A THYMOMA (ADENOMA OF THE THYMUS) FROM AN UNUSUAL CASE OF MYASTHENIA GRAVIS, WITH OBSERVATIONS ON THE GENERAL PATHOLOGY

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In 1936 I presented a report of four cases of myasthenia gravis, in two of which gross thymic lesions were found. At that time in a review of the literature only 80 cases of myasthenia gravis which had come to autopsy were found, and among these were 35 in which a lesion of the thymus constituted a prominent anatomic feature. It appears that progress toward a more exact understanding of myasthenia gravis has been largely hindered because of the small number of cases that have been studied by the pathologist. The importance of having recorded all cases of myasthenia gravis with definite pathologic findings I have previously emphasized.

During the past year another case, which will be described here, came to my attention. Moreover, there was found a case reported by Lównenthal which had escaped notice and failed of inclusion in the tabulation in the earlier study; this case also is briefly summarized below. The addition of these 2 cases to those previously tabulated increases the total to 37 instances of thymic lesions in reported autopsied cases of myasthenia gravis.

**CASE OF LÖWENTHAL, 1932:** The patient was a sixty-three-year-old woman with severe muscular changes. At autopsy the thymus weighed 26 grams and measured $8 \times 4.5 \times 1.25$ cm. Microscopically it had a lobulated structure but showed no differentiation of cortical and medullary zones. In some areas, however, a greater proportion of lymphocytes were present. Numerous Hassall's corpuscles in various stages of development were found, and the author describes the development of pseudocysts from these.

**AUTHOR'S CASE:** On Feb. 15, 1933, the patient whose case forms the basis of this report came under the observation of the staff of the University Hospitals of the University of Minnesota. The following is an abstract taken from the hospital records.

**First Hospital Admission (2/15/33–3/27/33):** The patient was a male farmer, fifty-two years of age. Apparently the first symptom of his long illness was a severe headache on the evening of Sept. 29, 1932, which lasted for six hours. On Oct. 4, 1932, the patient noticed epiphora from the left eye and on Oct. 7 a ptosis of the left eyelid appeared; the ptosis persisted but the epiphora soon disappeared. At about this same time the patient noticed weakness in abducting the right arm at the shoulder and this disability rapidly increased in severity. During October he experienced a numbness on the lateral sides of the right little and ring fingers; in fact the whole right hand seemed slightly numb to the wrist. After November 1932 he found that he tired quickly when walking and there was a sensation of weakness in the lower extremities, but no loss of movement. In February some indefinite lower abdominal discomfort was noticed and on two occasions there was fecal incontinence.

In the earlier history nothing of importance was noted except that the right shoulder blade had been fractured in 1913, when an 85-pound weight fell on the patient's back.

The patient was well developed and well nourished. There was ptosis of the left eyelid, some inability to move the left eye nasally, slight horizontal nystagmus in the direction of the gaze, and no exophthalmos or strabismus. The pupils were equal and regular.

1 Read before the American Association for Cancer Research, Chicago, Ill., March 24, 1937.
and reacted to light and accommodation. There was deformity of the right shoulder with atrophy of the muscles about both shoulder girdles. Both deltoid muscles, both biceps, and the right triceps showed the greatest degree of atrophy. The patient was unable to abduct the right arm from his side, or to raise the left arm to a horizontal position. Biceps and triceps reflexes were hyperactive; Babinski negative. The heart was not enlarged; pulse 76; blood pressure 120/78. The abdominal and rectal examinations were negative. There was no deformity of the spine, but some tenderness was noted at the level of the third thoracic vertebra.

The blood showed hemoglobin 85 per cent; white blood cells 6000; polymorphonuclears 70 per cent; lymphocytes 29 per cent; basophils 1 per cent. The Wassermann reaction was negative.

The urine was clear and of amber color; sp. gr., 1025; acid; no sugar; no albumin; an occasional hyaline cast and epithelial cell.

The spinal fluid pressure varied from 90 to 150. There was no block, and the color was clear. The Wassermann and colloidal gold reactions were negative.

X-ray study of the cervical and thoracic spine suggested a congenital deformity of the spinous processes of the cervical vertebrae; but no evidence of any tumor of the spine was seen and no other pathology was made out. A roentgenogram of the skull was negative. There was a roentgen shadow in the hilus region of the left lung which was thought to be due to a deformity of the pulmonary vessels (Fig. 1).

Diagnostic Impressions: (1) Spinal cord tumor; (2) mediastinal malignancy with metastases.

Therapy and Course: Due to the fact that the diagnosis was not clear, the patient was given a test course of four deep x-ray treatments over the cervical spine. Before leaving the hospital he showed some decrease in general weakness and in the inability to move his right arm; the ptosis had disappeared.

