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Coexistence of primary renal clear cell carcinoma with primary breast invasive lobular carcinoma: a literature review and case report

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Abstract

Introduction. *The concept of concomitant co-existing malignancies has been expanding since the report from Warren and Gates in 1932, and its aetiology remains controversial. Despite it being a rare occurrence, the frequency of Multiple Primary Malignant Neoplasms (MPMNs) is increasing. MPMNs are considered synchronous when they present simultaneously or within 6 months of one another. If the second cancer has been diagnosed after six months, they are known as metachronous.* ***Case report.*** *In this paper we present a case of synchronous primary breast invasive lobular carcinoma and renal clear cell carcinoma in a 75 years old patient. (Gerontol Pol 2018; 26; 229-235)*

Key words: *renal clear cell carcinoma, breast invasive lobular carcinoma, nephrectomy, wire-guided wide local excision, oestrogen, letrozole*

Introduction

The diagnosis of two or more origin independent primary cancers with unrelated histopathological features in a patient, is called Multiple Primary Malignant Neoplasms (MPMNs). The term MPMNs was first used by Billroth in 1889, before being defined by Warren and Gates in 1932 [1].

MPMNs are considered synchronous when they present simultaneously or within 6 months of one another. If the second cancer has been diagnosed after six months, they are known as metachronous.

The co-existence of different primary malignancies is rare. This implies important diagnostic and therapeutic challenges, as the different cancers could be misdiagnosed as one disease progression.

The MPMNs detection rate is rising, most likely due to an increase in the aging population, more clinician awareness of MPMNs, better reporting facilities and improvement in diagnostic techniques. Most synchronous multiple primary tumours are seen in the genitourinary system and gastrointestinal system [2], although they may also be seen in other organs.

As breast cancer is the most common cancer in females [3], it has been reported to be diagnosed with other primary cancers. The sites of reported synchronous or metachronous cancers associated with breast cancers are the contralateral breast [4], thyroid [5,6], prostate [7], colon [8,9], kidney [10-12], lung [13], skin [1,13,14], lymphoma [1], oesophagus [15,16], stomach [17] and urinary bladder [14].

Case report

A female patient aged 75 years, presented with a recent history of a painful right breast lump. She had longstanding breast asymmetry, but no risk factors for breast carcinoma apart from her age. She underwent a hysterectomy and bilateral oophorectomy at age 51 for benign fibroids. She suffered from vertigo and hypertension only. Clinically she had obvious breast asymmetry where the right was larger than the left. There was a clinically palpable lump measuring about 6 x 5 cm in the right breast upper outer quadrant (P3), but there was no associated lymphadenopathy.

Mammogram showed right breast soft tissue density with spiculated margins, in addition to benign calcifications (figures 1 & 2). This was reported as an M5 score in the BIRAD System (*Breast Imaging Reporting and Data System)*.

In the right breast ultrasound, there was an irregular hypoechoic lesion measuring 50 x 34 x 34 mm. It was suspicious of malignancy (Figure 3) and a BIRADS score of U5 was given.

An imaging guided biopsy revealed an invasive mammary carcinoma. Staining for E-Cadherin was negative, in keeping with lobular type carcinoma and Ki-67 pro-

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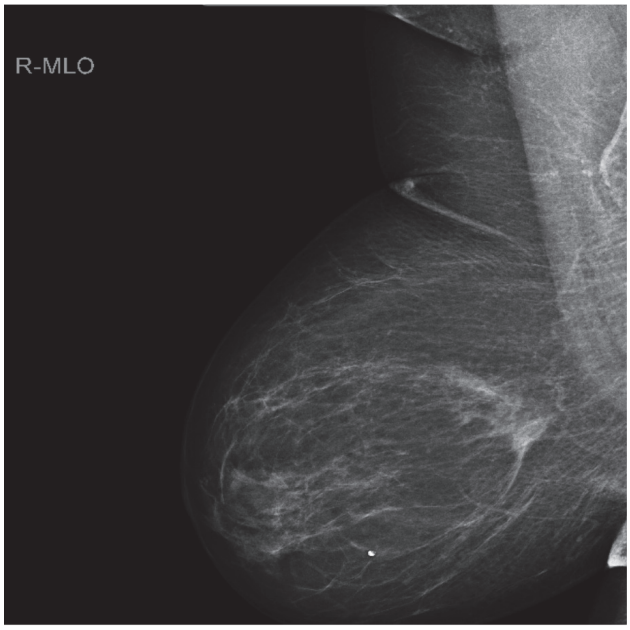

