**Case report**

**Soft tissue metastasis of mediastinal non-functioning paraganglioma with unusual TTF-1 expression: A potential diagnostic pitfall**

Michal Beneš1, Iva Zamo2, Ondřej Bilek1, Ivan Capov1

1First Department of Surgery, Medical Faculty, Masaryk University and St. Anne’s University Hospital, Brno, Czech Republic
21st Department of Pathological Anatomy, St. Anne’s University Hospital, Brno, Czech Republic
3Clinic of Comprehensive Cancer Care, Masaryk Memorial Cancer Institute, Brno, Czech Republic

Metastatic extra-adrenal paragangliomas are very rare and can represent diagnostic challenges. We report a case of 69-year-old man with a tumor of the right shoulder. Histologic and immunohistochemical examinations confirmed the diagnosis of paraganglioma. Sporadically, tumor cells were diffusely thyroid transcription factor 1 (TTF-1) positive. Succinate dehydrogenase complex subunit B (SDHB) deficiency has not been detected. Inherited syndromes associated with paragangliomas were ruled out. The primary tumor was identified in the mediastinum. This is the first report of TTF-1 expression in paraganglioma. To avoid misdiagnosis, careful clinical and pathological examination of any tumor with organoid growth pattern is necessary.

**Key words:** neuroendocrine tumor, malignant paraganglioma, hereditary syndromes, thyroid transcription factor 1.

**Introduction**

Paragangliomas (PGLs) are very rare neuroendocrine tumors arising from the extra-adrenal autonomic paraganglia. Intra-adrenal PGL is called pheochromocytoma. While sympathetic PGLs usually secrete catecholamines, and therefore clinically manifest with hypertension, tachycardia, episodic headache and sweating, most parasympathetic PGLs are nonfunctional, thus difficult to diagnose. Besides distinct clinical features, sympathetic and parasympathetic PGLs also differ in their anatomical distribution. Sym pathetic PGLs arise anywhere along sympathetic chain from the base of the skull to the bladder and prostate, most often in the abdomen. Parasympathetic PGLs are located along the branches of the vagus or vagal nerves and typically arise from the carotid body or less commonly from jugulotympanic, vagal or laryngeal paraganglia [1]. Up to one-half of cases can be associated with an inherited syndrome, in particular with the succinate dehydrogenase (SDH) gene mutations, multiple endocrine neoplasia type 2, neurofibromatosis type 1, von Hippel Lindau, or Carney-Stratakis dyad. Sporadic PGLs arise predominantly in females, but hereditary PGLs develop equally frequently in males and females [2, 3]. The vast majority of PGLs are benign. Malignant PGLs are extremely rare. Depending on the type of tumor, 0-56% of patients with PGL develop metastases [4, 5]. Chronic hypoxia in patients living in high altitudes and chronic obstructive lung disease represent a well-known risk factors for development of sporadic PGL [6, 7].

Here we report an unusual case of a 69-year-old man with a metastatic sporadic non-functional PGL of mediastinum initially presenting as a painful soft tissue tumor of right lateral supracavicular region. Absence of clinical symptoms at diagnosis, atypical location of the resected tumor and aberrant immunohistochemical highlighted the diagnostic challenges in establishing the correct diagnosis.

**Case description**

A 69-year-old male patient presented with a 3-year history of slow growing, somewhat painful mass in the right supracavicular area. Ultrasound examination confirmed a well-circumscribed ovoid tumor not exceeding 2.0 cm in size. The patient’s medical history was significant for arterial hypertension due to chronic tubulointerstitial nephritis stage 3 which was perhaps associated with chronic non-steroidal anti-inflammatory drugs (NSAIDs) overdose due to the bilateral coxarthrosis and chronic low back pain. Apart from the chronic pain of the hips and varicose veins in lower extremities, general physical examination was unremarkable. There was no personal and/or familial history of cancer.

