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First reported case of multiple endocrine neoplasia type 1 in an Australian Aboriginal

Edward Mignone[1] and Kirsten Neal[2]

[1]Royal Adelaide Hospital, Adelaide, South Australia, Australia
[2]Alice Springs Hospital, Alice Springs, Northern Territory, Australia

Correspondence should be addressed to E Mignone: edward.mignone@sa.gov.au

Summary

Multiple endocrine neoplasia type 1 (*MEN1*) requires a high level of suspicion, and late diagnosis can lead to dire outcomes. Genetic counselling is an important part of management, with a lack of evidence surrounding an optimal approach in Aboriginal Australian populations. Our case surrounds a remote-dwelling 48-year-old Aboriginal Australian female who was reviewed by an inpatient endocrine team in 2020 for persistent hypercalcaemia on a background of a parathyroidectomy in 2011 for primary hyperparathyroidism (PHPT), while she was admitted to a local hospital for acute chronic abdominal pain. Relevant medical history included multiple pulmonary embolisms/deep vein thrombosis, myocardial infarction, atrial fibrillation, chronic thromboembolic pulmonary hypertension, right heart failure, human T-lymphotropic virus 1, recurrent abdominal pain, and gastro-oesophageal reflux disorder. Gastroscopies from 2013 and 2015 demonstrated chronic gastritis with hundreds of gastric polyps. Subsequent laboratory studies, neuroendocrine tumour (NET) screening, and CT imaging demonstrated a recurrence of PHPT and a new diagnosis of Zollinger–Ellison syndrome. A 68-gallium-DOTATATE PET/CT was in keeping with metastatic NET. Pituitary studies were normal. Genetic testing confirmed a rare heterozygous variant of *c.207dupC in exon 2* of the *MEN1* gene. Treatment was symptom based due to terminal comorbidities. Genetic counselling was attempted; however, cultural and logistical barriers were identified and the family declined further testing. Unfortunately, she died in 2021 from multifactorial respiratory failure. This case highlights the need for better approaches to genetic counselling systems for remote Aboriginal Australians and emphasizes the importance of early recognition and the challenges faced in remote areas in making such rare diagnoses.

Learning points

- Remote healthcare systems often lack access to adequate specialist care, resulting in delayed diagnosis of rare conditions and leading to morbidity and mortality.
- Further research and work need to be done to provide culturally appropriate genetic counselling systems in remote Aboriginal Australians.
- A high index of suspicion is required to diagnose *MEN1*.
- Consider *MEN1* in any patient diagnosed with primary hyperparathyroidism, with age <40, and/or with the presence of multiglandular disease or with the presence of Zollinger–Ellison syndrome.
- *MEN1* may be under-recognized in Aboriginal Australians.

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Background

Multiple endocrine neoplasia type 1 (MEN1) is a rare autosomal dominant inherited syndrome characterized by the development of multiple tumours in endocrine glands, most commonly the parathyroid, pancreas, and pituitary (1). The incidence of MEN1 is estimated to be 1 in 30 000 individuals with a mean age of diagnosis around 20–25 years old (2). Hyperparathyroidism is the most common presentation of MEN1, affecting almost 95% of patients (3) with a younger onset compared to non-familial primary hyperparathyroidism (PHPT). It is estimated that 1 in 10 with PHPT under the age of 40 have a tumour syndrome, and genetic testing is recommended (4). Pancreatic tumours occur in up to 80% of patients with MEN1, the most common functioning pancreatic neuroendocrine tumour (NET) being gastrinomas leading to Zollinger–Ellison syndrome (ZES) (5). Early recognition and suspicion of MEN1 in young patients with hyperparathyroidism and/or ZES are crucial for prompt diagnosis and management of the disease as well as for identifying and treating potential complications (6). Long-term morbidity and mortality of MEN1 patients are significantly increased in comparison to the general population predominantly due to the malignant potential of the disease. We present a case that demonstrates the effect of delayed diagnosis of MEN1 in a remote-dwelling Aboriginal Australian person in terms of morbidity and mortality and the challenges in providing timely, culturally appropriate, and safe genetic counselling. For the context, the visiting genetics team visits every 6 months and does not generally have the resources to provide ad hoc counselling for patients who do not attend appointments nor is the service resourced to provide appropriate counselling in terms of culturally appropriate content, language, and written resources to a population where health beliefs are varied, literacy is low, and English is often a fourth or fifth language. To the best of our knowledge, it is also the first reported case of MEN1 in an Australian Aboriginal person. The case highlights the challenges in the diagnosis of genetic conditions in indigenous Australian people due to cultural and social reasons and emphasizes the clear gap still present between Australian Aboriginal people and the general population of Australia.

