Ectopic Hamartomatous Thymoma:

Clinicopathologic, Immunohistochemical, and Histogenetic Considerations in Four New Cases

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Four new cases of ectopic hamartomatous thymoma are presented. The tumor occurred either superficially or deep in the area of the sternoclavicular joint and consisted of solid islands of squamous epithelium which blended with spindled cells. Cysts lined by squamous epithelium, small glands, and fat also occurred in variable amounts. Both the spindled and epithelial regions of the tumor expressed keratin and muscle actin, but neither desmin nor S100 protein. The tumor probably originates from thymic anlage associated with the third pharyngeal pouch (thymus III), although origin from other structures such as thymus IV and the cervical sinus of His are discussed. Our experience indicates that the large size and extreme cellularity of the spindled portion of some tumors may result in the mistaken diagnosis of sarcoma. HUM PATHOL 21:662–668. © 1990 by W.B. Saunders Company.

We are reporting four new examples of a rare entity simultaneously described in English language literature by Smith and McClure as "an unusual subcutaneous mixed tumour exhibiting adipose, fibroblastic and epithelial components",[1] and by Rosai et al as "spindle cell thymic anlage tumor".[2] The latter authors subsequently suggested the term "ectopic hamartomatous thymoma".[3] Both groups discussed a possible origin from ectopic cervical thymus. To this collective experience we add four new cases with clinicopathologic and immunohistochemical findings. Our data extend the previous findings by indicating that the tumor may occur well into adult life and achieve such large proportions and possess such cellularity that a diagnosis of a biphasic synovial sarcoma or adnexal carcinoma may be entertained.

MATERIALS AND METHODS

The four cases comprising this study were retrieved from the Soft Tissue Registry of the Armed Forces Institute of Pathology and had been referred to one of us (S.W.W.) in consultation. Representative hematoxylin and eosin-stained slides were reviewed in each case. Immunohistochemistry was performed for keratin, S100 protein, muscle-specific actin (two cases), and desmin (two cases) using either the peroxidase-antiperoxidase method of Sternberger[4] or the avidin-biotin complex method of Hsu and colleagues.[5] Sources of the reagents and methods used in our immunopathology laboratory are cited in a previous publication.[6]

RESULTS

Clinical Findings

All patients in our series were male and ranged in age from 37 to 79 years (Table 1). The lesions presented as slowly increasing masses in the vicinity of the sternoclavicular joint. In one case the lesion lay beneath the sternocleidomastoid muscle, whereas in the other three cases the lesions were superficially located. The duration of the lesion was quite variable; in one case the patient noted its onset over the past year, whereas in two cases slow growth over a period of 30 years had been observed. In one of these two cases the mass reached the size of 19 cm.

Gross and Microscopic Features

All four lesions were well-circumscribed, grossly lobulated masses ranging in size from 3.5 cm to 19 cm in greatest dimension. The color varied from white to tan to pink and in one case the cut surface was described as "fasciculated".

The tumor had a distinct biphasic appearance consisting of sheets of spindled cells punctuated with occasional epithelial elements, usually showing squamous and rarely glandular differentiation (Figs 1 and 2). The proportion of the two elements varied from case to case, although in general the spindled component predominated. It consisted of slender fibroblast-like cells arranged in long fascicles sometimes intersecting one another in a herring-bone pattern (Fig 3, left). Vague nuclear palisading was present in one case. Although the spindled areas were usually densely cellular, some degree of hyalinization or even myxoid change was seen focally. In one case psammoma bodies were noted within the spindled zones (Fig 3, right). Neither pleomorphism nor significant mitotic activity was present. Necrosis was also not observed.

