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Case report

Paraganglioma with highly malignant potential involving the rib - Case report and review of the literature ☆

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ABSTRACT

Paragangliomas are rare neuroendocrine tumors arising from paraganglion cells in sympathetic or parasympathetic chains, which may develop in the abdomen, chest, skull base, and neck. As paragangliomas have a wide range of imaging features, the diagnosis often requires tissue sampling. We present a unique case of a paraganglioma which originally presented as a rib tumor.

A 64-year-old male with right flank pain for 2 months' was referred for a noncontrast renal colic CT. He was found to have a 3.7 × 3.5 cm soft tissue mass invading the left posterior 9th rib and paraspinous muscle. This was fluorodeoxyglucose F 18, (¹⁸F-FDG) avid, with no other distant metabolic activity. He underwent ultrasound-guided core biopsy which revealed a diagnosis of paraganglioma. A right thoracotomy with chest wall resection of 8, 9, and 10 ribs were subsequently performed. The tumor was removed along with a small portion of adherent lung. The tumor was positive for CD56, synaptophysin and chromogranin. S-100 highlighted occasional sustentacular cells, consistent with a pathologic diagnosis of a paraganglioma. The patient remains symptom free for 6 months' after the operation.

Our case highlights that, when paragangliomas occur within the chest wall, they may present as a rib tumor and can mimic metastasis, myeloma or other primary neoplastic etiologies originating from ribs. Both imaging and pathologic diagnosis can be challenging.

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Introduction

Paraganglia are clusters of neuroendocrine cells dispersed throughout the whole body. They are divided into sympathetic and parasympathetic cells according to their location and neural association. The largest cluster of these cells is found within the medulla of the adrenal gland, and a tumor arising from these cells are referred to as a **pheochromocytoma** [1]. Smaller clusters are located elsewhere in the abdomen, thorax head, and neck; tumors developing at these sites are called paragangliomas [2].

In the mediastinum, paragangliomas arise most commonly in the anterior mediastinum in association with a group of paraganglia anatomically near the pulmonary artery and aortic arch. Paragangliomas are much less frequently located in the posterior mediastinum, originating from the group of paraganglia along the sympathetic chain [3]. Most paragangliomas are thought to be benign in nature, but a small percentage of these tumors produce distant metastases or invade nearby structures [4]. Even without metastatic spread, multifocal or progressive disease can have significant morbidity and mortality [5]. Although the widespread distribution of paraganglia allows paragangliomas to occur at virtually all locations in the body, chest wall involvement by a paraganglioma is still extremely rare [5,6].

This case report describes a patient who initially underwent work up for right flank pain and was subsequently found to have a paraganglioma involving the rib. A review of the literature was performed summarizing radiographic, pathologic, and clinical findings associated with paraganglioma involving the rib.

Case presentation

A 64-year-old male, who had a prior abdominal wall paraganglioma resected 12 years earlier, presented with right flank pain and underwent a noncontrast CT for renal colic which demonstrated an incidental soft tissue mass with considerable cortical destruction of the posterior right 9th rib which was not present on a CT study performed 12 years ago (Figs. 1A and B). The image findings were concerning for a metastatic deposit or possibly myeloma and/or plasmacytoma. A dedicated contrast enhanced CT of the entire thorax and abdomen was subsequently performed to better evaluate the mass. It showed again a lytic lesion of the posterior 9th rib with an associated enhancing soft tissue mass which abutted the adjacent right-sided paraspinal musculature (Figs. 1C and D). No other primary malignancy was observed within the chest or abdomen. The primary diagnostic considerations being considered at this point were solitary plasmacytoma or metastatic disease to the chest wall from an unknown primary. A subsequent PET scan with ^{18}F fluorodeoxyglucose (^{18}F -FDG) was performed. This showed a hypermetabolic right posterior thoracic mass with a standardized uptake value (SUV) of 14.1, in keeping with malignancy (Figs. 2A, B and C). No other worrisome PET abnormalities were seen to suggest a primary tumor elsewhere. Additional

sonographic examination demonstrated color Doppler flow within the mass (Figs. 2D and E).

Under ultrasound guidance, 2 18-gauge core biopsies of the mass were obtained. Microscopically, the cores showed a neoplasm composed of nests and trabeculae of cells in a prominent vascular network, imparting a zellballen pattern (Data not shown). The tumor cells were polygonal, uniform with moderate amount of cytoplasm and round centrally located nuclei. The cells were positive for CD56, synaptophysin and chromogranin A and negative for ERG, CD31, CD34, actin, desmin, and pancytokeratin. S-100 highlighted occasional sustentacular cells (Data not shown).

