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Independent primary cutaneous and mammary apocrine carcinomas with neuroendocrine differentiation: Report of a case and literature review

Running title: Apocrine carcinoma with neuroendocrine differentiation

Key words: Apocrine carcinoma; neuroendocrine differentiation; cutaneous metastasis; molecular pathology

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Abstract

Cutaneous apocrine carcinomas share common features with their counterparts in the breast, hence metastatic mammary carcinoma must be excluded before such lesions can be designated primary cutaneous neoplasms. Primary tumors from either source rarely exhibit neuroendocrine differentiation. We report a case of a 72-year-old female with a painless 1.2 cm scalp nodule. An incisional biopsy revealed dermal involvement by an invasive apocrine carcinoma juxtaposed to a benign apocrine cystic lesion. Immunohistochemically, the carcinoma expressed neuroendocrine proteins including synaptophysin, chromogranin, and CD56. A primary cutaneous apocrine carcinoma with neuroendocrine differentiation was favored, but additional investigations to exclude breast origin were recommended. These revealed a 1.1 cm nodule in the right breast, which proved to be an invasive ductal carcinoma, morphologically and immunophenotypically similar to the scalp lesion. This confounded the case, yet factors militating against metastatic breast carcinoma to skin included (i) the small size of the mammary tumor, (ii) absence of other metastatic disease, and (iii) juxtaposition of the scalp carcinoma to a putative benign precursor. Molecular studies were undertaken to resolve the diagnostic quandary. SNP microarray analysis revealed distinct patterns of chromosomal copy number alterations in the two tumors, supporting the concept of synchronous and unusual primary neoplasms.

Key words: Apocrine carcinoma; neuroendocrine differentiation; cutaneous metastasis; molecular pathology

Introduction

Apocrine carcinoma (AC) of the skin is an uncommon primary skin malignancy, occurring most commonly in the axilla.[1–4] Neuroendocrine differentiation in cutaneous AC has rarely been reported.[5–8] Ductal/apocrine carcinomas of the breast can also express neuroendocrine markers,[9] hence detection of such a tumor in the skin calls for exclusion of metastatic disease of mammary origin.[1,3,4,10]

Herein, we present a case with several points of interest: (i) evidence of neuroendocrine differentiation in an apocrine carcinoma of the scalp, a site which harbors ordinary, but not mammary-type, apocrine glands, (ii) the synchronous occurrence of two similar unusual primary tumors in the skin and breast, raising the possibility of an underlying biological propensity for development of such tumors, and (iii) the value of molecular studies in clarifying the sources of such tumors with significant clinical implications.

Case Report

Patient consent was obtained, in accordance with local Research Ethics Board protocols, for presentation of this case. A 72-year-old female presented with an asymptomatic 1.2 cm nodule on the right posterior scalp, present for 4-6 months. An incisional biopsy showed dermal involvement by an invasive adenocarcinoma (Figure 1A) characterized by poorly circumscribed nests and nodular aggregates of cells with ovoid, vesicular nuclei, and moderate amphophilic cytoplasm (Figure 1I). Architecturally, aggregates contained areas of glandular/cribriform growth (Figure 1D) with apocrine differentiation evidenced by decapitation secretions (Figure 1E), as well as zones of solid growth. Features suggestive of neuroendocrine differentiation were absent. The invasive carcinoma was immediately juxtaposed to a collection of apocrine

cystic structures. Their inner lining ranged from a single layer of bland cuboidal epithelium to focal areas with luminal papillae and cribriform growth. These features combined with a surrounding myoepithelial layer were suggestive of a benign apocrine cystic precursor the precise classification of which could be debated (Figure 1F-H). Immunohistochemical findings are outlined in Table 1. Notably, the carcinoma expressed cytokeratin 7, GATA3, synaptophysin (Figure 1B), chromogranin, ER, and PR, but was negative for GCDFP-15 (Figure 1C). Alcian blue and mucicarmine stains revealed no evidence of mucin. Cytokeratin 5/6, p63, and p40 highlighted a preserved myoepithelial layer surrounding the adjacent cystic lesion (Figure 1G), the cells of which also exhibited focal expression of synaptophysin and chromogranin. A primary cutaneous apocrine carcinoma with immunophenotypic evidence of neuroendocrine differentiation was favored, but additional investigations to exclude breast origin were recommended. Subsequent re-excision due to positive margins demonstrated residual carcinoma with focal lymphovascular invasion.

A computed tomography scan showed an area of right breast skin/nipple retraction and a few mildly enlarged right axillary lymph nodes. Mammography revealed a 1.1 cm nodule in the right breast, with ill-defined margins and scattered microcalcifications. Positron emission tomography scan (performed prior to complete excision of the scalp tumor) showed mild to moderate fluorodeoxyglucose uptake in the scalp tumor, with mild uptake in the breast nodule and in axillary lymph nodes. Core needle biopsy of the breast nodule was pursued, followed by wire localization excision and sentinel lymph node biopsy. The core biopsy showed an invasive ductal/apocrine carcinoma, Nottingham grade 2, associated with focal ductal carcinoma in situ (Figure 2). There was morphological and immunophenotypic (Table 1) overlap with the

concurrent scalp tumor, the only IHC discrepancy being the expression of GCDFP-15 in the mammary carcinoma alone. Lymphovascular invasion was not identified. Sentinel lymph node biopsy was negative for metastatic ductal carcinoma but did reveal incidental involvement by clinically occult metastatic lobular breast carcinoma, a tumor which is morphologically and immunophenotypically distinct from ductal carcinoma.

