A case of co-existing paraganglioma and thymoma

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Abstract

Background: Head and neck paragangliomas are rare tumours and can arise as a part of inherited syndromes. Their association with thymic tumour is not well known.

Case description: This report describes a female patient who presented with right sided neck paragangliomas. The histology of the tumour was consistent with paraganglioma. Few years later her MRI scan of the chest revealed presence of an anterior mediastinal mass that corresponded to the location of the thymus. Review of her previous scans showed that the mass was present all along and had gradually increased in size. Patient developed symptoms including fatigue, dyspnoea, migratory polyarthritis, Raynaud’s phenomenon and erythema nodosum. She had sternotomy and excision of mediastinal mass. The histology was consistent with cortical thymoma (WHO type B2) and she had radiotherapy. After treatment her constitutional symptoms improved. Her paraganglioma susceptibility genes are negative.

Discussion and evaluation: To our knowledge this is only the second case report in the literature of coexistence of carotid body tumour and thymoma. The first case reported was bilateral carotid body tumour, thyroid gland adenoma and thymoma. This case also highlights the importance of long term surveillance, multidisciplinary management and being aware of associated pathologies in patients with isolated paraganglioma.

Keywords: Hereditary paragangliomas, Thymoma, Carotid body tumour, Mediastinal mass, Succinate dehydrogenase (SDH) subunits

Background

Head and neck paragangliomas (HNPGGLs) are tumors of the autonomic system. They arise from specialised neural crest chromaffin cells of the parasympathetic paraganglia of the skull base and neck, and are also called glomus tumors. HNPGGLs account for approximately 3 % of all paragangliomas (PGLs). Most often, HNPGGLs progress slowly are benign and nonsecreting with some carotid body tumors being reported to exist for many years as a painless lateral mass on the neck. They can be widely distributed and prominent locations are the carotid body tumour (CBT) along with the vagal, jugular, and tympanic glomus. Symptoms depend on the specific locations (Taïeb et al. 2014; Boedeker et al. 2005). HNPGGLs have been identified with many susceptibility genes: NF1, RET, VHL, SDHA, SDHB, SDHC, SDHD, SDHAF2 (SDH5), IDH1 and TMEM127. Hereditary HNPGGLs are mostly caused by mutations of the SDHD gene, but SDHB and SDHC mutations are not uncommon in such patients. Multiple head and neck paragangliomas are common in patients with SDHD mutations, while malignant head and neck paraganglioma is mostly seen in patients with SDHB mutations (Burnichon et al. 2010; Neumann et al. 2011; Schiavi et al. 2005).

The treatment of choice is surgical resection but this can be challenging because of the tumors' location in the vicinity of important blood vessels and cranial nerve.

We report a 49 year old female who presented with a right sided neck mass and earache. After standard
diagnostic procedures and surgical removal the diagnosis of paraganglioma was confirmed. She was found to have an anterior mediastinal mass on a screening MRI and 5 years later this turned out to be a cortical thymoma (WHO type B2). We also present a brief review the literature regarding the coexisting neck and mediastinal masses. To our knowledge this appears to be only the second case of paraganglioma associated with thymoma described in the literature.

**Subjects and methods**

**Case history**

The patient is a 49 year old lady who initially presented with right sided earache and right sided neck swelling. Following ear, nose and throat (ENT) assessment, surgical excision of the mass together with an adjacent lymph node was performed. At operation the mass was consistent with a glomus vagale tumour. The histology revealed organised growth pattern in which tumour cells formed characteristic nests (Zellballen pattern) separated by fibrovascular connective tissue septa. The tumour cells were polygonal with large nuclei, many with prominent nucleoli and plentiful eosinophilic granular cytoplasm. The tumour stained positively for synaptophysin, NSE and chromogranin A. No obvious metastatic features were found. The lymph node histology revealed reactive changes. The histology was consistent with paraganglioma (Figs. 1, 2). Post-operatively she suffered the complications of vagal nerve palsy and pulmonary embolism.

Five years later she was seen in Genetic Endocrine clinic and had an ultrasound scan of the neck, MRI scan of the abdomen and thorax as a part of screening for paraganglioma follow up. MRI scan revealed the presence of a 4 × 2 cm anterior mediastinal mass (Fig. 3). This mass corresponded to the location of the thymus and had central calcification. Review of her previous CT pulmonary angiogram (CTPA) done following her neck surgery 5 years earlier revealed that the mass was ever present on this scan. This mass had only marginally increased in size during this time (Fig. 4). It was decided to manage it conservatively and follow up with serial MRI scans. She had normal concentrations of urinary fractionated metanephrines.