Figure 1. Right mammogram – MLO view, showing soft tissue density with spiculated margins

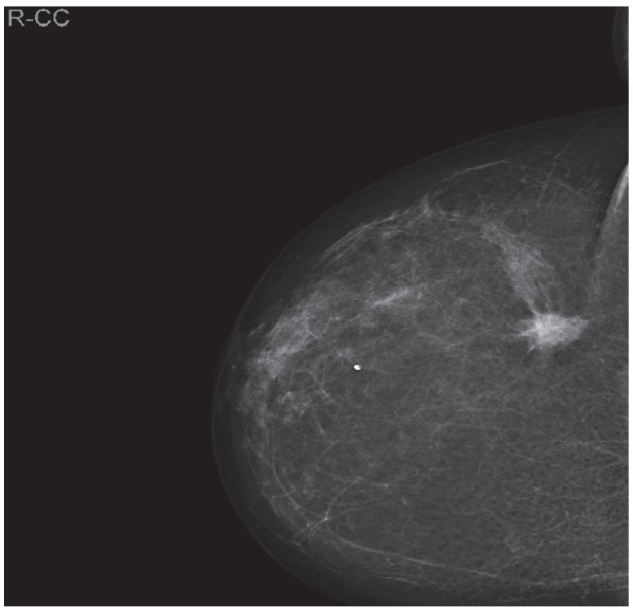

Figure 2. Right mammogram – CC view, showing soft tissue density with spiculated margins in the upper outer quadrant area

liferation index was 10%. The oestrogen receptors (ER) and progesterone receptors (PR) were positive, with both scores 8/8. Her-2 receptor status was borderline (2+). After FISH (Fluorescence in situ hybridization) testing, Her-2 was not amplified, so this case was regarded as negative for Her-2 overexpression.

The patient also had a staging CT chest abdomen pelvis, and breast MRI, in addition to a whole body scan. The breast MRI confirmed unifocal right breast disease and no suspicious areas in the contra-lateral breast. The CT reported a large left kidney nonhomogeneous mass lesion in the mid-pole area measuring 50 x 63 x 46 mm (figures 4-6). Imaging guided left renal mass biopsy showed sheets of cells with clear cytoplasm, compartmentalized into solid acinar structures by delicate, vascularized septa. The tumour cells were positive for CD10, vimentin and negative for MELA-A. The morphology and immune-profile were in keeping with renal clear cell carcinoma (Furhman grade 1).

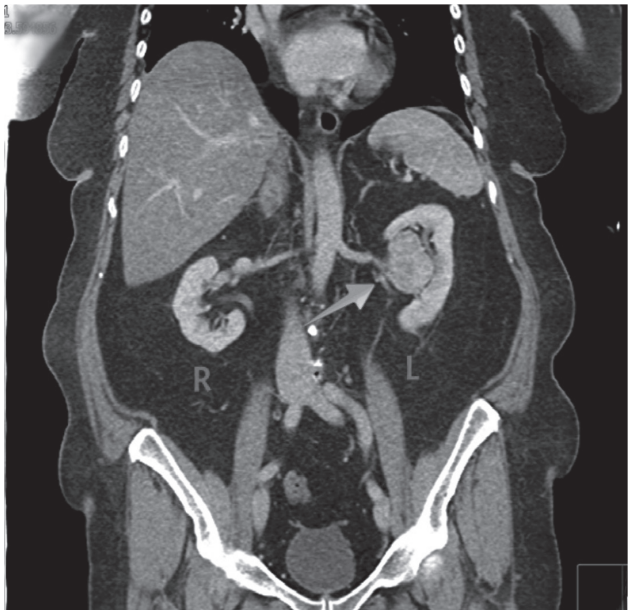

Figure 4. Coronal view abdomen CT scan, showing a large nonhomogeneous mass lesion in the mid-pole area