The case was discussed during multidisciplinary tumor board. The patient subsequently underwent right chest wall resection including a portion of the 8th, 9th, and 10th ribs with en bloc resection of adjacent paravertebral muscle. Grossly, a 4.3 × 4.0 × 3.2 cm nodular mass was attached to fibrofatty tissue, skeletal muscle and 3 ribs (Fig. 3A). The pathologic section of the mass showed a tan to red cut surface with hemorrhage. The mass had invaded the fibrofatty tissue and 9th rib (Fig. 3A). Sections from the surgical specimen demonstrated similar histologic features to the biopsy (Figs. 3B-D). Furthermore, the tumor occasionally showed large irregular nests (Figs. 3E). Comedonecrosis and lymphovascular invasion was identified (Figs. 3F and G). The mitotic rate was 2/10 high power fields (HPF) without atypical mitotic figures. Ki-67 proliferative index was 10%. The tumor involved the rib and adjacent soft tissue (Fig. 3H). Resection margins were negative.

Discussion

Our case highlights that, when a paraganglioma occurs within the chest wall, it may present as a rib tumor, and can mimic metastasis and/or multiple myeloma and/or plasmacytoma or other primary neoplastic etiologies related to ribs. Thoracic involvement by paraganglioma is however infrequent and most commonly arises from aorticopulmonary paraganglia or in the costovertebral gutter and/or paravertebral sympathetic chain [3]. The majority of paragangliomas are benign, although a small number can demonstrate aggressive features [5]. Local rib invasion is extremely rare. Very few case reports of paraganglioma with rib invasion are found in the literature, consisting of lesions in 3 adults (2 female and 1 male) and 1 female child [7-10]. All cases showed posterior rib involvement [7-10]. These tumors are typically located in the upper thorax with a left-sided predominance (3 out of 4 cases) [8-10]. All 4 cases reported previously showed metastasis [7-10].

Unlike pheochromocytomas, paragangliomas are rarely functional, and clinical presentation is often delayed until compression of nearby structures causes pain or shortness of breath [3]. Many imaging modalities, such as chest CT, MRI, and angiography, have played roles in the detection of these tumors and have assisted diagnosis [2,3,11,12]. A typical but non-specific CT finding is a strongly enhancing soft tissue mass along the sympathetic chain. In our case, MRI was not performed since the mass was thought to be a lytic rib lesion and the feeling was that MRI would not add any further useful information. MRI is actually often useful in the diagnosis

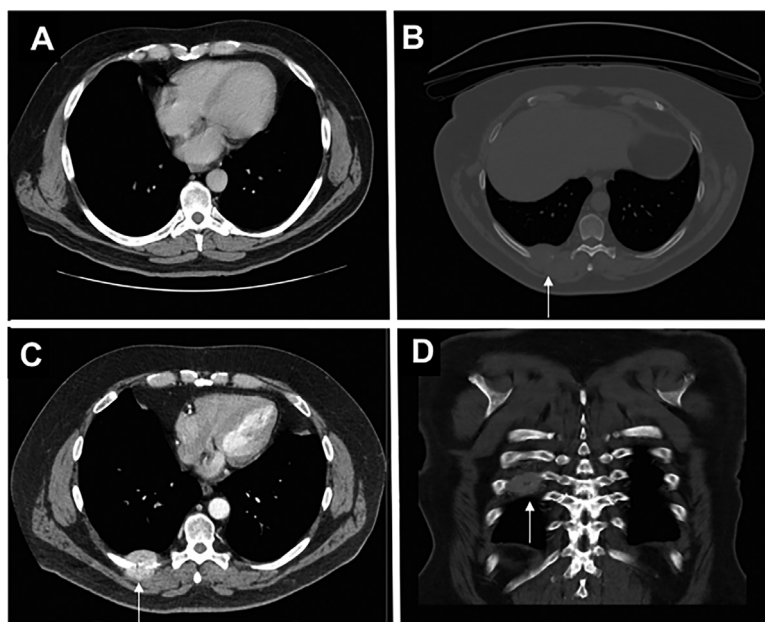


Fig. 1 – (A) Normal remote contrast-enhanced computed tomography (CT) from 12 years ago, and no rib abnormality is seen. (B). A noncontrast CT for renal colic showed interval development of a soft tissue mass with lytic destruction involving the posterior right 9th rib (white arrow). (C, D) Axial and coronal images of contrast-enhanced CT for metastatic workup from October 2020 again demonstrates the lytic bony lesion with an associated soft tissue mass involving the posterior right 9th rib (white arrow).

