# Breast cancer in multiple endocrine neoplasia type 1 (MEN1)

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## Summary

A 38-year-old female was identified as carrying a heterozygous pathogenic *MEN1* variant (c.1304delG) through predictive genetic testing, following a diagnosis of familial hyperparathyroidism. Routine screening for parathyroid and pituitary disease was negative. However, cross-sectional imaging by CT revealed a 41 mm pancreatic tail mass. Biopsy via endoscopic ultrasound confirmed the lesion to be a well-differentiated (grade 1) pancreatic neuroendocrine tumour (pNET) with MIB1<1%. Biochemically, hyperinsulinaemic hypoglycaemia was confirmed following an overnight fast, which was subsequently managed by diet alone prior to definitive surgery. Pre-operative work-up with octreotide SPECT CT demonstrated avid tracer uptake in the pancreatic lesion and, unexpectedly, a focal area of uptake in the left breast. Further investigation, and subsequent mastectomy, confirmed ductal carcinoma *in situ* pT2 (23 mm) grade 1, N0 (ER positive; HER2 negative). Following mastectomy, our patient underwent a successful distal pancreatectomy to resect the pNET. Loss of heterozygosity (LOH) at the *MEN1* locus was found in both the breast tumour and pNET, thereby in keeping with a 'two-hit' hypothesis of oncogenesis, a suggestive but non-definitive clue for causation. To obtain further support for a causative relationship between MEN1 and breast cancer, we undertook a detailed review of the published literature which overall supports the notion that breast cancer is a *MEN1*-related malignancy that presents at a younger age and histologically, is typically of ductal subtype. Currently, clinical guidance regarding breast cancer surveillance in MEN1 does not exist and further research is required to establish a clinical and cost-effective surveillance strategy).

### Learning points:

- We describe a case of pNET and breast cancer diagnosed at a young age of 38 years in a patient who is heterozygous for a pathogenic *MEN1* variant. Loss of the wild-type allele was seen in both breast tissue and pNET specimen.
- Breast cancer may be an under-recognised *MEN1*-associated malignancy that presents at a younger age than in the general population with a relative risk of 2–3.
- Further research is required to determine the cost-effectiveness of breast cancer surveillance approach at a younger age in MEN1 patients relative to the general population .

## Background

MEN1 is a rare autosomal dominant condition resulting from inactivating mutations of the *MEN1* gene, which normally encodes for menin, a 610-amino acid protein responsible for tumour suppression (1). MEN1 is associated with a spectrum of endocrinological disorders that classically includes primary hyperparathyroidism (PHP), duodenopancreatic neuroendocrine tumours (pNETs) and pituitary adenomas. Among this triad, primary hyperparathyroidism is the most common clinical manifestation of MEN1, with almost complete penetrance by 50 years of age (2). pNETs have a lifetime penetrance of 30–75%, while pituitary adenomas have a penetrance of 30–40% (3). Given the prevalence of these conditions and the importance of their early diagnosis and timely intervention, recommendations regarding their respective surveillance strategies are the focus of the most recent clinical practice guidance for MEN1 (3). However, it is increasingly recognised that the spectrum of MEN1-related tumours also includes a number of less prevalent tumours including small bowel neuroendocrine tumours, adrenal tumours (adenomas and adenocarcinomas), lipomas, angiofibromas, collagenomas and meningiomas. Clearly, a heightened awareness of these associations and an early diagnosis of these conditions are critical for preventing morbidity and/or premature mortality in this patient group (3). In addition to these rare tumours, several studies have also reported an increased prevalence of breast cancer in MEN1 compared with the general population (4,5). However, whether breast cancer is truly a *MEN1*-related malignancy has been contested (5,6). Here, we report a case of breast cancer co-existing with an insulin-secreting pNET in a young female with MEN1. We have demonstrated *MEN1* LOH in both tumours, which, supported by a review of the published literature, provides further evidence that breast cancer is a *MEN1*-related malignancy that should be considered for inclusion tumour surveillance strategies for MEN1.