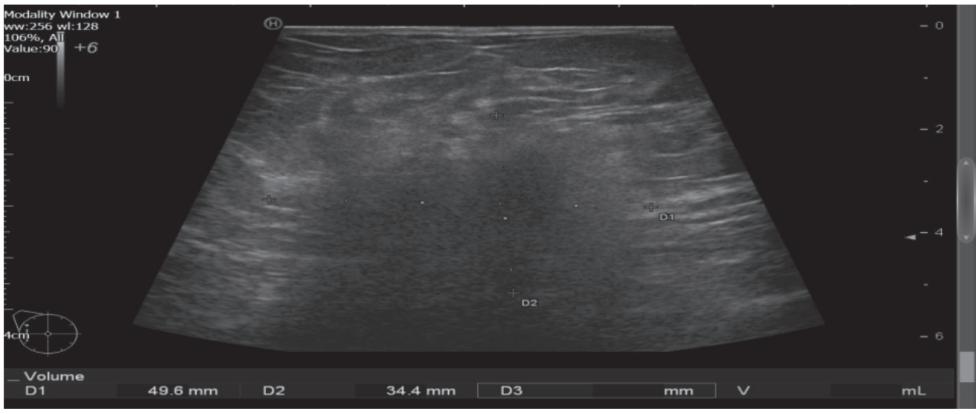

Figure 3. Right breast ultrasound, showing an irregular hypoechoic lesion measuring 50 x 34 x 34 mm; it was suspicious of malignancy

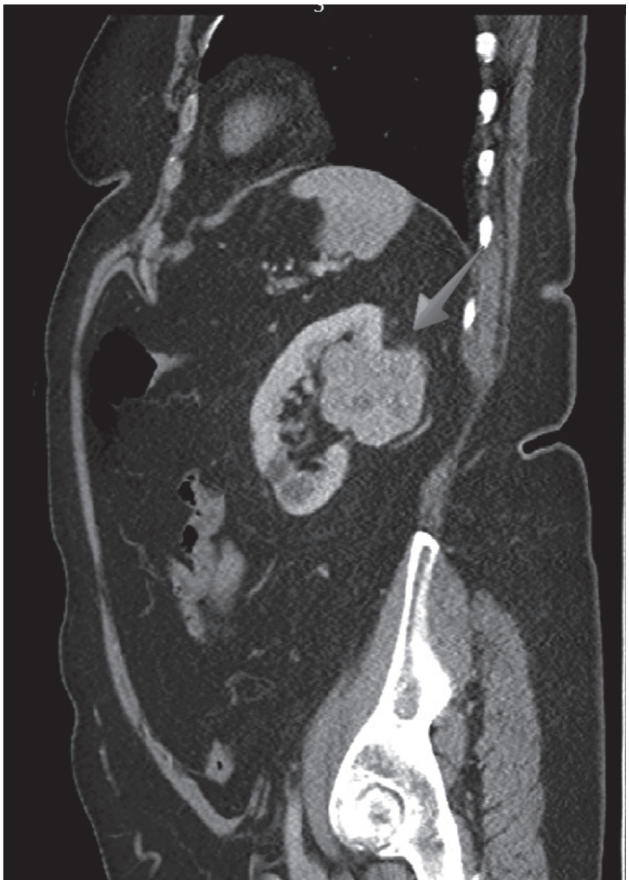

Figure 5. Sagittal view abdomen CT scan, showing a large nonhomogeneous mass lesion in the mid-pole area

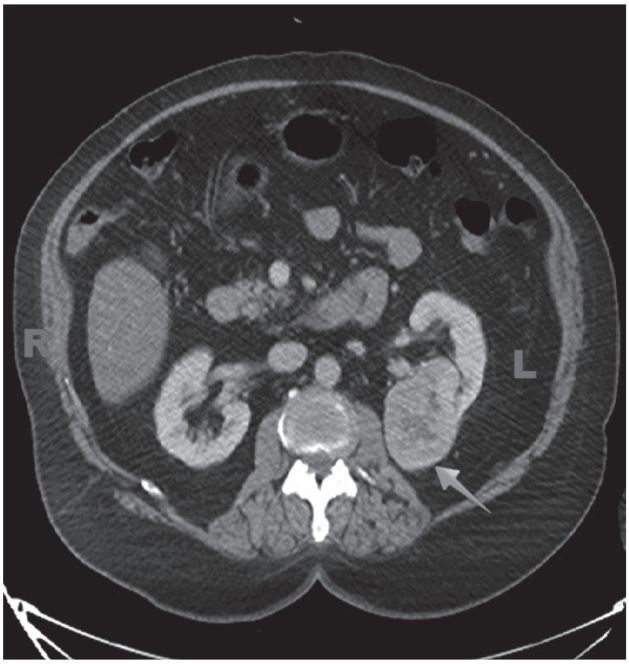

Figure 6. Axial view abdomen CT scan, showing a large nonhomogeneous mass lesion in the mid-pole area