Scattered throughout the spindled areas were epithelial elements consisting of small solid islands of mature squamous epithelium possessing intercellular bridges but no keratin pearls. These epithelial nests in many areas stood in stark contrast to the spindled zones (Fig 4), but more typically formed long adamantinoid cords which blended gradually with the latter areas (Figs 2 and 5). However, unlike a true adamantinoma, the peripheral basaloid and the central loose stellate zones were not present. In three of

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TABLE 1. Clinicopathologic Features of Hamartomatous Thymoma

Case No./Age/Sex	Location of Tumor	Size	Duration	Treatment	Follow-up
1/79/M	Superficial chest wall	19 cm	30 y	local excision	Died-NED
2/38/M	Beneath SCM, above medial clavicle	5.5 cm	—	local excision	—
3/37/M	Superficial	3.5 cm	1 y	local excision	—
4/65/M	Superficial	10.0 cm	30 y	local excision	—

Abbreviation: NED, no evidence of disease.

the four cases cystically dilated epithelial structures were evident. These were usually lined by squamous epithelium and rarely by glandular epithelium (Figs 6 and 7). In a few areas adamantinoid cords of epithelium originated from the epithelial cysts (Fig 6). Intraluminal eosinophilic secretion was seen in association with these cystic epithelial structures. Several of the glandular structures had a double layer of cells with an outer basal layer possibly showing myoepithelial differentiation.

Although mature fat has been described as an integral part of these tumors, it was prominent in only one case. In that instance the uniform intermingling of fat and spindled cells brought to mind the appearance of a dermatofibrosarcoma when it infiltrates normal fat at its base (Fig 8). Lymphocytes, described as a minor component of these tumors, were sparse and identified only in two of our four cases in association with plasma cells. Lymphoid aggregates with or without follicles were absent altogether.

Immunohistochemical stains confirmed the epithelial nature of these lesions. Immunoreactive cytokeratin was identified both within the epithelial as well as the spindled regions of this tumor. Immunostaining was most intense when a polyclonal antiserum directed against epidermal human callus was

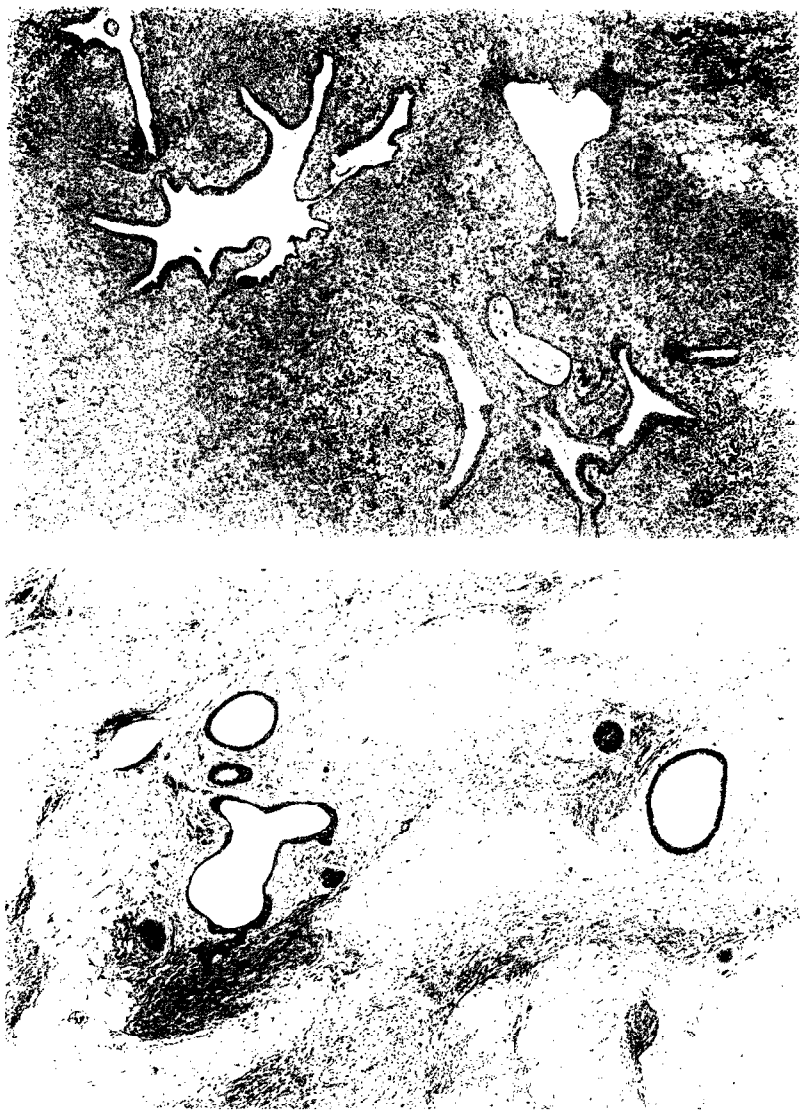

FIGURE 1. Two different ectopic hamartomatous thymomas illustrating variability in the components. One is highly cellular with only rare fat cells (top), whereas the other (bottom) contains large amounts of fat and only scattered cysts with associated spindled regions. (Magnification × 25.)

