Review Article

The pathology of the thymus in myasthenia gravis

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Abstract: Myasthenia gravis (MG) is an autoantibody mediated autoimmune disease characterized by skeletal muscle fatigability and weakness through different types of immune attacks against various proteins of the postsynaptic membrane or in the neuromuscular cleft of the neuromuscular junction. In a subset of patients with autoantibodies against the muscle type acetylcholine receptors (AChRs) there is strong evidence that the thymus is involved in the pathogenesis of MG, while its role is questionable or unknown in MG due to autoantibodies against muscle specific kinase (MuSK), lipoprotein receptor like protein 4 and agrin. Here we describe the thymic alterations that have repeatedly been encountered in MG, i.e., thymic follicular hyperplasia (TFH) (thymitis), 'thymic atrophy', thymoma and thymolipoma. The potential link of non-thymic tumors [e.g., follicular dendritic cell (FDC) sarcoma] with MG will be discussed.

Keywords: Thymoma; thymic hyperplasia; thymic atrophy; thymolipoma; follicular dendritic cell (FDC) sarcoma; rhabdomyosarcoma (RMS); pathogenesis; autoimmune regulator (AIRE)

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Introduction

Myasthenia gravis (MG) is an autoimmune disease eliciting muscle fatigability and weakness by an autoantibody attack against various proteins that physically and functionally cooperate and stabilize the highly ordered and dense array of acetylcholine receptors (AChRs) on the tips of the postsynaptic folds of the neuromuscular junction as a prerequisite to maintain highly efficient neuromuscular signal transduction (1,2). This "target heterogeneity" of the various autoantibodies is accompanied by somewhat different clinical presentation, different pathogenic mechanisms, different genetic risk factors and different accompanying thymic alterations (3). Currently, MG is classified into:

(I) MG with anti-AChR autoantibodies (AChR-MG), i.e., the most prevalent MG subtype that occurs in 70–80% MG patients and is due to mainly complement activating IgG1 autoantibodies against the muscle-type AChR (1,4). This subset now includes patients that were up to recently considered as 'sero-negative', because their autoantibodies do not bind solubilized AChRs (the targets used in conventional radio-immuno-assay) but recognize AChRs only in its clustered configuration, requiring cell based assays for recognition (5);

(II) MG with antibodies against the MuSK (MuSK-MG) (6) that is mainly due to IgG4 antibodies that complement-independently interfere with the MuSK/low-density lipoprotein receptor-related protein 4 (LRP4) interaction (7);

(III) MG due to mainly complement activating IgG1 and IgG2 antibodies to LRP4 (LRP4-MG), an interaction partner of MuSK (8-10);

(IV) MG due to autoantibodies against the motor

neuron-derived LRP4 ligand, agrin (Agrin-MG) (11,12) and;

(V) MG without known target autoantigen(s) (tentatively called "quadruple sero-negative MG", qSN-MG) (13,14).

In addition, there are small subsets of "double-sero-positive" MG patients with more than one of the above myasthenogenic autoantibodies, such as AChR/LRP4-MG (13,15), AChR/agrin-MG (12,13), MuSK/LRP4-MG (8,16) and, rarely AChR/MuSK MG (17,18). Switches from AChR-MG to AChR/LRP4-MG after thymoma removal (19) and many years after thymectomy for early onset myasthenia gravis (EOMG) (20) have been observed as well.

Another dimension of MG complexity results from the heterogeneity of AChR MG that is subdivided on epidemiological, genetic, clinical and thymic pathological grounds into, thymoma-associated MG (TAMG) and the non-thymomatous subtypes, EOMG, and late onset MG (LOMG). Furthermore, in many patients with AChR-MG various autoimmune targets other than the AChR are attacked by autoantibodies as well, resulting in accompanying diseases that are clinically highly relevant and potentially life-threatening, such as autoimmune thyroid disease, SLE or type I diabetes in EOMG patients; autoimmune pure red cell aplasia, cytopenias, hypogammaglobulinemia (good syndrome), encephalitis and many others in TAMG (21,22). Despite the diametrically different thymic pathologies in TAMG (thymic tumor) and EOMG (thymic 'atrophy'), there is a surprisingly strong immunological overlap between TAMG and LOMG in terms of the diagnostically important anti-titin autoantibodies and autoantibodies against various cytokines (23,24).

The prevalence of MG among the rare patients with thymolipoma appears to be higher than among members of the healthy population: in a recent study 4.4% of 267 MG-related thymectomies revealed thymolipoma, and stable remission of MG after thymectomy was achieved in a proportion of patients that was similar to that observed in EOMG patients (about 42%) (25). All thymolipoma patients with associated MG (TLAMG) described to date appear to have suffered from AChR-MG. This small subgroup of MG patients has not been studied sufficiently to allow for meaningful speculations in terms of disease mechanisms.

Detailed descriptions of the epidemiological, immunological and clinical heterogeneity of AChR-MG are given in recent reviews (1,2). Interestingly, several epidemiological studies revealed a real increase of LOMG, i.e., AChR-MG in the elderly, for unknown reasons (26,27). Reported incidence rates of AChR-MG varied widely between <1–14 (average 7) per million population (27).

The description of the largely unknown etiologies and the different pathogenetic pathways that lead to the various MG subtypes is beyond the scope of this article and available in recent reviews (1,7,28). Our focus here is on the pathology of the various thymic alterations that have recurrently been encountered in MG patients and are considered to be of pathogenetic relevance (*Table 1*). We shall also shortly address MG associated with extrathymic tumors. By contrast, we shall not cover thymic carcinomas (TCs). TCs are also derivatives of thymic epithelial cells but resemble carcinomas elsewhere and are labelled as such, e.g., as squamous cell carcinomas. Since TCs usually lack thymic functions (e.g., intratumorous thymopoiesis), associated autoimmunity is rare (e.g., polymyositis) or almost non-existent (e.g., MG). Reports on MG-associated TCs could result from the fact that (I) B3 thymomas were once called "Well differentiated thymic carcinomas" (36) and can be difficult to distinguish from TCs; and (II) myasthenogenic thymoma components accompanying TCs in heterogeneous cancers were not appreciated (37).

