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Thymic Carcinoid Tumor Combined with Thymoma

— Neuroendocrine differentiation in Thymoma? —

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A carcinoid tumor of the thymus combined with thymoma in a 62-year-old man is described. The mediastinal tumor had been present for 13 years and was associated with pure red cell aplasia. Carcinoid tumor occupied the central two-thirds of the tumor, consisting of nests and trabeculae of monotonous round cells, which ultrastructurally showed many intracytoplasmic dense-core granules. Typical spindle cell type thymoma surrounded the carcinoid area. Clinico-pathologic findings of this unique case suggested that the carcinoid tumor developed within a preexisting thymoma, illustrating a possibility of neuroendocrine differentiation of thymic epithelial cells.

Key Words: *thymus, carcinoid tumor, neuroendocrine carcinoma, thymoma*

INTRODUCTION

Carcinoid tumor of the thymus has recently been regarded as a distinct tumor from thymoma, and is probably Kultschizky cell origin, since the first collective study by Rosai et al. in 1972(Rosai & Higa, 1972). We recently experienced coexistence of typical carcinoid tumor and thymoma in a huge mediastinal tumor in a 62-year-old man. We present the clinico-pathologic findings of this unique case and discuss the histogenesis of thymic carcinoid tumor.

CASE REPORT

A 62-year-old man visited the Emergency Room in February 1992 because of aggravating dyspnea. He had been told about his mediastinal mass 13 years previously when he had first felt shortness of breath. A chest CT scan showed a 20x12x12cm-sized well demarcated mass with internal calcification in the right anterior mediastinum. Multiple foci of pleural calcification were noted on the right side, and both lungs were unremarkable. Preoperative laboratory tests revealed that he had normochromic normocytic anemia (Hb 6.4) without increase in reticulocytes. Scarce erythroid precursors were observed on bone marrow biopsy though granulopoiesis and megakaryopoiesis were normal. A diagnosis of pure red cell aplasia, associated with thymoma, was made. No other endocrine abnormality was found. The anemia was preoperatively corrected up to a Hb level of 10.4 by packed cell transfusion. A total mass excision was performed without difficulty and was followed by an uneventful post operative course. In April 1992 he revisited the hospital becuase of dyspnea on exertion, easy fatigability, palpitation and dizziness. Anemia (Hb 6.4) was again revealed, and chemotherapy with prednisolone and cytoxan was started. The red cell aplasia was not responsive until 2 months later when a bout of pneumonia developed. The pneumona of the right lower lung was controlled by antibiotics treatment. The patient still has intractable red cell aplasia with decreasing Hb down to 4.5, and is on conservative medication with occasional transfusion.

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PATHOLOGIC FINDINGS

The excised tumor was well encapsulated and measured 20x13x10cm. On cross section, nodu-

larities with fibrous septa were shown, and the largest nodule, measuring 15x12cm, occupied about two-thirds of the tumor. Its cut surface was more homogeneous, whitish, and friable than surrounding smaller nodules with yellowish glistening appearance (Fig.1)

Microscopic examination of the large nodule revealed typical features of carcinoid tumor, consisting of solid nests, ribbons, festoons, and pseudorosette formations of monotonous small round cells, separated by thin fibro-vascular or hyaline septa (Fig.2). Pseudorosette and festoon-like arrangements were occasionally present. No lymphocytic component was noted. On immunostaining, these cells showed diffuse reactivity for chromogranin A and neuron-specific enolase. The smaller nodules were microscopically composed of mixtures of lymphocytes and spindle-shaped epithelial cells. The number of lymphocytes varied, from scant to predominant, area by area (Fig.3). Predominantly lymphocytic areas showed germinal center formations. Abundant fibrous tissue ran between cellular areas. Microcystic formations were observed in both lesions. These two different lesions were relatively well demarcated in many areas, but focally transitional (Fig. 4).