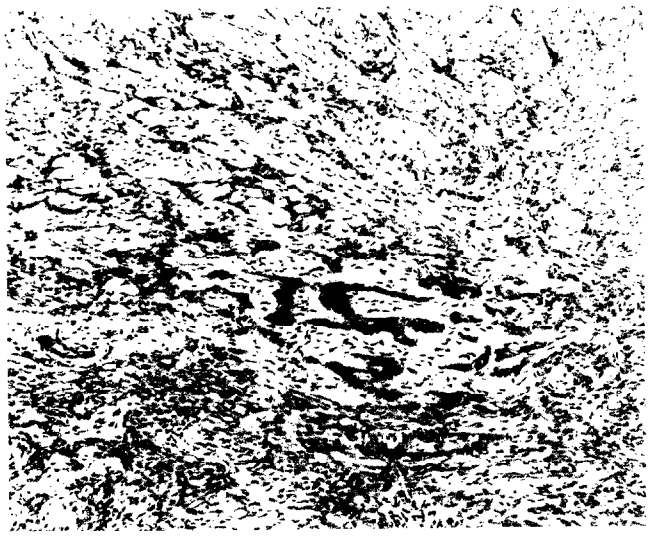

FIGURE 2. Ectopic hamartomatous thymoma illustrating the blending of the spindled and epithelial regions. (Magnification × 54.)

used and was less intense using a cocktail of monoclonal antibodies (AE1/3) which recognizes a wide range of keratin proteins. Immunoreactivity for a muscle-specific actin was identified within smooth-muscle cells associated with blood vessels and to a lesser extent within the tumor itself. However, in our hands this antigen may be demonstrated within myofibroblasts and myoepithelial cells, as well as in some epithelial tumors with striking spindled features. Desmin and S100 protein were not identified within the spindled or epithelial areas of the tumor. Mucin stains (periodic acid-Schiff with diastase and mucicarmine) highlighted the secretion within the cysts and glands.

DISCUSSION

The "ectopic hamartomatous thymoma" is a rare tumor apparently first described in 1982 by Smith and McClure as "an unusual subcutaneous mixed tumour exhibiting adipose, fibroblastic, and epithelial components,"[1] and by Rosai et al as "spindle cell thymic anlage tumor."[2] Shortly thereafter Rosai et al published five cases, including the original case reported by Smith and McClure, and suggested the above designation.[3] Our report brings the collective experience in the English literature to nine cases and reinforces the principal findings of the previous authors.

The tumor presents during adult life as a mass in the vicinity of the sternoclavicular joint or suprasternal area. It is located either superficial or deep to the sternomastoid muscle. Although all of the previous cases have been 8 cm or less when detected, one of our tumors, a slowly enlarging mass of 30 years, achieved the size of 19 cm. The tumor has a biphasic

