Phaeochromocytoma: back to the basics

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Abstract

We present a 53-year-old man who was admitted to ITU with shortness of breath and a massive pulmonary haemorrhage, with a history of new-onset hypertension, and unremarkable examination. CT scanning showed an 8 cm mass in the right adrenal gland, suspected to be a phaeochromocytoma (PHEOs). This was further supported by blood tests and avidity on MIBG radiology. Histological examination of the adrenalectomy and nephrectomy specimen showed a circumscribed tumour composed of small nests of small to medium sized, pale to basophilic cells with features suggestive of a phaeochromocytoma with borderline metastatic risk, and a pathological stage of pT2. Stratification of metastatic risk of PHEOs is crucial as those tumours that metastasise have a <50% 5-year survival rate. In addition, risk stratification facilitates management of these tumours, and this can be achieved by employing PASS and GAPP scores, amongst others.

Keywords chromaffin; GAPP; paraganglioma; PASS; phaeochromocytoma

Presentation

We present a 53-year-old man who was admitted with shortness of breath and a massive pulmonary haemorrhage, requiring ITU input. He had a past medical history of sudden onset hypertension, and no family history of rare endocrine disorders. The patient is an ex-smoker who stopped more than 10 years ago, and his alcohol intake was within recommended daily limits. He was taking phenoxybenzamine and propranolol at the time of examination (prior to the surgery). On examination, the patient had no obvious signs of any illness, and so the cause of his hypertension remained unclear.

Investigations

Blood test

The patient had multiple blood tests conducted with the results as follows: highly raised plasma metanephrines (59,013 pmol/L [normal <510]) and normetanephrines (77,393 pmol/L [normal <1180]). Blood tests for calcitonin and CEA were normal.

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Radiology

An emergency CT scan showed an incidental finding of a mass arising from the right adrenal gland, separated by a clear fat plane from the right kidney, and abutting the infero-medial surface of the right liver lobe. The mass was reported as a well-defined, heterogeneously enhancing mass measuring 8.8 cm in maximum dimension. The mass was seen to compress the right liver lobe superiorly and the right kidney upper pole inferiorly. The top differential diagnosis in this case was a phaeochromocytoma. Thereafter, an MIBG scan showed that the mass was in fact 11 cm in maximum dimension with high avidity, further supporting a diagnosis of phaeochromocytoma.

There was no radiological evidence of metastasis, and the left adrenal gland was normal. An MRI scan of the liver showed a small haemangioma within segment 6, with no evidence of hepatic metastases. The cause of the pulmonary haemorrhage was found to be bronchial artery rupture; however, the patient was referred to the respiratory medicine team for further review.

The patient underwent a right adrenalectomy with partial right upper pole nephrectomy, and the results of histological examination of the resection specimens will be outlined and discussed below.

Histology and immunohistochemistry

The sample showed a circumscribed tumour, surrounded by an intact capsule. The tumour was found to be mainly composed of small nests of small to medium sized, pale to basophilic cells, with no obvious spindle forms, showing focal hypercellularity and profound nuclear hyperchromasia and pleomorphism. Rare mitoses were seen (as previously reported no more than 3 per 10 HPF [high power fields]). Foci of necrosis were seen; however, no areas of confluent necrosis were noted. There was no evidence of lymphovascular or perineural invasion, and no tumour thrombi were identified. The tumour was confirmed to be a phaeochromocytoma and given a PASS (Pheochromocytoma of the Adrenal gland Scaled Score) score of 4 (borderline) and a GAPP (Grading of Adrenal Pheochromocytoma and Paraganglioma) score of 3 (moderately differentiated). The pathological stage was pT2.

Immunohistochemical staining showed diffuse positivity for chromogranin and synaptophysin, further supporting the diagnosis of phaeochromocytoma. Ki-67 was estimated as 2%. S100 highlighted the loss of sustentacular cells. Figure 1 shows the histological findings mentioned above.

