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Original contribution

Frequency and extent of cytokeratin expression in paraganglioma: an immunohistochemical study of 60 cases from 5 anatomic sites and review of the literature

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Summary The absence of cytokeratin expression in paraganglioma helps to differentiate it from other neuroendocrine neoplasms such as carcinoid tumor. Although rare cytokeratin positive paragangliomas have been reported, there are no large systematic studies of this phenomenon. The aim of this study was to determine the frequency and extent of cytokeratin expression in paragangliomas using a large cohort of cases from multiple anatomic sites. Immunohistochemical staining for keratin AE1/AE3 (mouse monoclonal, MAB3412; Millipore) and CAM 5.2 (mouse monoclonal, 349 205; Becton-Dickinson) was performed on whole-tissue sections from 60 resected paragangliomas from the head and neck (36), thorax (10), abdomen (8), intradural/epidural spine (5) and bone, left iliac (1). Cytokeratin expression was identified in only 2/60 (3.3%) cases. One was a mediastinal paraganglioma with moderate to strong expression of keratin AE1/AE3 and CAM 5.2 in <5% tumor cells. The other was a lumbar intradural paraganglioma positive for CAM 5.2 (moderate to strong, 80% of tumor cells) but negative for keratin AE1/AE3. All other paragangliomas (58/60, 96.7%) were negative for keratin AE1/AE3 and CAM 5.2. This study — the largest series of cytokeratin-stained whole-tissue sections of paragangliomas to date — supports the dictum that most paragangliomas are cytokeratin negative. Rare exceptions may be site-related.

1. Introduction

Paragangliomas are neuroendocrine neoplasms derived from the autonomic nervous system [1,2]. When these tumors arise from the adrenal medulla they are termed pheochromocytoma [2]. Separation of paraganglioma from other neuroendocrine neoplasms such as well-differentiated neuroendocrine carcinomas (such as typical and atypical carcinoid tumor) is important for therapy and

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prognosis. Furthermore, since greater than 30% of paragangliomas/pheochromocytomas are associated with inherited cancer susceptibility syndromes [3,4], the accurate diagnosis of paraganglioma helps to identify patients who may benefit from genetic testing.

The distinction of paraganglioma from neuroendocrine carcinoma is aided by immunohistochemistry. Both tumor types express neuroendocrine markers such as synaptophysin, chromogranin, and the nuclear neuroendocrine marker INSM1 [2,5-7]. However, in contrast to neuroendocrine carcinomas, paragangliomas do not express cytokeratin and contain sustentacular cells that stain for S100 and SOX10. Although it is true that the majority of paragangliomas lack cytokeratin expression [1,8-14], there are notable exceptions in the form of a few case series and case reports that demonstrate cytokeratin expression in paragangliomas, particularly of the cauda equina [15-27]. To our knowledge, no large or systematic studies have analyzed cytokeratin expression in paragangliomas from multiple anatomic sites. The aim of this study was to systematically examine the frequency and extent of cytokeratin expression in extra-adrenal paragangliomas from a range of anatomic sites.

2. Materials and methods

2.1. Case selection and literature review

After institutional review board approval, our archives were searched for resected paragangliomas over an 11-year period (2007–2017). All available hematoxylin–eosin (H&E)-stained slides were reviewed by two pathologists (JKD, AAS). In order to qualify as a paraganglioma, tumors were expected to have characteristic morphologic features including epithelioid cells with moderate amounts of eosinophilic to amphophilic cytoplasm, nested growth pattern, expression of neuroendocrine markers (synaptophysin and/or chromogranin), and presence of sustentacular cells demonstrated immunohistochemically by S100.

We also performed an English literature PubMed-indexed search using the search terms “paraganglioma” and “cytokeratin” or “keratin” to analyze the data related to cytokeratin expression in paragangliomas. Additional reports were found through references of original searched articles.

2.2. Immunohistochemical staining

Immunohistochemical stains were performed on a Ventana Benchmark Ultra automated immunostainer (Ventana Medical Systems [VMS], Tucson, AZ). Formalin-fixed, paraffin-embedded (FFPE) tissue sections, cut at 4 microns, were treated with online deparaffinization, followed by online epitope retrieval, if required. Localization of the antigen–antibody complex was achieved using the VMS OptiView DAB detection kit.

