Editorial

A curious rarity of the thymus gland: the microscopic thymoma

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In 1976, Rosai & Levine (1) opened a novel and interesting niche in the variegated field of the morphology of thymus gland in myasthenia gravis (MG). These authors firstly described a microscopic lesion having the histological features of a thymoma, occasionally observed in thymus gland removed during cardiac operations. They introduced the term "microscopic thymoma" to define these lesions histologically characterized by epithelial proliferation, smaller than 1mm in diameter, usually multifocal, sited in the cortex or medulla, in absence of a macroscopically evident thymic tumor (1-4). These lesions are observed in patients suffering from MG (5), an autoimmune disease that often shows several thymic abnormalities such as lymphoid follicular hyperplasia (15–85%) resulting from an abnormal activation of thymic B lymphocytes, or thymoma (10–25%), which originates from epithelial cells abnormally activated (6). Both features may coexist (7). In the remaining myasthenic patients the thymus appears involuted or normal.

Interestingly, according the 2004 WHO histological classification of the thymic epithelial tumor, these lesions are classified as A type thymoma. Indeed, hitherto 14 out of 18 cases already described belongs to type A thymoma (8), the remaining 4 reported by Vaideeswar *et al.* are not specified (3). This relationship is surprising because the A type tumor is not frequently associated with MG (9). The role of MG in the pathogenesis of the microscopic thymoma is not yet unveiled, particularly in the absence of lymphoid hyperplasia. Similarly, the pathogenesis and functional significance of microscopic thymoma of the thymic epithelium remains unclear. The rarity of the lesion does not favor the deepening of this essential issue.

Clinically, there are not evident symptoms referable to the lesion, whereas myasthenic signs and symptoms dominate the clinical scenario. Similarly, the imaging studies performed during the workup of the myasthenic disease did not allow the discovery of the lesions or thymic abnormalities.

The lack of morphological features of classic thymoma such as a lobulation and perivascular spaces as well as medullar differentiation and immature T-cells and the absence of data regarding the role in the development of the classic thymoma has suggested to define the microscopic thymoma as a nodular hyperplasia of the epithelium of the thymus (10,11). Hence, in the literature some author prefer to use the term of thymic nodular epithelial hyperplasia (3,12,13), but the latter would be a different pathologic entity according to Cheuk *et al.* (14).

The first clinical cases of microscopic thymoma were reported in 1992 by Pescarmona *et al.* 15 years after the first description, evidencing of the rarity of the pathology (15). These authors found multifocal microscopic thymomas in thymus of patients thymectomized for MG. The incidence of microscopic thymoma in autopsy specimens among myasthenic patients ranged between 4% and 15% in absence of clinical symptoms (15,16).

Fukuhara *et al.* (9) should be congratulated for their review focused on this niche of thymus morphology in myasthenic patients. We acknowledge the authors for having listed all cases reported in the literature since the very first description by Rosai and Levine (1). They have accurately collected the data from 18 patients outlining the

Table 1 Demographic and clinical details of the study group

N.	Age (years)	Sex	MG class	AchRAb preop (nmol/L)	AchRAb postop (nmol/L)	Approach	Computed tomography images	WHO histology	Focality	Follow up postop (years)	Outcome	Remission time (years)
1	16	Female	III	67	12	Sternal	Normal	A	Multi	30	Remission	11
2	33	Female	II	34	21	Sternal	Normal	A	Multi	21	Remission	6
3	26	Male	III	27	11	Sternal	Hyperplasia	A	Multi	17	Remission	4
4	54	Male	III	61	28	VATS	Hyperplasia	A	Multi	10	Remission	3
5	35	Female	II	47	13	VATS	Normal	A	Multi	7	Improvement	–
6	61	Male	II	21	9	Redo VATS	Residual	A	Mono	4	Improvement	–

AchRAb, acetylcholine receptor antibodies; WHO, World Health Organization classification of thymic tumors.

clinical and morphological features described in each paper retrievable in the literature (9).

An evident homogeneity emerges within the analyzed cases. First of all, they result very infrequent. Apart from the 5 cases described by the authors themselves only another 13 were observed during a very long interval since the first three described by Pescarmona *et al.* in 1992 (15). All patients were myasthenic and they were all thymectomized. Nobody presented radiological signs at computed tomography. In the reported cases, a long lasting clinical improvement after thymectomy were observed (2,12,13,15). Most of them presented multifocal lesions (15,16) whilst solitary lesions may be considered sporadic.

Furthermore, respect to the other authors, Fukuhara *et al.* signaled the significant postoperative decrement of circulating anti-acetylcholine receptor antibodies thus demonstrating the advantages of extended thymectomy in reducing the antibodies (9).