Thymic follicular hyperplasia (TFH)

Thymuses with TFH show increased numbers of lymphoid follicles in the medulla and perivascular spaces. Cortico-medullary architecture is adequate-for-age in corticosteroid-naïve patients. While single lymphoid follicles can occur in healthy persons (38-40), follicles in more than a third of thymic lobules are likely pathological (41).

Many autoimmune diseases can be associated with TFH (3) but TFH is commonest in EOMG, i.e., in patients with non-thymomatous AChR-MG that are mostly less than 50 years of age, but may rarely be up 55 (males) and 65 (females) (29). TFH due to EOMG has an incidence of 1–10 per 1,000,000 per year (42). TFH is also common (30–50%) in remnant thymuses adjacent to thymomas in TAMG and thought to be of a source of autoantibodies (43). By contrast, the reported frequencies of TFH in MuSK-MG (21%), LRP4-MG (0–31%) and AChR(–)/MuSK(–)/LRP4(–) triple-negative MG (22%) (16) need validation. The initiating trigger(s) of TFH are unknown, while many later steps of the intrathymic pathogenesis of EOMG have been resolved, leading to intrathymic autoantibody production (1,43). Since production of autoantibodies in EOMG is higher inside than outside the thymus, the thymus is thought

Table 1 MG subtypes and major associated thymic pathologies

MG subtype	Frequency[a] (%)	MG-related autoantigen	Thymic pathology (% of cases)
EOMG[b]	30	AChR	Thymic follicular hyperplasia (TFH; 100%)[c]
LOMG[d]	40	AChR	Thymic atrophy (age-related thymic involution?) (100%)[d]
TAMG	10–20	AChR (>99%)[e]	Thymoma (100%); TFH in remnant thymus (50%)
TLAMG	Rare	AChR(?)	Thymolipoma
MuSK-MG	0–10[f]	MuSK	None? Few with TFH?[ff]
LRP4-MG	Rare[g,gg]	LRP4	Thymic follicular hyperplasia (30%)[h]; thymic atrophy/normal for age (70%)
Agrin-MG	Rare[g]	Agrin	Unknown[g]
Quadruple sero-negative MG	Rare[g]	Unknown	Unknown[g]

Of note, most MG subtypes can apparently occur at young age including childhood (i.e., "early") or in the elderly (i.e., "late"). However, EOMG and LOMG are not 'baskets' for MG subtypes occurring in the young and elderly, respectively, but well-defined entities according to the criteria given in the table (i.e., EOMG is a "non-thymomatous AChR-MG in the 'young' with thymic follicular hyperplasia"). [a], Percentage of all MG patients; [b], including patients with antibodies exclusively against clustered AChRs; [c], by definition; [d], in an apparent 'biological grey zone' either EOMG or LOMG can occur between 50 and 65 years of age, with "early LOMG" occurring mainly in men, and 'late EOMG' occurring mainly in women (29); [e], single cases had anti-MuSK autoantibodies (30), were labeled 'sero-negative' in the pre-LRP4 and pre-agrin era (31,32) or showed "double AChR/LRP4 seropositivity" (15); [f], prevalences of MuSK-MG show a striking geographic gradient from virtual non-existence in northern countries (e.g., Norway) to increasingly higher prevalence toward the equator (1); [ff], whether reported frequencies (16,33,34) are higher than in the general population is unclear; [g], since LRP4-MG and Agrin-MG have been distinguished only recently and can be diagnosed only in specialized centers, their true frequency and the frequency of 'quadruple sero-negative MG' is currently not exactly known; [gg], the frequencies varied widely among AChR(−)/MuSK(−) double negative MG patients (9-12); [h], the reported frequencies of thymic alterations varied in two recent studies (13,16), apparently relied on local pathologists' diagnoses and need validation according to standard criteria (35). MG, myasthenia gravis; EOMG, early onset MG; LOMG, late-onset MG; TAMG, thymoma-associated MG; TLAMG, thymolipoma-associated MG; MuSK, muscle specific kinase; LRP4, low-density lipoprotein receptor-related protein 4.

to be the primary site of autoimmunization in EOMG (44), providing the rational for early thymectomy (35).

Clinical considerations: in contrast to thymomas und "true thymic hyperplasia" (45), TFH does not cause local symptoms. Systemic symptoms in TFH result from the underlying autoimmune diseases.

Macroscopy: thymic weight and size are normal or slightly increased for age (38). After corticosteroid treatment, strong thymic shrinkage is common.

Histology and immunohistochemistry: in corticosteroid-naïve patients thymuses show a normal-for-age cortex with terminal deoxynucleotidyl transferase (TdT) + immature T cells, while medullary areas are expanded at sites where lymphoid follicles occur (*Figure 1*). Follicles show CD21+/CD23+/CD35+ follicular dendritic cell (FDC) networks and may or may not show reactive germinal centers. The number of Hassall corpuscles is normal. Lymphoid follicles disrupt the normally continuous, epithelial network that separates the medulla from epithelial-free perivascular spaces, leading to fusion and expansion of both compartments in which mature B cells and T cells are increased (46). Prolonged TFH can induce thymic epithelial hyperplasia. Corticosteroid treatment leads to a starry sky pattern and shrinkage of the thymic cortex, and collapse of germinal centers and FDC networks. Prolonged, high dose corticosteroid and azathioprine treatment can completely abolish cortical structures and TFH (47), induce shrinkage of the medulla and may efface Hassall's corpuscles. A grading system of TFH has been proposed (41). Staining of FDC networks for CD21, CD23 or CD35 helps to detect early TFH and remnant follicles after corticosteroid treatment (41).