Case presentation

Our patient was a 46-year-old Aboriginal female who presented to her local remote Australian hospital in 2020 for recurrent abdominal pain, and during this stay, endocrinology was consulted for persistent asymptomatic hypercalcaemia. Her medical history included parathyroidectomy at age 40 for PHPT, three discrete episodes of pulmonary embolism (PE)/deep vein thrombosis (DVT) with negative anti-phospholipid and thrombosis screen, thromboembolic pulmonary hypertension requiring home oxygen, chronic right heart failure, myocardial infarction, coronary artery dissection, atrial fibrillation, human T-lymphotropic virus 1, gastro-oesophageal reflux disease, and peptic ulcer disease poorly controlled on oral proton pump inhibitor therapy.

The consulting endocrine team had a high level of suspicion for familial syndromes, having discovered a high calcium dating back to 2001 when the patient was 29 years old. Review of her file raised suspicion for ZES, with multiple previous endoscopies demonstrating gastritis and hundreds of gastric polyps as far back as 2009. Specifically, endoscopy in 2009 showed mild eosinophilic lamina of the colon; endoscopy in 2013 showed nodular gastritis, thickened folds, and diffuse stomach wall thickening; and endoscopy in 2015 demonstrated hundreds of gastric fundic gland polyps and mild chronic inflammation. In 2018, a CT abdomen performed to investigate abdominal pain revealed a 25 mm hypervascular caudate liver lesion, a 22 mm rim-calcified mass in the superior–inferior vena cava (IVC), a bulky left adrenal gland, and small nephrolithiasis. These were monitored with CT, MRI, and ultrasound imaging over the next few years and were thought to be benign. Neck ultrasound in 2018 revealed two likely parathyroid adenomas: one bilobed hypoechoic lesion at the previous parathyroidectomy site measuring 16 × 14 × 16 mm and a small hypoechoic 6 × 11 × 7 mm structure adjacent to the left carotid artery.

On further questioning, there was no prior family history of confirmed *MEN1* or hyperparathyroidism; however, her mother died of renal failure under the age of 50 years old with a known history of hypercalcaemia in the context of a renal transplant. The patient has six siblings, of whom five have experienced multiple significant DVTs and/or PEs in the past. One male had pseudogout confirmed in his late 20s but no evidence of hypercalcaemia. The family history is somewhat incomplete, as members were difficult to locate and/or not willing to discuss with the team.

Investigation

At the time of referral in March 2020, serum-corrected calcium fluctuated between 2.8 and 3.0 mmol/L (2.15–2.57 mmol/L), serum parathyroid hormone (PTH) level was 31.5 pmol/L (1–7 pmol/L), vitamin D level was 20–41 nmol/L (60–160 nmol/L), 24-h urinary calcium was normal to high across 2019 to 2020: 9.64, 3.1, 4.8 mmol/day (2.50–7.50 mmol/day). Calcitonin, plasma metanephrines, PTH-related protein, and pituitary function were all within normal limits. NET markers were markedly elevated in June 2020; gastrin was 14 042 ng/L (<100 ng/L), pancreatic polypeptide was 2905 pmol/L (<55 pmol/L), chromogranin A was 1031.0 nmol/L (<3.0 nmol/L), and urinary 5-hydroxyindoleacetic acid (5HIAA) ratio was 8 mmol/L (<4 mmol/L); vasoactive intestinal peptide and glucagon levels were normal.

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A repeat CT scan in 2020 of the abdomen again demonstrated thickened gastric folds, hepatosplenomegaly, and slight enlargement of the liver lesion to 29 × 16 mm and inferior cava (IFC) lesion (which is now 25 mm). The IVC lesion was thought to be chronic thrombus, and hepatosplenomegaly was presumed secondary to congestive right heart failure. A 68-gallium-DOTATATE PET/CT scan was delayed due to patient factors, remote location, and restricted travel associated with the coronavirus disease 2019 pandemic. It was subsequently performed in September 2021, demonstrating multiple avid pancreatic, gastric, nodal, and liver lesions with high somatostatin receptor expression, suggestive of the presence of a neuroendocrine malignancy. High uptake was seen in the pancreatic head, peripancreatic lymph node and 5 cm caudate liver lesion, and diffuse gastric activity with a more focal area in the antrum/pylorus (Krenning 4). The diagnosis of ZES was confirmed.

Eventually, genetic testing was positive for a rare heterozygous variant of c.207dupC in exon 2 of the *MEN1* gene. This single base duplication results in a frameshift, p.(Asp70Argfs*47), and generation of a premature stop codon, leading to a truncated *MEN1* protein with a predicted loss of *MEN1* protein function. This variant has not been reported in ClinVar or LOVD databases previously.