## Case presentation

A 38-year-old female was identified as being heterozygous for a *MEN1* pathogenic variant (c.1304delG) through predictive genetic testing, following a diagnosis of familial hyperparathyroidism in her mother and maternal aunt, who harboured the same mutation. Her maternal grandparents were deceased; however, her grandmother was known to have breast cancer and died at age 62, and her grandfather had a brain tumour diagnosed at age 41.

Our patient has two healthy sons (aged 5 and 7) neither of which has been tested for *MEN1* (Fig. 1).

In addition to a recent diagnosis of primary hyperparathyroidism, our patient's medical history was significant for anxiety and panic attacks for which she took sertraline.
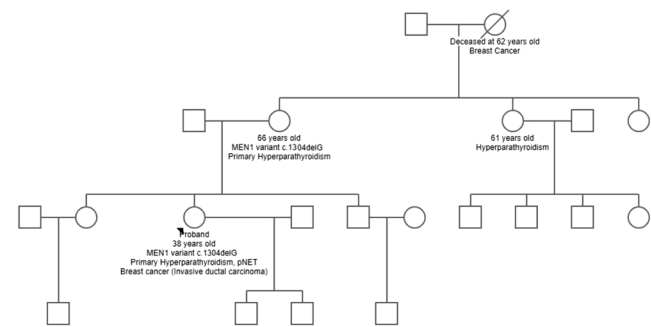
During her first consultation in the neuroendocrine tumour outpatient clinic following genetic confirmation of *MEN1*, a focused systems review revealed clinical features suggestive of hypoglycaemia that included episodic sweating, confusion and reduced consciousness, which quickly reversed the following ingestion of carbohydrate and were precipitated by missed meals or physical activity.

Clinical examination revealed a body weight of 55 kg and BMI of 22 kg/m². Our patient did not manifest any overt clinical features of pituitary hormone dysfunction. She was clinically euthyroid and her visual fields were unremarkable.
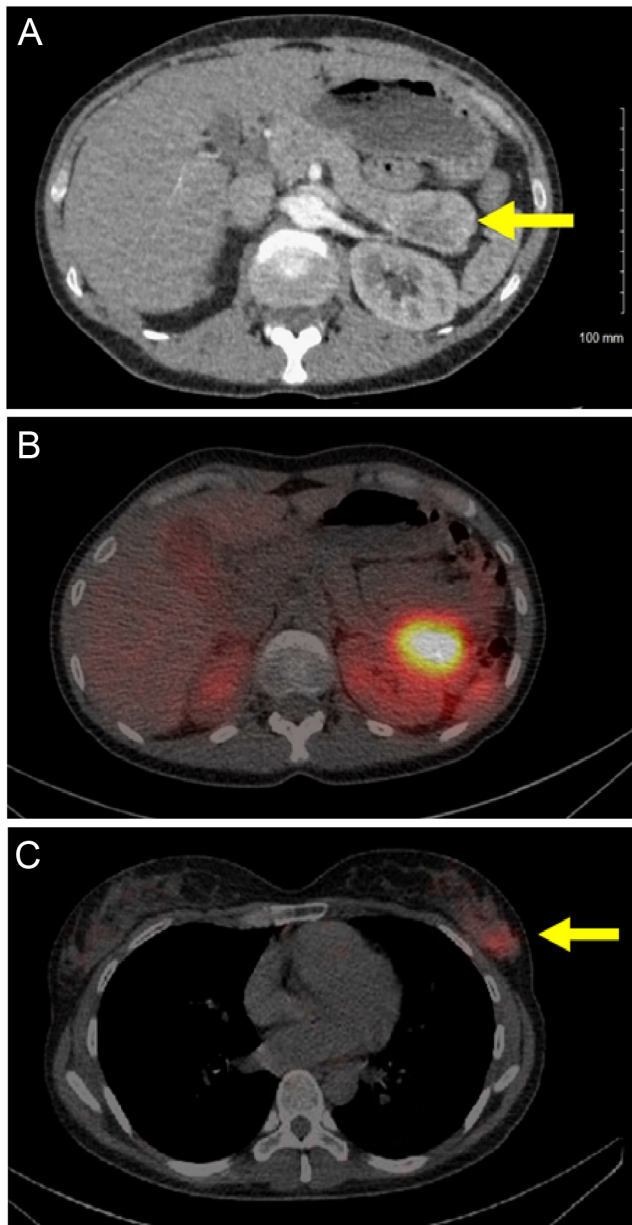
## Investigation