Two years later her annual scan revealed an increase in the size of mediastinal mass to 5.8 by 3.1 cm (Fig. 4) Whole body metaiodobenzylguanidine (MIBG) scintigraphy showed no uptake in the mass (Fig. 5). At this stage patient had noticed some additional symptoms including fatigue, hoarse voice and dyspnoea. She also described migratory polyarthritis of the small joints, Raynaud’s phenomenon and erythema nodosum. She was referred
to the neurology team to exclude myasthenia gravis in view of her mediastinal mass. Acetylcholine receptor antibodies were negative.

In view of the enlargement of the mass and constitutional symptoms patient was discussed in a multidisciplinary meeting and the decision was made to operate. She underwent median sternotomy and excision of mediastinal mass. The mass was completely excised. The histology showed intermediate-sized lymphocytes with admixed epithelial cells with cytoplasmic processes. Immunohistochemistry revealed the presence of reactive T lymphocytes; TdT, CD1a and CD5 positive (Fig. 6). The histology was consistent with cortical thymoma (WHO type B2). She made a good postoperative recovery and was referred for radiotherapy. Patient is currently very well with no symptoms and 1 year after operation, imaging investigations are still normal.

**Genetic testing**

Patient signed a written informed consent for the test. Screening for germline mutations of the \textit{RET}, \textit{VHL}, \textit{SDHB}, \textit{SDHC}, \textit{SDHD}, \textit{SDHAF2} and \textit{TMEM127} was negative. Analysis of the Paraganglioma/Phaeochromocytoma gene panel was undertaken in the West Midlands Regional Genetics Laboratory. The panel uses an Illumina MiSeq platform to capture the coding regions of the SDHAF2, SDHB, SDHC, SDHD, RET (exons 10, 11, 13–16), MAX, TMEM127 and VHL genes using the TruSight Cancer Panel target enrichment system (v1, Illumina). Sanger sequencing is used to confirm any
variants identified. MLPA analysis of all exons of the VHL gene (MRC-Holland Kit: P016-C2) and SDHB/C/D (MRC-Holland Kit: P226-C1) is undertaken.

Discussion

HPGLs overall are rare tumours and are known to have hereditary-familial tendency. Their association with thymic tumour is not well known. To our knowledge thymoma associated with paraganglioma has been reported only once before in the literature (Refior and Mees 2000) and we report this second case of HPGL coexisting with a thymic tumor in an adult patient. Her mediastinal tumour was initially growing slowly and she was asymptomatic. 5 years after her initial surgery for paraganglioma she developed symptoms suggestive of compression of anterior mediastinal structures, autoimmune pathology and her imaging showed increase in the size of her mediastinal tumour. The tumor was presumed to be benign as there was no metastasis (i.e., lymph node or distant metastases) after imaging. Our patient had extensive biochemical testing. The mediastinal mass was not MIBG avid and her urinary metanephrines were normal. Her genetic testing for hereditary paragangliomas has been negative so far. For the coexistence of HPGLS and such tumors a common neuroectodermal origin has been proposed as an explanation. The hypothesis is supported by combined (mixed) thymoma-neuroendocrine tumours and the occurrence of either thymomas or thymic neuroendocrine tumours in MEN1 syndrome patients (Rashid and Cassano 2013).

