CHAPTER 11: MEN 1 and associated neuroendocrine neoplasms

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Practice Points

Multiple Endocrine Neoplasia Type 1 (MEN 1)

- MEN 1 is a highly penetrant autosomal dominant disorder with a broad spectrum of benign, hyperplastic, dysplastic and malignant manifestations.
- Predictive genetic testing is a critical step in managing families with established MEN 1.
- Routine MEN 1 surveillance screening should be offered to all patients with a diagnosis of MEN 1 commencing by age 12 years.
- With the exception of thymic carcinoid (a Grade 3 NEC/Neuroendocrine Carcinoma), neoplasms arising in the endocrine pancreas, gastroduodenal tissue, bronchial mucosa and adrenal cortex are typically either benign adenomas or Grade 1 neoplasms.
- Pancreatic lesion resection should only be considered after carefully weighing risks and benefits against a conservative surveillance or medical management strategy.
- Hypergastrinaemia and Zollinger Ellison Syndrome typically results from multifocal submucosal duodenal carcinoids rather than pancreatic neoplasms that are optimally managed medically with SSA and PPI therapy.

Phaeochromocytoma and Paraganglioma

- Diagnosis of phaeochromocytoma or thoraco-abdominal (sympathetic) paraganglioma is generally an indication for surgery.
- All phaeochromocytomas and thoracoabdominal paragangliomas should have careful pre-operative evaluation for catecholamine excess (fasting plasma metanephrines or urinary fractionated metanephrines). Functioning tumours require pre-operative alpha-blockade to achieve blood pressure control.
- Head and neck (parasympathetic) paragangliomas should ideally be managed by expert centres with multidisciplinary care.
- PET imaging (particularly using ^{68}Ga-DOTATATE) is useful to diagnose metastases and/or multifocal disease and is recommended for younger patients (<40y), all paragangliomas and for patients with familial syndromes.
- All patients with phaeochromocytoma or paraganglioma should be offered genetic counselling towards testing for hereditary predisposition genes.
- Management options for metastatic phaeochromocytoma include: resection of the primary tumour; targeted therapies; systemic therapies (chemotherapy, radionuclide therapies); and medical management of catecholamine excess.

Multiple Endocrine Neoplasia Type 1 (MEN 1)

Overview

Familial Multiple Endocrine Neoplasia Type 1 (MEN 1) is a highly penetrant autosomal dominant disorder associated with a broad spectrum of benign, hyperplastic, dysplastic and overtly malignant manifestations (***see Appendix, Table 1***) (1,2,3). The prevalence of MEN 1 ranges from 2-10 per 100,000 with higher rates associated with founder effects in relatively isolated communities (3,4). Whilst benign pituitary lesions and parathyroid hyperplasia (resulting in primary hyperparathyroidism) develop in up to 30% and >95-100% of gene carriers respectively, more aggressive Neuroendocrine Neoplasms (NENs) involving endocrine pancreatic, gastroduodenal, thymic, bronchial and adrenocortical tissues are also observed (2,3,4). With the exception of thymic carcinoid (a Grade 3 NEC/Neuroendocrine Carcinoma), neoplasms arising in the endocrine pancreas, gastroduodenal tissue, bronchial mucosa and adrenal cortex are typically either benign adenomas or Grade 1 neoplasms (4). Most gastroenteropancreatic neuroendocrine neoplasms (GEP NENs) in MEN 1 arise in a field of hyperplasia with multicentric benign nodules of varying sizes. The diversity in lesion size, number and neoplastic potential leads to a range of diagnostic, prognostic and treatment challenges when approaching the management of any particular lesion (4,5).

