Case report

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

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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. Surprisingly, 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 growths 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. Sympathetic 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 glossopharyngeal and 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 types 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, 0-36% 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].

Herein, 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 supraclavicular region. Absence of clinical symptoms at diagnosis, atypical location of the resected tumor and aberrant immunoprofile 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 supraclavicular 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 with angiopathic complications, chronic renal failure due to chronic tubulointerstitial nephritis stage 3 which was perhaps associated with chronic non-steroidal anti-inflammatory drugs (NSAIDs) overdose due 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 supraclavicular mass was performed. On macroscopic examination, the lesion measured 1.7 × 1.5 × 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 inconspicuous 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, PEComa, and hemangioendothelioma.

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, prostatic 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 neoplastic cells. Based on the histological features and immunophenotype, 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 subcarinal 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 a pulmonary metastasis. Furthermore, osteolysis 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. MetaIodoBenzylGuanidine (I^{131}MIBG) 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 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 blade pain. A drainage of right sided fluidothorax was necessary. According to these facts and low Karnofsky index score, the radical surgical or oncological therapy was refused and the patient was managed in palliative mode with low-dose analgesic radiotherapy (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 sympathethic 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 parasympatetic ones, as well as sporadic cases from those associated with hereditary syndromes. However, parasympathetic and sympathetic PGLs somewhat differ in their anatomic 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 base 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 a known genetic syndrome in about one-half of cases [3, 8]. The non-functioning PGLs may be diagnosed

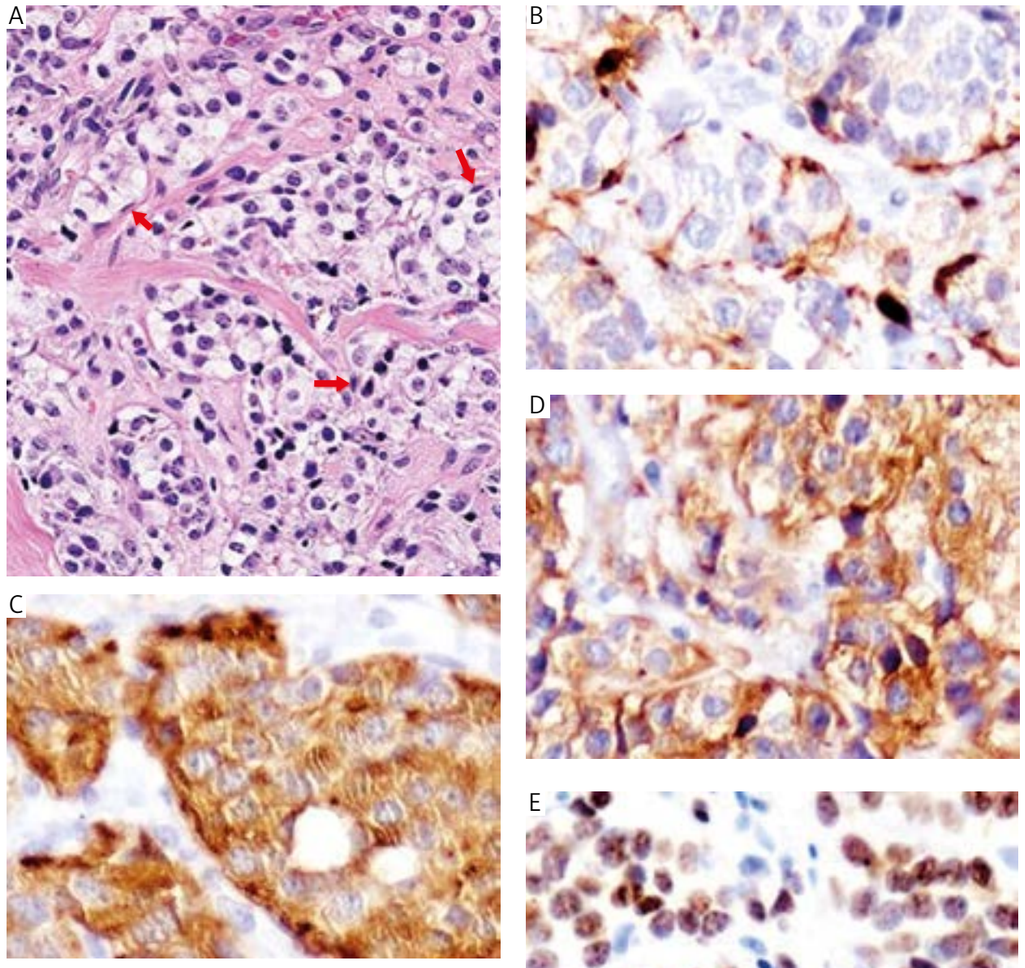

Fig. 1. Histopathological findings of metastatic paraganglioma. A) Nested organoid pattern of relatively uniform epithelioid cells with focal clear cell change, with inconspicuous spindle-shaped sustentacular cells (arrows) (HE, 400×). Immunohistochemical analysis revealed B) S-100 positivity in the network of sustentacular cells, C) diffuse chromogranin A and D) synaptohysin expression in the chief cells, and E) diffuse nuclear TTF-1 expression (B-E, 200×)