Between 1986 and 2015 we performed more than 300 extended thymectomies through transsternal or video-assisted thoracoscopic (VATS) approaches for nonthymomatous MG. After having reviewed our series we found microscopic thymomas in 6 instances only and the features of these patients do not differ from those already described in literature as shown in *Table 1*.

We incidentally discovered our first patient in occasion of a histological re-analysis performed for other reasons in 1996 within our own archival specimens of resected thymus for nonthymomatous MG. She was 16-year-old girl who in 1987 underwent a transsternal extended thymectomy for a IIB Osserman MG retrospectively judged as class III disease. The patient had an uneventful postoperative course and gradually achieved complete medication-free stable remission within 11 years from the procedure. She is still well without radiological evidence of the onset of a new thymoma at periodical controls.

Our sixth—at the moment last—case was detected in 2013 in a 61-year-old man class II myasthenic patient already operated 3 years before through a right-sided extended VATS thymectomy. This patient was reoperated through contralateral VATS given the persistence of the disease and the computed tomography image evidence of fat tissue residual in the aorto-pulmonary window. The histological examination revealed ectopic thymic tissue in the aorto-pulmonary mediastinal fat as well as a monofocal microscopic thymoma. After this second operation myasthenic symptoms had a progressive and significant improvement.

Finally, we would like also mention an adjunctive and more recent case of monofocal microscopic thymoma found in the neighboring tissue of a thymic cyst removed through VATS. In this case the patient had neither clinical symptoms nor electrophysiological sign and not even serological evidences of MG. Thus we did not include this case among of those listed in present publication.

According to our results we elaborated some hypothesis about the genesis of these tumors. Given the simultaneous occurrence of the lesions in both medullary and cortical compartments we agree with Pescarmona *et al.* who hypothesize a multifocal origin of microscopic thymoma from different epithelial clones hosted in different areas of the thymus (15). However, we also found these tumors freely growing in the mediastinal fat as a probable neoplastic evolution of ectopic thymic tissue.

Due to the rarity of the lesion it is difficult to predict the evolution of a microscopic thymoma. However, only

the extensive removal of all perithymic fat tissue allows the detection and the elimination of all microscopic thymomas incidentally present. Furthermore these patients deserve a stricter regimen of follow up with yearly computed tomography in order to discover other lesions or thymic residual.

Extended thymectomy is has been already evoked to maximize the effect of thymectomy because of the elevate incidence of ectopic thymic tissue within the mediastinal fat (17-21). In our experience we observed an incidence of 80% (17,18) especially in pericardio-phrenic angle bilaterally, in aorto-caval groove and aorto-pulmonary window. The presence of multifocal microscopic thymoma is an additional reason to re-affirm that all thymic tissue, pericardial fat should be completely removed and many histological sections should be carefully examined.

The relationship between microscopic thymoma and MG are probable but obscure. Indeed, microscopic thymomas are discovered in thymuses resected in patients suffering with MG, but the genesis of MG, as well as clinical evolution and prognosis appear independent from the microscopic thymoma itself.

The benefit of thymectomy in myasthenic patients was highlighted by Blalock approximately 80 years ago (22). This author removed a cystic tumor of the thymus gland in a young woman who thereafter experienced the remission of the myasthenic symptoms (23). Recently, the randomized trial of thymectomy in MG (2) demonstrated that extended thymectomy improves clinical outcomes in non thymomatous MG. Although sternotomy allows the extended or maximal thymectomy both in non-thymomatous MG and thymomas, the persisting pain, the serious complications and the non cosmetic sequelae made this approach progressively less used. Thus, over the years, less invasive approaches have increasingly gained the preference of surgeons, patients and physicians. Less postoperative pain, reduced surgical trauma, better cosmesis and subsequent better postoperative quality of life had enhanced the use of minimally invasive approach. More recently, a subxiphoid single port thymectomy has been used to accomplish thymectomy (24). It is associated with lesser pain because there is no intercostal nerve damage and it permits an excellent cosmetic outcome (25) since only a single 3 cm abdominal skin incision is done.

Conclusions

Similarly to others, we conclude that the discovery of a microscopic thymoma may derive from an attentive microscopical and histological study of the areas including the thymic proliferation. The rarity of the lesion hinders both the morphological and clinical speculations. Further knowledge will probably occur during the coming years with the progressive accrual of new cases. According to this attainment a careful examination of all macroscopic non-neoplastic thymus resected as well as the analysis of the whole perithymic fat tissue in myasthenic patients becomes absolutely mandatory. Obviously, in order to facilitate the detection is necessary to perform many paraffin-embedded blocks of the surgically resected specimen.

To date, there is a certain data: microscopic thymoma is a rare, asymptomatic and occasionally discovered lesion that by the way necessitates of a better knowledge. On these bases the extended thymectomy becomes of pivotal importance.

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