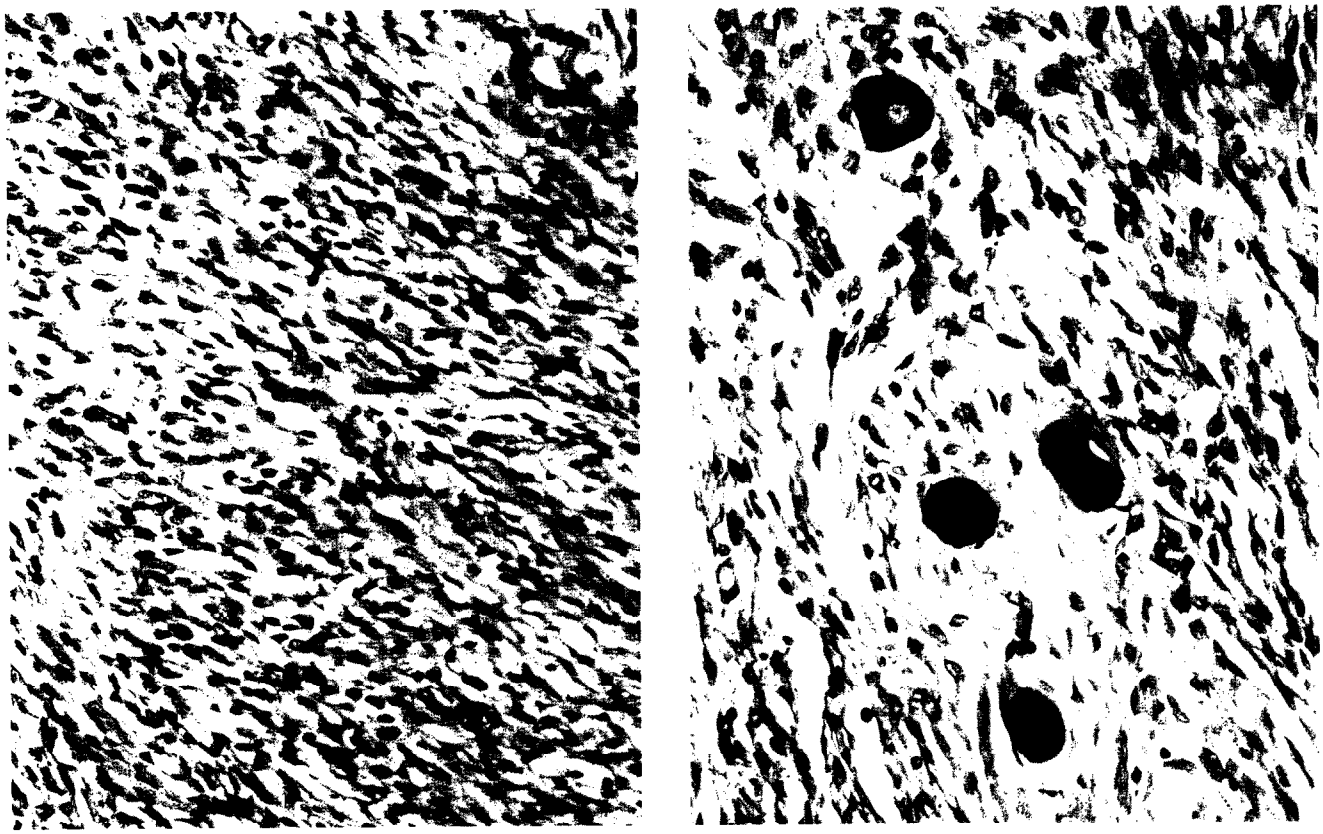

FIGURE 3. (Left) Spindled component of hamartomatous thymoma showing cellularity approaching that of a sarcoma; (right) psammoma bodies may also be present within these regions. (Magnification × 250.)