Keratin AE1/AE3 is a cocktail of two mouse monoclonal antibodies from Millipore, cat# MAB3412. Epitope retrieval was performed using VMS Protease 2 (~0.1 mg/mL alkaline protease activity) for 4 minutes. AE1/AE3 at 1:200 dilution is incubated for 12 minutes at 37°C. Cytokeratin mouse monoclonal CAM 5.2 was from Becton-Dickinson, cat# 349205. Epitope retrieval was performed using VMS Protease 2 (~0.1 mg/mL alkaline protease activity) for 4 minutes. CAM 5.2 at 1:10 dilution is incubated for 16 minutes at 37°C. Both the AE1/AE3 and CAM 5.2 antibodies are broad spectrum antibodies that recognize acidic and basic keratins with a broad spectrum of molecular weights. Specifically, the AE1 antibody recognizes the 56.5, 50, 50′, 48, and 40 kilodaltons (kD) keratins of the acidic subfamily; the AE3 antibody recognizes all members of the basic subfamily (65, 67, 64, 59, 56, 52 kD). The CAM 5.2 antibody has a primary reactivity with keratin peptides of 53 kD, but also demonstrate a weaker but distinct reactivity against keratin peptides of 54 kD. Synaptophysin was mouse monoclonal Snp88 from Biogenex, cat# AM363-5 M. Heat induced epitope retrieval (HIER) was performed using VMS Cell Conditioning 1 (CC1) (high pH buffer) for 32 minutes. Ready-to-use synaptophysin was incubated for 12 minutes at 37°C. Chromogranin A was mouse monoclonal DAK-A3 from Agilent, cat# M0869. HIER was performed using VMS CC1 for 32 minutes. Chromogranin A at 1:100 dilution was incubated for 16 minutes at 37°C. S100 was a rabbit polyclonal antibody from Dako (now Agilent), cat# Z0311. No epitope retrieval was required. S100 at 1:800 dilution was incubated for 4 minutes with no heat.

In cases with either keratin AE1/AE3 and/or CAM5.2 expression, GATA3 was performed using a mouse monoclonal antibody from Biocare Medical, cat # CM405C. HIER was performed using VMS CCI for 32 minutes. GATA3 at 1:100 dilution was incubated for 24 minutes with no heat. All stains were compared to the appropriate positive and negative controls during interpretation. Immunohistochemical stains were reviewed by two authors (JKD, AAS) and the percentage and intensity of tumor cell staining was documented.

3. Results

We retrieved 60 paragangliomas from 60 patients (46 women, 14 men) with an age range of 18–86 years (median 51 years). Most of the tumors were located in the head and neck region (36), followed by the thorax (10), abdomen (8), intradural/epidural spine (5), and bone, left iliac (1). Details of anatomic site of the paragangliomas in this study are listed in Table 1. The vast majority of paragangliomas (58/60, 96.7%) were negative for both keratin AE1/AE3 and CAM 5.2. Only two cases, described below, showed cytokeratin positivity.

Table 1 Anatomical distribution of paragangliomas in this study

Location	Cases (%)
Head and neck	
Ear, middle	20 (33.3)
Carotid body	14 (23.3)
Thyroid	2 (3.3)
Intrathoracic	
Mediastinal	8 (13.3)
Heart, atrium	2 (3.3)
Abdominal	
Retroperitoneal	5 (8.3)
Bladder	3 (5.0)
Spinal	
Intradural	3 (5.0)
Epidural	2 (3.3)
Bone, left iliac	1 (1.7)
Total	60

The first patient was a 45-year-old woman who presented with a 6.5 cm mediastinal mass. Grossly, the mass was solid and tan-pink. Histologic sections demonstrated a pleomorphic epithelioid to spindled neoplasm composed of markedly atypical cells with prominent cytoplasmic clearing and a rich vascular network with a nested architecture. Mitotic activity was low despite the pleomorphism. Nuclear chromatin was granular with many intranuclear pseudoinclusions. The neoplastic cells were positive for synaptophysin, chromogranin and GATA3, and negative for ERG, CD31, TTF1, PAX8, CEA and calcitonin. S100 highlighted scattered sustentacular cells. The tumor showed focal positivity for keratin AE1/AE3 and CAM 5.2, with moderate-to-strong staining in less than 5% of the neoplastic cells (Fig. 1).

The second patient was a 65-year-old woman with a recurrent intradural paraganglioma of the lumbar region. The tumor formed a 4.5 cm tan-red and soft mass with white fibrous streaks. Histologic sections showed a cellular lesion with a nested pattern and perivascular sclerosis. The neoplastic cells were strongly positive for synaptophysin and chromogranin. S100 highlighted scattered sustentacular cells. Keratin AE1/AE3 was negative, but CAM 5.2 was positive, with moderate to strong staining in 80% of tumor cells (Fig. 2). The primary tumor was diagnosed 10 years previously in the same location. The original tumor was also negative for keratin AE1/AE3. CAM 5.2 was not performed during the initial diagnosis and the paraffin block was not available for current testing. The neoplastic cells were negative for GATA3.

