative disorders and tumors arising in the mediastinum such as extragonadal germ cell tumors and sarcomas. In this review we focused on the classification, histopathology and molecular pathology of thymic epithelial tumors, mainly thymoma and thymic carcinoma.

Thymomas affect all age groups most commonly middle-aged adults (40-50 years) with an in-

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cidence 0.2 -1.5% among all malignant neoplasms [7]. They are slow-growing tumors with an overall recurrence rate around 10% (2% for the encapsulated and 20 to 40% for the invasive thymomas) with a mean time to recurrence being 6 years (range 1-16) [8,9]. 10-year survival after recurrence is up to 65% with a more favorable one in completely excised tumors, independent of stage or type. Metastases are rare (1-2% of cases) and are associated with a poor prognosis. In contrast, thymic carcinomas are highly aggressive tumors with poor therapeutic responsiveness and survival depending on the carcinoma type [10].

Thymoma is frequently associated with autoimmune and paraneoplastic disorders such as neuromuscular disorders (myasthenia gravis, limbic encephalopathy, polymyositis), immunodeficiency disorders (hypogammaglobulinemia), hematological diseases (pure cell aplasia, haemolytic anaemia), collagen diseases (systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome), dermatological disorders (pemphigus, lichen planus) [11,12].

Classification and staging

The histopathologic classification of thymic epithelial neoplasms is a controversial issue in thoracic pathology due to the wide variety of histopathological features displayed by these neoplasms. Histopathological classification schemes for these tumors based on the morphology, the lymphocyte content or the histogenetic background have been proposed but failed to correlate successfully the morphologic findings with the prediction of clinical behavior and thus the right therapeutic approach.

Among the 24 histopathologic classifications that have been proposed within the last century the most important are: the Traditional (Bernatz) classification (1961), the Kirchner and Muller-Hermelink classification (1989), the Suster and Moran classification (1999) and the WHO classification (1999, 2004, 2015).

In 1961 Bernatz et al from the Mayo Clinic proposed a classification based on 4 basic morphological types; lymphocyte-predominant, epithelial-predominant, mixed (lymphoepithelial), and spindle cell thymoma, known as the traditional classification of thymoma [13].

In 1985 Marino and Muller-Hermelink proposed another classification (histogenetic or functional) that divided thymic epithelial tumors into three categories: cortical, medullary, and mixed types, based on the anatomical and functional thymic compartment that the neoplastic cells are derived [14]. The latter classification was modified in 1989 introducing 2 more categories, the predominantly cortical thymoma (organoid) and the well-differentiated thymic carcinoma [15].

In 1999, Suster and Moran proposed a 3-tiered classification based on morphologic features of differentiation that classified thymic epithelial tumors according to their degree of cell atypia, presence of organotypic features of thymic differentiation and resemblance to benign thymus. According to this classification the well-differentiated tumors were designated as thymoma, the intermediate differentiated as atypical thymoma and the poorly differentiated tumors as thymic carcinoma [16].

In 1999, and later on 2004 and 2015, WHO divided thymic epithelial neoplasms, preserving the distinct categories of the histogenetic classification, into the following categories : A, Atypical type A variant, AB, B1, B2, B3, and C (thymic carcinoma) based on morphological, functional, genetic and clinical evidence [17-19]. Most of the epidemiologic and prognostic data for the WHO classification were derived from the International Thymic Malignancy Interest Group (ITMIG) database in which data from 6000 cases worldwide have been stored [20]. The different classification schemes are displayed in comparison on Table 1.

Thymic epithelial tumors can be staged based on the presence and extent of invasion to the gland capsule and/or adjacent tissues, serosal dissemination, lymph node involvement, and/or distant

Table 1. Classification schemes of thymic epithelial tumors

Traditional (Bernatz)	*Muller-Hermelink*	*Suster & Moran*	*WHO*
Spindle cell	Medullary	Thymoma	Type A
–	Mixed	Thymoma	Type AB
Lymphocyte-rich	Predominantly cortical	Thymoma	Type B1
Mixed	Cortical	Thymoma	Type B2
Epithelial-rich	Well-differentiated Carcinoma	Atypical thymoma	Type B3
–	Carcinoma	Thymic carcinoma	Thymic carcinoma (previously Type C)