Biochemical screening for hyperparathyroidism and pituitary disease was unremarkable during the initial clinic visits. However, a cross-sectional imaging by CT revealed a 41 mm pancreatic tail mass (Fig. 2A). Subsequent fine needle aspiration and cytological examination during an endoscopic ultrasound confirmed the diagnosis of a well-differentiated (grade 1) pancreatic neuroendocrine tumour (pNET) with MIB1<1%.

Given the clinical history suggestive of hypoglycaemia, the patient underwent an overnight fasting test. After 11 h of fasting, she developed hypoglycaemia at a plasma glucose level of 2.2 mmol/L, with paired insulin measurement at 51 pmol/L and C-peptide of 801 pmol/L, confirming hyperinsulinaemic hypoglycaemia. This was managed effectively by diet modification prior to definitive surgery.



**Figure 1**
Family tree with background familial hyperparathyroidism.

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**Figure 2**
(A) Cross-sectional CT revealed a 41 × 29 mm heterogeneous mass in the tail of the pancreas. (B) Octreotide SPECT CT showing avid uptake in the pancreatic mass. (C) Octreotide SPECT CT showing avid uptake in the left breast (lower panel, yellow arrow).

In preparation for surgery, a pre-operative Octreotide SPECT CT was performed which demonstrated avid tracer uptake in the pancreatic lesion (Fig. 2B). Unexpectedly, however, an area of focal uptake was also seen in the left breast (Fig. 2C), and following biopsy, the diagnosis of breast carcinoma was made.

## Treatment

Following clinical review, and multidisciplinary discussion involving the patient, the decision was made to first undertake a left mastectomy followed by distal pancreatectomy. The rationale for this decision reflected the increased potential of post-operative complications following a distal pancreatectomy and prolonged recovery period which may have delayed the planned mastectomy which was deemed to be the clinical priority. Reassuringly, her blood glucose levels were adequately supported by diet alone and closely monitored, which mitigated against the risk of severe hypoglycaemia whilst waiting for pNET resection. Therefore, the patient proceeded to an uncomplicated left mastectomy.

Subsequent histological examination confirmed a grade 1 ductal carcinoma *in situ* of 23 mm (pT2), with no metastasis to lymph nodes (N0) or distant organs (M0). The patient was commenced on tamoxifen in light of oestrogen receptor (ER) immunopositivity. The tumour was not immunopositive for progesterone receptor (PR) expression or Herceptin-2 receptor (HER2) expression.

Eight weeks following mastectomy, our patient underwent successful and uncomplicated distal pancreatectomy and splenectomy. Multifocal grade 1 well-differentiated neuroendocrine tumours were identified histologically. They were of varying sizes with diameters of 35, 20, 14, and 8 mm, respectively. There was no local lymphatic spread and the tumours were focally less than 1 mm from the posterior margin. The MIB-1 index was <1%. Immunohistochemical staining for insulin was described as patchy. According to the ENET (European Neuroendocrine Tumour Society) staging criteria, the pNET was staged at pT2, N0, M0, recognising that breast cancer is a histologically distinct entity ([7]).

## Outcome and follow-up

Both surgical procedures were successful in achieving disease clearance and the patient has remained euglycaemic. The well-differentiated nature of her low-grade pNET, the absence of lymph node spread on both disease sites and pre-operative octreotide SPECT CT which did not show additional uptake elsewhere, is favourable for her prognosis. However, being a *MEN1* carrier, disease recurrence in the remaining pancreas remnant is possible and the patient will continue to receive lifelong biochemical and radiological surveillance.