An uncomplicated removal of the supracavicular mass was performed. On macroscopic examination, the lesion measured 1.7 x 1.5 x 1.2 cm and was solid, with a whitish yellow cut surface. Histologically, a well-vascularized tumor was composed of relatively uniform, round epithelioid cells arranged in compact clusters of varying size with focal clear cell change (Fig. 1A). In places, the inopaculous spindle-shaped cells were apparent. Sporadic mitotic figures were noted. Intervening extracellular matrix was variably fibrous to hyaline. The tumor infiltrated the vaguely formed fibrous capsule, however, the soft tissue margins were microscopically free of tumor. Various differential diagnoses came into consideration such as malignant melanoma, metastatic clear cell carcinoma, PECa, and hermangioendothelioma.

The immunohistochemical analysis revealed the S-100 protein positive incomplete network of sustentacular cells (Fig. 1B) and groups of neuroendocrine cells which strongly expressed CD56, neuron-specific enolase (NSE), chromogranin A, and synaptophysin (Fig. 1C, D). Surprisingly, tumor cells were also diffusely thyroid transcription factor 1 (TTF-1) positive. (Fig. 1E) whereas no immunoreactivity was detected with antibodies against thyroglobulin, calcitonin, vimentin, pan-cytokeratin (AE1/AE3), high molecular weight cytokeratin (HMWCK), cytokeratins 5, 7 and 20, phosphatase specific antigen (PSA), HMB-45, Melan A, smooth muscle actin (SMA), CD34, CD31, CD10, and placental alkaline phosphatase (PLAP). The Ki-67 labeling showed less than 5% of neuroendocrine cells. Based on the histological and immunophenotypic features, the diagnosis of PGL was determined. Because of atypical location of tumor, the metastatic origin of the lesion was suggested. Subsequently, SDHB deficiency has not been immunohistochemically detected.

In order to locate the origin of the metastatic disease, the patient was subjected for computed tomography (CT) of thoracic and abdominal cavity. CT chest showed a large solid mass lesion measured 14.7 cm in the greatest dimension, arising in the subcardiac region with particular compression of the right main bronchus (Fig. 2). In addition, a small 5 mm nodule in the right lung was revealed, suspected to be the right hilar lymph node metastasis of the seventh rib on the right side and ground glass opacity in the upper and lower lobe were confirmed. Adrenal glands on the both side did not exceed normal size variability. MetastadoBenet/Gumi- dine (1%MBG) scintigraphy revealed activity also in right hip joint and in the soft tissues around the right scapula. Post-operative 24-hour urine catecholamine secretory test and plasma metanephrines were negative. Taken together, the tumor was considered as a non-functioning. The multiple endocrine neoplasia syndrome (MEN) or Carney syndrome were excluded. No clinical signs associated with neurofibromato- sis type 2, neurofibromatosis type 1 were presented. Shortly after diagnosis, the patient’s clinical condition deteriorated rapidly with increasing fatigue, progressive dyspnea, loss of appetite, and the right shoulder pain increased. A diagnosis of right sided fluidthorax was necessary. According to these facts and low Karnofsky index score, the radical surgery or oncological therapy was refused and the patient was managed in palliative mode with low-dose analgesic radiortherapy (a total dose of 20 Gy with 2.5 Gy per fraction). One year after diagnosis, the patient died of disease progression.

**Discussion**

PGLs represent rare neuroendocrine tumors that arise from sympathetic or parasympathetic paraganglia. Up to one-half of cases can be associated with a genetic syndrome [2]. At the microscopic level, it is not possible to distinguish sympathetic PGLs from the parasympathetic ones, as well as sporadic cases from those associated with hereditary syndromes. However, parasympathetic and sympathetic PGLs share features different from the diagnostic distribution, clinical features and frequency of an underlying hereditary syndrome. Sympathetic PGLs tend to secrete catecholamines, arise anywhere along the sympathetic chain from the skull to the pelvic cavity, and in approximately 25% are part of a genetic syndrome. Parasympathetic PGLs are located along the glossopharyngeal and vagal nerves, they are more often non-functional, and arise in association with known genetic syndromes [3, 8]. The non-functioning PGLs may be diagnosed