FIG. 1. X-RAY FILM OF CHEST TAKEN ON MARCH 8, 1933

Note the sharply outlined shadow cast by the thymoma as it protrudes from the left hilus region below the shadow of the aortic arch.

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Second Hospital Admission (8/14/33-9/5/33): The condition was unchanged. One deep x-ray treatment was given over the cervical and thoracic spine.

Third Hospital Admission (2/12/34-2/28/34): The patient had remained fairly well until September 1933, when he began to be troubled by choking and coughing spells and asthmatic symptoms. On his third admission he showed: slight ptosis of the left eyelid; slight incoordination of the finer movements of the left hand; some decrease in muscle and tendon pain, especially on the right side; marked reduction in the ability to abduct both arms, most marked on the right side, extreme atrophy of both deltoid muscles and a lesser degree of atrophy of the supra- and infra-spinaus muscles. The muscles of the forearms, thighs, and legs were apparently normal. The biceps and triceps were markedly atrophied, although the strength in the upper arm seemed good.

One more deep x-ray treatment was given over the cervical and thoracic spine.

Fourth Hospital Admission (6/29/34-7/13/34): After the previous discharge the patient had had severe "bronchitis and asthma" and had not been as well since. He had not been able to raise his arms and had become weaker. Sometimes on stooping over he was unable to regain the upright position without the aid of a cane.

Slight ptosis of the left eyelid persisted. The muscular atrophy and reflexes were about as before. X-ray examination of the chest with lipiodol revealed bilateral obliterative bronchitis and a slight degree of cylindrical bronchiectasis on the left side. A note at the time of discharge reads as follows: "The patient says he is much stronger in his arms and body but seems weaker in the muscles of his thighs. The diagnosis is still obscure. Progressive muscular atrophy, progressive muscular dystrophy and cord neoplasm have been considered, but none of these seems to fit the condition. The patient has good reflexes and no sensory changes. Progressive muscular dystrophy seems the most likely except for the age, the ptosis, and the fact that the proximal and not the distal muscle groups are involved." The patient was put on ephedrin.

Fifth Hospital Admission (11/21/35-12/5/35): The patient was in the hospital with lobar pneumonia.

Sixth Hospital Admission (7/30/36-9/11/36): The patient was admitted because of pain in the lower back and sacro-iliac region. He also complained of paroxysmal dyspnea and orthopnea. He developed a hyperesthesia of the skin so that he was unable to bear even the sheets on his legs. The physical findings were as before with the exception of the following: pulse 100; blood pressure 176/140; heart enlarged to the left and fibrillating; râles in both lung bases; liver palpable.

The patient was treated for hypertensive heart disease with mild congestive failure and auricular fibrillation but failed to respond to either digitalis or quinidine. He was discharged to a rest home unimproved. He died on Sept. 28, 1936, at the age of fifty-five years, after an illness of four years' duration.

Post-mortem Findings (A-36-1832): The body is that of a well developed, well nourished white male, 183 cm. in length and weighing about 165 pounds. There is atrophy of the shoulder girdle musculature, involving the deltoid, biceps and triceps muscles of both sides, but more marked on the right side.

The peritoneal and pericardial cavities are negative. Both pleural cavities are obliterated by old adhesions.

There is a flattened, ovoid tumor occupying the anterior portion of the superior mediastinum; this tumor weighs 63 grams, measures 9 × 6 × 3.5 cm., and is surrounded by a capsule of tough fibrous tissue (Fig. 2). The cut surface shows a grayish fleshy tissue which is beset with numerous cysts of variable size (Fig. 3). The substance of the tumor is divided by dense, broad bands of connective tissue in which yellow areas of softer consistence are present.

The heart weighs 425 grams. Except for moderate hypertrophy of the myocardium, it shows no gross lesion.

The lower portions of the lungs are firm but the findings are obscured by the embalming. Many of the bronchi seem dilated, and some purulent exudate is expressed from them.

The spleen weighs 250 grams and is congested.

The liver weighs 1800 grams. Its cut surface appears normal. The gallbladder is not
thickened and contains no stones. The gastro-intestinal tract, pancreas, and adrenals show no gross lesions.

Each kidney weighs 250 grams, and the cut surfaces appear normal. The urinary bladder, ureters, and renal pelves show no gross lesions. The prostate shows a grade 2 hypertrophy.

There is a grade 2 atherosclerosis of the descending aorta.

Two lymph nodes in the anterior mediastinum adjoining the tumor appear to be enlarged; otherwise there is no lymphadenopathy.

Figs. 2 and 3. Ventral View of the Thymoma (Left) as it was Removed at Autopsy and a Coronal Section (Right)

The tumor had been incised and a block removed for microscopic study before the photograph on the left was taken. Note the well encapsulated nature of the mass. Along the right side is some soft tissue which is closely adherent to the fibrous capsule of the thymoma. Fig. 7 was taken from this extra-capsular tissue. The coronal section shows the dense fibrous septa dividing the tumor and numerous cysts of variable size.