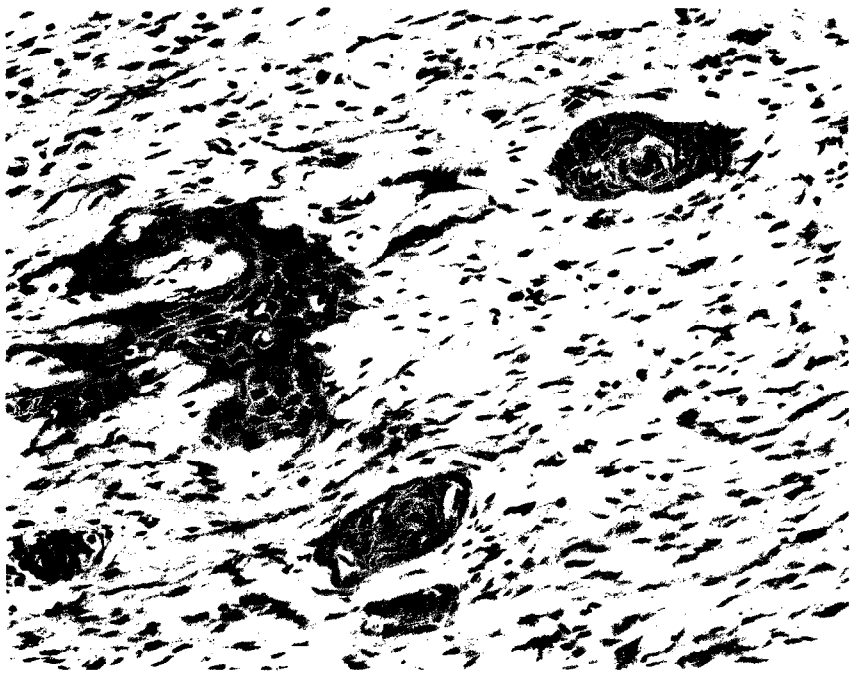

FIGURE 4. Squamous islands within thymoma which are sharply demarcated from spindled component. (Magnification × 250.)

appearance and consists of a cellular, but differentiated, spindled component punctuated with a combination of solid islands of mature squamous epithelium, cysts lined by squamous epithelium, and/or glands lined by cuboidal or columnar epithelium which may produce mucin. However, of the mature epithelial elements, the solid nests of squamous epithelium predominate. Although Smith and McClure believed the spindled and epithelial components to be quite distinct because of the failure to identify desmosomes and tonofilaments within the spindled stroma,[1] Rosai et al provided convincing immunohistochemical and electron microscopic evidence that the spindled cells possess epithelial features.[3] Both the subtle blending of the two elements and the immunohistochemical findings support the latter idea. In our experience immunoreactive cytokeratin was strongly expressed by both the spindled and epithelial cells, although the intensity was influenced by the type of keratin antibody used. Strong immunoreactivity was noted using polyclonal antibodies directed against human epidermal callus as opposed to the weaker immunoreactivity using monoclonal antibodies (AE 1/3) directed against a broad spectrum of keratins. This probably indicates that the tumor produces high-molecular weight keratins similar to strat-

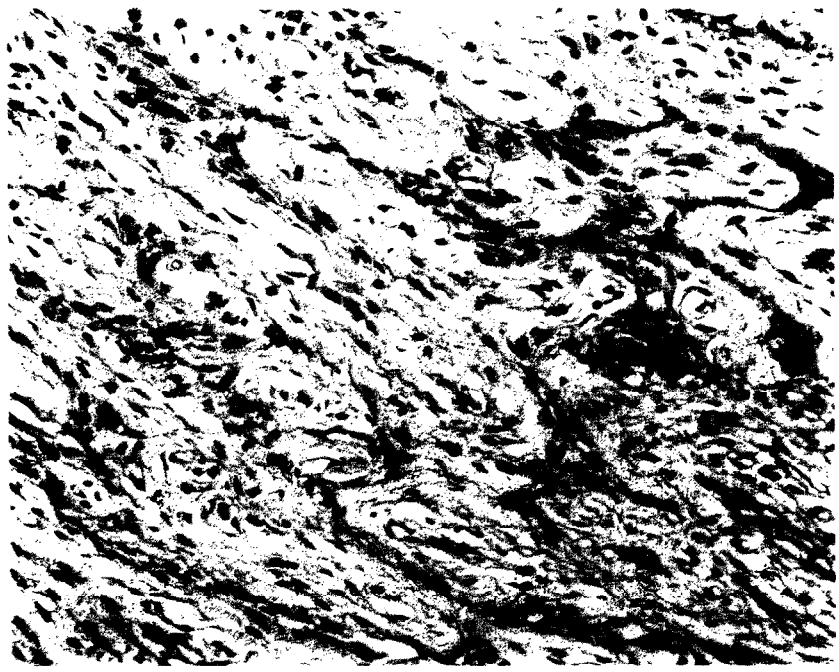

FIGURE 5. Hamartomatous thymoma showing subtle blending of the epithelial and spindled zones with formation of adamantinoid cords of cells. (Magnification × 250.)