of paraganglioma, which characteristically are quite hyperintense on T2-weighted images and show with flow voids with avid gadolinium enhancement. Moreover, MRI can be valuable in determining the local extent of the tumor [2,12]. A meta-iodobenzylguanidine (mIBG) scan can provide an additional method of detecting unusual or unexpected locations of paraganglioma, even if they are not functional tumors [13]. In addition, ^{18}F -FDG PET has shown superiority over mIBG as an indicator for tumor dedifferentiation and for the detection of metastatic lesions [14,15]. Angiography may be performed preoperatively for surgical planning or embolization [16]. In many cases, it is difficult to obtain a biopsy of mediastinal paragangliomas because of the locations. Often the diagnosis is obtained after surgical resection [17]. However, in our case, the mass was fairly accessible because of its superficial location.

The diagnostic considerations of a lytic rib lesion on CT scan would include solitary plasmacytoma or metastatic disease to the chest wall [18]. Chondrosarcoma could produce similar findings [18]. A chest wall lipoma is a benign neoplasm with characteristic fatty attenuation and/or signal and would not be associated with rib destruction. Fibrous tumors of the pleura, mesenchymal primary tumors of the visceral pleura or the localized form of mesothelioma are also rare. On imaging, mesothelioma typically presents with multiple tumor masses involving predominantly the parietal pleura and to a lesser degree the visceral pleura. The disease progresses to confluent masses resulting in lung encasement. In our case, given the non-specific CT findings, a biopsy was required to make the final diagnosis.

Morphologically, the most characteristic feature is Zellballen pattern, within highly vascularized fibrous stroma (Figs. 3A and 5A). Large and irregular nests and pseudorosettes are especially important patterns due to histologic grading which will be discussed later [19,20]. The uniform polygonal tumor cells demonstrated abundant pale cytoplasm and centralized hyper chromatic nuclei and are almost always positive for CD56, synaptophysin, and chromogranin. Sustentacular cells are S-100 and SOX10 positive (Figs. 3B and C) [20]. Mitotic figures are usually rare. There are also spindled, slender sustentacular cells at periphery of nests (Figs. 3D).

Previously, paragangliomas were divided into benign and malignant paragangliomas based on status of distant metastases. However, according to WHO classification of Tumor of Endocrine Organs, all paragangliomas have some metastatic potential. Therefore, it is felt that the concept of benign and malignant paragangliomas are outdated and a new approach named GAPP (Grading of Adrenal Pheochromocytoma and Paraganglioma) is advocated to grade paragangliomas based on risk stratification [21]. The GAPP predicts the likelihood of metastasis and the prognosis of patients with pheochromocytoma and paraganglioma [19]. It is a scoring system based on histologic grading with a total of 10 possible points. The 6 parameters assessed are the histologic pattern, cellularity, comedo necrosis, capsular, and/or vascular invasion, Ki67 labeling index and catecholamine phenotype. A score of 0-2 is well-differentiated, 3-6 is moderately-differentiated and 7-10 is poorly-differentiated as the 3 subtypes. Although the catecholamine phenotypes