Differential diagnosis: lymphoid follicles adjacent to TdT+ lymphocyte-rich cortical structures can occur in MG-associated type B1 and B2 thymomas. In small biopsies, thick fibrous capsular structures or medullary islands (MIs) abutting fibrous septae may hint to a B1 thymoma, while increased numbers and clusters of epithelial cells suggest B2 thymoma (48). While 'pure' micronodular thymoma (MNT) with lymphoid stroma is usually not associated with MG, type A or AB thymomas with a micronodular component can be accompanied by MG. In small biopsies nodules of

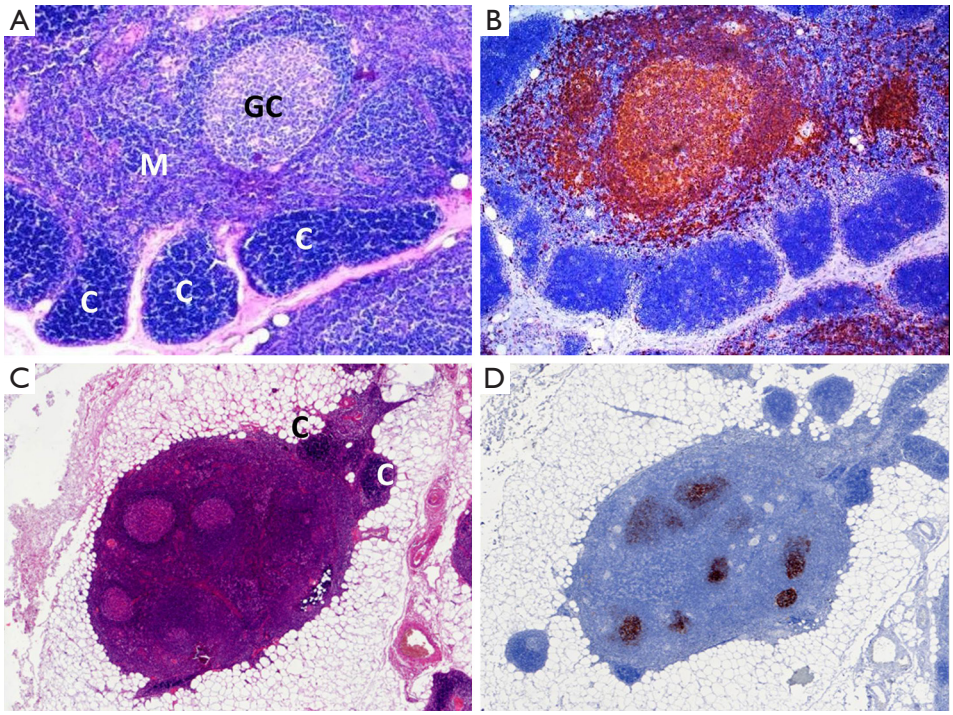

Figure 1 TFH. (A) lymphoid follicle with florid GC in an expanded thymic medulla [M] and close to fully preserved cortical areas [C] with little interstitial fat is typical of an EOMG thymus in a corticosteroid-naïve patient in her twenties or younger (HE, ×100); (B) CD20 staining of a serial section highlights the B cell-rich follicle and other medullary B cells (×100); (C) Massive TFH with more than three follicles per lobule at low-power (HE, ×50) corresponding to grade 4 TFH (34); substantial cortical atrophy and interstitial fat fit to a patient who was over 40 years of age and not corticosteroid-naïve; (D) CD23 staining of a serial section highlights follicular dendritic cell networks (brown) in even more lymphoid follicles (×50). Immunoperoxidase (B,D). TFH, Thymic follicular hyperplasia; GC, germinal center; EOMG, early onset myasthenia gravis; HE, hematoxylin and eosin.

spindle epithelial cells can hint to the correct diagnosis. Sampling of remnant thymus with TFH adjacent to an MG-associated thymoma is a pitfall in small biopsies, underlining the necessity to correlate histology with imaging findings. In many other mediastinal diseases associated with lymphoid follicles, MG is typically not present, including mediastinal cysts (if not associated with EOMG or TAMG) (49), 'pure' TCs (see above), germ cell tumors, lymphomas, and 'LESA-like' thymic hyperplasia (50), showing that information on the MG status helps interpreting small thymic biopsies.

Thymoma

Ten to 20% of MG patients have a thymoma and 30% of thymoma patients have TAMG. TAMG typically occurs after age 40 but may affect children. Thymomas are epithelial tumors that the World Health Organization (WHO) classification (51) subdivides into the malignant A, AB, B1, B2, and B3 rare other types. They usually maintain thymic functions (e.g., intratumorous thymopoiesis). Since this thymopoiesis fails to induce immunological tolerance, thymomas are often associated with autoimmune diseases, the commonest being MG (3). Here we shall cover the potentially MG-associated A, AB, B1, B2 and B3 thymomas (*Table 2*).