Electron microscopic study was performed on the two areas using formalin-fixed tissue, revealing numerous intracytoplasmic membrane-bound structures, which were compatible with degenerated dense core granules, in the carcinoid cells (Fig.5). Well-developed desmosomes and basal lamina were observed in the thymoma cells.

DISCUSSION

Rosai and Higa first described carcinoid tumors of the mediastinum, and considered their origin as Kulchitsky cells in the thymus (Rosai & Higa, 1972). They reviewed many further cases in the literature and concluded that the tumors previously interpreted as spindle cell thymoma, or epithelial thymoma with Cushing's syndrome, were related to these tumors. Salyer et al. reemphasized the clinico-pathological difference between thymoma and carcinoid tumor of the thymus (Salyer et al., 1976). Thereafter many unequivocal cases of thymic carcinoid have been described, characterized as being more aggressive tumors than thymomas, not associated with myasthenia gravis or red cell hypoplasia, and showing various neuroendocrine markers and neurosecretory granules immunohistochemically and ultrastructurally (Herbst et al., 1987; Levine & Rosai, 1976; Müllerer-Her-

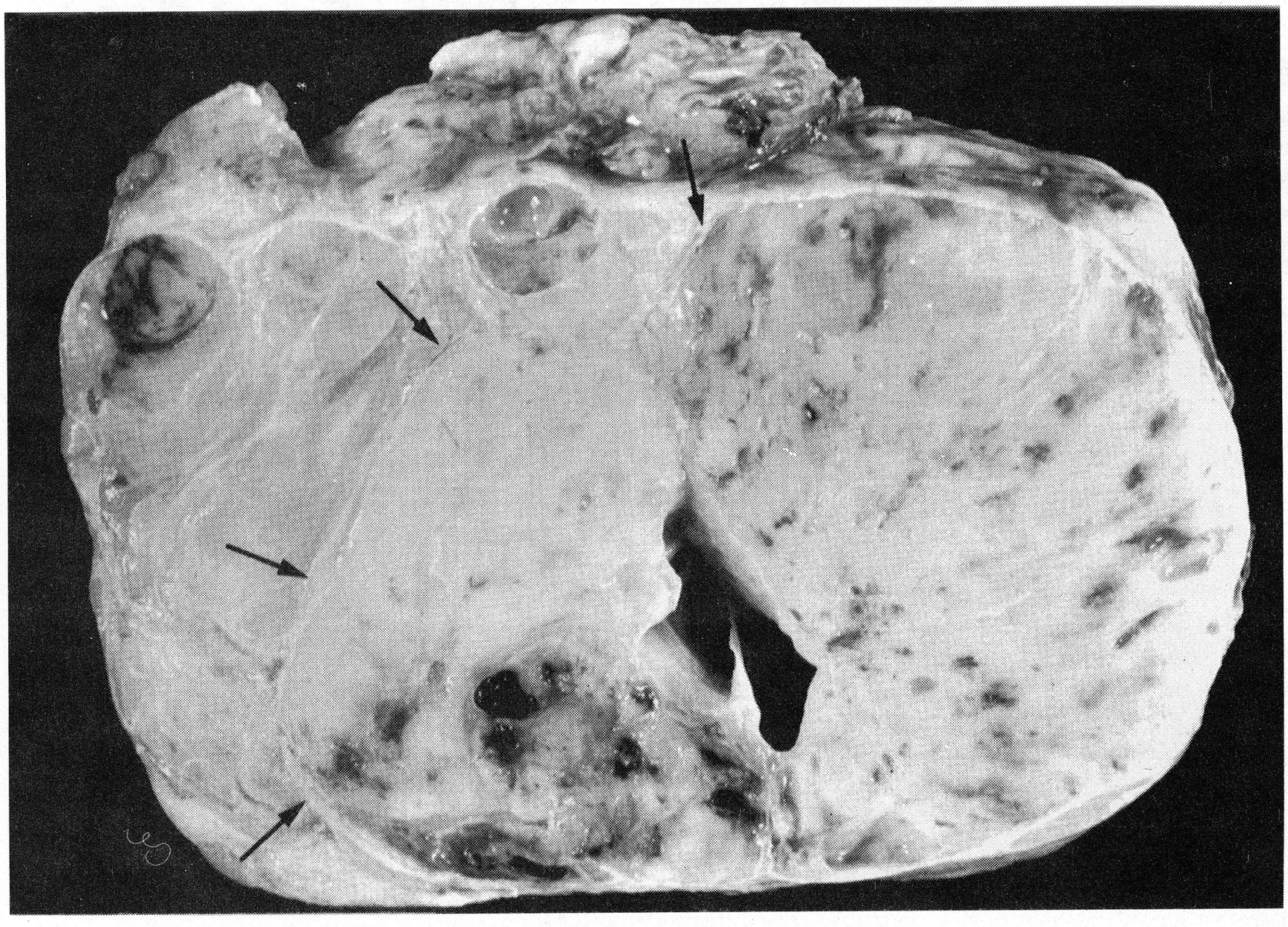

Fig. 1. Gross photograph of the tumor, showing several yellow tan nodules intervened by thin fibrous septa. The largest nodule (arrows) proved to be a carcinoid tumor.