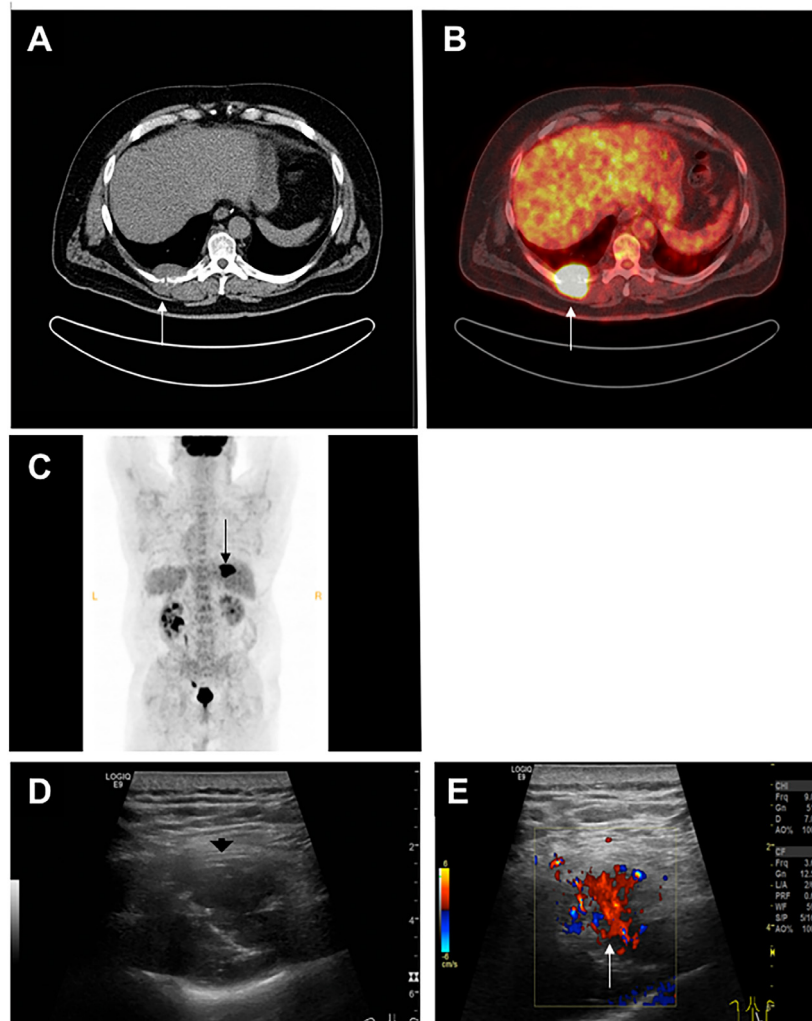


Fig. 2 – (A, B and C) Positron emission tomography/computed tomography (PET/CT) scan with ^{18}F ^{18}F fluorodeoxyglucose 500 MBq IV showed marked hypermetabolic activity in the mass consistent with malignancy (A,B white arrows; C black arrow). No other worrisome PET abnormalities were seen elsewhere. (D, E) The mass involving the right posterior 9th rib was identified on a sonographic examination (black arrowhead). It demonstrated marked color Doppler flow (white arrow). Under ultrasound guidance, a fine needle aspiration (FNA) and 2 18-gauge core biopsies of the mass were obtained.

were unknown in our current case, according to the scores of all the other 5 parameters, this case had already scored at least 7. In addition, this case showed infiltrative growth so it should be graded as poorly differentiated type and its pathologic risk stratification is high risk.

Paragangliomas are mostly sporadic and about 30%-40% arise in the setting of tumor syndromes, such as multiple endocrine neoplasia type II (MEN2) syndrome, von Hippel-Lindau syndrome, neurofibromatosis type I (NF1) and Carney-Stratakis syndrome [22]. About 25% of paragangliomas harbor the succinate dehydrogenase (SDH) mutation followed by VHL (4%-10%) and NF1 (1%-5%) [19,23,24]. Since patients with paragangliomas have high rate of germline susceptibility, it is now recommended that all patients undergo at least some degree of genetic screening to evaluate molecular risk stratification, even patients without other syndromic manifestations or family history [23-25]. Our current case had a previous history

of an abdominal wall paraganglioma resected in 2010, which was therefore highly suspicious for an underlying predisposing germline mutation.

Pathologically, the differential diagnosis includes alveolar soft part sarcoma, well differentiated neuroendocrine tumor (NET), carcinoma, and metastatic melanoma. Alveolar soft part sarcoma is a rare malignant mesenchymal neoplasm that predominantly affects children and young adults in the lower extremity. The tumor shows characteristic alveolar soft part sarcoma chromosome region 1 - transcription factor E3 (ASPSR1-TFE3) fusion. Patients with paragangliomas and NET express characteristic biomarkers: Patients with NETs of the small bowel and abdomen are routinely followed with urinary serotonin derivative 5-HIAA (5-hydroxyindoleacetic acid), whereas patients with paragangliomas can instead be monitored with more specific measurements of catecholamines. [5,20,26].

