Genomic imbalances and *MYB* fusion in synchronous bilateral adenoid cystic carcinoma and invasive lobular carcinoma of the breast

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Abstract. The incidence of synchronous bilateral breast carcinomas (BBCs) has increased with a more frequent use of magnetic resonance imaging screening of the contralateral breast in women with newly diagnosed breast cancer. A total of 30% of all BBCs occur synchronously. In the present study, we describe a unique case of synchronous BBC in a 59-year-old previously healthy woman with no known family history of breast or ovarian cancer. At the time of diagnosis the patient had an invasive lobular carcinoma (ILC) in the right breast and an adenoid cystic carcinoma (ACC) in the left breast. To the best of our knowledge, this is the first published case of bilateral, simultaneously occurring ACC and ILC of the breast. Genome-wide genomic profiling of the tumors revealed that they had distinctly different genomic imbalances. The ACC had a 5.7 Mb interstitial 6q deletion with a breakpoint located in the 3'-part of *MYB*, resulting in loss of the last coding exon of *MYB* and its 3'-UTR. RT-PCR analysis confirmed that the tumor expressed an ACC-specific *MYB-NFIB* fusion transcript. In contrast, the ILC had no rearrangements of 6q or *MYB-NFIB* gene fusion but showed instead gain of 1q21.1-qter, loss of 16q11.2-qter, and 22q12.2-q12.3 as the sole genomic imbalances. Notably, concurrent gains of 1q and losses of 16q are characteristic features of ILC. Collectively, our findings indicate that the ACC and ILC had originated independently of each other and

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that the *MYB-NFIB* fusion is a specific biomarker for breast ACC.

Introduction

The definition of synchronous bilateral breast carcinomas (BBC) varies in the literature. Some investigators regard tumors in both breasts as synchronous if they are diagnosed within an interval of 12 months, whereas others regard them as synchronous if they occur within 6 or 3 months (1-3). From a biological point of view, 12 months is considered the most reasonable time period (4,5). The incidence of synchronous BBCs has increased with the use of magnetic resonance imaging screening of the contralateral breast in women with newly diagnosed breast cancer (6). A total of 30% of BBCs occur synchronously, which constitutes <2% of all breast cancers (7). Breast cancer patients have a 2- to 6-fold higher risk for developing contralateral breast cancer compared to the risk of developing breast cancer for women in the general population (8,9). Risk factors for BBC include young age, family history (e.g., *BRCA1/2* germline mutations), lobular type of cancer, and multicentric tumors (8,10-12).

Before a diagnosis of BBC can be established, contralateral metastatic spread has to be excluded. Synchronous and metachronous BBC with highly concordant genetic profiles strongly suggest contralateral metastasis (13). On the other hand, presence of a carcinoma *in situ* component in an invasive cancer suggests a primary tumor. The distinction between BBC and breast-to-breast metastasis is important and forms the basis for the choice of therapy and ultimately also for patient outcome. Recent studies using genome-wide genomic profiling methods have facilitated the molecular characterization of synchronous and metachronous BBCs and have made it possible to rule out whether they are separate tumors or have a common origin. Thus far, available data indicate that the majority of BBC evolve independently and have distinct genotypes (13,14).

In the present study, we describe a unique case of synchronous BBC in a patient with an invasive lobular carcinoma (ILC) of solid type in the right breast and an adenoid cystic carcinoma (ACC) in the left breast. Genomic profiling revealed

that the tumors had few but distinctly different genomic imbalances and that only the ACC expressed the *MYB-NFIB* gene fusion. These observations are consistent with an independent origin of the two tumors.

Case report

Clinical history. The patient was a 59-year-old previously healthy woman with no known family history of breast or ovarian cancer. In January 2015, she had a routine mammography screening at which bilateral breast tumors were detected. Fine needle aspiration cytology (FNAC) of the right breast lesion confirmed the presence of an adenocarcinoma, whereas the FNAC of the left breast lesion was inconclusive and showed only epithelial atypia. A subsequent core biopsy of the left lesion confirmed the presence of an invasive carcinoma, possibly an ACC. Both tumors were located cranially close to the mamilla. In March 2015, bilateral partial mastectomies were performed combined with bilateral axillary sentinel node biopsies. Both tumors were clinically staged as T2N0M0, anatomic stage/prognostic group IIA. The patient was subsequently subjected to a multi-disciplinary conference for post-operative oncologic adjuvant treatment. She received post-operative, bilateral radiotherapy of the mammary glands with 2.66 Gy/fraction in 16 fractions, and endocrine treatment with an aromatase inhibitor (1 mg/day of anastrozole during a 5-year period).