Mutations responsible for familial MEN 1 are typically identified in the *MEN1* gene in Chromosome 11 coding for a 610 amino transcription regulator (1,4). Whilst mutations in *MEN1* are identifiable in approximately 80% of families with MEN 1, for 20% the responsible gene either cannot be identified or is rarely associated with other gene mutations such as in *CDKN1B* (4,5,6). Individual patients presenting with non-familial MEN 1 phenotypes are also recognised, occurring as a consequence of multi-site sporadic endocrinopathy (5). Recognising the distinction between familial MEN 1 (based on confirmatory genetic testing) and phenocopy MEN 1 is critical given differences exist in relation to patient prognosis, management and the approach to counselling and follow-up (4,5,6).

Mortality and Prognosis

Familial MEN 1 leads to a moderate reduction in life expectancy (~10-15 years). Historical studies of MEN 1 natural history and prognosis described malignancy, peptic ulcer disease and renal failure secondary to hyperparathyroidism as common causes of death, with the median age of death <60 years (7,8). However, more recent data indicate that early intervention with parathyroidectomy and control of hypercalcaemia, as well as control of Zollinger Ellison syndrome and prevention of severe peptic ulcer disease, have been associated with both improved life expectancy as well as a substantial reduction in the morbidity and mortality associated with hypercalcaemia and hypergastrinaemia (4,7,8). While overt neuroendocrine neoplasia (malignancy and hypersecretory hormonal syndromes) remains an important cause of death in MEN 1, other non-neoplastic processes such as vascular risk and premature cardiovascular disease are increasingly important (9,10).

Diagnosis of familial MEN 1

Predictive genetic testing is a critical step in managing families with established MEN 1 (4,11,12). However, for patients without a family history, but exhibiting two or more MEN 1 associated clinical diagnoses (e.g. parathyroid, gastroenteropancreatic and pituitary disease) the potential for non-familial sporadic neoplasia (phenocopy MEN 1) must also be considered (4,5,6,11). Drawing a distinction between familial MEN 1 and sporadic phenocopy MEN 1 is essential for providing effective patient investigation and management (5,6,11). In such circumstances, referral to a clinical genetic service for evaluation, counselling and genetic testing is recommended. Genetic counselling and testing should be offered to patients presenting a typical MEN 1 polyendocrine phenotype, particularly if a family history of MEN 1 associated endocrinopathy is identified (4,11).

In established MEN 1 families, predictive MEN 1 genetic testing should be offered at 10-12 years of age if the child is asymptomatic, or earlier if there is concern regarding the possibility of an emergent MEN 1 phenotype in childhood (4,11). Whilst MEN 1 is highly penetrant, onset of clinical disease prior to puberty is uncommon and typically limited to primary hyperparathyroidism, occasionally pituitary adenoma, and uncommonly insulinoma (2,11). Malignancy and NENs related to MEN 1 (GEP NENs, thymic carcinoid, adrenocortical lesions and bronchopulmonary carcinoid) are rare prior to age 30 years (4,11).

Routine cycle of surveillance for patients with confirmed familial MEN 1

Routine MEN 1 surveillance screening should be offered to all patients with a diagnosis of MEN 1 commencing at age 12 years (4,11). A typical primary screening paradigm is:

- From age 12 years
  - annual fasting ionised calcium, albumin correct calcium, PTH, glucose, insulin, prolactin and chromogranin A
  - biannual abdominal ultrasound.
- From age 16 years
  - 4th yearly MRI pituitary.
- From age 20 years
  - annual abdominal ultrasound
  - annual fasting gastrointestinal hormone profile (as for age 12 plus gastrin, pancreatic polypeptide, glycoprotein alpha subunit, creatinine, TSH, FT4 and IGF-1)
  - assessment for evidence of active Helicobacter pylori infection
  - 4th yearly MRI pituitary, FDG PET/CT, gastroduodenoscopy and endoscopic pancreatic surveillance.
- From age 30 years
  - bone densitometry and gastro-duodenal endoscopy with EUS 3-5th yearly.
- Other hormonal evaluation as clinically indicated (e.g. urinary cortisol, aldosterone).