Table 2. Masaoka-Koga staging system

Stage I.	Grossly and microscopically completely encapsulated tumor. A noninvasive thymoma, tumor has not spread beyond the thymus - T1 N0 M0 according to TNM
Stage II	The thymoma invades beyond the capsule of the thymus) and into the adjacent adipose tissue or to the mediastinal pleura or pericardium but not breaking trough. It is divided into:
Stage IIa	Microscopic transcapsular invasion - T2 N0 M0.
Stage IIb	Macroscopic capsular invasion or into the surrounding adipose tissue or adherent to the mediastinal pleura or pericardium but not breaking through - T2 N0 M0.
Stage III	Macroscopic invasion into neighboring organs. The thymoma extends into the neighboring tissues or organs of the lower neck or upper chest area, including the pericardium, the lungs, or the great blood vessels leading into or exiting from the heart - T3 N0 M0.
Stage IVA	Pleural or pericardial dissemination. The thymoma has spread widely throughout the pleura and/or pericardium - T4 N0 M0.
Stage IVB	Hematogenous or lymphogenous metastases. The thymoma has spread to distant organs - Any T >N0 or >M0.

Table 3. TNM classification and staging system

T – Primary tumour			
TX	Primary tumour cannot be assessed		
T0	No evidence of primary tumour		
T1	Tumour completely encapsulated		
T2	Tumour invades pericapsular connective tissue		
T3	Tumour invades into neighbouring structures,such as pericardium, mediastinal pleura, thoracic wall,great vessels and lung		
T4	Tumour with pleural or pericardial dissemination		
N – Regional lymph nodes			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in anterior mediastinal lymph nodes		
N2	Metastasis in other intrathoracic lymph nodes excluding anterior mediastinal lymph nodes		
N3	Metastasis in scalene and/or supraclavicular lymph nodes		
M – Distant Metastasis			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
WHO stage grouping			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1	N1	M0
	T2	N1	M0
	T3	N0, N1	M0
Stage IV	T4	Any N	M0
	Any T	N2, N3	M0
	Any T	Any N	M1

metastases.Till now 14 staging systems have been proposed among which the Masaoka-Koga and the TNM systems are the most commonly used [22-24]. These systems are displayed on Table 2 and Table 3 respectively.

Pathologic features and incidence

Thymoma type A (spindle cell, medullary) is a well circumscribed, encapsulated tumor with a lobulated cut surface with thick fibrous septa and focal cystic change occasionally. It consists of spindle or oval and rarely polygonal cells without cytologic atypia and inconspicuous nucleoli. Mitotic activity is low (<4 mitoses /mm^2).The growth pattern is storiform with or without rosette-like, pseudoglandular or glomeruloid structures. Hassall's corpuscles are absent. Immature terminal deoxynucleotidyl transferase positive (TdT +) T lymphocytes are rare or absent [25-27]. Nevertheless, a small percentage (5-10%) of type A thymomas can display foci of micronodular thymoma with stroma containing lymphocytes [28]. Lymphocyte dense areas or lymphocyte infiltrate more than 10% of the tumor area classify the neoplasm as a type AB thymoma [29].

Thymoma type A is rare in relation to all thymomas (relative mean incidence 11.5%) and most of them are stage I (60%) according to the Masaoka-Koga staging system. A percentage of 30% of them are stage II, while stage III is rare (8%) [30,31].

Atypical type A variant is a rare form of type A thymoma that preserves some organo-typical characteristics of thymic differentiation, but associated with hypercellularity, cytologic atypia, increased number of mitoses and focal areas of necrosis. The predominant component consists of epithelial cells with a tendency to squamous metaplasia. Atypical thymoma can invade adjacent structures more frequently than the conventional thymoma and can co-exist with other types of thymoma or/and thymic carcinoma. The clinical significance of this type is under investigation [29,32].

Thymomas can display different histological patterns in the same tumor showing tissue heterogeneity and because of this, extensive sampling should be performed from the resection specimens [33]. All these histological types should be mentioned in the diagnostic report commencing with the predominant component and following with the percentage of minor ones. This rule does not apply for the distinct entity of type AB thymoma. Tumors that have a thymic carcinoma component along with any thymoma type should be labelled thymic carcinoma mentioning the histological type and the percentage of both thymic carcinoma and accompanying thymoma(s) [19,41].