Two years after diagnosis, the patient was relapse-free with no clinical, mammographic or ultra-sound evidence of disease in the mammary glands. In June 2016, FNAC of both breasts revealed normal breast tissues without signs of cancer. The study was approved by the Local Scientific Ethics Committee in Gothenburg (Dnr: 287-15). The requirement for informed consent was waived by the ethical committee since the patient material was stripped from direct subject identifiers.

Histopathological and immunohistochemical findings. Microscopic examination of the 26-mm large lesion in the right breast revealed an ILC of solid type, grade 2 (BRE-score 7: tubulus formation 3, nuclear pleomorphism 3, and mitotic activity 1) (Fig. 1A and B). Immunohistochemically, the tumor was negative for E-cadherin and positive for estrogen (95%) and progesterone (80%) receptors (Fig. 1C and D). The Ki-67 index was 20% and HercepTest was negative. No metastases were found in the sentinel node from the right axilla.

Microscopic examination of the lesion in the left breast revealed an uncommon type of breast cancer, i.e., an ACC measuring 23 mm at its largest diameter. Histologically, the tumor was composed of epithelial, basaloid, and myoepithelial cells forming typical tubular and cribriform structures (Fig. 2A and B). Combined Alcian blue-PAS staining showed clear blue-stained mucin in the luminal spaces and there was eosinophilic material in the pseudolumina. Immunohistochemically, the tumor was triple negative (estrogen and progesterone receptors and HercepTest were negative) and had a low Ki-67 proliferation index (10%). The tumor was positive for E-cadherin, p63 (Fig. 2C), α-SMA, CD10, and KIT (CD117) (Fig. 2D). Analysis of the sentinel node from the left axilla showed no signs of metastases.

Genomic profiles of the ACC and ILC. Genome-wide array-based comparative genomic hybridization (arrayCGH) analysis of DNAs isolated from the formalin-fixed paraffin-embedded (FFPE) blocks of the ACC and ILC lesions (containing >75% tumor cells) was performed with the Human Genome CGH Microarray 244K oligonucleotide arrays (G4411B; Agilent Technologies, Palo Alto, CA, USA) as previously described (15,16). Data analysis was performed with the Nexus Copy Number software version 8.0 (BioDiscovery Inc., El Segundo, CA, USA). Regions partially or completely covered by a previously reported copy number variation were excluded from the analysis.

ArrayCGH analysis of the ACC revealed a single genomic imbalance, that is a 5.7 Mb deletion in 6q23.2-q24.1. The centromeric breakpoint was located in the 3'-part of the *MYB* gene with deletion of the last coding exon of *MYB* including the 3'-UTR and flanking sequences (Fig. 3A). The telomeric breakpoint was in an intergenic region in 6q24.1.

The ILC had also relatively few but different genomic imbalances compared to the ACC. It was characterized by gain of a 104.3 Mb segment in 1q21.1-qter, loss of a 43.8 Mb segment in 16q11.2-qter, and loss of a 4.8 Mb segment in 22q12.2-q12.3 (Fig. 3B). There was no evidence of amplifications or homozygous deletions in any of the tumors.

To further characterize the ACC and ILC genomically, we screened both tumors for expression of the ACC-specific *MYB-NFIB* gene fusion (17,18). Reverse transcription polymerase chain reaction (RT-PCR) analysis was conducted on RNAs isolated from the FFPE blocks of both tumors using PCR-primers located in *MYB* exon 14 and *NFIB* exons 8a, 8c, and 9 as previously described (19). As shown in Fig. 4, the ACC was strongly positive for the *MYB-NFIB* fusion whereas the ILC was negative.

Discussion

The present study describes a unique case of synchronous BBC with two histologically different carcinomas. At the time of diagnosis the patient had an ILC in the right breast and an ACC in the left breast. The tumors were detected by routine mammography screening. The histopathological diagnoses of both lesions were unequivocal (Figs. 1 and 2) and there was no evidence of ILC or carcinoma *in situ* component in the surgical specimen from the left breast. To the best of our knowledge this is the first case of bilateral, simultaneously occurring ACC and ILC of the breast. Morphologically and immunohistochemically, the two tumors showed the typical picture and immunoprofile consistent with the respective histological subtype. Thus, the ILC was estrogen and progesterone receptor positive and E-cadherin negative whereas the ACC was triple negative and strongly positive for KIT.