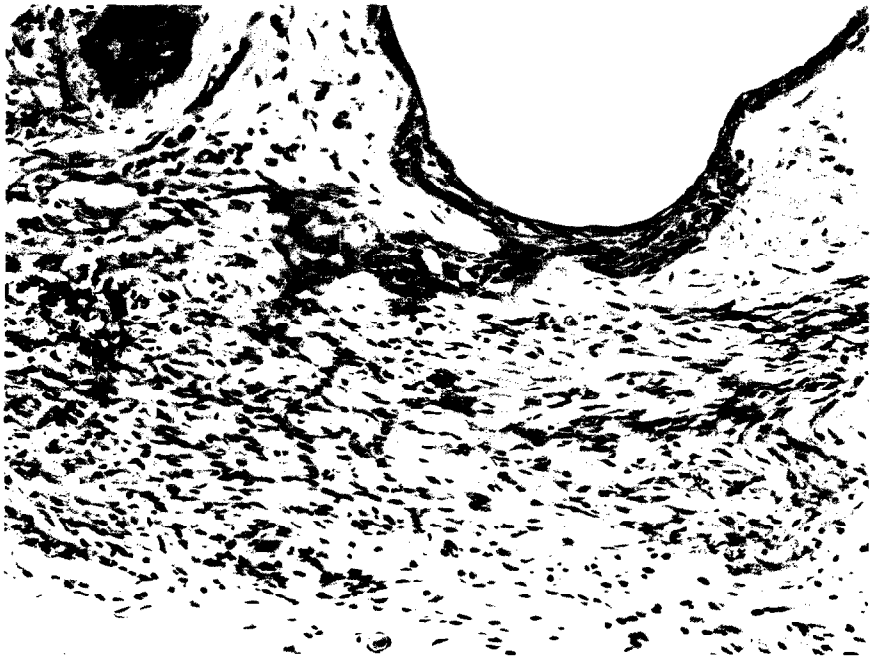

FIGURE 6. Epithelial cords taking origin from squamous-lined cyst within hamartomatous thymoma. (Magnification × 100.)

ified squamous epithelium. Both the epithelial and spindled cells also expressed muscle actin, but to a lesser extent than was noted in surrounding smooth muscle of vessels. Since we have noted similar staining in epithelial tumors which show spindled cell change, we believe this finding relates to functional changes of the epithelium rather than the presence of a population of smooth muscle cells contributing to the tumor. Desmin, moreover, was not identified within the lesions. Although mature fat does, indeed, appear to be part of this lesion, it is more difficult to necessarily accept lymphocytes as an integral component. They are inconspicuous and do not exceed the number seen in a variety of tumors.

The most interesting aspect of this tumor is its histogenesis. Both earlier reports suggested that the lesion may be derived from ectopic thymic tissue.[1,3] Rosai et al proposed origin from thymic anlage of the third pharyngeal pouch (thymus III). This is an attractive hypothesis since the location of this lesion in the sternoclavicular area coincides with one of the points along the path of migration of the thymus III. Fragmentation of its tail can result in development of thymic rests at any point in this path.[7-9] Neoplasms of the thymus, furthermore, can consist of a mixture of spindled and epithelial elements. Glandular elements, while seemingly an unusual feature for a thymoma, have been reported and could be explained