Thymoma type AB (mixed) is usually encapsulated with a nodular cut surface displaying fibrous thick septa. It has a lobulated growth pattern and is characterized by lymphocyte-poor type A areas and T immature TdT + lymphocyte-rich type B-like areas. The two different components of the tumor may be delineated by fibrous septa or the transition between them can be gradual. Hassall's corpuscles are absent and medullary islands can be seen rarely [32-34].

Thymoma type AB shows a relative mean incidence of 27.5% in relation to all thymomas and most of them are stage I (67%) according to the Masaoka-Koga staging system. A percentage of 26% of them are stage II, while stage III is rare (6%) [30,31].

Thymoma type B1 (lymphocyte-rich, lymphocytic, cortical) is well circuscribed with capsule and nodular cut surface separated by fibrous bands. The mean diameter is between 5.1 to 7.5 cm. It has normal functional non-involuted thymus architectural pattern and consists mainly of cortical areas (that predominate) and few medullary islands. The lobules are larger than in normal thymus and are separated by collagenous, hypocellular bands. Medullary islands are usually round and may contain clusters of epithelial cells, Hassall's corpuscles or myoid cells together with an increased number of B lymphocytes and mature T lymphocytes. Perivascular spaces are rarely present and less prominent than in other thymoma types [19,33,34].

Thymoma type B1 has a relative mean incidence of 17.5% in relation to all thymomas and most of them are stage I (50%) according to the Masaoka-Koga staging system. A percentage of 37% of them are stage II, while stage III is less common (9%) and stage IV is rarely seen (3% for IVa and 1% for IVb) [30,31].

Thymoma type B2 (cortical) is an encapsulated tumor or can invade the mediastinal adipose tissue or adjacent organs. Its mean diameter ranges from 4 to 6.2 cm. The cut surface is lobulated with fibrous septa. Necrotic areas, haemorrhage or cystic changes can be found. It consists of poorly formed lymphoepithelial irregular lobules separated by delicate fibrous septa. It is characterized by the abundance of immature T lymphoid cells interspersed among them isolated or small aggregates of polygonal epithelial cells with round or oval nuclei and small prominent nucleoli [19,35]. The number of epithelial cells is higher than in the normal cortex and B1 thymoma. The immature lymphocytes have large nuclei, relatively abundant cytoplasm and high proliferation rate (Ki67 index

>80%) [35]. Perivascular spaces are present around a central venule and contain proteinaceous fluid or lymphocytes. Medullary islands with or without Hassall's corpuscles are few or absent. A percentage of 42% of this tumor may co-exist with thymoma B3 and rarely with thymoma B1 (4% of type B2 thymomas) [30].

Thymoma type B2 accounts for an average incidence of 26% in relation to all thymomas and its distribution, according to the Masaoka-Koga staging system, is 32% in stage I, 29% in stage II and 28% in stage III. Stage IV is rarely seen (8% for IVa and 3% for IVb) [30,31].

Thymoma type B3 (epithelial, atypical, well differentiated thymic carcinoma) is usually poorly circumscribed and extends into the mediastinal adipose tissue or adjacent organs. Its average diameter is between 5.1 to 6.8 cm. The cut surface is grey to yellowish, nodular and separated by fibrous septa. Haemorrhagic and necrotic areas can be seen. It has a lobulated architectural pattern with fibrous septa, pushing tumor invasive front, abundant perivascular spaces with epithelial palisading and rare Hassall's corpuscles. It consists of abundant epithelial cells that are polygonal with round or elongated, occasionally grooved nuclei and inconspicuous or prominent nucleoli. The epithelial component form solid cell sheets and the tumor is characterized by paucity of immature T lymphocytes [9,19]. This tumor may co-exist with thymoma B2 (2-16% of all thymomas) and rarely with thymic carcinoma [34].

Thymoma type B3 accounts for an average incidence of 16% in relation to all thymomas and its distribution, according to the Masaoka-Koga staging system, is 19% in stage I, 36% in stage II, 27% in stage III, 15% in stage IVa and 3% in stage IVb [30,31].

Rare types of thymoma have been described such as micronodular thymoma with lymphoid stroma, metaplastic thymoma, microscopic thymoma and sclerosing thymoma [19].

Micronodular thymoma with lymphoid stroma consists of multiple epithelial islands of spindle or oval cells surrounded by a epithelial cell-free lymphoid stroma which occasionally contain lymphoid follicles [37].

Metaplastic thymoma has a biphasic architectural pattern and is characterized by solid sheets of epithelial cells merging sharply or gradually with bland looking spindle cells [38].