Genome-wide genomic profiling of the tumors provided additional evidence in support of an independent origin of the BBCs. Thus, the ACC had an interstitial 6q deletion with a centromeric breakpoint located in the 3'-part of *MYB*, resulting in loss of the last coding exon of *MYB* including its 3'-UTR. The deletion, which spanned a 5.7 Mb segment in 6q23.2-q24.1, was the sole genomic imbalance. Previous findings have unequivocally shown that rearrangements of *MYB* is the main genomic hallmark of ACC (15,17,18,20,21). The most common *MYB*
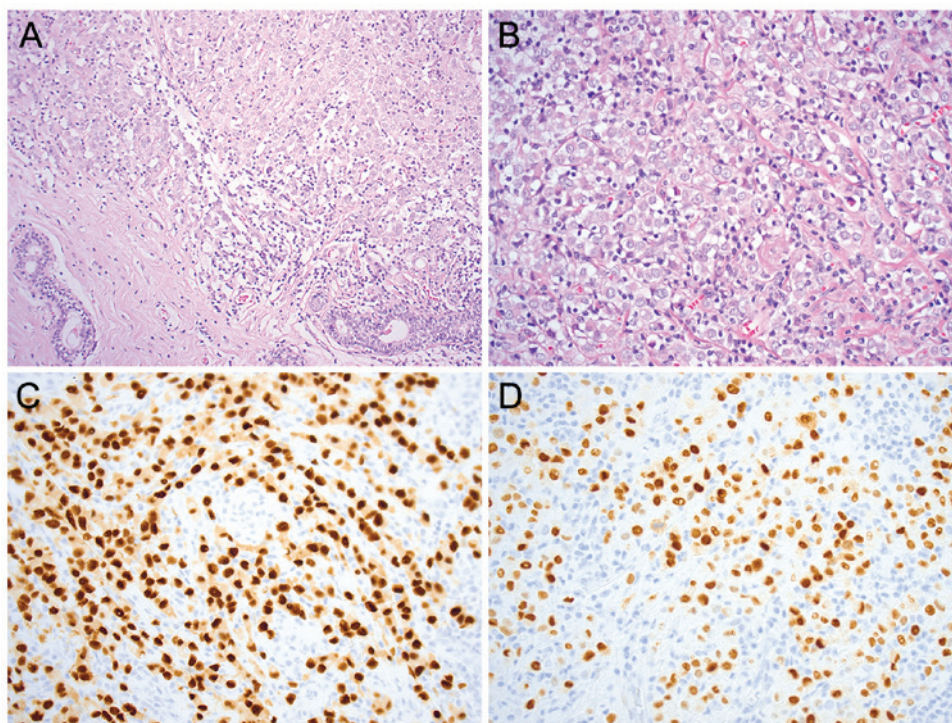
Figure 1. (A and B) ILC of solid type with cords forming sheets of tumor cells, with focal lymphocytic infiltration (H&E staining; original magnification, x100 and x200, respectively). (C and D) The tumor cells are diffusely positive for estrogen (C) and progesterone (D) receptors (original magnification, x200). ILC, invasive lobular carcinoma.
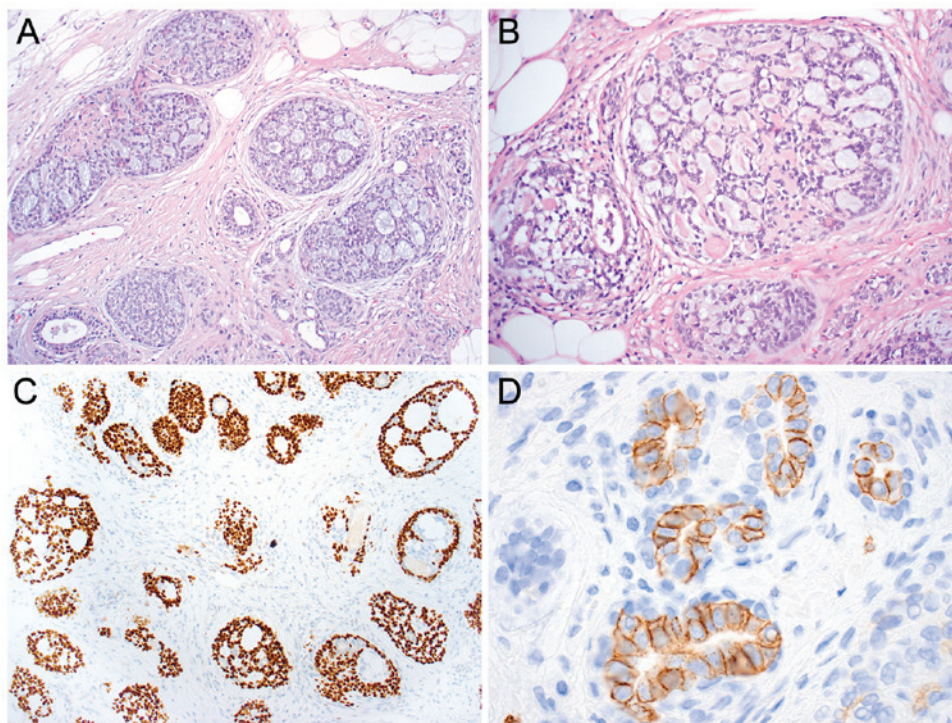