4. Discussion

According to the most recent WHO classification of endocrine tumors, paragangliomas are non-epithelial neoplasms that originate from neural crest-derived paraganglia. Microscopically, the tumor cells are arranged in an organoid (Zellballen) pattern [1]. They are typically composed of chief cells characterized by abundant pale cytoplasm and hyperchromatic nuclei, and spindle-shaped sustentacular cells located peripherally around the nests [1,2]. A prominent vascular network usually separates tumor cell nests [1,2]. Neuroendocrine markers, such as synaptophysin, chromogranin and CD56, are almost always positive in the chief cells, while S100 and SOX10 highlight sustentacular cells [1,2].

Despite the dictum that paragangliomas do not express cytokeratin, occasional reports have documented rare examples of cytokeratin expression in these tumors [15-27]. Table 2 summarizes the literature findings of cytokeratin expression in paragangliomas. A handful of reports have shown focal to strong cytokeratin staining in paragangliomas of the cauda equina [15-18,27], leading to the hypothesis that cauda equina paragangliomas are biologically distinct. However, cytokeratin positivity in paragangliomas from other anatomical locations have also been reported. For example, one of the largest studies of head and neck paragangliomas with comprehensive immunohistochemical profiling of 29 tumors detected cytokeratin positivity using keratin AE1/AE3 and CAM 5.2 in two glomus jugulare tumors and one carotid body tumor [19]. Another study of 18 extra-adrenal paragangliomas, showed keratin AE1/AE3 and CAM 5.2 expression in an intravagal, an orbital, and a cauda equina paraganglioma [20]. In a recent case report, similar to one of our cases, diffuse AE1/AE3 expression was reported in an intradural paraganglioma at the lumbar region [21]. In the thorax, a case diagnosed as endobronchial gangliocytic paraganglioma was reported to stain positively for keratin AE1/AE3 and CAM 5.2 [22]. Three additional case reports have described primary pulmonary paragangliomas with at least focal reactivity to AE1/AE3 and/or CAM 5.2 [23-25]. On the other hand, a study of 16 cases of mediastinal paraganglioma found no examples of cytokeratin positivity [9].

Most of these anecdotal observations have been based on a limited number of cases. In view of the absence of systematic data on this issue, we sought to study cytokeratin expression in a relatively large series of paragangliomas across a broad anatomical distribution. Only 2/60 cases in our study showed cytokeratin expression (CAM 5.2) - one case each from the mediastinum and lumbar region - supporting the dictum that most paragangliomas are negative for cytokeratin. However, as seen in the single cytokeratin (CAM 5.2)-positive paraganglioma from an intradural lumbar region, positivity in these tumors can rarely be strong and diffuse. However, neither of our cases had strong and diffuse expression of both cytokeratins.

In practice, in difficult cases, GATA3 and tyrosine hydroxylase are additional immunohistochemical markers that can assist in supporting the diagnosis [28-32]. Although positivity for these markers is helpful, negative staining does not exclude the diagnosis, since the sensitivity for

