TUMORS OF THE THYMUS GLAND

Benjamin Castleman, M. D.

TUMORS OF THE THYMUS GLAND

Benjamin Castleman, M. D.

ARMED FORCES INSTITUTE OF PATHOLOGY

TUMORS OF THE THYMUS GLAND

TABLE OF CONTENTS

ATLAS OF TUMOR PATHOLOGY

Section V—Fascicle 19

TUMORS OF THE THYMUS GLAND

by

Benjamin Castleman, M. D.
Chief, Department of Pathology and Bacteriology
Massachusetts General Hospital
Clinical Professor of Pathology, Harvard Medical School
Boston, Massachusetts

Published by the
ARMED FORCES INSTITUTE OF PATHOLOGY
Under the Auspices of the
SUBCOMMITTEE ON ONCOLOGY
of the
COMMITTEE ON PATHOLOGY
of the
NATIONAL RESEARCH COUNCIL
Washington, D. C.
1955

For sale by the American Registry of Pathology
Armed Forces Institute of Pathology
Washington 25, D. C. - Price $1.00

ATLAS OF TUMOR PATHOLOGY

Sponsored and Supported

by

AMERICAN CANCER SOCIETY

ANNA FULLER FUND

ARMED FORCES INSTITUTE OF PATHOLOGY

JANE COFFIN CHILDS MEMORIAL FUND FOR MEDICAL RESEARCH

NATIONAL CANCER INSTITUTE, U.S. PUBLIC HEALTH SERVICE

UNITED STATES VETERANS ADMINISTRATION

ACKNOWLEDGMENTS

The author is extremely grateful to Dr. Averill A. Liebow, professor of pathology, Yale University School of Medicine, who generously consented to act as special critic, and who not only made helpful suggestions in both the selection and arrangement of the material, but also provided the author with interesting interpretations of the origin of the cells in the thymomas.

The author also wishes to thank Dr. Lalla Iverson, Washington, D. C., for reviewing a great deal of the material; she made many very valuable suggestions and helped in the selection of many of the cases that are described in the text as "tumors resembling thymomas."

The author is grateful to Dr. John R. McDonald for permission to study the thymoma material of the Mayo Clinic; to Dr. Samuel H. Rosen, Washington, D. C., for reviewing the manuscript and making many helpful suggestions; to Dr. G. F. M. Hall, of the Kings College Hospital, London, England, for the use of the microscopic slides of his case of thymolipoma; to Dr. A. B. Bratton, London, England, and Dr. Douglas Hubble, Derby, England, for their slides of cases of Cushing's syndrome with thymoma; to Dr. M. J. Schlesinger and Dr. L. Reiner of the Beth Israel Hospital, Boston, Mass., for use of their slides of two cases of thymoma with pulmonary involvement and their cases of squamous cell carcinoma; to Dr. Nathan B. Friedman of Cedars of Lebanon Hospital, Los Angeles, Calif., for permission to use material previously submitted to the Armed Forces Institute of Pathology; to the staff of the Armed Forces Institute of Pathology for making most of the photomicrographs and for help in many respects; and especially to Dr. Mary Ruth Oldt and her staff for their invaluable editorial assistance.

Grateful acknowledgment is made to the following for allowing the use of illustrations previously published:

Dr. W. DeW. Andrus and Dr. N. C. Foot. For our figure 79

Dr. E. E. Arnheim and Dr. B. L. Gemson. For our figures 2, 3

Dr. G. F. M. Hall. For our figure 80

Dr. R. C. McBurney, Dr. O. T. Clagett, and Dr. J. R. McDonald. For our figure 61

Dr. R. W. Weller, Dr. A. E. Pearse, and Dr. M. Rapoport. For our figure 77

Permission to use copyrighted illustrations has been granted by:

C. V. Mosby Co.:

Surgery, 27: 603–608, 1950. For our figures 2, 3

J. Thoracic Surg., 6: 648–659, 1937. For our figure 79

Williams & Wilkins Co.:

Medicine, 28: 27–58, 1949. For our figures 10, 12, 13, 14, 15, 16, 18, 19, 26, 27, 28, 30, 31, 60, 63, 64

Massachusetts Medical Society:

New England J. Med., 250: 26–30, 1954. For our figures 70, 72

American Medical Association:

A. M. A. Arch. Path., 52: 569–573, 1951. For our figure 77

Dr. G. F. M. Hall:

Brit. J. Surg., 36: 321–324, 1949. For our figure 80

All illustrations are the author's own unless otherwise acknowledged. The A. F. I. P. numbers are for the identification of negatives at the Armed Forces Institute of Pathology.