Type A thymoma, including the 'atypical type A thymoma' variant

Type A thymoma is a clinically indolent tumor composed of bland spindle/oval epithelial cells, with few or no admixed immature T cells. The more aggressive atypical variant can display hypercellularity, high mitotic activity and focal necrosis, of which the latter is correlated with increased invasiveness (48). For stage distribution see ref. (51). Since it is a tumor that is lymphocyte-poor or lymphocyte-free

Table 2 Epidemiological data of thymoma histological subtypes

WHO histological thymoma subtype	Mean relative frequency (%)	Age (y); range (average)	Gender (male: female)	Percentage of TAMG(+) cases: range (mean)
Type A	11.5	8–88 [64]	1:1.4	0–33 [17]
Type AB	27.5	11–89 [57]	1:1.4	6–42 [18]
Type B1	17.5	6–83 [50]	1:1.6	7–70 [44]
Type B2	26.0	4–83 [49]	1:1	24–71 [54]
Type B3	16.0	8–87 [55]	1:0.8	25–65 [50]
Others	<1.0	28–80 [60]	1:0.8	Very rare (<5%)

Epidemiological data of thymoma histological subtypes according to the WHO classification and proportion of cases with TAMG (51). Due to the revised definition of type A thymoma as a consistently immature lymphocyte-poor tumor, the diagnosis of type A thymoma is now rare (<10%) and the proportion of TAMG(+) type A cases is low (<10%), while the reverse is true for type AB thymoma that is a focally or diffusely immature lymphocyte-rich tumor. 'Pure' thymic carcinoma is likely not associated with myasthenia gravis. WHO, World Health Organization; TAMG, thymoma-associated myasthenia gravis.

throughout, type A thymoma is rarely associated with MG.

Macroscopically, type A thymoma it is usually encapsulated or well circumscribed (stage I or II). The atypical variant may be poorly circumscribed, invade adjacent organs and show metastasis (52-54).

Histologically (*Figure 2A,B,C,D*), type A thymomas show fascicular, storiform, glandular/adenoid, solid, rosette-forming, hemangiopericytoma-like and paraganglioma-like patterns. Bland spindle or oval cells with small, spindly or oval nuclei with fine chromatin and inconspicuous nucleoli, and thin-walled hemangiopericytomatous vessels are found in almost all cases. Polygonal tumor cells are an optional feature. Lymphoid cells are scarce. Mitoses, apoptotic cells and perivascular spaces are rare. Coagulation necrosis is typical of the atypical variant. Hassall corpuscles are absent.

Immunohistochemically, type A thymomas harbor no or rare TdT(+)/CD99(+)/CD1a(+) immature T cells, with TdT being the preferred marker. Any "crowded" immature T cells or moderate numbers of immature T cells in >10% of the evaluable tumor area imply a diagnosis of AB thymoma. Epithelial cells consistently stain for CK19 and p63/p40, are commonly CD20(+) (focally) but negative for CK20, CD5 and CD117. The Ki67 index is <2% in the conventional type A thymoma (55), and may be higher in the atypical variant (own observation).

Genetically, recurrent structural genetic alterations are rare (56), while a unique point mutation in the *GTF2I* gene (L404H) shows the highest prevalence (80%) among all thymomas (57).

Differential diagnoses comprise other spindle cell 'lesions': AB thymoma, focally spindling B3 thymoma, sarcomatoid carcinoma, spindle cell carcinoid; melanoma, synovial sarcoma, solitary fibrous tumor, inflammatory myofibroblastic tumor, nerve sheath tumors, mesothelioma and dendritic cell tumors.

Complete surgical removal is the only definite treatment that may be difficult in 'atypical' cases (54). Ten-year survival rates reach 80–100% (58,59) but are unknown for the atypical variant.

Type AB thymoma

AB thymomas are indolent epithelial tumors with a lymphocyte-poor (type A) und lymphocyte-rich (B-like) component in variable proportions. The B-like component must not be subtyped (e.g., as B1-like or B2-like). Stage distribution is given in ref. (51). MG occurs in 20–40% of cases, and other autoimmune diseases are also frequent (22).

Macroscopically, most cases are well circumscribed. Atypical cases that resemble 'atypical A thymoma' (e.g., with necrosis, extensive invasion, metastasis) are rare (<5%) (52).

Histologically and immunohistochemically (*Figure 2C,D,E,F*) type A areas resemble type A thymomas. The B-like areas show spindly, oval or rarely polygonal tumor cells with small nuclei and inconspicuous nucleoli, i.e., they do not look like tumor cells in B thymomas. Light staining 'MIs' can occur. Rarely, AB thymomas are immature T-cell-rich throughout, i.e., type A areas and a biphasic pattern are not obligatory for the diagnosis. Spindly and CD20(+) tumor cells are helpful to recognize such cases. In contrast to B1