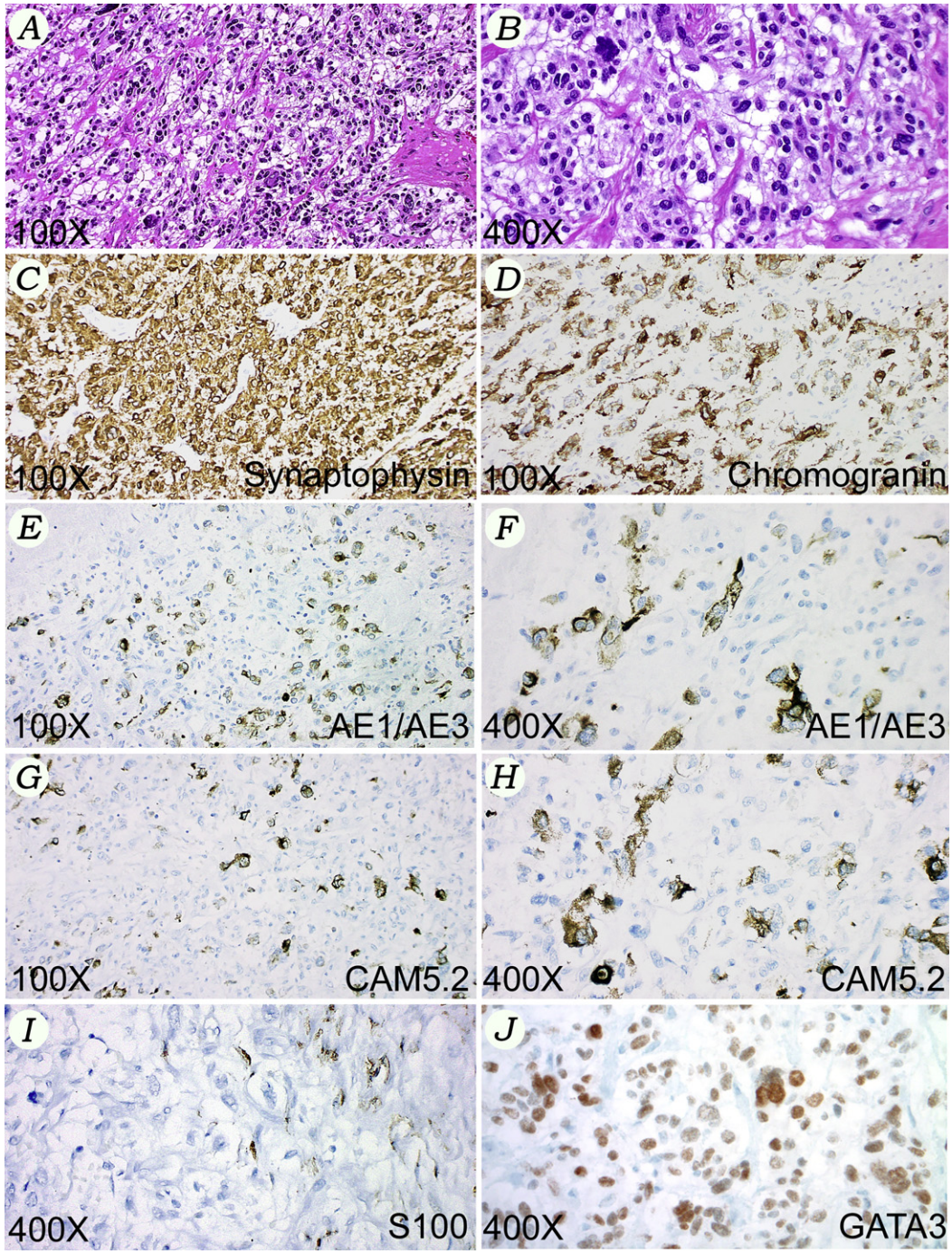

Fig. 1 Paraganglioma from a 6.5 cm mediastinal mass. A and B, Tumor demonstrates a pleomorphic epithelioid/spindled cells in a nested architecture (hematoxylin and eosin). C and D, The neoplastic cells are strongly and diffusely positive for synaptophysin (C) and chromogranin (D). E-H, AE1/AE3 (E-F) and CAM 5.2 (G-H) show focal, moderate-to-strong staining intensity in less than 5% of tumor cells. I, S100 highlights a few sustentacular cells. J, The neoplastic cells are strongly and diffusely positive for GATA3 (magnification indicated on individual image).

GATA3 for paragangliomas is not perfect (70–90%) [28-30]. Tyrosine hydroxylase, an enzyme involved in catecholamine synthesis, has been reported as a useful marker particularly for the diagnosis of paragangliomas in unusual sites. However, this marker is not available in our laboratory [31,32]. We also acknowledge that the literature contains studies in which a rigid distinction between paraganglioma and other neuroendocrine neoplasms was not based on complete biomarker profiling. For instance, a significant proportion of previous series did not use GATA3 and tyrosine hydroxylase. Therefore, one should assess this information with caution.