Figure 2. (A and B) ACC with characteristic cribriform structures and well-defined round spaces containing basophilic material (H&E staining; original magnification, x100 and x200, respectively). (C) Positive nuclear immunostaining for p63 (myoepithelial marker; original magnification, x200). (D) Membrane staining of the KIT oncoprotein (original magnification, x400). ACC, adenoid cystic carcinoma.

alteration in ACC is a *MYB-NFIB* gene fusion generated by a t(6;9) translocation (22,23). In the resulting fusion gene, the 3'-part of *MYB* is replaced by the 3'-part of *NFIB* leading to the overexpression of *MYB* (17,18). Activation of *MYB* through gene fusion or juxtaposition of strong enhancer elements to *MYB* occurs in 80-90% of ACCs (18,24,25) irrespective of anatomical localization (salivary gland, breast, skin, lacrimal gland, tracheobronchial tree, digestive tract, prostate, and
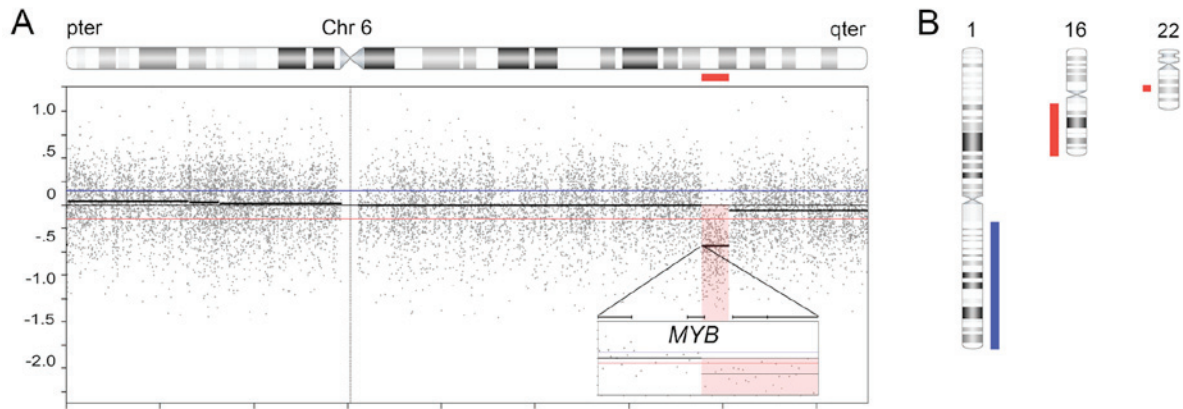
Figure 3. Genomic imbalances in synchronous BBC. (A) ArrayCGH analysis of the breast ACC demonstrating segmental loss of a 5.7 Mb fragment in 6q23.2-q24.1 including the 3'-part of the *MYB* gene and its 3'-UTR (horizontal red line). (B) Copy number alterations in the ILC, including gain of 1q21.1-qter (vertical blue line) losses of 16q11.2-qter and 22q12.2-q12.3 (red vertical lines). BBC, bilateral breast carcinomas; arrayCGH, array-based comparative genomic hybridization; ACC, adenoid cystic carcinoma; ILC, invasive lobular carcinoma.
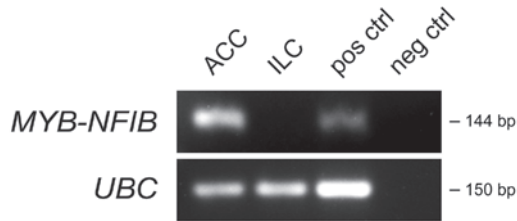