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The synchronous identification of breast cancer prompted us to investigate the genetic makeup of the breast lesion and its relation to the *MEN1* carrier state. DNA sequencing of the *MEN1* locus was performed using a germline sample, from the patient, breast tumour tissue and pNET specimen after informed consent was obtained (REC 14/EE/105). Tumour microdissection of the relevant paraffin-embedded tumour samples was performed. Tissue slides were deparaffinised and DNA was extracted using the Covaris Adaptive Focused Acoustics™ (AFA) based DNA extraction and purification technique. DNA was sequenced using a modified AmpliSeq cancer hotspot panel, containing 142 Cancer Hotspot Panel v2 (catalogue number 4475346) by the staff at the Stratified Medicine Core Laboratory within the Department of Medical Genetics, Cambridge University. Tumour DNA from the breast tumour was also sequenced using SeqCap EZ HyperCap workflow (Roche Sequencing Solutions, Inc.), utilising a targeted sequencing method containing a 350 gene panel in collaboration with colleagues from the Cancer and Molecular Diagnostics Laboratory in Cancer Research UK Cambridge. Variant filtering was performed on variant calling files (VCF). Variants were removed if the variant allele frequency was <5%. Synonymous variants were removed as presumed not to be pathogenic. Benign variants, variants of uncertain significance and those variants that had coverage of less than two standard deviations below the mean coverage were also removed.

Biallelic loss in the breast tumour and pNET at the *MEN1* locus were suggested by the finding of higher reads of the mutant allele identified in the breast tumour (variant allele frequency 73%) and the pNET (variant allele frequency 90%) compared with the germline (variant allele frequency 51%). Somatic pathogenic truncating variants in *BRCA2* and *TP53* were also identified in the breast tumour in our patient but the variant allele frequency was < 10% for both variants, suggesting that these variants were sub-clonal mutations rather than a primary driver mutation. No further pathogenic or likely pathogenic driver somatic variants were identified on either of the two gene panels utilised for sequencing of the breast tumour.

### Reported cases and series

We sought to correlate the clinical, histological and genetic characteristics of our case to other reported cases of *MEN1* related carcinoma and performed a literature search using PubMed and Google Scholar. MeSH search terms applied in PubMed included 'Breast Neoplasms'

and 'Multiple Endocrine Neoplasia Type 1'. Search terms applied in Google Scholar were 'breast', 'cancer', 'carcinoma', 'adenocarcinoma', 'MEN', 'MEN1' and 'multiple endocrine neoplasia type 1'. Features of interest to us were the age of breast cancer diagnosis, histological type, staging, hormone receptor expression, LOH status, and *MEN1* genetic variant and these are listed in Table 1. Due to the relative rarity of the condition, we have included abstracts, case reports and reported series of varying quality, and we accept that some of the features are variably reported depending on the availability of local genetic services and the nature of the reporting literature.

## Discussion

Menin, a protein coded by *MEN1* is a ubiquitously expressed nuclear protein that has no intrinsic enzymatic activity, but it regulates transcription either as a co-activator or co-repressor. Dreijerink *et al.* have described menin's role in regulating antiproliferative genes in mammary progenitor cells, which may lead to oncogenesis (8).

### Features of reported MEN1 related breast cancer

Despite the variability in reporting, the majority of breast cancer in MEN1 patients were diagnosed at a relatively younger age and the most common histological subtype was ductal carcinoma with variablity of ER/PR and HER2 expression (Table 1). They are usually diagnosed at early stages and no cases of metastatic disease have been reported thus far.