**References**


FDG-PET or MIBG scintigraphy may be helpful. 
I123MIBG is structurally similar to noradrenaline and is actively transported to catecholamine storage vesicles of adrenergic nerve endings [9]. Mediastinal PGLs predominantly arise in two locations. Aorto-copulmonary PGL of superior and middle mediastinum occurs in patients with mean age of 49 years and catecholamine secretion is detected in only 3% of cases. The paravertebral PGLs of posterior mediastinum arise in younger patients with a mean age of 29 years and almost half of these tumors are hormonally active [10, 11]. Mediastinal PGLs tend to invade to neighboring organs, thus becoming harder to remove [12, 13]. Posteriorlateral thoracotomy or median sternotomy represent the recommended surgical approaches. In a case of great vessel ingrowth or high risk of bleeding, cardiopulmonary bypass may be required incidentally or can manifest with symptoms caused by local pressure. 
PGLs can be localized by CT or magnetic resonance imaging (MRI). Functional imaging with 18F-Fluoro-2-deoxyglucose positron emission tomography (FDG-PET) or MIBG scintigraphy may be helpful. 111MIBG is structurally similar to noradrenaline and is actively transported to catecholamine storage vesicles of adrenergic nerve endings [9]. Mediastinal PGLs predominantly arise in two locations. Aorto-copulmonary PGL of superior and middle mediastinum occurs in patients with mean age of 49 years and catecholamine secretion is detected in only 3% of cases. The paravertebral PGLs of posterior mediastinum arise in younger patients with a mean age of 29 years and almost half of these tumors are hormonally active [10, 11]. Mediastinal PGLs tend to invade to neighboring organs, thus becoming harder to remove [12, 13]. Posteriorlateral thoracotomy or median sternotomy represent the recommended surgical approaches. In a case of great vessel ingrowth or high risk of bleeding, cardiopulmonary bypass may be required incidentally or can manifest with symptoms caused by local pressure. 
PGLs can be localized by CT or magnetic resonance imaging (MRI). Functional imaging with 18F-Fluoro-2-deoxyglucose positron emission tomography (FDG-PET) or MIBG scintigraphy may be helpful. 
Histologically, the diagnosis of PGL is usually straightforward, especially when the tumor arises in the usual location and is associated with catecholamine secretion. However, metastasis of non-functioning PGL can by histologically mistaken for a variety of tumors, including metastatic carcinoma, malignant melanoma, hemangioendothelioma, sclerosing PEComa, perivascular tumors, and clear cell sarcoma. Immunohistochemistry using a broad panel of antibodies should be performed to rule out above-mentioned possibilities. PGLs typically show strong diffuse expression of neuroendocrine markers such as synaptophysin, chromogranin A, and NSE. There is variable vimentin positivity. An inconspicuous network of sustentacular cells is positive for S-100 protein in the network of sustentacular cells, diffuse nuclear TTF-1 expression (B-E, 200×).

In summary, malignant PGL is a very rare neoplasm. At initial biopsy, unusually localized metastasis can be a potential source of a diagnostic error. Such lesions require extended and careful clinical and pathological examination to rule out the metastatic...
spread of various carcinomas with clear cell change, malignant melanoma, and sarcomas. However, if appropriate microscopic features are present, PGL should be included in the differential diagnosis. With regard to this possibility, the immunohistochemical panel should contain neuroendocrine markers, S-100 protein, SDHB and/or HIF2α. Simultaneously, it is necessary to search for primary tumor and the possible association with an inherited syndrome. In the case of inoperable tumor, palliative chemotherapy as well as analgesic radiotherapy can be administered.

The authors declare no conflict of interest.

References


Address for correspondence
Iva Zambo
1st Department of Pathological Anatomy
St. Anne’s University Hospital
Pekarska 53
65691 Brno, Czech Republic
e-mail: iva.zambo@fnusa.cz