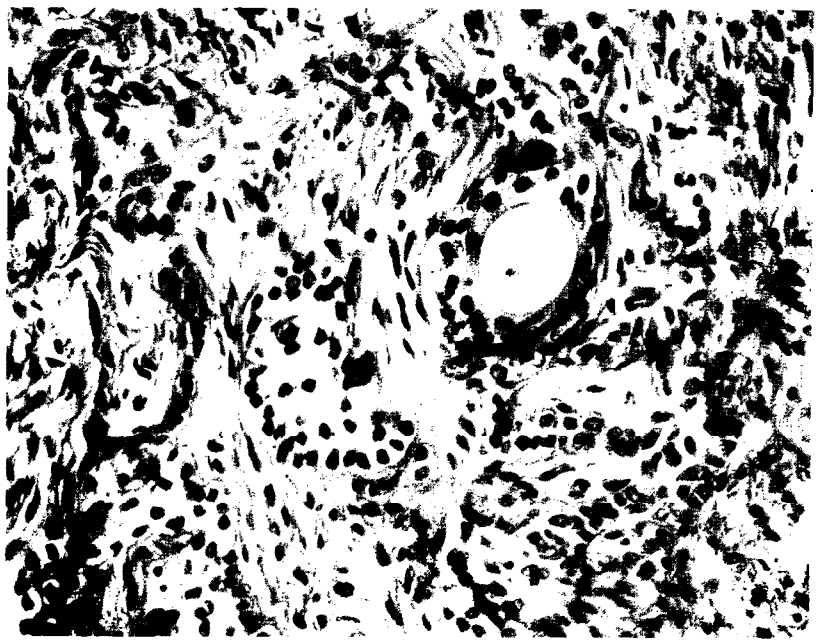

FIGURE 7. Glands within ectopic hamartomatous thymoma. (Magnification × 300.)

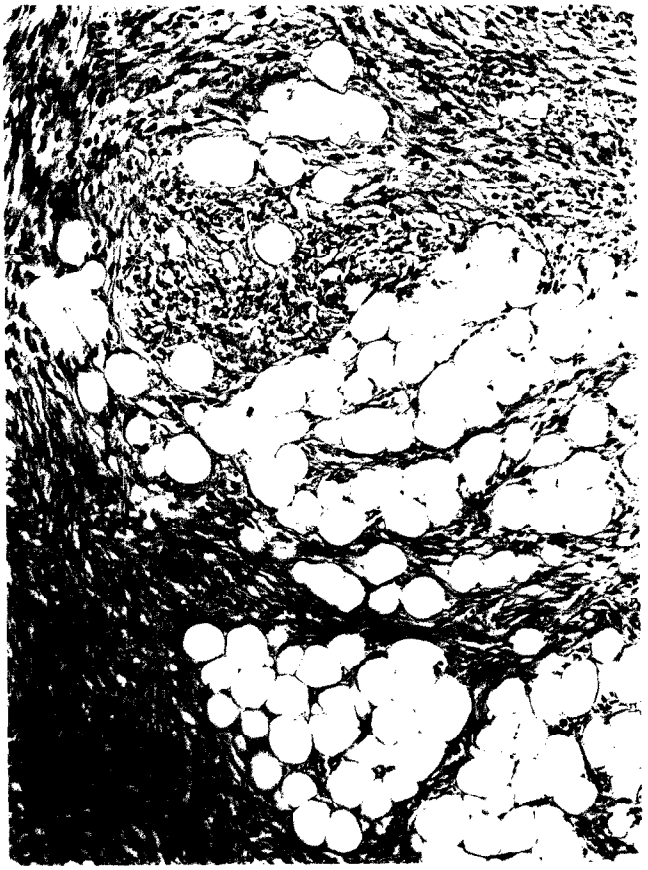

FIGURE 8. Blending of spindled cells and fat within hamartomatous thymoma simulates the pattern of a sarcoma infiltrating fat. (Magnification × 100.)

on the basis of thymic or parathyroid duct remnants, also derived from the third pharyngeal pouch. These gland-like structures, referred to as the canals of Kursteiner, have been identified in fetuses and may persist into adult life.[10,11] They occasionally enlarge and give rise to mucous filled cysts sometimes lined by columnar epithelium.[10]

There are, however, alternative histogenetic explanations, depending on the location of the tumor. The fourth pharyngeal pouch has the capacity to produce small amounts of thymic tissue (thymus IV).[7,11,12] Van Dyke identified thymic IV tissue in 42% of fetuses studied.[12] It was most frequently located adjacent to or in continuity with the parathyroid (IV) glands (derived from the same pouch) or the thyroid gland. Under normal circumstances thymic IV tissue regresses without contributing to the adult thymus gland.[7] However, it may persist[9] and, on rare occasions, apparently can give rise to an intrathyroidal thymoma.[13,14] In fact, one of the reported intrathyroidal spindle cell thymomas bears a striking resemblance to the lesions under discussion. This tumor, reported as "thyroid spindle cell tumor with mucous cysts,[11,13] consisted of a cellular spindled stroma with mucinous glands and calcifications.