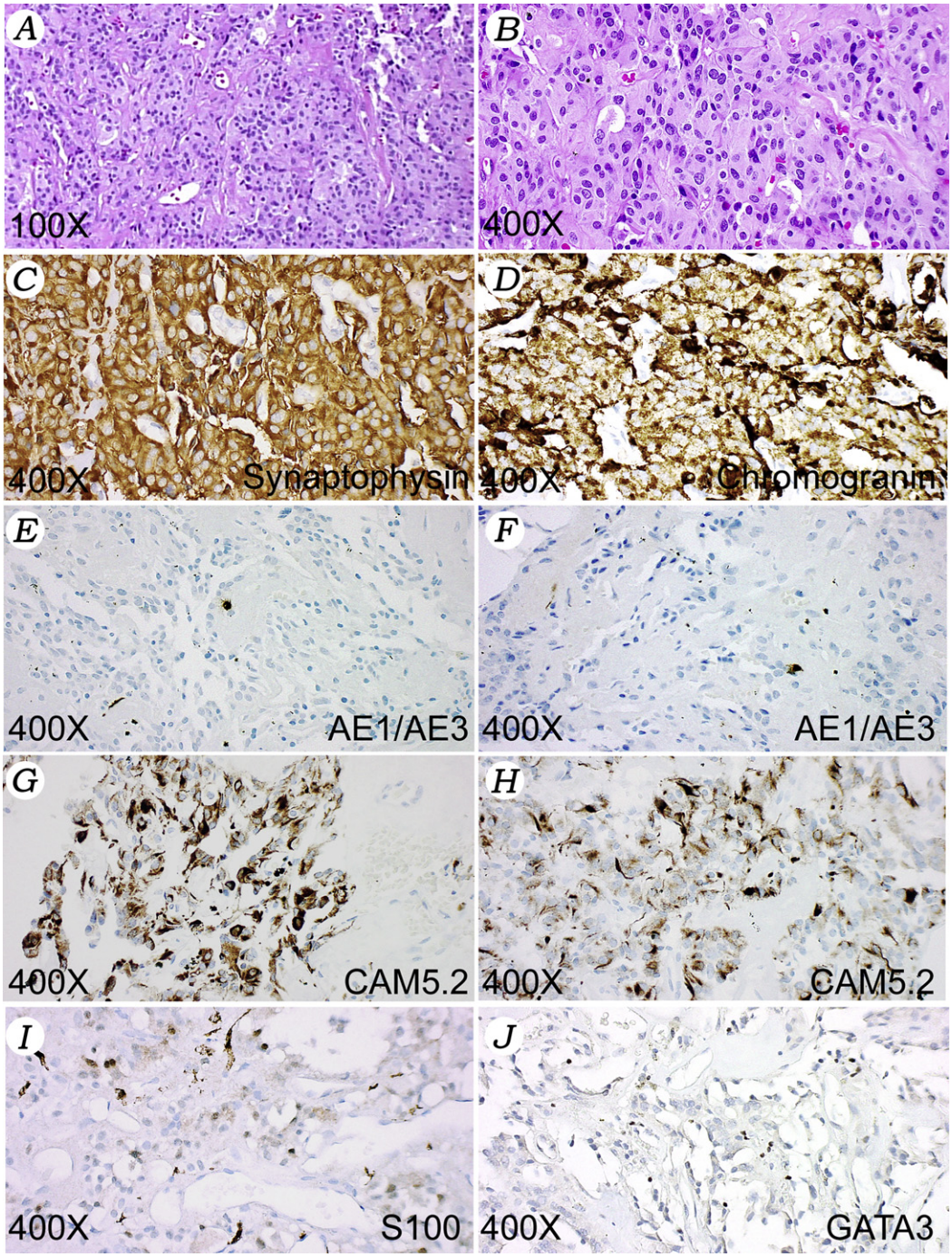

Fig. 2 Intradural paraganglioma from a 2.5 cm lumbar mass. A and B, Tumor consists of epithelioid cells in a nested pattern (hematoxylin and eosin). C and D, Synaptophysin (C) and chromogranin (D) are both strongly and diffusely positive in tumor cells. E-H, The cells are negative for AE1/AE3 (E-F). However, CAM5.2 (G-H) shows moderate-to-strong staining intensity in 80% with a few sustentacular cells staining positive for S100. I, S100 highlights a few sustentacular cells. J, The neoplastic cells are negative for GATA3, there are rare scattered non-tumoral cells with expression of GATA3 (magnification indicated on individual image).

In summary, based on our findings, cytokeratin expression in extra-adrenal paragangliomas is rare and generally limited to tumors arising in non-head and neck sites, such as the mediastinum and lumbar spine. The basis of cytokeratin expression in these sites remains unclear, and should be addressed in future studies. The findings of this study support the dictum that cytokeratin expression is useful in distinguishing paragangliomas from other low to intermediate grade neuroendocrine neoplasms such as carcinoid tumor.