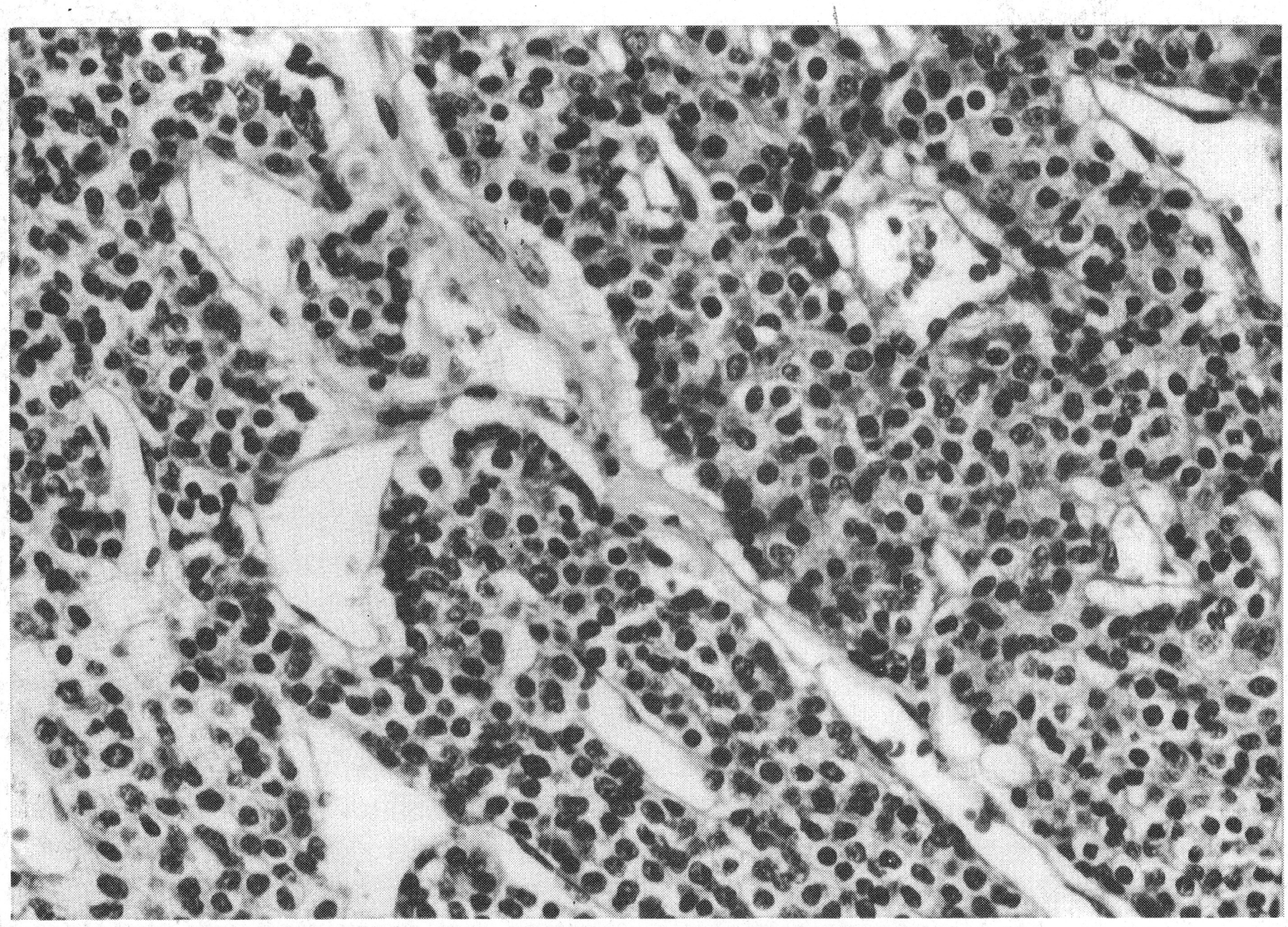

Fig. 2. Photomicrograph of the carcinoid tumor, showing trabecular arrangement of monotonous round cells separated by thin fibrovascular septa (H & E, original magnification x100).