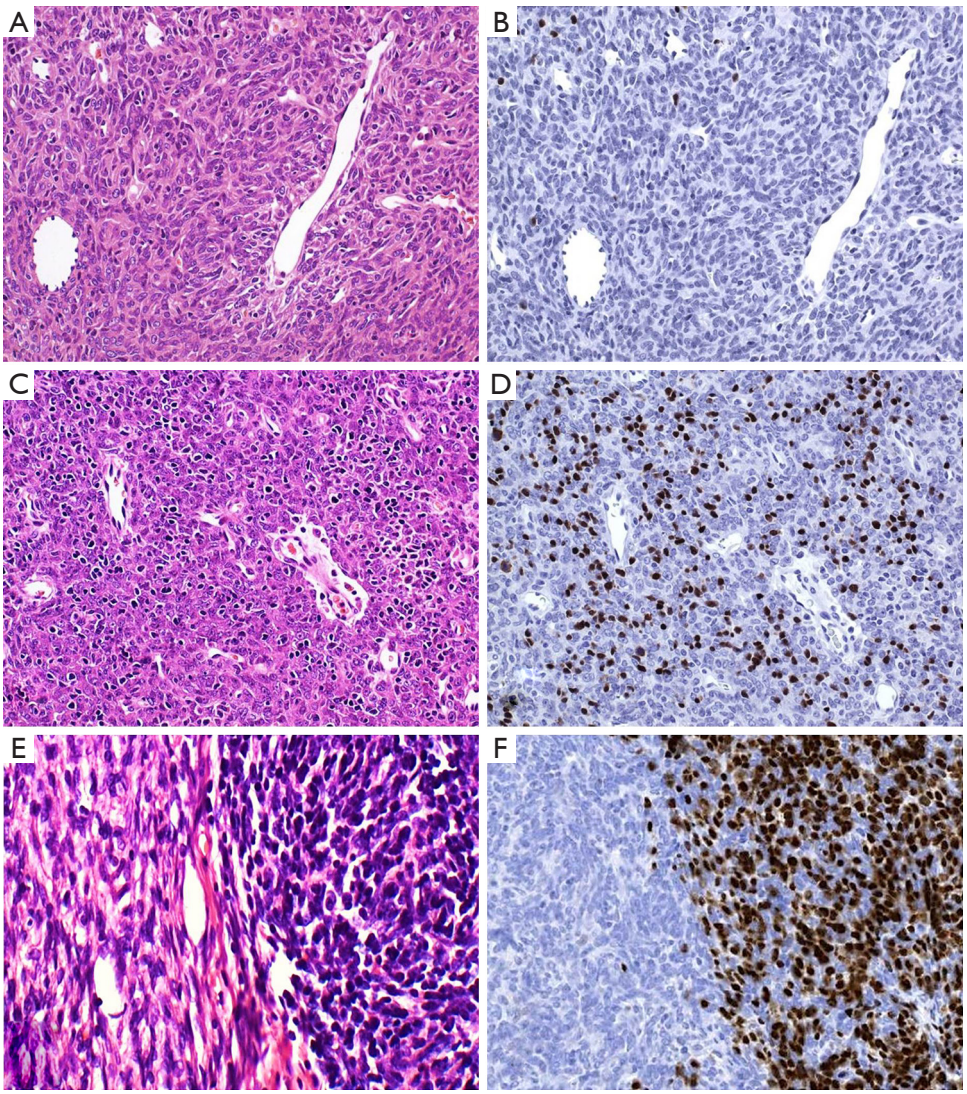

Figure 2 Prototypic and difficult to classify WHO type A and AB thymoma. (A) Prototypic spindle cell type A thymoma with very few interstitial lymphocytes and hemangiopericytoma-like vessels without perivascular spaces (HE, ×100); (B) TdT stain highlights paucity of interstitial immature T cells in a serial section (×100); (C) HE; (D) TdT. Tumor area with a "borderline" quantity of lymphocytes that immunohistochemistry (D) shows to be immature, TdT(+) T cells. Depending on whether such regions comprise more than 10% of the investigated tumor area or less, a given thymoma is classified as AB or A thymoma, respectively (×100); (E) HE stain; (F) TdT stain. Prototypic biphasic type AB thymoma with sharp separation of lymphocyte-poor (left) and lymphocyte-rich (right) areas; immunohistochemistry reveals 'crowded' immature, TdT(+) T cells (×200). Immunoperoxidase (B,D,F). WHO, World Health Organization; TdT, terminal deoxynucleotidyl transferase; HE, hematoxylin and eosin.

thymomas, AB thymomas are epithelial-rich throughout on keratin and p63/p40 stains. Focal epithelial CD20 positivity occurs in 50% of cases. Epithelial membrane antigen (EMA) positivity in septal structures is another helpful feature (60). Lymphocytes outside medullar islands are mainly immature, CD3+ TdT(+) T cells with a Ki-67 index >90%.

Genetically, structural alterations are more common than in type A thymomas (56), while the hot spot *GTF2I* mutation is similarly prevalent (74–80% of cases) (57).

Differential diagnoses comprise A, B1, B2 and MNT with lymphoid stroma. In MNTs the lymphoid component is localized outside the epithelial component. Tumors

featuring type A or AB thymoma and an MNT component are common and may be MG associated.

Complete resection is the only curative therapy and usually achieved due to the common low tumor stage. Ten-year overall survival rates are over 80% (58,59).

Type B1 thymoma

B1 thymoma resembles the normal childhood thymus with respect to abundance of immature T cells, paucity of epithelial cells, absence of epithelial cell clustering and the "organoid" concurrence of prevailing cortical areas over minor 'MIs'. Hassall corpuscles are not obligatory. As to stage distribution, see ref. (51). MG is frequent (–45%), other autoimmune diseases are rare (5%). Pure B1 thymomas usually are indolent tumors (stage I and II in >80%) (58,59).

Macroscopically most B1 thymomas are well circumscribed. The mostly firm capsule confines a soft interior. Tumor nodules are typically large and separated by delicate or coarse fibrous septae.

Histologically and immunohistochemically (*Figure 3A,B*), B1 thymomas show little or no lobulation. Dark cortical regions dominate over lighter MIs. MIs are, however, not consistently 'buried' in cortical areas like in pediatric thymuses, but are often misplaced to the periphery of tumor lobules or fibrous septae. Hassall corpuscles occur in 50% of cases and usually not in all MIs in a given case. The abundance of epithelial cells must be similar to that of the normal pediatric thymus and clustering (i.e., 3 or more contiguous tumor cells) must be absent (best appreciated in p40/p63 stains). Tumor cells show vesicular chromatin and variably prominent nucleoli. Immunohistochemical stains show a delicate cytokeratin positive epithelial network that is attenuated in MIs. While CD3(+)TdT(+) T cells dominate in cortical regions, CD3+/TdT(–) T cells prevail over CD20(+) B cells in MIs. Desmin(+) myoid cells and autoimmune regulator [AIRE(+)] epithelial cells occur in (some) MIs in 50% of cases.

Genetically, chromosomal gains and losses are less frequent than in the more aggressive B2 and B3 thymomas (56). The *GTF2I* mutation occurs in 32% of cases (57).