The multidisciplinary team recommended commencing hormonal manipulation of breast cancer with aromatase inhibitor letrozole. This was followed by laparoscopic left nephrectomy. The postoperative histopathology revealed 50 x 30 x 20 mm grade 2, clear cell carcinoma without involvement of the renal vein, renal pelvis or ureter (figure 7). There was also no small vessel lympho-vascular invasion. One lymph node removed was free from cancer cells. After 6 months from the initial diagnosis and hormonal manipulation of the right breast cancer, a repeat right breast ultrasound was consistent with a possible partial radiological response. The tumour measured only 19 mm in maximum diameter. The patient underwent wire guided wide local excision of the breast cancer with sentinel lymph node biopsy (figure 8). The postoperative histology results were consistent with 25 mm grade 2, invasive lobular carcinoma admixed with invasive lobular carcinoma in situ (figure 9). The abnormality was completely excised and no lympho-vascular invasion was detected. Three removed lymph nodes were free from metastatic disease. The patient had an uneventful recovery and is currently under surveillance.

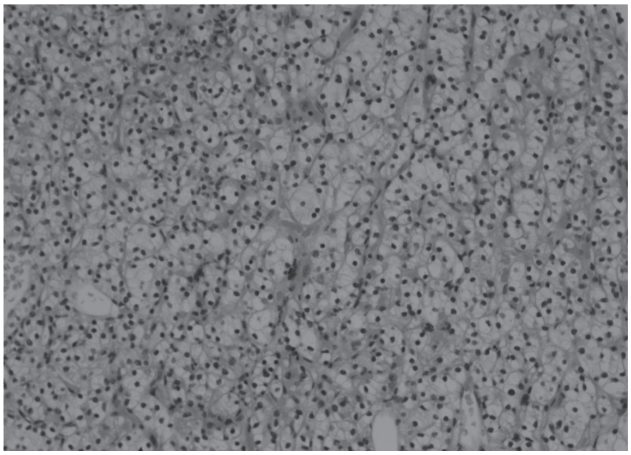

Figure 7. Clear cell renal carcinoma

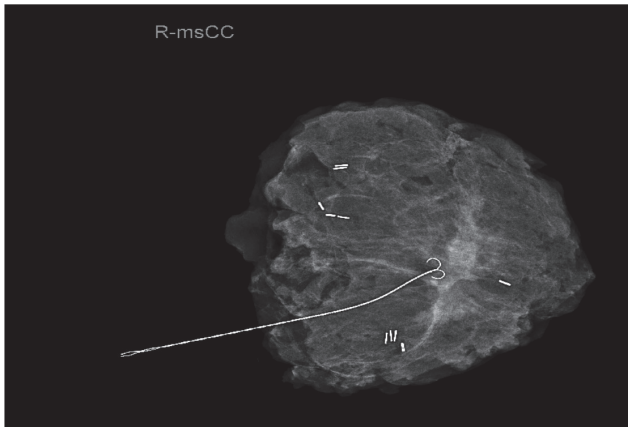

Figure 8. Lumpogram of a wire guided wide local excision of right breast cancer, showing the removed breast cancer with good radiological resection margins

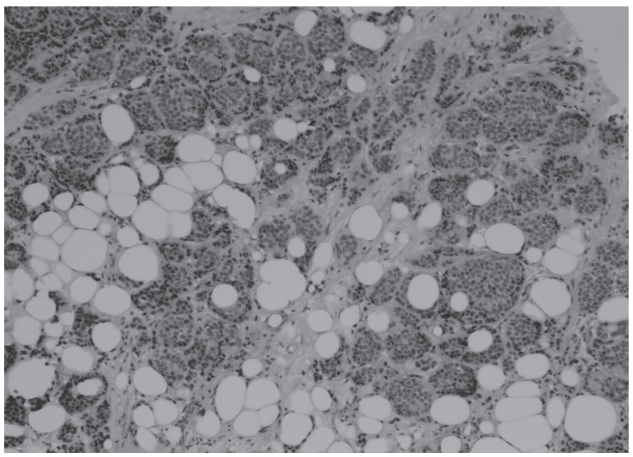

Figure 9. Breast tissue infiltrated by a lobular carcinoma

Discussion

The coexistence of two or more primary carcinomas simultaneously or within six months of each other are known as synchronous tumours. If the tumours develop consequently after six months, they are called metachronous [18]. Up to eight primary malignancies have been diagnosed in a single patient, two were synchronous and the other six were metachronous [19].