Microscopic thymoma is defined as a conventional thymoma with a diameter <1cm and composed of aggregates of bland looking thymic epithelial cells less than 1mm in diameter arranged multifocally [39].

Sclerosing thymoma exhibits histological features of conventional thymoma with collagen rich stroma [40].

Thymic carcinomas are rare thymic epithelial tumor that display histologic features observed in malignant epithelial neoplasms of other organs. They exhibit prominent cytologic atypia and lack immature lymphocytes. Mature lymphocytes of T and rarely B lineages admixed with plasma cells may be present. In contrast to conventional thymomas, thymic carcinoma is rarely associated with autoimmune diseases such as myasthenia gravis. Thymic epithelial tumors may exhibit both thymoma and thymic carcinoma morphologic features and tumors that have both components should be labelled as thymic carcinoma reporting the histological type and the percentage of both thymic carcinoma and accompanying thymoma(s) [19,41,43].

Thymic carcinomas account for 22% of all thymic epithelial tumors and a variety of histologic types have been described including the following:

Squamous cell thymic carcinoma accounts for 70% of all thymic carcinoma cases. It consists of infiltrative keratinizing or non keratinizing forms with large cells of squamous differentiation and obvious cytologic atypia [50,51].

Basaloid thymic carcinoma accounts for <5% of all thymic carcinomas. It is exhibits a cystic-papillary and nesting growth pattern. It is composed of tumor cells with peripheral palisading, basophilic staining pattern and absence of keratinisation [47].

Mucoepidermoid thymic carcinoma has morphologic features similar to salivary glands mucoepidermoid carcinoma. It consists of squamous cells admixed with mucinous cells forming nests or lining cystic spaces [52].

Lymphoepithelioma-like thymic carcinoma consists of anastomosing islands and cords of poorly differentiated carcinoma cells admixed with abundant lymphocytes and plasma cells [53].

Sarcomatoid or spindle cell thymic carcinoma consists of an admixture of conventional type A thymoma spindle cells and areas of cytologically malignant spindle cells resembling sarcoma [48,49].

Clear cell thymic carcinoma shows a lobulated infiltrative growth pattern and is composed predominantly of polygonal cells with clear cytoplasm [45,46].

Thymic adenocarcinoma. This type of thymic carcinoma displays a variety of growth patterns and is divided in four categories: papillary, adenoid cystic-like, mucinous and NOS (not otherwise specified) in a papillary fashion [44].

Undifferentiated thymic carcinoma is a very rare type of thymic carcinoma that grows in

a solid infiltrative islands and sheets with large polygonal cells exhibiting pleomorphic features. Coagulative necrosis areas may be found [43].

NUT carcinoma is a poorly differentiated carcinoma with t(15;19) NUT gene translocation. It is composed of small to intermediate sized cells arranged in sheets and nests which are positive for nuclear protein in testis (NUT) immunohistochemically [42].

Pathologic features of thymoma after preoperative treatment with corticosteroids

Corticosteroids are used preoperatively in advanced stage thymomas in order to reduce their size and facilitate the surgical operation. The administration of corticosteroids may induce degenerative changes in the epithelial cells and lymphocytes of thymic epithelial tumors and change the typical histologic patterns of these neoplasms raising diagnostic problems for the pathologist. Very few studies have addressed this issue and have shown that there are significant histologic changes between thymic specimens before and after corticosteroid treatment. Corticosteroid administration, depending on the dose and duration, can cause morphologic changes to the neoplastic thymic epithelial cells like condensation of nuclei, spindle-shaped or bizarre features and formation of glandular-like or haemangiopericytoma-like structures. It has been observed a dramatic depletion of the lymphoid component of immature T cells with the presence of few lymphocytes showing fragmented nuclei. Cystic degeneration, presence of multinucleated giant and bizarre cells, necrotic areas, foamy histiocytes and prominent fibrosis have been reported. Pathologist should be informed for any preoperative medication in order to avoid possible diagnostic confusion [54].

Immunohistochemical and molecular genetic pathology findings

Immunohistochemical analysis may be used to solve differential diagnostic problems such as the distinction of thymoma type A from other spindle cell neoplasm or the differential diagnosis between type B1 thymoma from lymphoblastic lymphoma. The most commonly used antibodies are against antigens of thymic epithelial cells and lymphoid cells, as well as antibodies against compartment-specific targets (cortical or medullary differentiated cells) like claudin 4, Cathepsin V, CD40, PRSS16, Involucin, Beta 5t and Autoimmune Regulator AIRE [19,57].