Differential diagnoses comprise normal thymus, rebound hyperplasia, true thymic hyperplasia, and T-lymphoblastic lymphoma (T-LBL), all of with are not associated with MG. In small biopsies distinction between normal thymus, TFH and B1 thymoma (with lymphoid follicles) may be impossible. Excess of cortical over medullary areas, misplaced MIs and deficient Hassall corpuscles favor a diagnosis of B1 thymoma. B-like areas of AB thymomas are distinguished by spindle cells and numerous keratin(+) epithelial cells that are CD20(+) in 50% of cases. B2 thymomas show increased numbers or clusters of tumor cells.

Over 90% of B1 thymomas are cured by resection; 10-year and 20-year survival is 85–100% (58,59).

Type B2 thymoma

B2 thymomas are TdT(+) T cell-rich, aggressive tumors with increased numbers of polygonal and dendritic tumor cells compared to B1 thymomas. Spindle tumor cells are absent.

As to stage distribution, see ref. (51). Occurrence in children is rare (61). MG occurs in up to 50% of cases (59), pure red cell aplasia and hypogammaglobulinemia are infrequent (5%). Pleural effusions and the superior vena cava syndrome are commoner than in A, AB and B1 thymomas.

Macroscopically B2 thymomas often infiltrate mediastinal fat, pleura, lung, heart or large vessels. The cut surface is grey-white and firm and may show poor septation, necrosis, haemorrhage and cysts.

Histologically and immunohistochemically (*Figure 3C,D*), fibrous septae mostly delineate small tumor lobules. Dominant, TdT+ T cells impart a blue impression. Tumor cell nuclei have vesicular chromatin und prominent nucleoli. Perivascular spaces and MIs with or without Hassall corpuscles may occur. Intratumorous lymphoid follicles are common in MG(+) cases. Keratin/p40(+) tumor cells are more numerous than in B1 thymoma and may occur in clusters (3 or more contiguous epithelial cells). Minor B3 or B1 thymoma component occur in 40% of B2 thymomas.

Genetically, the number of alterations in B2 thymomas is intermediate between AB and B3 thymomas (56). 22% of B2 thymomas show the hotspot *GTF2I* mutation (57).

Differential diagnoses comprise B1 thymomas and T-LBL (see above). Rarely, B2 thymomas show a loss of keratin expression (62). Since expression of p40 is mostly maintained in such cases, a p40 stain is recommended if the differential diagnosis between B2 thymoma and T-LBL is difficult.

Complete resection is achieved in 70–90% of cases and 10-year recurrence rates reach 32% and 41% in R0 resected stage II and III B2 thymomas, respectively. Overall, 10-year