The scalp and calvarium appear normal. The meninges and vessels at the base of the brain are negative. The surface of the brain and serial sections through this organ reveal no gross lesion. Serial cross-sections of the spinal cord from the cervical to the lumbar level show multiple, small, irregular, brownish areas.

The trunks of the brachial plexus show no gross lesions.

Sections from the triceps muscles appear grossly normal.

Microscopic Findings: The liver and spleen are normal except that thorotrast, which had been given three years before death, is present in the reticular cells.

The lungs show a diffuse bronchiectasis.

The mediastinal and bronchial lymph nodes and the pancreas, adrenals, and heart muscle are normal. The coronary arteries show moderate atherosclerosis with calcification.
FIG. 4. A MUSCLE FASCICULUS FROM THE RIGHT TRICEPS

Note the vacuolar condition of two swollen fibers and the relatively normal appearance of the other fibers. Medium magnification.

FIG. 5. HIGH-POWER PHOTOMICROGRAPH OF MUSCLE FIBERS IN THE LOWER LEFT CORNER OF FIG. 4

Note the extreme degree of vacuolization in the large fiber and the lesser degrees of alteration in some of the adjacent fibers.

FIG. 6. MUSCLE FIBERS IN A FASCICULUS FROM THE RIGHT TRICEPS

Four fibers are included in which varying degrees of vacuolization may be seen. This microscopic field represents the largest number of closely associated vacuolated fibers which were found. High magnification.

FIG. 7. SECTION THROUGH SOFT AREolar TISSUE ATTACHED TO SURFACE OF TUMOR CAPSULE

This section shows the presence of thymic tissue of the normal adult type. Low magnification.
The skeletal musculature shows the presence of numerous typical lymphorrhages. No definite atrophy of muscle fibers can be recognized, but the impression is strong that the fibers in many fasciculi from the muscles of the shoulder girdle group are smaller than normal. A few fibers show a peculiar vacuolar structure (Figs. 4, 5 and 6). This vacuolar change is not a common finding but in those muscle fasciculi in which this lesion is found several fibers are regularly affected (Figs. 4 and 6). No bacteria are found in the muscles.

**Fig. 8. High-power View of the Least Differentiated Part of the Thymoma**

Note the large syncytial epithelial cells and the relatively few small lymphocytes. Near the upper right hand corner and near the lower left hand corner are two whorls of endothelial cells; these represent young, incompletely developed capillaries and are the only vascular structures included in this field.

**Fig. 9. High-power View of a Slightly Better Differentiated Part of the Thymoma**

Note that the epithelial cells tend to be smaller, that the syncytium is looser, and that lymphocytes are more numerous than in Fig. 8. This field includes three vascular elements; one of these has developed a lumen and the other two are solid.

Sections from numerous regions of the brain and from the trunks of the brachial plexus show no lesion. Sections from the various levels of the spinal cord show the presence of a few irregularly distributed petechial hemorrhages. These are most numerous in the cervical cord and are almost entirely confined to the gray matter (anterior and posterior horns). No degeneration of nerve cells or tracts can be recognized.

Microscopic examination of the fleshy portion of the thymic tumor shows some variation of structure. The essential cells of the tumor are epithelial cells arranged in the form of a syncytium. They have indistinct cell outlines, more or less homogeneous, acidophilic cytoplasm, and ovoid or irregularly block-shaped vesicular nuclei in which the chromatin is distributed in a delicate network; a definite nucleolus is frequently present. A relatively small number of small lymphocytes are rather regularly distributed in the interstices of the epithelial syncytium (Fig. 8). A few Hassall’s corpuscles are present.

The structure of the tumor varies in different areas depending upon the degree of
vascularization which has developed. In the younger parts of the tumor there are very few capillaries and the epithelial cells are large and disposed in broad sheets (Fig. 8). Slightly older portions are recognized by the presence of endothelial whorls and solid vascular buds in the epithelial expanses (Fig. 9). Still older areas show greater numbers of these young vessels (Fig. 10). In the oldest and best differentiated parts nearly one-half of the tumor tissue is made up of well formed and rather wide capillaries which anastomose freely but which, for the most part, appear to maintain a parallel course; in such areas the epithelial cells come to be arranged in narrow cords which are separated by the intervening capillaries (Fig. 11). Together with the increasing age of the tumor tissue and the better vascular
devvelopment, a change in the cytology of the epithelial elements is to be noted. In the areas where the vascular structures are best differentiated the thymic epithelium is made up of much smaller cells and these have narrow processes which form a loose syncytium. This makes a reticular structure and the cell types and their arrangement correspond more closely to those of the epithelium found in the adolescent or adult thymus. The rich vascular network and the intervening cords of syncytial epithelium form a structure which suggests the splenic pulp (Fig. 11). Within the broader dense fibrous septa there is some necrosis.