Benjamin Castleman

TUMORS OF THE THYMUS GLAND

TABLE OF CONTENTS

TUMORS OF THE THYMUS GLAND

INTRODUCTION

Normal Thymus Gland

EMBRYOLOGY. The thymus gland is derived embryologically from the third pharyngeal pouches on each side, as are also the lower parathyroid glands. During the downward migration the parathyroid glands remain in the neck near the lower poles of the thyroid, and the right and left thymic portions descend into the anterior mediastinum, where they join but do not completely fuse and are thus easily separable. Occasionally, bits of thymic tissue break off during the descent and remain in the neck, thus accounting for the rare occurrence of ectopic tumors of the thymus gland. It is even possible for an entire lobe not to descend at all but remain in the neck (fig. 1); one such case required thymectomy because of a bulge in the neck and choking spells in a 9-month-old infant (Arnheim and Gemson; figs. 2, 3).

GROSS. A great deal of the prevalent confusion as to whether a thymus gland is enlarged, hyperplastic, neoplastic, involuted, persistent, or even absent seems to be due to insufficient knowledge about the size and appearance of the normal gland. It is important to realize that the thymus gland never disappears entirely. It may show extensive involution with replacement by fat, but some thymic tissue is always present. From birth until puberty the thymus gland increases in weight, although it is well known that infections and malnutrition will produce a marked decrease in its size (accidental involution). The apparently large thymus gland sometimes observed radiologically in infants and children is normal, does not represent true hyperplasia, and there is no evidence that it ever is the cause of sudden death—the so-called status thymicolymphaticus (Potter). Possibly most important, since the thorough series of studies of the weights of the normal thymus gland by Hammar, by Sloan, and by Murray and McDonald, is the realization of the great variations in thymic weights for any given age. Figure 4 is a graph, based on Hammar's figures, of the variations in weights of the normal gland at different ages. This graph makes it plainly evident that many cases of so-called hyperplastic and persistent thymus are really variations of the normal.

MICROSCOPIC. For a detailed description of the histology of the normal thymus gland, the reader is referred to the standard texts of histology. Briefly, the two thymic lobes are divided into lobules by loose connective tissue. The lobular character is more prominent in glands with little or no involution and is retained in many of the thymomas. Each lobule has a peripheral cortical layer and a central medulla. The medullas of the lobules are connected centrally like the connective tissue stalk of an intestinal polyp, each projection of medulla being covered on all sides by cortex (fig. 5). This clear-cut separation of cortex from medulla is best seen up to and before the end of puberty.

The peripheral cortical layer is composed almost entirely of densely packed lymphocytes ("thymocytes") with a scattering of pale reticular cells. Since most anatomists agree that the small cell of the thymus gland has the same properties as the ordinary lymphocyte, there is no need to continue using the term "thymocyte." The origin of the reticular cells in the cortex has not been certainly settled, although most authorities believe that the great majority of the cells are epithelial. Maximow and Bloom state in their chapter on the thymus: "Most of the reticular cells are of endodermal origin, although there are a few reticular cells of mesenchymal origin around the blood vessels." Although some of these reticular cells are undoubtedly mesenchymal, in the postnatal gland it is very difficult to identify them, because the epithelial cells are often flattened and spindle shaped. The lymphocytes of the cortex become less densely packed as they reach the medulla, which stains much lighter because of the sparsity of lymphocytes and a predominance of the reticular cells. Normally no germinal centers are present. The well known distinctive Hassall's corpuscles, composed of epithelial cells in various stages of keratinization, degeneration, and cyst formation are scattered in the medulla (fig. 6.).

Normal involutionary changes usually begin around puberty with a gradual decrease of lymphocytes, followed by adipose tissue replacement and atrophy of the epithelial cells (fig. 7). It is at this stage, when the epithelial cells so closely resemble connective tissue cells, that a tumor arising from these cells is often called mesenchymal or endothelial rather than epithelial (fig. 8). Further discussion of the origin of the cells comprising the tumors will be taken up under Thymoma.

References

Arnheim, E. E., and Gemson, B. L. Persistent cervical thymus gland; thymectomy. Surgery, 27: 603–608, 1950.