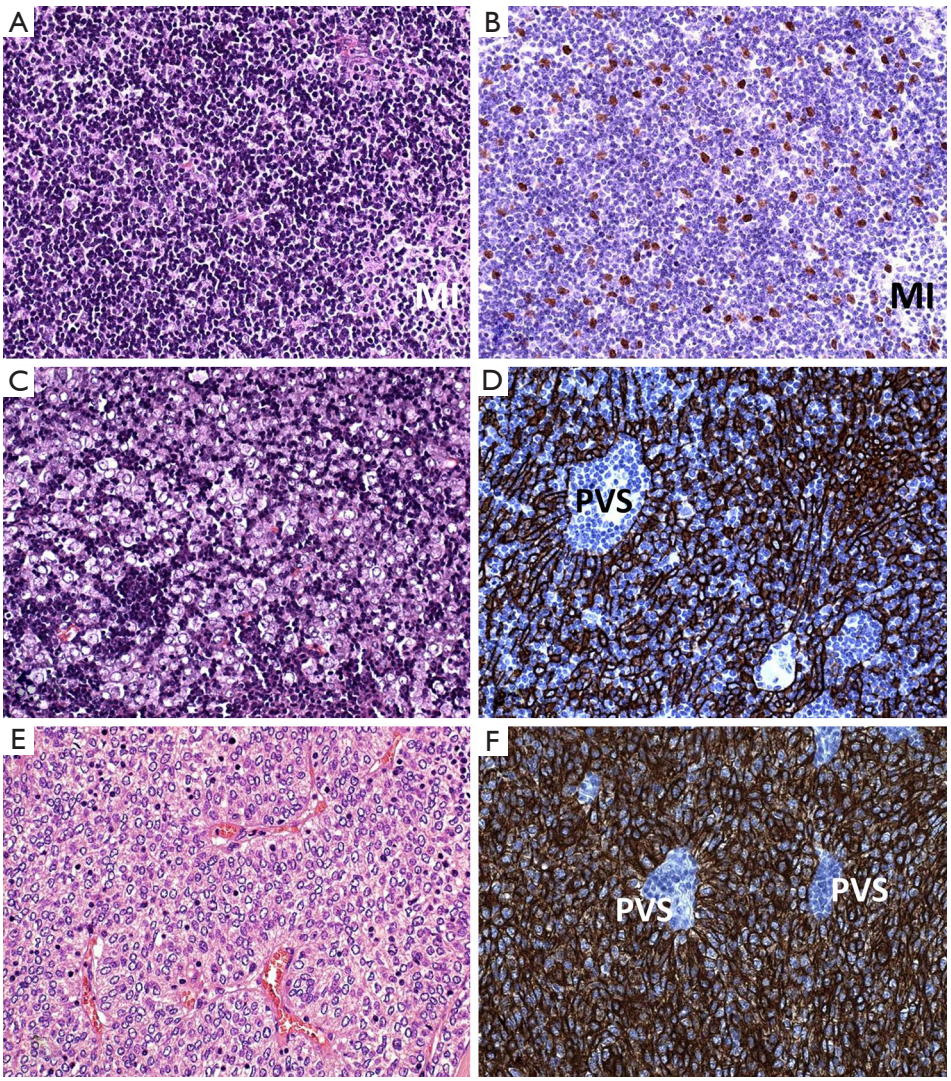

Figure 3 Prototypic WHO type B thymomas. (A) Classical B1 thymoma with obligatory predominance of dark cortical areas, a minor but distinct, lighter medullary island (MI) and barely visible neoplastic epithelial cells (HE, ×100); (B) The sparse and dispersed, non-clustering tumor cell nuclei in a serial section are best recognized in a p40 stain; (C) HE; (D) keratin 19. B2 thymoma with obvious clustering of pale polygonal tumor cells against a lymphocyte-rich background that imparts a blue impression to the HE stained section. Higher-than-normal density of keratin 19(+) network outside typical PVS; (E) HE; (F) keratin 19. B3 thymoma with obligatory dominant number of polygonal, keratin(+) tumor cells that form sheets and impart a pink impression to the HE stained section; PVS and rare but distinct interstitial lymphocytes [TdT(+), not shown], are typical but not obligatory. Immunoperoxidase (B,D,F). WHO, World Health Organization; TdT, terminal deoxynucleotidyl transferase; HE, hematoxylin and eosin; PVS, perivascular spaces.

survival rates are 70–90% (58,59,63).

Type B3 thymoma

B3 thymomas are epithelial-predominant tumors that show at most a few or no immature, TdT(+) T cells. Tumor cells have largely lost cortical and medullary features (64).

For stage distribution see ref. (51). Occurrence in children is rare (61). MG occurs in 40–50% of cases, other autoimmune diseases are rare. Local symptoms are commoner than in other thymomas.

Macroscopically, B3 thymomas often infiltrate into

mediastinal fat and adjacent organs. On the firm or hard, grey/white cut surface, hemorrhage, necrosis and cysts are common.

Histologically and immunohistochemically (*Figure 3E,F*), tumor lobules are composed of sheets of polygonal tumor cells that impart a pink impression. At the invasion front, lobules are mostly sharply delineated without single cell infiltration that is more common in TC. Tumor cell nuclei are either bland (with inconspicuous nucleoli) or moderately atypical with prominent nucleoli. Among the tumor cells there are usually a few or rarely no lymphocytes that may or may not be TdT(+). Perivascular spaces are often conspicuous. Hassall corpuscles, focal spindle cells and clear cells can occur. There is diffuse and dense expression of keratins and p40/p63; only focal expression of GLUT1 (65) and EMA and no CD20 expression. Focal expression of CD5 and CD117 is rare.

Genetically, B3 thymomas show the highest prevalence of genetic alterations among thymomas (56), while the *GTF2I* hotspot mutations is as common (21%) as in B2 thymomas (57).

Differential diagnoses: The distinction of B2 thymomas relies on the pink expression of B3 (*Figure 3E*) versus blue expression of B2 cases (*Figure 3C*) in HE sections. B3 thymomas with focal spindling and type A thymomas may be impossible to distinguish in small biopsies, if areas with typical features are not sampled (CD20 expression, glandular structures, prominent perivascular spaces). Thymic squamous cell carcinomas (TSQCC) may be difficult to delineate as well, since they can rarely show perivascular spaces and sharply contours at the invasion front. In the presence of MG, a diagnosis of TSQCC should be made with caution and complemented by a search for a thymoma component. Prominent intercellular bridges, expression of CD5 and CD117 (in 80% of TSQCCs), diffuse positivity for GLUT1, and absence of TdT+ T cells suggest a diagnosis of TSQCC (51). Neuroendocrine and germ cell tumors, sarcomas, mesothelioma, and parathyroid adenoma can potentially be misinterpreted as B3 thymoma or TC.

Therapy is like in B2 thymomas. Thirty percent of B3 thymomas recur within 10 years (58). 10-year overall survival rates are 50-70% (59,63). Prognosis of MG(+) cases may be better due to earlier detection (66).

Thymic atrophy

Thymic atrophy has for long been described as the typical 'pathology' associated with LOMG, i.e., the non-thymomatous AChR-MG in the elderly [reviewed in ref. (3)]. The lympho-epithelial tissue of the aging thymus is gradually replaced with fat, the cortico-medullary architecture gets distorted (with medullary structures bordering on adipose tissue) (*Figure 4A,B*), but residual parenchyma continues to export some T-cells at least into middle age (29,67). In LOMG, morphometric analysis of these remnants did not show significant differences between LOMG and normal thymuses (38). Thymic myoid cells are sparse in LOMG (68), decline with age and become barely detectable been 60 and 70 years of age, with considerable variation between patients (69). The number of AIRE positive cells is also declining (own observation), however, again with no clear difference between LOMG and age-matched control thymuses, suggesting that "atrophy" in the LOMG setting may better be labeled as (physiological) "involution". Nevertheless, there are currently non-histological features of LOMG patients that strongly hint to an involvement of the thymuses in the pathogenesis of LOMG. These features comprise (I) the unique immunological overlap in terms of anti-striational muscle (mostly anti-titin) and anti-cytokine autoantibodies between TAMG (in which an involvement of the neoplastic thymic tissue is certain) and LOMG (23,24); and (II) the observation that the thymus in LOMG patients appears to export significantly less naïve T cells than age-matched controls (29). Understanding these functional peculiaritis of LOMG thymuses might reveal tissue markers that might allow recognition of thymic abnormalities at the immunohistochemical level in the future.

Recently, thymic atrophy has also been mentioned as "pathology" in the context of at least subsets of patients with either MuSK-MG (34,46) or LRP4-MG (13,16). As is the case with LOMG, thymectomy has not generally been beneficial in MuSK-MG (70) and LRP4-MG (2), with few exceptions (71). These observations parallel largely unchanged histology findings in MuSK-MG thymectomy specimens (34,46), while analogous standardized morphological studies in LRP4-MG thymuses are still awaited, as are functional studies (e.g., in terms of thymic T cell export) in MuSK-MG and LRP4-MG patients.