Thymus has an important role in the development of an effective immune system as well as endocrine function. Thymus has two main components; the lymphoid thymocytes and the thymic epithelial cells. The thymic epithelium develops first from the third pharyngeal pouch as two flask-shaped endodermal diverticula and extend laterally and backward into the surrounding mesoderm and neural crest-derived mesenchyme. The mature thymus epithelium has two main cell types: cortical thymic epithelial (cTECs) and medullary thymic epithelial cells (mTECs) or stromal cells. These thymic stromal cells provide signals for T cell differentiation. During the late stages of the development of the thymic epithelium, hematopoietic bone marrow precursors migrate into the thymus. After this stage the normal thymic development is dependent on the interaction between the thymic epithelium and the hematopoietic thymocytes (Farley et al. 2013). Tumours of the thymus are extremely rare and comprise <1 % of all adult cancers. Thymoma is a benign tumour but has a malignant potential. There are two major types of thymoma depending on the neoplastic epithelial cell type. In type A thymoma the cells and their nuclei have a spindle or oval shape, and are uniformly bland. In type B thymoma the cells have a predominantly round or polygonal appearance. In 50 % of cases thymoma is detected as an incidental finding on imaging. It constitutes about 20 % of the mediastinal tumours so the differential diagnosis includes paraganglioma. In 95 % of cases it presents as an anterior mediastinal mass. Thymic tumours occur at almost all ages (range 7–89 years) with a peak incidence between 55 and 65 years. There is no pronounced sex predilection. Patients exhibit an increased incidence of second cancers irrespective of the histology of the thymic epithelial tumour. The etiology of thymic tumours is largely unknown. Some epidemiologic clustering of thymomas and neuroendocrine tumours has been observed among patients with multiple endocrine neoplasia (MEN1).
syndrome. Epstein–Barr virus (EBV) infection may play a role in a minority of thymic carcinoma. Symptoms can be due to local complications such as superior vena cava syndrome, pleural or pericardial effusions or patients may have systemic symptoms such as fever or weight loss (Mikhail et al. 2012). In addition, thymomas can cause parathyroid syndrome in 40 % of cases. These syndromes are often typical for a specific tumour type and may precede or follow thymoma resection. Thymomas can exhibit a spectrum of autoimmune phenomena, comprising neuromuscular, haematopoietic, dermatologic, rheumatic/vascular, hepatic and renal diseases. These are more commonly seen in type A and B thymomas as in our patient. Myasthenia gravis is more frequently associated with type B thymomas, while hypogammaglobulinaemia (Good syndrome) and pure red cell aplasia are more typical for type A thymoma. 20 % of patients can have non thymic cancers. Thymic carcinomas can occasionally be associated with syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Carcinoid neuroendocrine tumour of the thymus is well reported. One-third of these patients have Cushings syndrome due to ectopic ACTH production. 15 % of carcinoids can be associated with multiple endocrine neoplasia (MEN) syndromes mostly with MEN type 1 and some with MEN type 2. Thymic carcinoid tumours associated with MEN syndromes are mostly malignant and can present with bony metastasis (Kaltsas 2010).

Recurrent genetic alterations have so far been reported for thymomas as well as for thymic squamous cell carcinoma. Deletions of chromosome 6p are reported with type A thymoma and gains of chromosome 1q and losses of chromosomes 6 and 13q are reported with type B thymomas (Zettl et al. 2000).

Paragangliomas (PGLs) are found mostly in the neck and abdomen, less commonly in the pelvic sympathetic for thymomas as well as for thymic squamous cell carcinoma. Deletions of chromosome 6p are reported with type B thymomas, while hypogammaglobulinaemia (Good syndrome) and pure red cell aplasia are more typical for type A thymoma. 20 % of patients can have non thymic cancers. Thymic carcinomas can occasionally be associated with syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Carcinoid neuroendocrine tumour of the thymus is well reported. One-third of these patients have Cushings syndrome due to ectopic ACTH production. 15 % of carcinoids can be associated with multiple endocrine neoplasia (MEN) syndromes mostly with MEN type 1 and some with MEN type 2. Thymic carcinoid tumours associated with MEN syndromes are mostly malignant and can present with bony metastasis (Kaltsas 2010).

With complete surgical resection, the tumor is controlled locally in 89–100 % of cases. However, there is a possibility of postoperative cranial nerve dysfunction even in cases of successful surgical removal of CBT and complication rates are directly related to tumor size. Postoperatively our patient had vagal nerve palsy and patient is left with hoarse voice (Boedeker et al. 2005).

Complete surgical excision is the treatment of choice for non metastatic thymoma and thymic carcinoma, even when the tumor is locally advanced. This is followed by postoperative radiotherapy to decrease the incidence of local recurrence. In an advanced disease surgical debulking, radiotherapy, and chemotherapy are recommended (Berman et al. 2011). Our patient had surgical resection
followed by radiotherapy and till date remains symptoms free with normal imaging.

**Conclusion**

In conclusion this is the second case where carotid body tumour and associated thymoma has been reported. This case highlights the importance long term follow up of patients with HNPGLs that should be mandatory because of their association with other tumours.

Such cases should be seen in multidisciplinary clinic and should include geneticists as some of these cases are hereditary. Genetic tests should be offered to all of these patients so that proper surveillance by biochemical tests and imaging can be arranged and family members can be screened.

**Authors’ contributions**

GB managed and diagnosed the case, suggested hypothesis about the association and wrote the final version of paper. DS, MK and YK wrote the initial draft and helped with literature search. PW did the histology reporting. IH was the surgeon. KS, VT and SH helped with genetics. All authors read and approved the final manuscript.

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**Acknowledgements**

No funding was obtained for this study.

**Competing interest**

The authors declare that they have no competing interests.

**Consent**

Informed consent was obtained from the patient regarding publication of the case report.

Received: 3 February 2015 Accepted: 24 August 2015
Published online: 21 October 2015

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