Management of MEN 1 related disease

General considerations

MEN 1 is a phenotypically complex disease with pleotropic manifestations, all of which require contemporaneous screening and management (4,11). The general principles of disease management in MEN 1 parallels management of their sporadic disease counterparts. Identification and co-management of hormone-secretory benign neoplasms is essential to prevent morbidity and mortality due to metabolic complication of hypercalcaemia, prolactinoma, acromegaly, Cushing's syndrome, thyrotropinoma and insulinoma (4,11). Eradication of active Helicobacter pylori infection, if present, is recommended given the potential for this to aggravate hypergastrinaemia and subsequent development of gastrinoma (13).

Parathyroid Disease

Primary hyperparathyroidism (PHPT) in MEN 1 is typically all gland hyperplasia with asymmetric glandular enlargement (4,14). The PHPT is benign but recurrence due to remnant tissue hyperplasia is to be expected (15). Near-total parathyroidectomy (3.5 parathyroid resection) with transcervical thymectomy (preferably with autologous parathyroid autotransplantion to reduce iatrogenic hypoparathyroidism) is the preferred surgical approach (4,11,15). In cases of PHPT that is refractory to surgical intervention, control of hypercalcaemia using cinacalcet can be considered (16).

Pancreatic

Pancreatic lesion resection should only be considered after carefully weighing risks and benefits against a conservative surveillance management strategy (4,17). Most pancreatic neuroendocrine tumours (pNETs) are non-secretory, exhibiting a benign (or indolent) natural history (4,11,18). Pancreatic multinodularity and microscopic multifocality is typical in MEN 1, with lesions arising from islet cell lineage and/or possibly ductal and acinar precursors. Most are either microscopic or WHO Classification Grades 1-3 (typically Grade 1 with Ki-67 index <2%) pNETS (19,20). Resection of pancreatic lesions is appropriate for hormonally functional pNETs (e.g. insulinoma, glucagonoma, VIPoma), for non-functioning lesion > 2cm diameter, for lesions demonstrating rapid size increase, and for hypermetabolic lesions on FDG-PET (4,11.19,20). For the remainder of pNETs, typically those >1cm in size, either somatostatin analogue (SSA) therapy or observation can be considered (4,20,21). Peptide Receptor Radionuclide Therapy (PRRT) with ^{177}Lu-DOTATATE in addition to SSA therapy can be considered for 68Gallium Octreotate (GATAte)-PET positive aggressive lesions and metastatic disease not otherwise appropriate for conservative or surgical management (22).

Pathological Hypergastrinaemia (Zollinger-Ellison Syndrome)

Gastrinomas are typically indolent G1/G2 NEN in MEN 1, although their behaviour is unpredictable and loco-regional metastases not uncommonly present at diagnosis (4,23). Hypergastrinaemia arises from multifocal duodenal submucosal lesions rather than pancreatic neoplasms and is optimally treated medically with SSA (4,11,24,25) proton pump inhibition and normalisation of hypercalcaemia. Surgical resection of submucosal duodenal gastrinoma is typically ineffective for cure (due to multicentricity and

recurrence rates) and is best avoided (4,11). ^{177}Lutetium octreotate peptide receptor radionuclide therapy (PRRT), in addition to SSA therapy, can be considered for tumours expressing SSR (Somatostatin Receptors) as demonstrated by staging 68Ga Octreotate-PET imaging. positive neoplasia not otherwise appropriate for conservative or surgical management (4,22,24).

Type 2 Gastric Carcinoids

Gastric neuroendocrine tumours (Type 2 gastric carcinoid) develop in the context of hypergastrinaemia in patients with MEN 1 (25). Hypergastrinaemia drives enterochromaffin-like (ECL) cell hyperplasia, dysplasia and ultimately malignant gastric carcinoid formation (26,27). ECL cell lesions and gastric carcinoids often secrete glycoprotein alpha subunit, and serum alpha subunit may be a useful biochemical marker of ECL cell transformation in hypergastrinaemic patients (11,24). Control of hypergastrinaemia with SSA mitigates against gastric carcinoid formation and it is also a therapeutic intervention when they are present (4,26,27). Surgery and PRRT should be considered in the context of aggressive gastric lesions not otherwise controlled with SSA therapy.