Hammar, J. A. Die Menschenthymus in Gesundheit und Krankheit. Part I. Das Normale Organ. Jahrbuch für Morphologie und mikroskopische Anatomie, Section 2. Zeitschrift für mikroskopisch-anatomische Forschung. Vol. 6, Suppl., 1926.

Maximow, A. A. and Bloom, W. A Textbook of Histology. 6th ed. Philadelphia: W. B. Saunders Co., 1952.

Murray, N. A., and McDonald, J. R. Tumors of the thymus in myasthenia gravis. Am. J. Clin. Path., 15: 87–94, 1945.

Norris, E. H. The morphogenesis and histogenesis of the thymus gland in man: in which the origin of the Hassall's corpuscles of the human thymus is discovered. Contrib. Embryol., 27 (No. 166): 191–208, 1938.

UNDESCENDED THYMUS GLAND

(Figures 2 and 3 are from the same case)

Figure 1. Undescended thymus gland (arrow) found adjacent to trachea below right lobe of thyroid gland in a necropsy of a full term stillborn infant. A. F. I. P. Acc. No. 218955-89.

Figure 2.* Roentgenogram of the chest taken three weeks prior to the patient's admission to the hospital, showing a wide shadow in the superior mediastinum, and a displacement of the trachea to the right side. A. F. I. P. Acc. No. 218955-90.

Figure 3.* Undescended thymus gland. Photograph of surgically resected thymus gland, showing the cervical (A) and mediastinal (B) components of the gland. A. F. I. P. Acc. No. 218955-91.

---

* From Arnheim, E. E., and Gemson, B. L. Persistent cervical thymus gland; thymectomy. Surgery, 27: 603–608, 1950. Figures 1 and 2 are our figures 2 and 3.

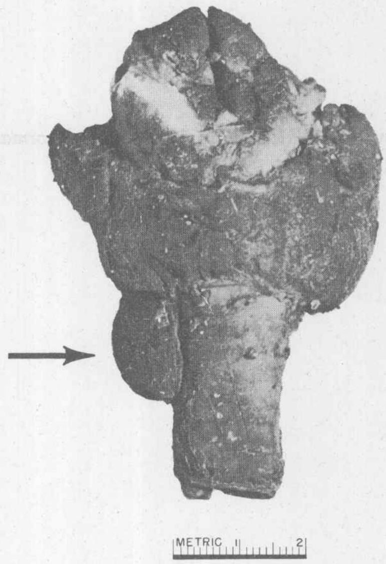

Fig. 1

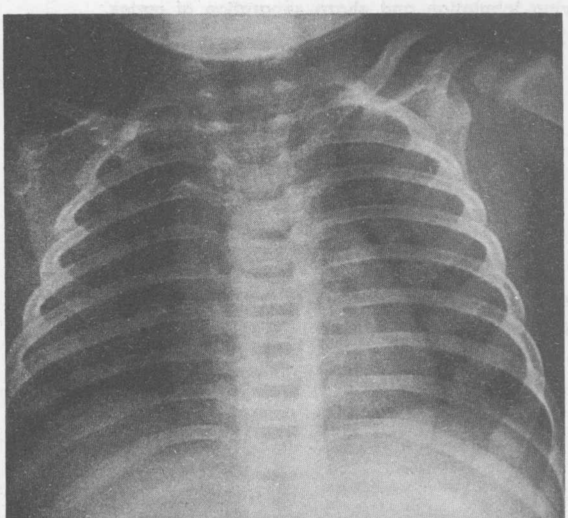

Fig. 2

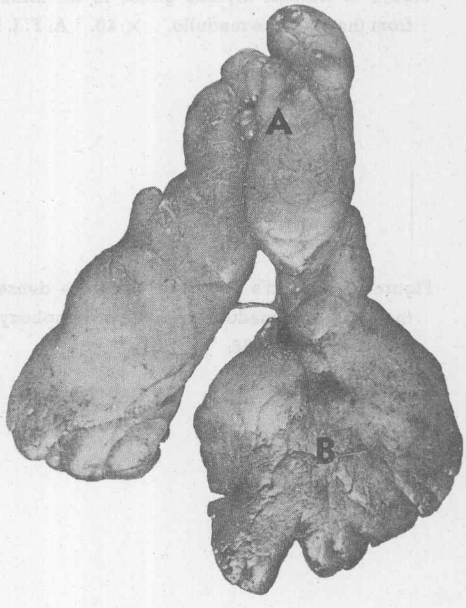

Fig. 3

NORMAL THYMUS GLAND

Figure 4. Variations in the weight of normal thymus glands at any given age, based on Hammar's* data. A. F. I. P. Acc. No. 218955–84.