The largest reported series was published by the Dutch MEN1 study group which includes over 90% of MEN1 Dutch population with 20 years of mean follow-up duration (2). From this cohort, 73% of female MEN1 patients who had breast cancer reported no family history of breast malignancy. Relative to control group, no significant differences were found for the presence of breast cancer risk factors including menarche age, menopause age, age at first delivery, practice of breast feeding, use of oral contraceptive pills, obesity, smoking and alcohol consumption. The same group reported that from a cohort of 190 MEN1 females, 12 cases (6.3%) of breast cancer were identified, resulting in a relative risk of invasive breast cancer of 2.83 consistent with similar findings in three other independent validation cohorts in US ($n$= 68, RR: 2.40, $P$=0.11), Tasmania ($n$= 71, RR: 2.31, $P$=0.22) and France ($n$= 536, RR: 2.33, $P$=0.03) (5). However, the comparisons were not statistically

**Table 1** Reported cases of breast cancer in MEN1 patients.

| No. | Age | Histology | TNM staging | ER | PR | HER2 | LOH | *MEN1* variant | Reference |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 44 | Scirrhous | T1N×Mx | NA | NA | NA | + | c.1621G>A | (18) |
| 2 | 45 | Ductal | T2N×M0 | + | + | − | NA | c.196_200dupAGCCC (frameshift) | (19) |
| 3 | 55 | Ductal | T1N1M0 | + | − | − | − | NA | (5) |
| 4 | 38 | Ductal | T3N1M0 | + | + | + | − | NA | (5) |
| 5 | 44 | Ductal | T1N0M0 | − | − | -- | − | NA | (5) |
| 6 | 61 | Ductal | T1N1M0 | + | − | + | − | NA | (5) |
| 7 | 52 | Lobular | T1N0M0 | + | + | − | − | NA | (5) |
| 8 | 53 | Ductal | T1N0M0 | + | + | − | + | NA | (5) |
| 9 | 45 | Micropapillary | T1N1M0 | + | − | − | + | NA | (5) |
| 10 | 42 | Ductal (bilateral) | T1N0M0 | − | + | | + | NA | (5) |
| 11 | 33 | Ductal | T1N1M0 | + | + | + | − | NA | (5) |
| 12 | 46 | Ductal | T1N0M0 | + | + | − | NA | NA | (5) |
| 13 | 36 | Ductal | NA | + | + | + | NA | c.1649insC | (20) |
| 14 | 41 | Ductal | T1N0M0 | − | − | − | NA | NA | (21) |
| 15 | 56 | Ductal | NA | NA | NA | NA | NA | c.628_631delACAG | (22) |
| 16 | 48 | Ductal | T1 N0M0 | + | + | − | NA | c.1365+1_1365+11 del, GTGAGGGACAG | (23) |
| 17 | 38 | Ductal | T2N0M0 | + | + | − | + | c.1304delG | This case |

A plus sign indicates positivity, and a minus sign negativity.
HER2, human EGF receptor 2; NA, not available.

significant between the later two cohorts, presumed to be due to the smaller sample sizes. Additionally, comparisons may be confounded by variable sample sizes and duration of follow-up between cohorts (6).

The Dutch cohort had early onset breast cancer diagnosed at a young median age of 48.0 ± 8.8 years, as compared to the age of 60–65 in general population (5). In relation to this, our patient was diagnosed with breast cancer at 38 years of age.

However, *MEN1* variants were not found to be significantly associated with breast cancer when a panel of 34 putative susceptibility genes was tested in a population-based study of 48 826 women with breast cancer and 50 703 controls. In this study, a truncating *MEN1 variant* was identified in two women with breast cancer and five controls with an odds ratio of 0.37 (95% CI: 0.07–1.97, $P = 0.24$), while a missense variant in *MEN1* was identified in 109 women with breast cancer and 130 controls, with an odds ratio of 0.86 (95% CI: 0.66–1.12, $P = 0.25$) (9).