Pituitary Disease

Pituitary lesions are often non-functioning, although prolactinoma are common, with somatotrophinoma, corticotrophinoma and thyrotrophinoma also features of MEN 1 (28,29). Whilst almost always benign lesions, pituitary neoplasia in MEN 1 is potentially more aggressive than observed for sporadic counterparts, but they are managed as appropriate for typical sporadic pituitary disease (4,28,29,30). Stereotactic radio-surgery/Gamma knife for aggressive and recurrent pituitary lesions unsuitable for, or unresponsive to standard pharmacological and neurosurgical intervention can be considered.

Adrenal Lesions

The majority of nodular adrenal lesions are benign (although adrenocortical carcinoma does present in the context of MEN 1), non-secretory and relate to underlying macronodular hyperplasia (4,11,31). Resection is appropriate if functional hormonal hypersecretion is demonstrated (Cushing's Syndrome), a lesion is FDG PET avid, displaying rapid size increase or >3-4cm in absolute size (4,11).

Bronchopulmonary Carcinoid

Bronchopulmonary carcinoids in MEN 1 are typically indolent and relate to multicentric, non-secretory, benign/G1 NENs. They can be considered for medical management (SSA) unless obstructive, FDG PET avid or rapidly progressive, in which case resection is recommended (4,32,33,34).

Thymic Carcinoid

Thymic carcinoid is typically an aggressive G3 NEN/NEC. Early detection and surgical resection is essential (4,11). Periodic (4th yearly FDG PET/CT) is a potentially useful screening modality for early detection of thymic carcinoid in MEN 1 (4,35). Whilst prophylactic transcervical thymectomy at the time of initial parathyroidectomy for hyperparathyroidism is recommended to reduce the risk of subsequent carcinoid

development, this approach does not assure prophylaxis against subsequent thymic malignancy (36).

Other Lesions

The management of other lesions identified in the context of MEN 1 should be considered with reference to existing guidelines appropriate for sporadic disease management (e.g. breast cancer, lipomata and melanoma) (4,37,38,39).

Phaeochromocytoma and Paraganglioma

Overview

Phaeochromocytomas (PCs) and paragangliomas (PGLs; and collectively termed PPGLs) are tumours of neural crest origin arising from the adrenal medulla and extra-adrenal paraganglia respectively. Thoracoabdominal PGLs arise from chromaffin tissue in sympathetic ganglia whereas head and neck PGLs arise from parasympathetic ganglia (e.g. the carotid bodies). Under the revised WHO classification (2018), PPGLs are now referred to as 'metastatic' or 'non-metastatic' rather than 'malignant' or 'benign' (40). Head and neck paragangliomas are more rarely metastatic (41). Incidence of PPGLs is approximately one per 200,000, although autopsy studies suggest a significant proportion are undiagnosed ante-mortem (42). PPGLs often present with typical features of catecholamine excess (headache, sweating , palpitations, hypertension), but are now being increasingly diagnosed after incidental discovery on abdominal imaging (43) or during surveillance programs for hereditary PPGLs in Family Cancer Centres (44).

PPGLs are highly heritable, with up to 40% cases associated with germline mutations in one of up to 16 driver genes (***see Table 2***)(45). Due to variable penetrance and/or parent-of-origin inheritance (*SDHD*, *SDHAF2*, *MAX*), family history may be negative. Multiple Endocrine Neoplasia Type 2 (MEN 2) usually presents with medullary thyroid cancer, occasionally PC is the first manifestation. PPGLs may also be the presenting feature in Von Hippel-Lindau syndrome (VHL), but rarely so in Neurofibromatosis type 1 (NF1)(46). Approximately 10% of all PPGLs present in childhood, 70-80% of which are associated with hereditary causes (usually *VHL* or *SDHB*)(47). The risk of bilateral and/or multifocal disease is gene-dependent (***see Table 2***).

