THYMOMA AND THYMIC GERMINAL CENTER

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The autoimmune diseases, for example myasthenia gravis and others, have been postulated as a significant complication of thymoma. The presence of "autoimmune thymitis," on the other hand, with the formation of lymph follicle or germinal center in the thymus has also been pointed out to be characteristic of autoimmune disorders.

A previous study of 70 cases of thymoma described in 1966 by the author reported that definite germinal centers were found in the normal thymic tissue attached to one case of thymoma associated with myasthenia gravis, and that this was very interesting from the point of view of whether thymoma or thymic germinal center was a more important occurrence of a myasthenic condition. Since then routine histopathological examinations have been directed not only on thymic neoplasms but also on thymic tissues attached to them, so that the relationship between thymomas and thymic germinal centers could be presented on the basis of ten collected cases with this view in mind.

MATERIAL, FINDING AND COMMENT

Ten cases, as listed in Table 1, in which the thymic tissues attached to thymomas were investigated were selected from 91 cases of thymoma, which consisted of 70 previously reported cases and an additional 21 cases, autopsied, resected and submitted. Because few germinal center have been generally accepted as being seen in thymomas themselves, the particular case in which a germinal center was distinctly demonstrated within the thymoma tissue was added as Case No. 11. Case No. 1 in this report was described as Case No. 57 in a previous report. One case, in which the thymic biopsy was performed five months prior to death revealed the histological finding of a marked involution without a germinal center. A small thymoma, 2.2 cm in diameter, mixed type in histology, was
accidentally found at autopsy associated clinically and pathologically with myasthenia gravis. This case was added as Case No. 10 although both thymoma and thymic tissue were histologically examined at a different time.

Several pieces of tumor and the attached thymic tissue were taken for histological observation utilizing various staining procedures such as hematoxylin-eosin, Mallory's trichrome stain, PAS reaction and Gomori's reticulum fiber staining after the routine gross examination.

The gross appearance of thymoma (49.9 gr., 7×4.5×3 cm) and the attached bilateral thymic tissues (r: 4.5×0.5×0.5 cm, l: 7×1.5×0.5 cm), which had been carefully resected by a surgical procedure, is shown as a representative case in Photo 1 (Case No. 2). Histological observations of this case revealed a typical pattern of a mixed type of thymoma and numerous germinal centers in the attached thymus as shown in Photo 2.

Germinal centers which are demonstrated variably in size and number in the attached thymic tissue are found in 7 of the 10 cases and are noted almost exclusively in the expanded medullary area of the thymomas as shown in Photo 3. The detailed structure of the germinal center is recognized to be similar to that observed pathologically in the thymus as described by Tamaoki and the author.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>No. of material</th>
<th>Age</th>
<th>Sex</th>
<th>Type of thymoma</th>
<th>M. G.</th>
<th>Attached thymus</th>
<th>G. C.</th>
<th>Note</th>
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M. G.: Myasthenia gravis
G. C.: Germinal center
Type of thymoma (M: mixed type, E: epithelial type, L: lymphocytic type)
* Previously reported
** Associated with Hashimoto's disease
*** Germinal center within thymoma tissue
There are plasmacytic infiltrations in the surrounding region of the germinal centers. Age, sex, histological classification of thymoma, complication of myasthenia gravis, presence of the attached thymic tissue and germinal center within the tissue in the 10 cases studied are briefly summarized in Table 1.

It is a well known fact that thymomas are frequently associated with myasthenia gravis. The frequency of myasthenia gravis complicated with thymomas is variable according to different authors and such a discrepancy supposedly results from the source of the data. In the previous study of 70 cases there were 11 cases of thymomas associated with myasthenia gravis including a few doubtful ones. Eight cases of thymomas in the present study are evidently associated with clinical conditions of myasthenia gravis and are histologically classified as follows; mixed type with the various proportions of both epithelial cells and lymphocytes in 6, epithelial type in 1 and lymphocytic type in the final case. There was no distinct difference with histological pattern in the previous report between thymomas with and without myasthenia gravis, though the pattern of thymomas associated with myasthenia gravis was observed to be mostly of the mixed type.