Thymoma type A. In type A thymoma epithelial cells show strong reactivity against AE1 acidic keratins and p63, and negative reactivity against AE3 basic keratins. They display negative expression of CK10 and CK20 and are positive for epithelial markers PAX8, FOXN1 and CD205, while CD117(c-Kit) and CD5 are negative. CD20 focal positive expression has been shown in 50% of the epithelial cells, while CD20 positive B lymphocytes and immature TdT+ positive T lymphocytes are absent [55,56,58,68].

Type A thymomas harbour consistent loss of heterozygocity in 6q25.2-25.3, also a common genetic finding in AB and B3 thymomas, as well as in thymic squamous carcinoma. Rare genetic aberrations are losses at chromosomal loci 2, 4, 6q, 13 and 6p21 and t(15;22)(p11;q11) translocation [63]. *EGFR, KIT, APC, RB1* and *TP53* mutations are absent and activating *HRAS* mutations are rare (67). Recently *GTF2I* transcription factor missense mutation has detected in 82% in type A thymomas [60].

Thymoma type AB. Same pattern of expression for cytokeratins and p63 as in type A thymoma has been observed with the exception of type B areas in which epithelial cells are CK14 positive. CD20 is positive in epithelial cells of both type A and type B areas, while CD20 positive B lymphocytes are absent. Few CD3 positive T lymphocytes can be seen and belong to the immature TdT+ T cells. Epithelial cells do not express CD5 and usually no expression of CK10 and involucin is seen. Markers of both cortical and medullary differentiation such as CD40, claudin 4, autoimmune regulator AIRE are expressed in the admixture of thymic epithelial cells [57,61,62].

Losses of genetic material on chromosomes 2. 4, 5q21-22, 6p21, 6q25.2-25.3, 7p15.3, 8p, 13q14.3, 16q and 18 are shared with other types of thymomas. Loss of heterozygocity at 5q21-22 is associated with *APC* gene and also found in type B thymomas [63]. *EGFR* and *KIT* mutations have not been described [66]. *GTF2I* transcription factor missense mutation has detected in 74% in type AB thymomas [59,60,63].

Recently, a large microRNA cluster on chr19q13.42 has been found to be overexpressed in all A and AB tumors and whose expression was not observed in B thymomas, thymic carcinomas and normal thymus. Furthermore, this cluster overexpression activates the PIK3AC/Akt pathway, suggesting the possible treatment of patients with these thymoma types by using PIK3AC inhibitors [64,65].

Thymoma type B1. The epithelial cells of type B1 thymoma are focally positive for CK8/18, CK14, CK7, diffusely positive for CK19 and negative for CK20 [62]. They also express p63 [61] and PAX8 [68]. The lymphocytic population consists mostly

of immature T cells with positive expression for TdT, CD1a, CD3, CD4, CD8 and negative for CD34. The medullary islands contain mature T lymphocytes with CD3, CD4 or CD8 positive expression and TdT and CD1a negative one [19]. In the same area B cell population can be found which is positive for CD20 and CD79a admixed with epithelial cells expressing CK19 diffusely [57].

Chromosomal aberrations, like losses at loci 1p, 2q, 3q, 4, 5, 6q, 8, 13 and 18, and a gain of chromosome 9q have been observed [63]. Missense mutation of *GTF2I* transcription factor gene is found in 32% of the cases [60].

Thymoma type B2. Similar pattern of keratin expression in thymic epithelial cells as type B1 thymoma but more dense. Abundance of highly proliferative (Ki-67 > 90%) immature TdT+ T lymphocytes admixed with epithelial cells expressing strongly cortical differentiation markers (PRSS16, Beta5t, Cathepsin V) [35,57].

Losses on chromosome loci 6q25.2-25.3 and 3p, and gain on 1q have deen detected. No mutations of *EGFR* or *KIT* have been reported [69]. Missense mutation of *GTF2I* transcription factor gene has been found in 22% of the cases [60].