### LOH analysis

LOH analysis is important to recognise if there is a presence of biallelic loss of a specific tumour suppressor gene. Possession of a single loss-of-function mutant *MEN-1* copy in the germline DNA will predispose to tumour development. In line with a 'two-hit hypothesis', if

subsequent somatic (acquired) loss-of-function of the second allele in a cell occurs, it will then result in *MEN1*-related tumour (10). Concomitant loss (mutation) of both copies of allele is termed LOH, a feature suggestive yet not conclusive of causation. In our patient, tumour sequencing has suggested biallelic loss in the breast tissue and pNET specimen, with a mutant allele frequency of 73 and 91%, respectively. Although, it should be noted that formal analysis for loss of heterozygosity was not performed and copy number analysis was not possible due to the nature of the sequencing performed (targeted gene panel sequencing).

Reports of LOH analysis in the reported cases of breast cancer in MEN1 have been varied (Table 1). This may reflect the variation in access to specialist genetic laboratory testing from one institution to another. Moreover, it appears that LOH at breast tissue level may be of low yield as suggested in the largest series from the Dutch group as only three out of nine breast specimens were demonstrated to have LOH (5).

Presence of tumour LOH is limited in proving causation as it can be a common secondary event in tumours. For instance, deletions or rearrangement of the long arm of chromosome 11 is commonly seen in other tumours. Therefore, the LOH analysis technique is important where the sequencing of *MEN1* in tumour DNA and a dosage assay (MLPA) of *MEN1* alone are probably

less fallible than dosage analysis of a larger section of chromosome 11 containing the *MEN1* gene locus (6,11).

## The role of BRCA

BRCA1 and BRCA2 are the main driver genes for breast carcinogenesis. There were reports of MEN1 females who also had mutations of BRCA1 (12) and BRCA2 (13). These cases did not present with breast cancer when they were reported. The Dutch cohort of MEN1 females with breast cancer was derived from ten different families, and of these, only two satisfied the Dutch national criteria for BRCA1/2 genetic screening and were proven negative (4). Our patient was not tested for BRCA1 and BRCA2 as her family history does not fulfil current NHS criteria for testing.

Somatic truncating *BRCA2* and *TP53* mutations were also identified at low variant allele frequency (<10%) in the breast tumour in our patient, and, therefore, they were identified as sub-clonal mutations rather than potential driver mutations. The interpretation of our sequencing results is limited by our inability to undertake genetic studies in deceased relatives with a history of breast cancer (Fig. 1) and as a targeted gene panel was employed rather than a whole exome sequencing approach, we cannot exclude the possibility of other causative genetic mutations in the breast tumour.

## Future research needs and clinical practice

In the UK, women aged 50–70 years are invited to breast screening programs every 3 years (14). This strategy may miss the opportunity of diagnosing breast cancer early in MEN1 patients who were reported to present younger. Early detection of young-onset malignancy may potentially be curative prior to disease progression. However, with inadequate evidence to ascertain association at the moment, it is not immediately obvious if enhanced breast cancer surveillance is justifiable. The prognostic significance of *MEN1* mutation upon breast cancer diagnosis is also unclear to inform surveillance and management.

The existing clinical practice guideline for MEN1 was published in 2012 before the evidence for potential breast cancer association started to emerge (3). Therefore, the guideline does not include specific recommendations with regards to breast cancer surveillance and management in MEN1. However, considering the younger age of diagnosis of breast cancer in MEN1 identified from data obtained from the Dutch MEN1 cohort, the authors have

suggested that biennial breast cancer screening from age 40 may be justifiable in MEN1 patients (15). This is in line with simulation modelling suggesting that screening breast cancer annually in women above 40 years of age who are at two- to four-fold increase risk of breast cancer had similar or more favourable harm-to-benefit ratios as biennial screening of 50- to 74-year-old women at average risk (16). This appears to be applicable for the MEN1 group, for whom the breast cancer risk was estimated to be almost three-fold higher by the Dutch group (5).

The evidence to date suggesting that the risk of breast cancer in women who are heterozygous for MEN1 pathogenic variants is two- to three-fold greater than in women in the general population with an earlier onset would fulfil criteria for moderate risk of breast cancer under current NHS breast screening guidelines (17). The recommended screening for this consists of annual mammography between the age of 40 and 50 years followed by the routine NHS breast screening programme from the age of 50 years.

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