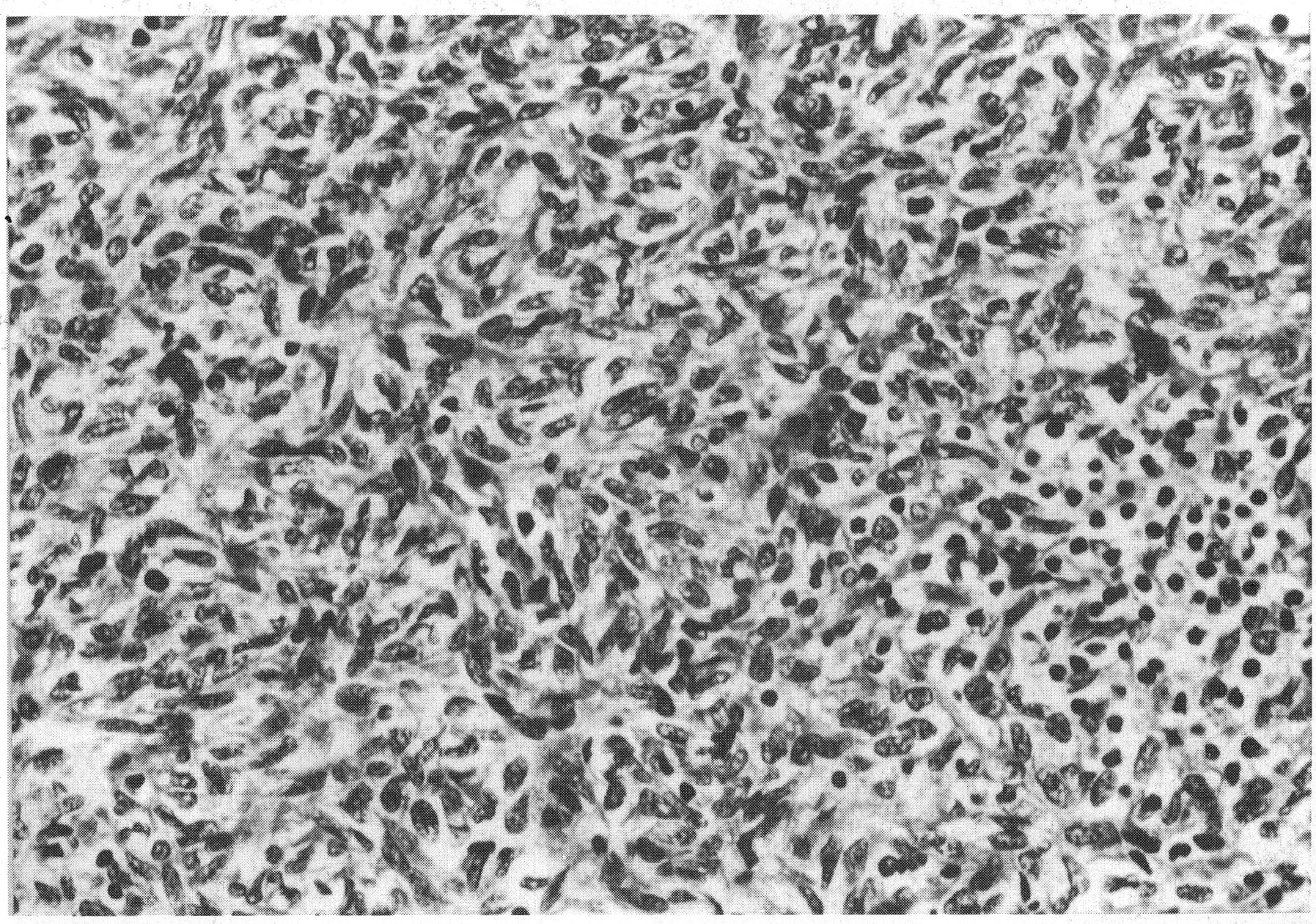

Fig. 3. Areas of thymoma consisting of predominantly spindle epithelial cells and varying numbers of lymphocytes(H & E, original magnification x 100).