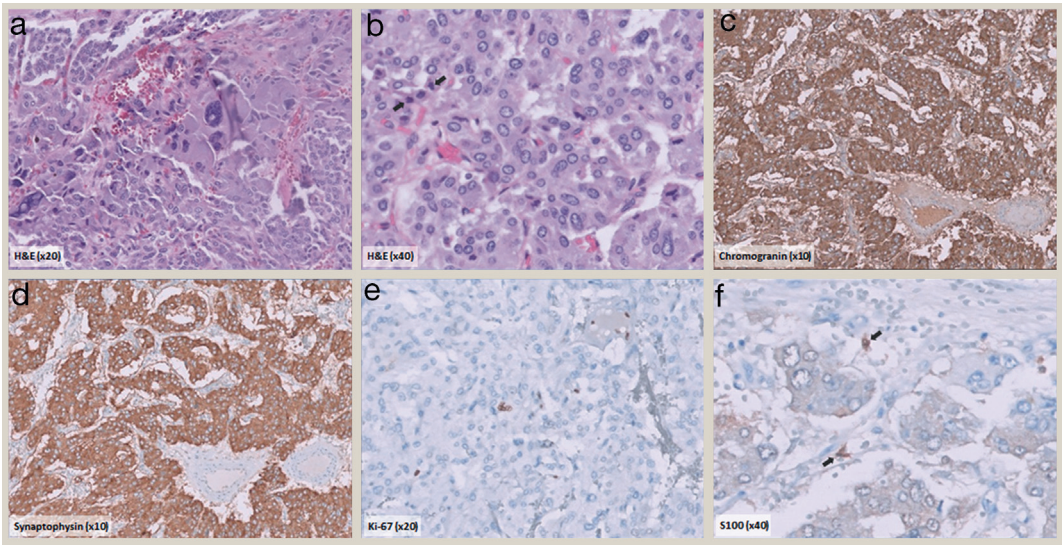

Figure 1 Histology images of the specimen showing (a) hyperchromasia and hypercellularity (×20), (b) Two mitotic figures (arrows) (×40), (c) diffusely positive chromogranin (×10), (d) diffusely positive synaptophysin (×10), (e) Ki-67 at 2% (×20), (f) S100 showing loss of sustentacular cells (arrows point to remaining sustentacular cells).

Discussion and conclusion

Phaeochromocytomas (PHEOs) are usually grouped with paragangliomas (PGLs) (abbreviated together as PPGL). PPGLs are rare neuroendocrine tumours that can arise from the catecholamine-producing chromaffin cells of the adrenal medulla (PHEOs) or extra-adrenal neural crest cells (PGLs) (sympathetic and parasympathetic ganglia, mainly of chest and pelvis), each representing 80% and 20% of PPGLs, respectively, with an incidence of 2–8 cases/million/year.[1] Patients usually present with pallor, excessive sweating, palpitations, and hypertension, with weight loss, nausea and vomiting seen in a minority of patients.[2]

The most recent WHO book of endocrine tumours (issued 2017) stated that all PPGLs can metastasise.[3] Metastasis of PPGLs can only be diagnosed as such in a non-chromaffin site, hence local invasion surrounding tissue is not considered as metastasis.[4] Approximately 10–15% of PPGLs metastasise,[5] months to decades following the initial diagnosis, with <50% of them surviving >5 years.

Prediction of prognosis (including risk of metastasis) is of paramount importance, especially at an early stage, as this will help to predict prognosis and guide further management of the patient. Staining for the S100+ sustentacular cells has been predict prognosis, as loss/reduction in their numbers has been shown -in early studies- to correlate with aggressiveness, but this finding was shown to be inconsistent.[6] Thus, several predictive grading algorithms were devised,[7] including: the COPPs (Composite Pheochromocytoma/paraganglioma Prognostic Score) scoring system, the grading system for adrenal pheochromocytoma and paraganglioma (GAPP), the modified grading system for adrenal pheochromocytoma and paraganglioma (M-GAPP), and the Phaeochromocytoma of the Adrenal Gland Scaled Score (PASS) grading system. The two commonly used scoring systems are PASS and GAPP, the former of which is the older of the two. Details of the PASS and GAPP systems are summarized in Table 1, and they can be further explored in the comprehensive publication by Kimura et al.[8]

In conclusion, PPGLs are rare tumours with relatively low metastatic potential overall; however, some features (highlighted, for example, in PASS and GAPP grading systems) can

Parameters with their corresponding scores for PASS (Pheochromocytoma of the Adrenal gland Scaled Score) and GAPP (Grading of Adrenal Pheochromocytoma and Paraganglioma) scoring systems

Parameters	PASS	GAPP
Nuclear hyperchromasia	1	—
Nuclear pleomorphism (profound)	1	—
Capsular invasion	1	—
Central/confluent tumour necrosis (in large cell nests)	2	—
Extension into adjacent fat	2	—
Mitotic figures >3/10 HPF	2	—
Tumour cell spindling (even focal)	2	—
Large nests/diffuse growth (>10% of tumour volume)	2	—
Cellular monotony	2	—
Hypercellularity	2	1 or 2
Vascular (or capsular [in GAPP]) invasion	1	1
Catecholamine type	—	1
Ki-67 labelling index (%)	—	1 or 2
Comedo-necrosis	—	2
Pseudorosette formation (even focal)	—	1
Large and irregular cell nests	—	1
Maximum score	20	10
Cut-off for high metastatic potential	≥4	≥3 (60% risk)

Table 1

help estimate the risk of metastasis in patients suffering from these tumours. ◆

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Self-assessment questions

1. Phaeochromocytomas and paragangliomas arise from which type of cells?

A. Chromaffin cells
B. Extra-adrenal sympathetic ganglion cells
C. Cells of the zona glomerulosa
D. Both A & B
E. All of the above

Correct answer: D

2. Which system(s) is used to estimate the risk of metastasis in PPGLs?

A. PASS
B. GAPP
C. M-GAPP
D. COPPs
E. All of the above

Correct answer: E

Practice points

- PPGLs are rare tumours of the adrenal gland.
- About 10–15% of PPGLs metastasise, and these show <50% 5-year survival rate
- Grading systems such as PASS or GAPP aid in planning further management