Another viable origin for tumors with this appearance could be from the cervical sinus of His. This structure forms when the second branchial arch caudally overgrows the third and fourth arches sequestering a small pocket of ectoderm. Normally this sinus loses its connection with the ectoderm and ultimately disappears altogether. However, persistence of the entrapped cystic portion of this structure results in the branchial (lateral) cysts of the neck, which usually occur in the upper neck in a line along the anterior border of the sternomastoid muscle. In animals a portion of this sinus may undergo thymic transformation.[15,16] While our cases do not contain areas morphologically resembling the typical branchial cleft cyst and occupy sites away from their typical location, this structure would seem to be a potential source for similar lesions. It has been suggested that it gives rise to heterotopic salivary gland tissue in the lower neck which also frequently resides in the vicinity of the sternoclavicular joint.[17] For a short period during embryogenesis the pharyngeal clefts, derived from ectoderm, and the pharyngeal pouches, derived from endoderm, appose one another resulting in the formation of cleft membranes. At these sites of contact, the potential for inclusion of pharyngeal pouch tissue into the pharyngeal cleft exists. Theoretically thymic "primordia" could be implanted at the sites of the third or fourth cleft membranes. The second, third, and fourth cleft membranes reside within the deepest recesses of the cervical sinus of His. The two deepest invaginations, derived from the second and fourth pharyngeal clefts, give rise to placodal vesicles which are the last portion of the cervical sinus of His to disappear and seem to have a greater predilection to persist.

The significance of this rare tumor resides in distinguishing it from other biphasic tumors, particularly malignant ones such as synovial sarcoma and malignant schwannoma with epithelial differentiation. However, other biphasic lesions which enter the differential diagnosis include adnexal tumors, soft-tissue adamantinoma, and ectopic salivary gland tissue of the lower neck region.[17,18]

Biphasic forms of synovial sarcoma contain a spindled component which may appear quite similar to regions of this tumor. In fact, this diagnosis was entertained in case 1 by several observers. However, the epithelial component within synovial sarcomas almost invariably consists of small glands containing mucin. Squamous metaplasia or squamous differentiation of the epithelial component is a rare occurrence within synovial sarcoma.[19] The majority of synovial sarcomas occur in deep soft tissue of the extremity. Those unusual ones occurring in the head and neck are usually distributed between the retropharyngeal space or prevertebral fascia.[19,20] Likewise, well-differentiated malignant schwannomas can recapitulate the appearance of those hamartomatous thymomas which have a predominantly spindled appearance. Care then should be paid to the distinctly wavy or irregular shape of the spindled cells in the malignant schwannoma and to the highly variable cellularity which characterize these areas. Epithelial glands may rarely occur within malignant schwan-

noma[21] but like those in synovial sarcoma are usually small and do not give rise to the adamantinoid ribbons of epithelium seen in hamartomatous thymomas. Since metastasis may occur even in differentiated forms of synovial sarcoma and malignant schwannoma, the distinction of these lesions from the hamartomatous thymoma is of more than academic interest. To date, neither recurrence nor metastases have been reported in the latter. Distinguishing this tumor from an adnexal carcinoma could be quite problematic to one unfamiliar with its features. However, the deep location of some of these tumors detract from the diagnosis of an adnexal tumor even though on purely histologic grounds it would be difficult to categorically exclude this possibility.

In summary, we present four cases of a distinctive biphasic tumor recently described as "ectopic hamartomatous thymoma." In at least one of our cases the extreme cellularity of the spindled areas resulted in the mistaken diagnosis of malignancy, a problem which has not been addressed previously in the literature. The pathologic features combined with the demonstration of immunoreactive keratin within both components of this tumor indicate an epithelial neoplasm, probably derived from thymic anlage. Possible sources of the ectopic thymic tissue include the third pharyngeal pouch, fourth pharyngeal pouch, and the cervical sinus of His. Possibly, on occasion, any of these sites could give rise to a tumor with this appearance. An accurate assessment of the location of the lesion with particular attention to the surrounding structures (ie, branchial cleft derivatives such as parathyroid glands) may help investigators to better understand the pathogenesis of this lesion. Our cases as well as those published in the literature have behaved in a benign fashion even though two of our four cases had been present as slowly growing masses for a period of 30 years.

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