Germinal centers which are usually numerous and large in size with a few exception are found in 5 cases in the thymic tissues of these eight cases of thymomas associated with myasthenia gravis. In Case No. 4 a few germinal center are noticed among all of the slides taken from the examined thymic tissue. Thymic germinal centers are recognized in the thymus of various diseases as reported by Okabe (1966), Tamaoki (1968) and others. However the thymic germinal center is found more frequently in diseases acceptably included in so-called autoimmune diseases than in other disorders. It will be described elsewhere by Habu and Tamaoki that the incidence, number, size and the relationship with the clinical condition of the germinal centers in the biopsied thymic tissues of myasthenia gravis are significantly different from those of other diseases. Germinal centers are also found in the thymuses attached to 2 thymomas, that is Case No. 6 and 9, associated with no myasthenic signs. A mediastinal tumor, with multiple cystic spaces in the cut surface, in Case No. 6 is histologically diagnosed as a lymphocytic type of thymoma. The associated diffuse struma with normal function of thyroid shows the characteristic microscopical findings, compatible with the histological pattern of Hashimoto’s disease. They are composed of oxyphilic changes of follicular epithelium and lymphocytic and plasmacytic infiltration frequently with germinal center formation in intralobular or interlobular tissue as shown in Photo 4. The thymic tissue attached to the thymoma in this case, numerous germinal centers are evidently observed with plasma cell infiltration. The autoimmune mechanism though not of myasthenia...
gravis, but of Hashimoto's disease might be considered to be responsible for the formation of thymic germinal centers in this case, because they have been noticed in Hashimoto's disease by Gunn and Michie (1965), and Tamaoki and the author (1967). One case of thymoma associated with a thyroid lesion compatible with Hashimoto's disease was described by the author in a previous report. However the attached thymic tissue was not microscopically investigated in that case. Another case in which numerous germinal centers are found in a thymic tissue resected with a thymoma not associated with myasthenia gravis is Case No. 9. This case is also suggestive of a complication of the autoimmune mechanism, but a record concerning this has not yet been placed in a clinical data report.

An encapsulated firm tumor mass with an uneven surface, measuring 7.5 × 8 × 3 cm, located in the anterior mediastinum, protruding into the right pleural cavity, was removed without the attached thymic tissue in Case No. 11 associated with no myasthenic symptoms. The tumor was histologically diagnosed as a typical mixed type of thymoma. One particular nodular lesion, resembling a germinal center structure, composed of an outer layer of small-sized lymphocytic accumulations and a central area of larger irregularly-shaped cells was accidentally observed within the thymoma tissue as shown in Photo 5. The nodular lesion was interpreted microscopically as a similar structure to germinal centers noticed in general lymphoid tissue and also in thymic tissue attached to the thymoma mentioned above. The germinal center was indicated to be formed actually in perilobular connective tissue of thymoma parenchyma, because a lesion with the surrounding network of postcapillary venules was distinctly demonstrated, as in Photo 6 by the reticulum fiber staining, out of the border of the basement membrane of the epithelial cell sheet. The area is easily recognized as connecting directly with the perivascular spaces which were postulated to be one of the characteristic findings of thymoma in a previous report. According to Castleman's or Lattes' collections of thymomas, the formation of lymph follicle or germinal center has been hardly noticed within the neoplastic tissue. However the case in the present study represents the possibility that the germinal center in the stroma area related to the perivascular spaces within the thymoma tissue might be formed by the same mechanism as that of the thymic germinal center observed in the thymus attached to the thymoma.

The experience that thymic germinal centers were also noticed in the thymic tissue attached to a mediastinal teratoma other than thymoma was previously reported by the author in 1967. The structural distortion of the whole thymic tissue due to the neoplastic growth within it was supposed to be respon-
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sible for the reactive mode of lymph follicle formation with a germinal center in that report.

However thymic germinal centers in the present study are so frequently observed in thymuses attached to thymomas, that the histological examination of both thymic neoplasms and the attached tissue might be required as routine; also that both thymomas and thymic germinal centers interpreted as the most noticeable changes of "autoimmune thymitis" are reasonable included under the concept of thymic abnormalities.

Although it has been generally known that there is a significant relationship between autoimmune diseases and thymic germinal centers as interpreted in this study, it may be an important question as to whether they are histologically manifested resulting from disturbances due to autoimmunity or represented by the existence of an autoimmune process itself. The unique hypothesis proposed by Kobayashi9 on the relationship between thymoma and pure red cell anemia in 1970 could be speculated as an explanation for the close relationship between thymic abnormalities and myasthenia gravis in the present study. Namely that immunoproliferative process within the concept of immunoproliferative disorders as summarized by Dameshek10 may be a common causal agent to both thymomas and pure red cell anemia; since the neoplastic growth can be interpreted as a morphological manifestation and the autoimmune disorders as an immunological representation of the same process.

SUMMARY

1. Ten cases in which the attached thymic tissues were histologically investigated from 91 cases of thymomas were reviewed with brief description of the gross appearance, histological findings and clinical complications.

2. Thymic germinal centers were found in 7 cases of which 5 cases were associated with myasthenia gravis.

3. One case of thymoma with the presence of a germinal center in the neoplastic stroma was added.

4. The significant relationship between thymomas and thymic germinal centers is postulated with a discussion of the relationship of thymic abnormalities and autoimmune diseases.
REFERENCES


EXPLANATION OF PLATES

Photo 1. Case 2. Gross appearance of thymoma and bilateral attached thymic lobes.
Photo 2. Case 2. Thymoma (TO), mixed type, and germinal centers (G) in the attached thymus (TH). H: Hassall's corpuscle.
Photo 5. Case 11. A germinal center (G) within thymoma tissue (TO), mixed type.
Photo 6. Case 11. Basement membrane between thymoma parenchyma (TO) and germinal center (G). Silver-impregnation.