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Original contribution

Thymic neuroendocrine tumors (paraganglioma and carcinoid tumors): a comparative immunohistochemical study of 46 cases☆

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Summary Twenty-two paragangliomas from different anatomical sites and 24 thymic neuroendocrine carcinomas (carcinoid tumors) were analyzed for traditional and novel immunohistochemical markers. In the paraganglioma group, there were 8 men and 14 women between the ages of 23 and 79 years (mean, 46 years). Their symptoms depended on the location of the tumor and included neck swelling and Horner syndrome for neck tumors, whereas abdominal and chest pain was present in tumors of the abdomen and mediastinum, respectively. One patient had Carney triad. In the carcinoid group, the patients were 20 men and 4 women between the ages of 25 and 78 years (mean, 48 years). These patients were symptomatic with chest pain, shortness of breath, and dyspnea. One patient presented with multiple endocrine neoplasia syndrome. Complete surgical resection was accomplished in all patients. The 46 neuroendocrine tumors were evaluated for GATA-3, pancytokeratin, thryoid transcription factor 1 (TTF-1), napsin A, chromogranin A, and synaptophysin. All paragangliomas were universally positive for chromogranin A and synaptophysin, but negative for pancytokeratin, TTF-1, and napsin A. GATA-3 was expressed in 12 (55%) of 22 tumors. The thymic neuroendocrine carcinomas (carcinoid tumors) were universally positive for pancytokeratin, but negative for GATA-3 and napsin A. Chromogranin A and synaptophysin were expressed in 92% and 88% of cases, respectively, and TTF-1 in 4 (17%) of 24 cases. Based on these results, we recommend that the workup of neuroendocrine tumors should include not only the conventional neuroendocrine markers and pancytokeratin but also other markers such as GATA-3 and TTF-1 in order to arrive at a better interpretation.

1. Introduction

The spectrum of neuroendocrine tumors is wide and includes a range of neoplasms that can occur in many organ systems. Paragangliomas and neuroendocrine carcinomas

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are among the most common neuroendocrine tumors and those that may pose problems in correct interpretation mainly when dealing with small biopsies [1,2]. These tumors can show striking similarity with regard to morphologic appearance and immunohistochemical phenotype characterized by an organoid growth pattern and neuroendocrine differentiation demonstrated by immunohistochemistry. One of the most effective discriminators to separate these tumors is the expression of cytokeratin in neuroendocrine carcinomas as opposed to paragangliomas [1–4]. There are, however, rare cases of paraganglioma that can show focal or diffuse positive staining for cytokeratin. Although most of these keratin-positive cases are located in the cauda equina or spinal canal, rare paragangliomas in other locations may also show this immunophenotype [5–8].

Most mediastinal paragangliomas follow an indolent clinical course [2], whereas carcinoid tumors of the mediastinum are aggressive tumors that, depending on grade, have survival rates as low as 50% and 25% at 5 years [1]. Thus, it becomes evident that accurate diagnosis is essential as the choice of therapy and clinical follow-up requires different approaches; although paragangliomas are most commonly treated with surgery alone [2], thymic carcinoid tumors may require additional medical therapy [9].

GATA-3 has recently emerged as a sensitive and specific marker for breast and urothelial carcinomas [10] and is also known to be expressed in up to 80% of paragangliomas [11], but there are no studies to date to investigate reactivity of this marker in thymic carcinoid tumors. In addition, detailed information about the use of napsin A and thryoid transcription factor 1 (TTF-1) in the context of separating paraganglioma and thymic carcinoid tumors is still lacking. In order to evaluate use of these antibodies in the differential diagnosis of mediastinal neuroendocrine tumors, we performed a comparative immunohistochemical study to include the aforementioned markers along with more the established ones such as pancytokeratin, synaptophysin, and chromogranin A.

2. Materials and methods

A search using the MD Anderson Cancer Center database identified 4 cases of primary mediastinal paragangliomas and 24 cases of primary thymic carcinoid tumors. In addition, 18 cases of paraganglioma of nonmediastinal sites (13 from the head and neck and 5 from the retroperitoneum) were selected using the same database. The thymic carcinoid tumors were classified as 12 well-differentiated (typical carcinoids) and 12 moderately differentiated (atypical carcinoids) carcinomas based on the classification schema proposed by Moran and Suster [1]. Clinical and radiologic correlation verified the absence of any tumor elsewhere confirming the thymus to be the primary site.

Tissue was obtained from resection specimens in all cases. For the purpose of the present study, representative unstained sections obtained from formalin-fixed and paraffin-embedded blocks were used to perform immunohistochemical studies. The sections were incubated with 3% H_2O_2 in methanol and fetal bovine serum to block endogenous peroxidase activity and nonspecific protein-protein interactions, respectively. Immunostaining was performed using a horseradish peroxidase–labeled polymer system. Tissue sections were incubated with antibodies against GATA-3, pancytokeratin, TTF-1, napsin A, chromogranin A, and synaptophysin (Table 1). Diaminobenzidine was used as a chromogen for antigen localization. Adequate positive and negative controls were run, respectively. Cytoplasmic (pancytokeratin, napsin A, chromogranin A, synaptophysin) or nuclear (GATA-3, TTF-1) staining in the tumor cells was scored on a sliding scale of 0 to 4+, according to the percentage of reactive cells (0, negative; 1+, 1%-25%; 2+, 26%-50%; 3+, 51%-75%; 4+, 76%-100%). The staining intensity was graded as weak, intermediate, or strong.

Clinical and follow-up information was obtained from the patients' medical records or from the referring physicians. The study was approved by the MD Anderson Institutional Review Board.

3. Results

3.1. Clinical features

The patients with paraganglioma were 8 men and 14 women with an age range from 23 to 79 years (mean, 46 years). The presenting symptoms depended on the primary site of the lesion and included neck swelling and Horner syndrome for patients with head and neck tumors, abdominal pain for patients with retroperitoneal lesions, and chest pain or incidental findings in patients with mediastinal paragangliomas. Some patients displayed functional symptoms (headache, hypertension, weight loss, and elevated catecholamine levels), which were unrelated to the site of the tumor. In 2 patients, the tumors arose on a background of *succinate dehydrogenase subunit B* (*SDHB*) gene mutation, whereas 1 patient had Carney triad (Table 2).

Among the patients with thymic carcinoid tumors were 20 men and 4 women aged 25 to 78 years (mean, 48 years). Chest pain, shortness of breath, and dyspnea were the main presenting symptoms; the tumors were incidental findings in 5 patients. One patient had multiple endocrine neoplasia (MEN) syndrome (Table 3).

Complete surgical resection was performed in all cases.

3.2. Histologic features

The paragangliomas had similar morphologic features irrespective of anatomical site. They were characterized by