Figure 5. Normal thymus gland in an infant, showing lobulation and sharp separation of cortex from the stalklike medulla. × 40. A. F. I. P. Acc. No. 218955–85.

Figure 6. A child's gland showing the dense cortex composed predominantly of lymphocytes and the less dense medulla with fewer lymphocytes. Note the Hassall's corpuscle. × 150. A. F. I. P. Acc. No. 218955–86.

---

*Hammar, J. A. Die Menschenthymus in Gesundheit und Krankheit. Part I. Das Normale Organ. Jahrbuch für Morphologie und mikroskopische Anatomie, Section 2. Zeitschrift für mikroskopischanatomische Forschung. Vol. 6, Suppl., 1926.

Fig. 4

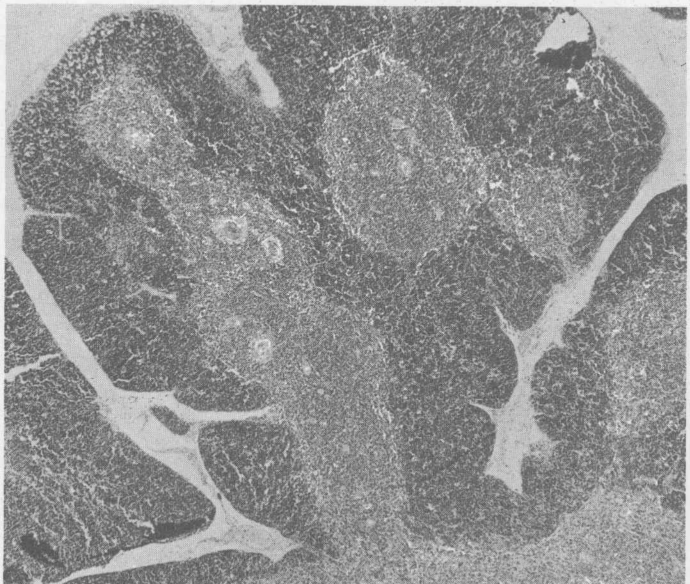

Fig. 5

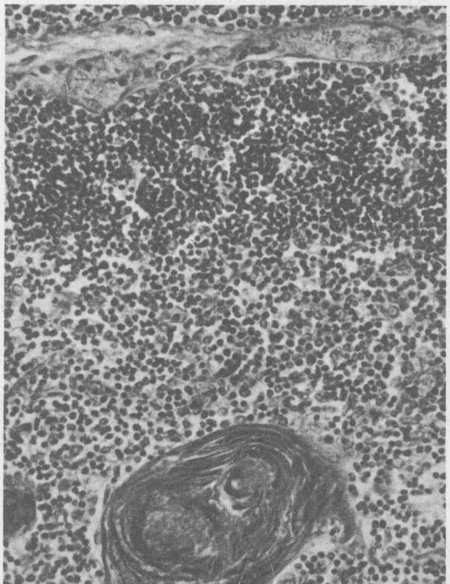

Fig. 6

NORMAL THYMUS GLAND

Figure 7. An adult's gland, showing involution with fat cell replacement. × 20. A. F. I. P. Acc. No. 218955–87.

Figure 8. Medulla of involuted gland, showing spindle-shaped epithelial cells. × 200. A. F. I. P. Acc. No. 218955–88.