Figure 4. Expression of the *MYB-NFIB* gene fusion in synchronous BBC. RT-PCR analysis revealed expression of a 144-bp fragment in the breast ACC corresponding to a chimeric *MYB-NFIB* transcript in which exon 14 of *MYB* is linked to exon 9 of *NFIB*. The ILC did not express the *MYB-NFIB* fusion. A known fusion-positive salivary gland ACC was used as a pos ctrl. Neg ctrl indicates a negative control PCR reaction with gene-specific primers but without cDNA template. *UBC* was used as a reference gene. The sizes (bp) of the amplified fragments are indicated to the right. BBC, bilateral breast carcinomas; RT-PCR, reverse transcription polymerase chain reaction; ACC, adenoid cystic carcinoma; ILC, invasive lobular carcinoma; pos ctrl, positive control.

female genital tract) (17,18,26,27). In the breast, >90% of ACCs have *MYB* activation (21,27). In keeping with this observation the present ACC was also strongly positive for the *MYB-NFIB* fusion (Fig. 4). The ubiquitously expressed gene *UBC* was used as a positive control for the PCR reaction.

In contrast to head and neck ACCs, breast ACCs are usually low-grade tumors with an indolent clinical course. A major reason for this difference is that breast ACCs have very few, if any, genomic alterations other than *MYB* rearrangements/activation (as identified in the present case), whereas head and neck ACCs have a much higher frequency of genomic imbalances some of which are associated with an aggressive clinical behavior and a poor prognosis (15,27). However, studies of the mutational landscape of breast and salivary gland ACCs have revealed a similar mutational profile with mutations targeting chromatin remodelling, cell adhesion, RNA biology, ubiquitination, and canonical signaling pathway genes (20,21,28). Furthermore, breast and salivary ACCs show very similar histologies with luminal, basaloid, and myoepithelial cells arranged in tubular and cribriform structures with or without the presence of solid structures (29-31).

ArrayCGH analysis of the present ILC revealed a genomic profile that was completely different from that of the breast

ACC. The ILC had no rearrangements of 6q, did not express the *MYB-NFIB* gene fusion, and showed gain of 1q21.1-qter, loss of 16q11.2-qter, and 22q12.2-q12.3 as the sole genomic imbalances. Notably, concurrent gains of 1q and losses of 16q are recurrent alterations in ILC (32-34). Taken together, our studies clearly demonstrate that the synchronous BBCs had different histopathologic and genomic characteristics and had developed independently of each other consistent with the classical molecular pathways known for sporadic ACC and ILC (18,34,35).

Previous findings have shown that synchronous BBCs are often of the same histological type and show an association between hormone receptor status and tumor grade (1,4). Despite these similarities, synchronous BBCs are commonly considered as two separate primary tumors evolving in a similar microenvironment and with the same genetic background (13,14,36,37). Notably, there are a number of cases on record with histologically different synchronous bilateral breast tumors. Thus, there is a rare case of pleomorphic adenoma of the breast and a synchronous invasive ductal breast carcinoma in a 58-year-old woman (38). Da Silva *et al* have also described an interesting case of ACC with synchronous tubular adenosis (39). Although the two tumors occurred in the same breast, genomic analysis indicated that they had an independent origin. The fact that synchronous BBCs are not always identical tumors suggests that they ideally should be treated individually in line with the concept of personalized cancer medicine.

In summary, we describe a unique case of synchronous BBC in a woman with an ACC in the left breast and an ILC in the right breast. Molecular analyses revealed that the two tumors had different genomic profiles and that the ACC expressed the tumor-type specific *MYB-NFIB* gene fusion. Taken together, our findings strongly indicate that the two tumors had originated independently of each other and that the *MYB-NFIB* fusion is a specific biomarker for breast ACC.

Acknowledgements

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