Mortality and Prognosis

Approximately 10% of phaeochromocytomas and ~40% of sympathetic paragangliomas will be associated with metastases (48). Median survival of metastatic PPGL is ~6 years, although the rate of progression is highly variable. Death is usually from metastatic progression, although it may also occur from excess catecholamines. Risk factors for metastases are tumour size, extra-adrenal primary, norepinephrine-secreting tumours and specific underlying genetic factors (*SDHB*, *FH*, *MAX*)(49). Risk factors for rapidly progressive disease include older age at diagnosis, tumour size and presence of synchronous metastases (50). Patients with skeletal-only metastases may have an indolent course, sometimes over decades (51).

Diagnosis of familial PPGL

All patients with PPGL should be offered genetic counselling towards testing for hereditary predisposition genes. The eviQ guidelines offer gene-specific recommendations for age at testing and surveillance (https://www.eviq.org.au/cancer-genetics). Surveillance of *SDHB*, *SDHD* and *VHL* gene mutation carriers has been shown to diagnose PPGLs at an early stage, and to improve survival (44).

Management of PPGL

General considerations

Diagnosis of PPGL is generally considered an indication for surgery, excepting head and neck PGLs which may be suitable for active surveillance (see below)(41). All PCs and thoracoabdominal PGLs should have careful pre-operative evaluation for catecholamine excess, ideally by fasting plasma metanephrine, normetanephrine and 3-methoxytyramine (after 30 mins supine posture)(51). Functioning PPGLs require pre-operative alpha-blockade (53). Pre-operative PET imaging (particularly using ^{68}Ga-DOTATATE) is useful to diagnose metastases and/or multifocal disease and is recommended for younger patients (<40y), all PGLs and for patients with familial syndromes (54). A proposed algorithm for management of PCs and TAPGLs is shown in ***Figure 1 (see Appendix)***. Rarely, PPGL may present with a catecholaminergic crisis – usually manifesting as either severe hypertension or cardiomyopathy. This medical emergency should be managed in intensive care with alpha-blockers or dihydropyridine calcium-channel blockers and/or nitroprusside, and extra-corporeal membrane oxygenation in selected cases.

Patients with metastatic PPGL may still benefit from resection of the primary tumour (55). Other therapeutic options for metastatic disease include: active surveillance +/- bisphosphonates (for indolent, bone-only metastases); targeted therapies (surgery, radiotherapy, radiofrequency ablation, cryoablation, transarterial chemoembolization); and systemic therapies (chemotherapy, radionuclide therapies)(56). Plasma metanephrine and/or normetanephrine should be monitored in all patients with metastatic PPGL. Clinical features from catecholaminergic excess include hypertension, tachycardia, constipation or (rarely) limb ischaemia and may require ongoing therapy with alpha-blockers (adding a beta-blocker only to control tachycardia).

Chemotherapies

Response rate for cyclophosphamide, vincristine, and dacarbazine (CVD) is approximately 30-40%, usually partial and associated with some improvement in symptoms of catecholamine excess (57,58). Patients with germline *SDHB* mutations may respond better to CVD (59). Treatment-related toxicity is often significant.

Temozolomide has also shown some efficacy, particularly in patients with germline *SDHB* mutations (60) but remains off-label for this condition. Limited efficacy has also been shown in Phase II trials for other chemotherapeutic agents including axitinib, cabozantinib, lenvatinib, pazopanib and sunitinib (61).

Radionuclide therapies

Meta-iodine-benzyl-guanidine (MIBG) labeled with Iodine-131 has been used to treat metastatic PPGL since 1980s. Only around 60% of metastatic PPGLs are MIBG-avid; partial responses to MIBG are seen in around a third of these (62). Greater response to high-specific activity MIBG (Ultratrace) is described, but is currently unavailable in Australia (63).

Peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-DOTATATE may achieve partial responses and control of catecholamine hypersecretion in some metastatic PPGLs (64-67).

Management of head and neck PGLs

These include carotid body and glomus vagale, jugulare and tympanicum tumours. They are usually non-functional, but may cause significant morbidity from compression of local structures (41). Management should ideally be in specialist centres with multidisciplinary input. The risk of aggressive behaviour is higher in patients with germline *SDHB* mutations (41). Although small carotid body tumours can be kept under active surveillance, active treatment should be considered for symptomatic cases, progressive disease and in cases with higher risk of metastasis. Surgical resection often carries a significant risk of lower cranial nerve palsies. External beam radiotherapy or radiosurgery has become an attractive alternative or adjunct to surgery in many cases. PRRT with ^{177}Lu-DOTATATE has been used for local disease control in some cases (66).

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APPENDIX

Table 1: Phenotype Penetrance and Malignancy Risk in Familial MEN 1

MEN 1 Phenotype	Overall Penetrance	Risk of Malignancy
Parathyroid hyperplasia	>95%	Non-malignant
Skin (angiofibroma, collagenoma, lipoma)	>80%	Non-malignant
Pituitary adenoma (non-functioning lesions, secretory [Prolactin, ACTH, GH, TSH])	20-30%	Extremely Rare
Adrenal macronodular hyperplasia (non-functioning lesions, Cushing's Syndrome)	25%	Uncommon
Leiomyomas (uterine, oesophageal, lung)	<20%	Uncommon
Bronchial carcinoid, Adrenal neoplasia	5-15%	Uncommon
Secretory pancreatic NENs (insulin)	30-50%	Uncommon
"Non-functioning" pancreatic adenoma	50-80%	Low-Moderate
Zollinger Ellison Syndrome (multifocal submucosal duodenal gastrinoma)		High G1/G2 NENs
Thymic carcinoid	2-5%	Malignant
Breast cancer	~5%	Malignant

References: 3,4,8,11,17,18,20,23,28,29,30,33,35,37,38,39

Table 2: Familial phaeochromocytoma and paraganglioma syndromes [45]

Gene	Syndrome	Penetrance for PPGL	Bilateral or multifocal disease	Risk of metastatic PPGL	Other features
VHL	VHL	10-30%	30-40%	5%	Retinal angiomas, cerebellar/spinal haemangioblastoma, renal cell cancer
RET	MEN2	20-50%	40-60%	3%	Medullary thyroid cancer, hyperparathyroidism
NF1	NF1	5%	<1%	9%	Café-au-lait, neurofibromas, lisch nodules, axillary freckling, optic glioma
SDHD	PGL1	85% (paternal)	56%	4%	Renal cell cancer, GIST
SDHAF2	PGL2	(high)	(high)	(low)	N/A
SDHC	PGL3	10%	low	low	N/A
SDHB	PGL4	30%	21%	30%	Renal cell cancer, GIST
SDHA	PGL5	5%	low	low	N/A
FH	HLRCC	?	?	(high)	Leiomyoma, renal cell cancer
TMEM 127	-	?	30%	4%	Renal cell cancer
MAX	-	? (high)	21%	11%	Pituitary adenomas
Other genes for which insufficient information to guide genetic counselling/surveillance: KIF1B, MDH2, GOT2, SLC25A11, DLST					

FIGURE 1. A proposed algorithm for management of PC and TAPGL
(adapted from [67])

TAPGL, thoraco-abdominal PGL. *Italics* refer to germline mutations in indicated gene. Somatic DNA testing is indicated for suspected *EPAS1* or *PHD1/2* mutations [45]. High or moderate *RET* mutations refer to ATA guidelines [68]. Neurofibromatosis type 1 (*NF1*) usually diagnosed on clinical grounds rather than genetic testing. *VHL, RET, NF1 are associated with additional syndromic features which require specific management beyond the scope of this chapter.

Fig 1. Proposed algorithm for management of PC or Thoraco-abdominal PGL