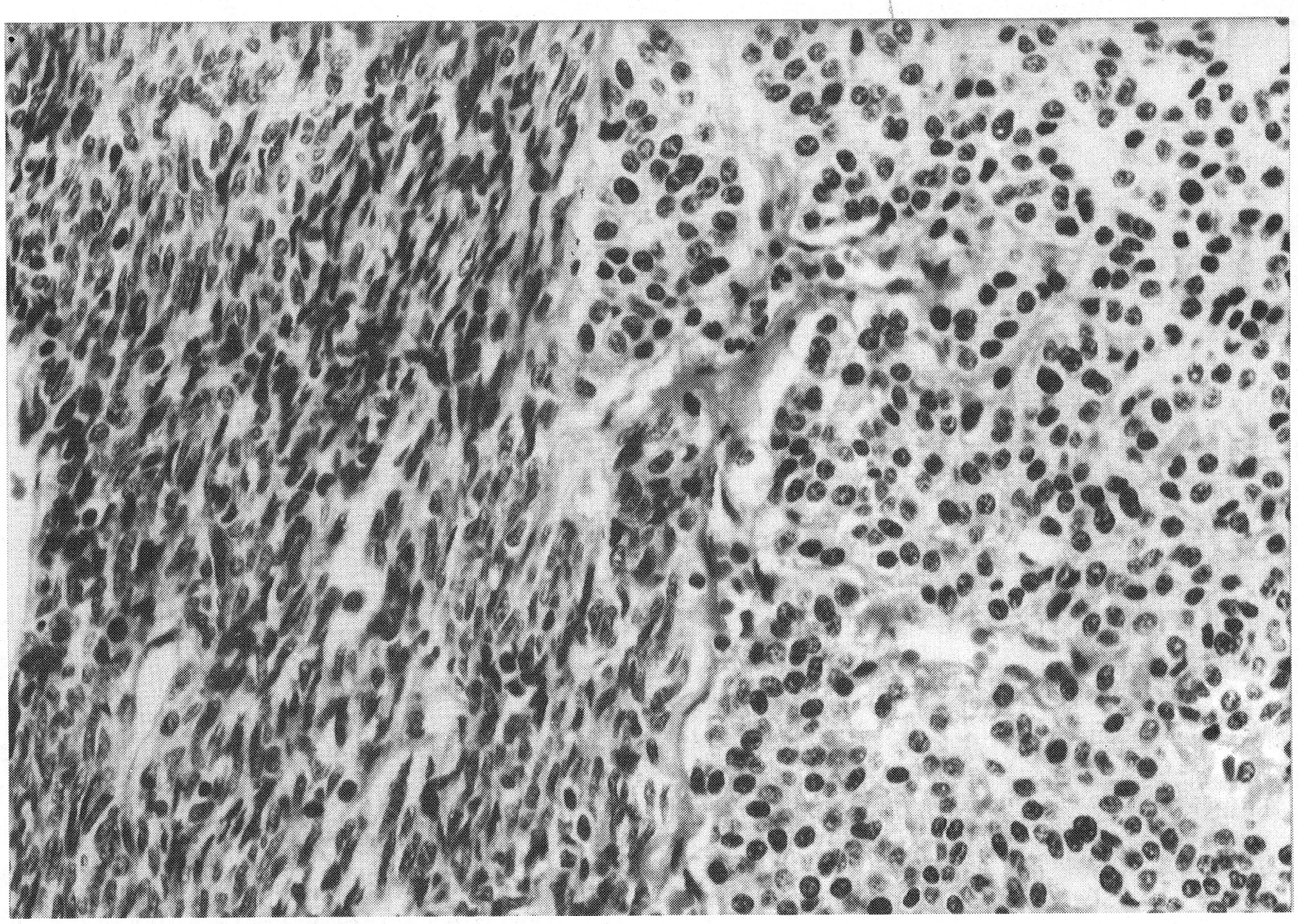

Fig. 4. Transitional border between typical thymoma and carcinoid tumor (H & E, original magnification x 100).