The few Hassall's corpuscles which are found within the tumor are vacuolated and,
FIG. 12. A LARGE PARTIALLY CYSTIC HASSALL'S CORPUSCLE FOUND WITHIN THE THYMOMA

FIG. 13. SECTION THROUGH THE WALL OF ONE OF THE MEDIUM-SIZED CYSTS FOUND IN THE THYMOMA

The lumen of the cyst corresponds to the clear area shown in the upper edge of this figure. Note the character of the cells which make up the lining of the cyst; these may be seen along the upper edge of the cellular mass and bordering upon the cyst cavity.
by a confluence of the vacuoles, these bodies are converted into small cysts (Fig. 12). Apparently the larger cysts have a similar origin, for they are lined with epithelial cells which resemble those of the Hassall's corpuscles (Fig. 13).

Sections taken through the areolar tissue attached to the outside of the main tumor show the presence of thymus tissue which has the appearance of that regularly found in the adult gland (Fig. 7). Hassall's corpuscles of the adult type are more numerous in this tissue than in that of the encapsulated mass. The medullary portions of these lobules are made up of closely packed thymic, epithelial cells and these are morphologically similar to the cells which make up the better differentiated areas of the tumor.

**Discussion**

Despite the fact that this patient was frequently under medical observation, the diagnosis of myasthenia gravis was not made during life. In retrospect it is doubtful whether the diagnosis could have been made on purely clinical findings, for the degree of muscular atrophy which was present introduced a very confusing feature. The clinical presence of muscular atrophy in myasthenia gravis is not in accord with the usual findings. The pathologic diagnosis in this case rests upon the findings of typical lymphorrhages in the muscles and the thymoma. From the pathologist's point of view the lymphorrhages are pathognomonic of myasthenia gravis, and this case emphasizes the diagnostic importance of the muscle biopsy in all doubtful cases where this disease entity might possibly be considered.

The vacuolar changes found in certain of the skeletal muscle fibers are probably best interpreted as a degenerative alteration. Apparently Buzzard (1905) and Mandlebaum and Celler (1908) observed similar but less marked vacuolar changes in the muscles. There is at present, however, no way of knowing whether or not this lesion is a significant finding peculiar to myasthenia gravis. When dealing with a malady so poorly understood as myasthenia gravis, a record of all the findings is of great importance. Finally, after many more cases have been thoroughly studied, a proper evaluation of the various lesions may be made. Only in this manner can progress toward an understanding of this disease be accomplished, for the rarity of the malady makes it likely that but few cases will come under the observation of any single investigator.

The petechial hemorrhages found in the gray matter of the spinal cord are also unusual and they are probably best explained as the result of some underlying toxemia which may be the basis for the other symptoms and findings. It seems strange, however, that if a general toxemia were present, these hemorrhages should be so completely confined to the spinal cord and that they should not appear in other organs also.

In our previous communication (1936) emphasis was placed upon the difficulties encountered in attempting to differentiate between a benign thymoma and an enlarged hyperplastic thymus. The morphologic evidence relevant to this feature was analyzed and it was concluded that the differences between these two conditions were only those of the varying degrees of epithelial hyperplasia which was found from case to case.

The case reported here is of particular interest because it supports our earlier interpretation and because it adds further evidence in that it presents
in the same tumor many different stages of histologic differentiation. The essential cells of the tumor were found to be morphologically characteristic of all possible stages of thymic histogenesis and, as has been pointed out, these successive cell types were found in different parts of the tumor in numbers proportionate to the associated and varying degrees of vascularization. Apparently, as this tumor grew and differentiated, a satisfactory development of vascular elements progressed. Thus the thymoma of myasthenia gravis seems best regarded as an adenoma of the thymus produced by an extreme degree of local hyperplasia of the thymic epithelium. In this connection, also, the finding of normal thymus outside the capsule of the tumor has significance; a morphologic relationship is here produced which is similar to that described for adenomatous growths in the hypophysis, the thyroid, the parathyroid and the adrenal.

As regards the cysts of the tumor I am in agreement with Löwenthal. The morphologic evidence indicates that they have their origin from the Hassall’s corpuscles.

**Summary**

1. Another case of myasthenia gravis associated with a thymoma is presented.
2. The thymoma of myasthenia gravis is best regarded as an adenoma of the thymus.
3. The cysts found in these tumors are apparently developed from Hassall’s corpuscles.
4. Certain vacuolar changes in the skeletal muscle fibers were found.
5. The diagnostic importance of lymphorrhages and the muscle biopsy is again emphasized.

**Bibliography**