Table 2 Literature review on cytokeratin expression in extraadrenal paragangliomas

Author/year	Gender	No. of cases	Age (y)	Tumor location (# of cases)	Cytokeratin expression	Cytokeratin antibodies
Dermawan/2019 (current study)	46 F, 14 M	60	18–86 (median 51)	See Table 1	Focally strong for AE1/3 and CAM 5.2 in 1 mediastinal, diffuse and strong for CAM 5.2 and negative for AE1/3 in 1 intradural case	AE1/AE3, CAM 5.2
Fraga/1993 [8]	7 F, 1 M	7	21–65 (mean 41)	CB (6), retroperitoneum RP (1)	Negative in all cases	AE1/AE3, CAM 5.2
Moran/1993 [9]	6 F, 10 M	16	16–69 (mean 43)	Mediastinum: posterior (12), anterior (3), unknown (1)	Negative in all cases	"broad-spectrum keratin"
Martinez-Madrigal/1991 [10]	10 F, 6 M	16	17–74 (mean 44)	Vagus (8), CB (3), jugulotympanic (2), Vagal/jugulotympanic (2), larynx (1)	Negative in all cases	KL-1
Aubertine/2004 [11]	1 M	1	40	Endobronchial (1)	Negative	AE1/AE3, CAM 5.2
Cheng/2000 [12]	6 F, 2 M	8	16–74 (mean 45)	Bladder (16)	Negative in all cases	AE1/AE3, CK7, CK20
Shibahara/2004 [13]	1 F	1	55	Intrapulmonary	Negative	AE1/AE3, CAM 5.2, KL-1
Noble/1997 [14]	2 M	2	14–71 (mean 43)	Skull base (2)	Negative	N/A
Orrell/1992 [15]	6 F, 2 M	8	41–63 (mean 47)	CE (3), CB (3), ear (1), RP (1)	Focal for AE1/3, strong and diffuse for CAM 5.2 and MNF 116 in 3 CE	MNF 116, AE1/AE3, CAM 5.2
Labrousse/1999 [16]	5 F, 6 M	11	12–73 (mean 49)	CE (3), CB (5), aortic arch (1), GJ (2)	Strong and diffuse in 3 CE, focal in one CB	"broad-spectrum keratin"
Pytel/2005 [17]	1 F	1	74	CE (1)	Moderate to strong and diffuse for AE1/3 and CAM 5.2	AE1/AE3, CAM 5.2
Hirose/1988 [18]	N/A	2	N/A	CE (2)	Focally positive in 1 case	N/A
Johnson/1988 [19]	N/A	29	N/A	GJ (20), CB (9)	Strong and diffuse for cytokeratin cocktail in 2 GJ and 1 CB	AE1/AE3 and CAM 5.2 cocktail
Chetty/1998 [20]	13 F, 5 M	18	7–74	Extraadrenal (18): CE (1), orbit, organ of Zuckerkandl, CB, vagus nerve	Strong and diffuse for CAM 5.2 and weaker staining for AE1/3 in 1 CE; strong and diffuse for both AE1/3 and CAM 5.2 in 1 orbit and 1 vagus nerve	AE1/AE3, CAM 5.2
Nowacki/2016 [21]	1 M	1	60	Intradural (1)	Strong and diffuse for AE1/3; negative for CK7 and CK20	AE1/AE3, CK7, CK20
Gucer/2014 [22]	1 M	1	61	Endobronchial gangliocytic (1)	Epithelioid cells positive for AE1/3 and CAM 5.2; spindle cells focally for AE1/3	AE1/AE3, CAM 5.2
Saeki/1999 [23]	1 F	1	38	Pulmonary (1)	Positive primarily in sustentacular cells but also focally in tumor cells	CAM 5.2
Kim/2000 [24]	1 M	1	34	Pulmonary (1)	Focally positive	AE1/AE3
Skødt/1995 [25]	2 F	2	33–69	Pulmonary (2)	Focally positive (punctate) for CAM 5.2 in 1 case; negative for cytokeratin in 1 case	CAM 5.2
Moran/1997 [26]	15 M, 15 F	30 (23 w IHC)	20–74 (mean 46)	Spine: lumbar (19), CE (6), filum terminale (2), thoracic (2), cervical (1)	Focally positive in 5/23 (21%)	"broad-spectrum keratin"
Ironside/1985 [27]	1 F, 1 M	2	42–50	CE (2)	Focally positive (10%) for cytokeratin in both cases	"cytokeratin"

Abbreviations: M, male; F, female; CB, carotid body; CE, cauda equina; GJ, glomus jugulare; RP, retroperitoneum; IHC, immunohistochemistry.

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