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. I^{123}MIBG 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. Aorticopulmonary 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]. Posterolateral 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

[9, 14]. If there is a suspicion of functioning PGL, a biopsy or resection can be performed only after alpha-adrenergic blockade medication, because surgery can cause severe hypertension from catechomalmine crisis. Due to the unpredictable malignant potential of PGLs, radical surgical excision is highly recommended with subsequent careful follow-up to rule out delayed metastatic spread. Complete resection of PGL seems to be a favorable prognostic factor. Lamy *et al*. evaluated clinical outcome of 79 patients with mediastinal PGLs over a period of 180 months. Among these patients, the overall survival rates after radical and incomplete resection were 84.6% and 50.0%, respectively [15]. The relationship between mediastinal localization and metastatic potential of extra-adrenal PGL has not yet been specified. At diagnosis, metastatic disease is already present in up to 10% of cases [4]. In malignant PGLs, cytoreductive resection of metastases can be considered. The majority of PGLs are relatively resistant to chemotherapy or to irradiation. Possible regimens of chemotherapy are cyclophosphamide, vincristine, dacarbazine (CVD) or temozolomide [16, 17]. Chemotherapy may decrease tumor size and facilitate blood pressure control in approximately 33% of patients with metastatic pheochromocytoma or sympathetic PGL [18]. Multikinase inhibitors such as sunitinib or pazopanib were also used in treatment of advanced pheochromocytoma or PGL [19]. Reported survival of patients with metastatic PGL depends on the study population, with 5-year overall survival ranges between 35 and 60% [20].

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 abovementioned 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. However, it is of note that vimentin and S-100 protein expression may be lost in malignant PGL [21]. At present, it is highly recommended to examine SDHB expression in newly diagnosed PGLs. Absence of SDHB protein was suggested as predictive of metastatic disease [22, 23].

Based on microscopic features, it is not reliably possible to determine biological behavior of PGLs. The most promising predictive marker for metastatic PGL seems to be the expression of hypoxia inducible factor 2α (HIF2α) [24]. A somatic *HIF2α* gain-of-mutation can be associated with PGL of the organ of Zuckerkandl, as has been recently reported [25]. However, according to the current diagnostic criteria for PGLs, the metastatic spread is still the only true indicator of malignant behavior [1]. The incidence of malignancy also depends on the genetic background. Development of metastatic disease in patients with extra-adrenal PGL is more frequent than in patients with pheochromocytoma [26].

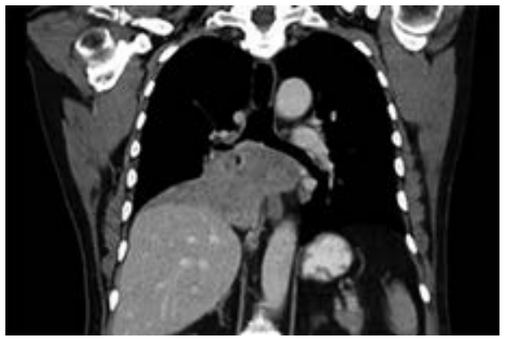

Fig. 2. CT scan. Tumor infiltration in the subcarinal region extending to the right costophrenic angle. Atelectasis of the right lung

In our case, extra-adrenal PGL of the right sided lateral supraclavicular region was diagnosed and suspicion of metastatic origin has been raised. Besides typical immunohistochemical expression of neuroendocrine markers in chief cells and S-100 protein in sustentacular cells, diffuse strong TTF-1 positivity was surprisingly detected. However, thyreoglobulin, calcitonin and a panel of cytokeratins were negative. The expression of TTF-1 is probably aberrant. According to our knowledge, TTF-1 has not yet been described in PGLs. In addition, an immunohistochemical expression of SDHB was retained. Based on the histopatological diagnosis, the primary mass lesion was identified in superior mediastinum, arising in the subcarinal region with partial compression of the right main bronchus. Clinical features suggestive of inherited PGLs were absent. Subsequently, multiple suspected metastatic foci in various right sided organs such as lung, the seventh rib, periscapular soft tissues and hip region were detected. A surgical intervention of the primary mediastinal mass lesion was not performed due to the advanced disease and the poor clinical condition of the patient and palliative low-dose analgesic radiotherapy was indicated. Patient died one year after diagnosis.

In summary, malignant PGL is a very rare neoplasia. 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.

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