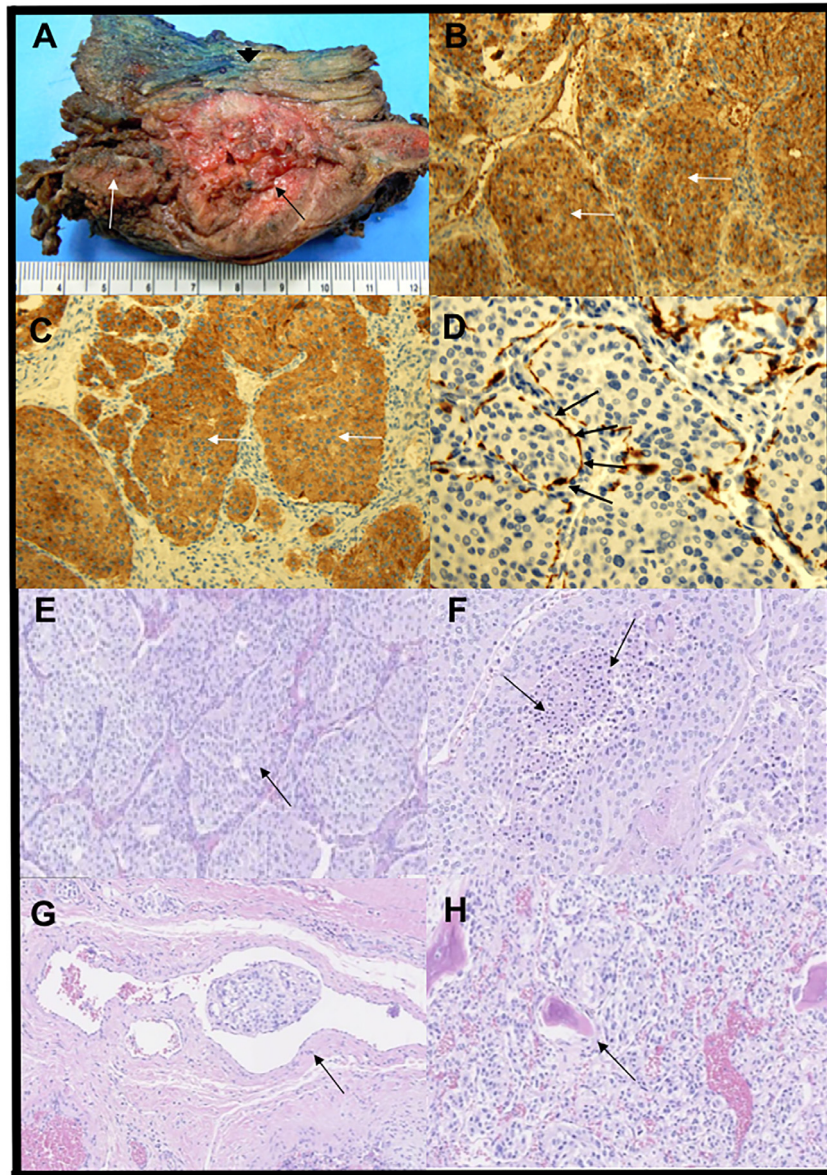


Fig. 3 – (A) Gross picture from the resection specimen demonstrated a nodular mass (black arrow) with surrounding fibrofatty tissue, skeletal muscle (black arrowhead) and 9th rib (white arrow). It showed a tan to red cut surface with hemorrhage. **(B-D)** The section from the resection specimen showed a neoplasm composed of nests of cells in a Zellballen pattern (white arrows). The uniform tumor cells had moderate amount of cytoplasm and round centrally located nuclei (X40). The tumor cells were positive for synaptophysin (B, X40) and chromogranin A (C, X40). S-100 highlighted that the tumor cell nests of Zellballen are surrounded by a layer occasional sustentacular cells (D, X40, black arrows). **(E-H)** Multiple X20 magnification H&E sections from the resection specimen demonstrated occasionally large irregular nests (E, black arrow), comedonecrosis (F, black arrows), lymphovascular invasion (G, black arrow), and bone involvement (H, black arrow).

Conclusion

In conclusion, given that imaging findings of the rare rib paraganglioma are non-specific, paraganglioma should be considered in the differential diagnosis of a chest wall and/or rib soft tissue mass. The final diagnosis of paraganglioma may be challenging for pathologists. Paragangliomas are no longer classified as benign, since it can have aggressive features and significant mortality even without metastatic spread. Long-

term follow-up after surgical resection is now felt indicated in all individuals.

Patient consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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