Thymolipoma

Thymolipoma is rare among thymic tumors, accounting for 2–9% of all cases, occurring at any age and without clear gender bias (25). Histologically (*Figure 4C,D*), the

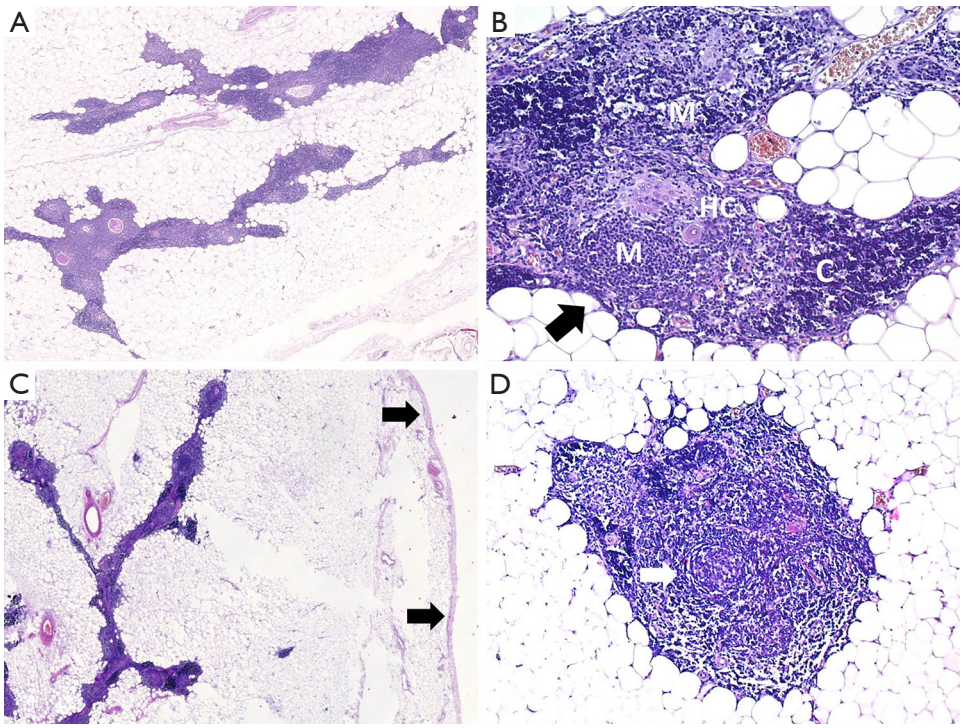

Figure 4 'Thymic atrophy' and thymolipoma. (A) Normal-for-age 'atrophic' thymus of a 56 year-old patient with MG without TFH; light blue medullary areas dominate over dark blue cortical areas (×25); (B) typical ('physiological') age-related architectural alteration with retraction of cortical areas [C], making medullary thymic regions [M] border directly on adipocytes (arrow); small HC (×100); (C) Thymolipoma commonly mimics 'thymic atrophy' at the microscopic level; a thickened fibrous capsule (arrow) can hint to the diagnosis; nevertheless, correlation with the 'lipoma-like' macroscopic aspect is indispensable to arrive at a correct diagnosis (×25); (D) a rare lymphoid follicle (arrow) hints to mild TFH in this thymolipoma (×100) (A,B,C,D,E: HE). MG, myasthenia gravis; TFH, thymic follicular hyperplasia; HC, Hassall's corpuscle; HE, hematoxylin and eosin.

tumors consist of a minor component of thymic tissue that is embedded in a dominant component of mature adipose tissue confined by a fibrous, epithelial-free capsule. The thymic component is often atrophic but may rarely show follicular hyperplasia and exceptionally neoplastic transformation (thymoma or carcinoid) (51,72).

Thymolipoma has repeatedly been found associated with MG while mediastinal/thymic lipoma has not, suggesting that there might be a pathogenetic (i.e., non-fortuitous) link between the thymic component and "thymolipoma-associated MG" (TLAMG) (25,73-75). On the other hand, the reported percentages of MG patients among those who suffer from thymolipoma vary widely (2–50%) in rare reports (73,75,76), making risk prediction a matter of speculation. TLAMG is apparently the commonest autoimmune disease associated with thymolipoma, while hypogammaglobulinemia (good syndrome) (77), erythropoietic hypoplasia (78), aplastic anemia, polymyositis (79) and Graves' disease have been reported less commonly (73). The latter rare autoimmune diseases in TLAMG patients suggest a similarity between TLAMG and TAMG, but there are no immunological data (e.g., in terms of anti-titin or anti-cytokine autoantibodies) to underpin this hypothesis. Finally, no consistent histological alteration (e.g., follicular hyperplasia or atrophy) has been reported in thymolipomas accompanied by TLAMG (80).

Concurrences of MG with other cancers

Extrathymic epithelial, mesenchymal and hematological cancers have rarely been reported in connection with MG, likely reflecting a fortuitous coincidence or the result of unspecific immune perturbation (81,82). However, in a rare MG-associated rhabdomyosarcoma (RMS) an autoimmunizing 'accident' against AChRs might have occurred (83). The reason for the 'accident' in this unique

RMS remained enigmatic, and cannot be explained by expression of the AChR, because almost all RMS express functional AChRs (84). MG-associated non-thymic cancers may deserve more attention as exemplified by rare AChR-MG-associated FDC sarcomas that occurred in the mediastinum (85) and mesentery (86). Both cases were the first non-thymic epithelial tumors described to exhibited "thymoma-like" intratumorous thymopoiesis, suggesting that this feature contributed to paraneoplastic MG.

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