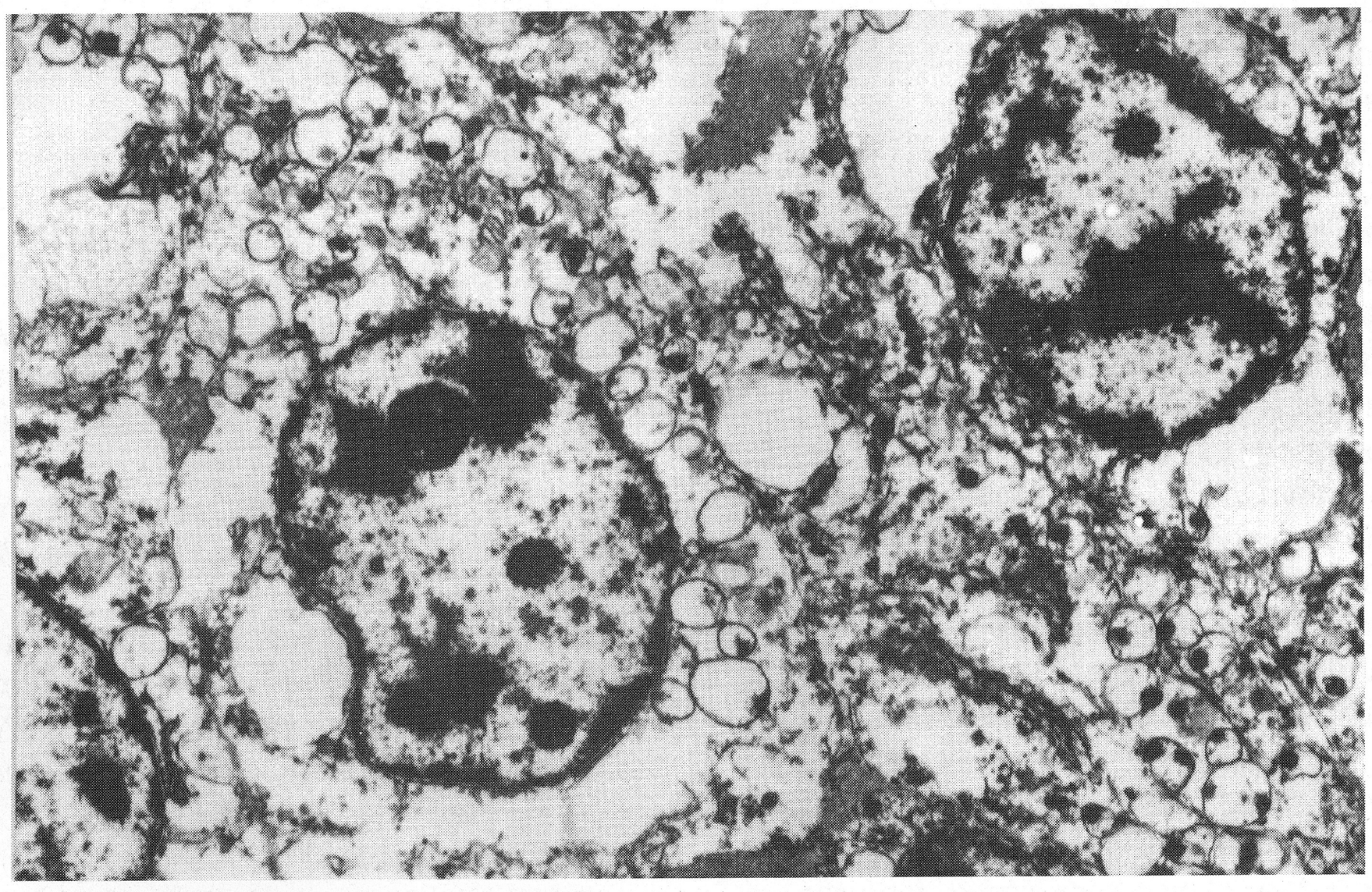

Fig. 5. Electron micrograph of areas of carcinoid tumor, showing numerous intracytoplasmic membrane-bound granules in degeneration (orginal magnification x 3000).

melink, 1985; Sidhu, 1979; Viebahn et al., 1985; Wich et al., 1982a; Wick & Scheithauer, 1984).

Now there is no doubt that carcinoid tumorrs occur in the thymus, however, their histogenesis remains unclear. Several facts raise questions about the hypothesis that thymic carcinoid tumors arise from the Kulchitsky cells present in the normal thymus. First of all, neuroendocrine cells in the thymus have not been precisely characterized in morphologic and functional aspects, although their presence has been demonstrated by argyrophil or immunohistochemical stains (Müller-Hermelink, 1985; Rosia & Higa, 1972). They are beliv-ed to be of neural crest origin by some authors (Levine & Rosai, 1976), though APUD cells of the digestive and respiratory tract have now been shown to be of endodermal origin (Sidhu, 1979). Thymic carcinoids frequently produce more than one peptide (Herbst et al., 1987; Wick & Scheithauer, 1984). Cusing's syndrome is one of the most commonly associated endocrine abnormalities, as in other carcinoid tumors arising from the foregut derivatives (Rosia et al., 1976). Müller-Hermelink suggested that neuroendocrine tumors of the thymus, as in other organs, might represent the result of neuroendocrine differentiation of endoderm derived tumor stem cells (Müller-Hermelink, 1985). The epithelial nature of tumor cells has been confirmed in many neuroendocrine tumors of the thymus (Kay & Wilson, 1970; Lagrange et al., 1987; Viebahn et al., 1985; Wick & Schethauer, 1982 & 1984), while Levine and Rosai stressed the lack of desmosomes, tonofilaments and basal lamina in thymic carcinoid tumor (Levine & Rosai, 1976).

In addition, many cases of thymic carcinomas with neuroendocrine differentiation have been described, illustrating the multiple capabilities of differentiation of thymic cells (Alguacil-Garcia & Halliday, 1987; Paties et al., 1991; Snover et al., 1982; Wick & Scheithauer, 1982; Wick et al., 1982c). The most common associates were undifferentiated small cell carcinomas, but features of carcinoid tumor could also be identified in some cases (Paties et al., 1991; Wick & Scheithauer, 1984). But exact morphology of the studied portions had not been clarified.

Considering the clinico-pathologic features of this case and the discussed facts, it is tempting to speculate that this carcinoid tumor of the thymus has arisen from a thymoma as a result of neuroendocrine differentiation of neoplastic thymic epithelium.

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