Thymoma type B3. Tumor epithelial cells are positive for CK5/6, CK7, CK8, CK10 and CK19, and negative for CK20. They also express p63, PAX8, CD57 an focally EMA [19,61,68]. There is no expression of medullary differentiation markers and only occasional expression of cortical differentiation markers [57]. Markers for thymic carcinoma (CD5 and CD117) are negative and rarely focal expression of GLUT1 and MUC1 has been observed [70]. CD20 and TTF1 are not expressed. Few immature TdT+ T cells can been seen among the tumor cells.

Gene copy number aberrations are more common in B3 thymomas than in other types. Chromosomal gains have been described on loci 1q, 4, 5, 7, 8, 9q,17q, and X . Copy number gain of *BCL2 (18q21.33)* and loss of *CDKN2A/B (9q21.3)* are associated with poor prognosis [71]. Chromosomal losses have been found on 3p, 6, 6q25.2-25.3, 9p, 11q42.qter, 13q, 16q, 17p. Translocation t(11;X) can also be found in some cases. *GTF2I* missense mutation is found in 21% of type B3 thymomas. In addition, genomic profiling analysed by hierarchical clustering algorithm revealed specific cluster for type B3 thymomas and thymic carcinomas that can distinguish them from type A and B2 thymomas [72,73].

Thymic carcinoma

Thymic squamous carcinomas display positive expression for p63/p40, PAX8, CD5, CD117, GLUT1 and MUC1. The latter four markers (CD5,CD117, GLUT1, MUC1) are expressed in almost all types of thymic carcinomas and very rarely in thymomas [50,70]. Epithelial markers for thymic organogenesis such as FOXN1 and CD205 are positive in thymic carcinomas but not in carcinomas of non-thymic origin and thus are useful for differential diagnosis between them [55]. Beta5t, a proteasome subunit, is negative in thymic carcinoma but shows a universal expression in type B thymomas [74]. Focal expression of neuroendocrine markers can be seen in thymic carcinoma. The lymphocytic infiltrate of thymic carcinoma consists of mature B and TdT- T cells and very rarely of immature T lymphocytes.

Chromosomal gains have been described on loci 1q, 4, 5, 7, 8, 9q, 12, 15,17q, 18 and 20. Copy number gain of *BCL2* and loss of *CDKN2A/B (p16)* are associated with poor prognosis [71]. Chromosomal losses have been found on 3p, 6, 6q25.2-25.3, 9p, 13q, 14, 16q, 17p. Activating *KIT* mutations can be seen in 2-11% of thymic squamous carcinoma and *GTF2I* missense mutation in 8% of the cases. Activating *KRAS, EGFR, BRAF, PIK3CA, APC, RET* or *PTEN* mutations are rare [67]. Amplification of *HER2* gene and TP53 mutations have been found in <4% and 50% of cases respectively [75].

Further molecular analysis is needed in order to define specific molecular targets for future therapeutic interventions.

Prognosis

Prognosis of epithelial thymic tumors is based mainly on the presence or absence of capsule invasion without penetration or with penetration and extension of tumor cells to the adjacent adipose tissue. Careful microscopic examination should be performed on serial tissue sections in order to check any tumor cell emboli in capsular venules in an otherwise intact capsule. Thymomas type A and AB show long-term survival rates and are considered of benign behaviour, while thymic carcinoma is of malignant behaviour. The prognosis of thymic carcinoma largely depends on the pathologic type. Among its different variants , better prognosis has been shown in well-differentiated squamous cell carcinoma, low-grade mucoepidermoid carcinoma and basaloid carcinoma, in contrast to poor prognosis that can be seen in lymphoepithelioma-like carcinoma, high-grade mucoepidermoid carcinoma, clear cell carcinoma, sarcomatoid carcinoma and undifferentiated carcinoma. Type B thymomas show a range of clinical behaviour between benign to malignant and thus more detailed studies should be performed in order to establish more consistent data [76,77].

According to SEER, ITMIG and the American Cancer Society, the overall survival rate of patients with thymoma, irrelevant of type, after 5-years follow-up based on the Masaoka-Koga staging system, is approximately as follows: for stage I is 74%, stage II 73%, stage III 64% and stage IV 45%. On the other hand, the overall survival rate of thymic carcinoma, independent of type, after 5-years follow-up is approximately as follows: for stage I and II 74%, stage III 33% and stage IV 24% [77,80,81]. Further studies should be performed on long series of patients by combining the Masaoka-Koga staging system with the histological types and taking into account a more precise reporting of possible tumor extension to adjacent tissues and organs [78,79].

Conflict of interests

The authors declare no conflict of interests.

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