Although there are no clear answers yet behind multiple malignancy aetiology, there are some theories that have been discussed. Exposure of multiple organs to carcinogenic factor is one of those theories [9]. This is seen in the relationship between smoking and lung, nasopharyngeal, oesophageal, colorectal [20], breast [21] and bladder cancer [22].

The second theory is the genetic predisposition to BRCA1 and BRCA2 mutations, which are associated with breast and ovarian cancer [10,23] (see table I). This is known as Hereditary Breast and Ovarian Cancer syndrome (HBOC). Another example is MEN2 or Sipple's syndrome, which is characterised by the presence of medullary thyroid carcinoma, pheochromocytoma, and parathyroid adenoma [24]. Patients with Lynch syndrome, also called hereditary non-polyposis colorectal cancer (HNPCC) are at high risk of developing endometrial ovarian, stomach, small intestine, pancreatic, renal, brain, and biliary tree cancer. Lynch syndrome can be caused by a mutation in any of the MMR (Mismatch Repair Genes), including MLH1, MSH6,PMS1 and PMS2 [25]. Li-Fraumeni syndrome is a rare hereditary autosomal dominant cancer disorder. It is due to a germline mutation in TP53. The patients may develop sarcoma, leukaemia, brain cancers, adrenal cortex cancers and breast cancers [26].

The third theory is the effect of a single primary cancer treatment. Chemotherapy and radiotherapy in breast cancer treatment results in an increased risk of developing acute non-lymphocytic leukaemia [27]. Solid organs of metachronous malignancy usually take longer to de-

Table I. Hereditary MPMNs (Multiple Primary Malignant Neoplasms)

Hereditary conditions	Related cancers
Neurofibromatosis type 1(NF1)	Breast cancer Pheochromocytoma
PTEN Phosphatase and Tensin homolog Gene /Cowden syndrome	Breast cancer Renal cell carcinoma Thyroid cancer
Lynch syndrome	Colonic cancer Endometrial cancer Gastric cancer Renal cancer Pancreatic cancer
Multiple Endocrine Neoplasia Type II [MEN2] [Sipple's Syndrome]	Pheochromocytoma Thyroid Medullary carcinoma Parathyroid adenoma
Li-Fraumeni syndrome	Endometrial cancer Ovarian cancer Gastric cancer Pancreatic cancer Renal cell carcinoma Bile duct adenocarcinoma
Breast and Ovarian Cancer syndrome (HBOC). BRCA1 & BRCA2 mutation	Breast carcinoma Ovarian cancer

velop, such as a breast secondary angiosarcoma after lumpectomy and radiotherapy [28-30]. Theodor Billroth (1829-1894) is a German surgeon. In 1863 he reported for the first time, the presence of multiple primary malignancies in the same patient [14]. Multiple Primary Malignant Neoplasms (MPMNs) may involve a single organ or multiple different organs [31]. The co-existence of renal cancer with other primary cancers has also been reported. The sites of such malignancies are the ovaries [32,33], colon [9,34], lymphoma [35], breast [11], prostate [31], pancreas [36] and urinary bladder [31,37]. Hereditary conditions known to have MPMN are neurofibromatosis type 1 (NF1), which is associated with an increased risk of breast cancer [38] and pheochromocytoma, [39,40] and Cowden syndrome (CS), associated with renal and breast cancer [41].

The sites of reported synchronous or metachronous cancers associated with breast cancers are the contralateral breast [4], thyroid [5,6,42], prostate [7], colon [**8**], kidney [10-12], lung [13,43], skin [1,13,14] , lymphoma [1], oesophagus [15,16], stomach [17], urinary bladder [14], uterus [19] and adrenal pheochromocytoma [40].

The rise in detection rate of multiple co-existing primary cancers could be related to several factors, such as an increase in the overall cancer risk in the aging population, better diagnostic modalities, increased reporting rate and more awareness of the existence of Multiple Primary Malignant Neoplasms (MPMNs).

Conclusion

The MPMNs detection rate is rising. This is most likely related to an increase in the aging population, more clinician awareness of MPMNs, better reporting facilities and improvement in diagnostic techniques.

In the case of diagnosed cancer, any suspicious additional abnormality, especially if not responding to systemic treatment, should be biopsied. Attention should be paid to differentiate between double primary and metastatic tumours; this will require proper clinical and pathological assessment.

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Conflict of interest
None

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