Treatment

Her case was discussed in an NET multidisciplinary meeting, and given her comorbidities, specifically her poor respiratory and cardiac function with limited life expectancy due to the same, her treatment was based largely on symptom control. A high-dose proton pump inhibitor was reiterated, histamine type 2 receptor antagonists were trialled with minimal effect, and subsequent subcutaneous octreotide was commenced, followed by a trial of lanreotide monthly; however, there was poor adherence due to conflicting priorities for the patient. She received minimal symptom improvement with this. Hypercalcaemia was treated with IV bisphosphonate therapy. Calcimimetic analogues were considered; however, the patient declined therapy as her medication regimen was already too complicated.

Outcome and follow-up

Genetic counselling for the patient and family was attempted multiple times by the endocrine and visiting genetics team, together with an Aboriginal liaison officer (ALO); however, this posed challenges as the patient did not have a working phone, moved between homes and communities, and did not attend outpatient appointments. It was agreed by the teams involved that the genetic diagnosis should be given by the endocrine team opportunistically should she present to the hospital, which occurred almost 5 months after the test had returned. Unfortunately, there was no available ALO or genetic counsellor to assist at this time, as quite often occurs remotely. The family has been contacted and declined testing. The authors wonder if the family would have been able to make a more informed decision had the counselling occurred with an ALO and genetic counsellor present and with culturally appropriate resources available. Unfortunately, the patient died in her sleep in late 2021, likely due to multifactorial type 2 respiratory failure.

Discussion

This MEN1 is a rare autosomal dominant genetic syndrome that affects multiple endocrine glands. The incidence of *MEN1* in Australian Aboriginal populations is not known. To the best of our knowledge, our case represents the first reported case of *MEN1* in an Aboriginal person. It depicts the still present disparity in health outcomes compared to the non-Aboriginal Australian population and the difficulties of genetic counselling in such settings.

Patients with *MEN1* are at a high risk of developing multiple tumours, and early diagnosis allows for prompt surveillance and management, which can improve patient outcomes and quality of life. The general incidence of *MEN1* has been reported in postmortem studies to be as high as 0.25% (7). Up to 95% of individuals with *MEN1* will have PHPT on presentation (8) and up to 30% of individuals with ZES will have underlying *MEN1* syndrome. Familial hyperparathyroidism occurs in <5% of the population; however, young age (<40 years old), positive family history, and multiple parathyroid gland hyperplasia should prompt consideration of tumour syndromes and warrant genetic testing (9). In this case, these were the relevant features that led to the suspicion of the disease. Unfortunately, the diagnosis of *MEN1* has not yet significantly benefited the patient or her family. The patient suffered from gastritis symptoms from ZES, prompting many hospital admissions, and possibly from hypercalcaemia, but succumbed to comorbidities likely unrelated to the MEN1 diagnosis, which are unfortunately all too common in remote Aboriginal Australians.

The family of this patient possibly remain at risk, and the extent to which we advocate for testing poses ethical and logistic challenges in an already resource-poor service. There has likely been significant additional stress on family members by confirmation of a genetic disorder with no tangible improved outcomes given the family's reluctance for further genetic testing. Further research into genetic counselling and the development of local culturally appropriate resources, specifically for Aboriginal Australians, is required with limited evidence-based guidelines currently available (10).

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This case demonstrates the importance of early recognition of this condition to avoid morbidity and mortality from the tumour syndrome and highlights the challenges of diagnosing rare genetic conditions within remote Aboriginal Australians. To our knowledge, no cases of *MEN1* have been reported in Aboriginal Australians, although there is a large *MEN1* kindred in Tasmania whose indigenous status could not be found by the authors. A high index of suspicion is always required, particularly with any patient diagnosed with PHPT, especially under the age under 40 with multiglandular disease or ZES. More culturally appropriate genetic counselling services need to be developed and employed to further support the diagnosis and surveillance of rare genetic conditions in Aboriginal Australians, and there needs to be continual work to improve access to culturally appropriate specialist services and resources for remote communities to recognize such conditions early to prevent associated morbidity and mortality.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the study reported.

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Patient consent

The patient verbally consented to publication with KN. Signed informed consent could not be obtained from the patient who died in 2021 or by any proxy but has been approved by the treating institution. Every effort was made to contact the next of kin of the deceased patient to obtain consent but was unsuccessful.

Author contribution statement

All authors made individual contributions to authorship. KN was involved with the diagnosis and management of this patient and manuscript submission. All authors reviewed and approved the final draft.

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