Fig. 7

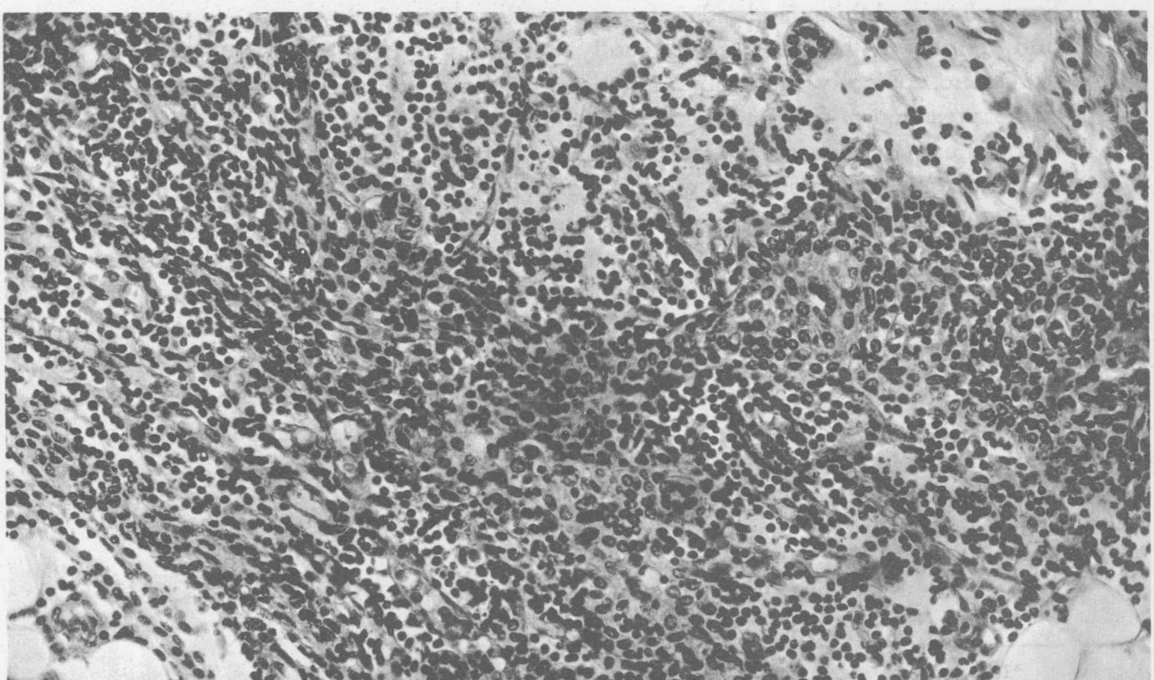

Fig. 8

Potter, E. L. Pathology of the Fetus and the Newborn. Chicago: The Year Book Publishers, 1952.
Sloan, H. E., Jr. The thymus in myasthenia gravis. With observations on the normal anatomy and histology of the thymus. Surgery, 13: 154–174, 1943.

Thymic Hyperplasia

Before discussing the true neoplasm of the thymus gland, it may be appropriate to attempt to clarify what is meant by thymic hyperplasia.

The established knowledge of the great variation in the weight of the normal gland makes weight alone an unreliable criterion of hyperplasia. The absence of involution in a thymus gland of an adult probably indicates that thymic cells have multiplied after previous involution, and replaced the loose stroma and fat cells. For example, the thymus gland in a patient with exophthalmic goiter, similar to that of a prepubertal child, has a cellular cortex and medulla (fig. 9). In a rare case of Graves's disease an occasional germinal center* has been observed in the medulla. Similar findings have been reported in Addison's disease and acromegaly (Sloan).

Thymic Hyperplasia in Myasthenia Gravis

Approximately 15 percent of patients with myasthenia gravis have true neoplasms of the thymus gland—tumors that we prefer to call thymomas. Of the remaining patients about 20 percent have thymus glands that, so far as can be determined grossly and microscopically, are completely within normal limits, showing varying degrees of involution. The other 80 percent have abnormal thymus glands microscopically, although the gross appearance and weights of the glands are usually within normal limits (fig. 10).

Microscopically, the striking finding in the thymus gland of these 80 percent is the presence of germinal centers in the medulla (fig. 11)—germinal centers that are exactly like those observed in any lymph node (fig. 12). The number of these follicles varies from gland to gland. Some have so many germinal centers in the medulla that any evidence of involution is oblite ated, and the cortex is so compressed that it appears like a cap over an expanding medulla. A distinct separation is produced between medulla and cortex in the most markedly affected glands; this is well brought out by reticulum stains in sharp contrast to its absence in the normal gland (figs. 13, 14), and even in the thymus gland as seen in Graves's disease, in which there is a gradual merging of medulla and cortex (fig. 9). The medulla is not otherwise changed, Hassall's corpuscles being in their usual numbers. In other cases of myasthenia gravis the germinal centers may be less numerous (fig. 15), and in some they have to be hunted for. The remainder of the gland in the cases with few to moderate

*The commonly used term "germinal centers" is employed throughout this fascicle, although it is admitted that these secondary nodules or follicles may have functions other than the production of lymphocytes, e. g., they may serve for the destruction of lymphocytes, or as reaction centers to disease.