After obtaining informed consent from the patient, to distinguish between metastatic disease and synchronous primary carcinomas molecular profiling studies were performed. The two tumors were subjected to Next Generation Sequencing (NGS) (Illumina TSO500 hybrid capture DNA panel, Illumina NextSeq550 instrument) and Single Nucleotide Polymorphism (SNP) microarray analysis (Affymetrix OncoScan™ FFPE Assay Kit, performed at the University of Michigan). NGS identified nine variants in common between the tumors (Table 2), with no pathogenic or likely pathogenic mutations identified in either tumor. This raised the possibility that the shared variants could represent rare germline SNPs and the analysis was hence considered inconclusive in assessing for clonality/relatedness. There were no pathogenic mutations in genes implicated in common hereditary tumor syndromes (e.g. *BRCA* genes). SNP microarray analysis of the breast tumor showed no copy number gains or losses, while the scalp tumor demonstrated greater than 20 copy number alterations/losses of heterozygosity involving nearly every chromosome (Table 3, Figure 3).

Discussion

AC is a rare skin malignancy, and the literature pertaining to this tumor is comprised of isolated reports and small series of cases.[1,3–7,10–16] Tumors are sometimes associated with adjacent hyperplastic, hamartomatous, or adenomatous benign apocrine proliferations,[1,3,4,11,13–15]

suggesting that these may represent precursors.[13,14] Occasionally, tumor cells have involved myoepithelial-lined spaces, reflecting either colonization of pre-existing adnexal structures or "in situ" carcinoma.[4,5,15] Some ACs have occurred in association with nevus sebaceus of Jadassohn.[4] Given the frequency of breast carcinoma relative to that of cutaneous AC,[1,3,4,10] and the fact that secondary deposits from this source feature in many reported examples of metastases to the skin,[17–19] mammary origin must be excluded prior to a diagnosis of primary cutaneous AC. In our case, histopathological and clinical factors favoring synchronous primary tumors over metastatic disease included (i) the small size of the mammary ductal/apocrine carcinoma, (ii) the absence of other metastatic disease from this tumor, and (iii) the association of the AC on the scalp with a putative benign precursor.

Apart from conventional ductal/apocrine carcinomas which can arise at both anatomic sites, certain tumor types, notably secretory carcinoma[20] and endocrine mucin-producing sweat gland carcinoma (EMPSGC) of the skin (versus solid papillary carcinoma of the breast),[8,21–23] can be of mammary or cutaneous origin. Similarly, neuroendocrine differentiation has rarely been described in 'conventional' primary apocrine/ductal carcinomas of the breast[9] and of the skin.[8] In two of three reported cases of cutaneous AC with neuroendocrine differentiation[5,6] the lesions were located on genital skin, raising the possibility of an origin from mammary-type glands at that site rather than ordinary cutaneous apocrine glands. The third case occurred on the lower abdomen.[7] Identification of neuroendocrine differentiation in a primary cutaneous AC on the scalp indicates that this can occur in non-mammary-type cutaneous apocrine glands. Moreover, it provides a putative link between such tumors and the rare, published examples of cutaneous undifferentiated large cell neuroendocrine carcinomas. These are known to be

distinct from Merkel cell carcinoma and they lack the routine histopathological features conventionally associated with neuroendocrine differentiation.[24] The synchronous occurrence of these two unusual primary neoplasms in the skin and breast of our patient raises the question of a potential underlying biological propensity to develop such tumors. Of interest, EMPSGC in the skin has rarely been reported to coincide with a synchronous primary breast carcinoma.[25,26] A case of EMPSGC occurring along with a ductal/mucinous breast carcinoma presents an analogous situation to our current case.[25]

Clinical and histopathological data in our case were more suggestive of two independent primary neoplasms than metastatic breast carcinoma, but a definite conclusion in this regard remained elusive. Given the importance of resolving this quandary, from treatment and prognostic perspectives, molecular studies were undertaken. In contrast to findings in an earlier report,[27] in which NGS was used to identify identical pathogenic somatic mutations in a urothelial carcinoma of the kidney and a tumor on the scalp, disclosing the metastatic nature of the latter, NGS results proved inconclusive in our case. NGS also failed to identify a putative germline pathogenic mutation predisposing to development of these unusual apocrine carcinomas at different sites.

In contrast, SNP microarray revealed a distinct pattern of chromosomal copy number alterations between the tumors, providing no evidence of relatedness. This technology uses hybridization probes at SNP sites throughout the genome to interrogate for sites of copy number alterations, and has been used in a research setting to distinguish primary versus metastatic tumors at other anatomical sites, including breast and ovarian adenocarcinomas,[28] head/neck and esophageal squamous cell carcinomas,[29] and germ cell tumors,[30] as well as in

patients with multiple cutaneous melanomas.[31] In two related tumors, one would ordinarily expect a degree of overlap in copy number alterations, while independent primary neoplasms would demonstrate distinct patterns.

In conclusion, the main points of interest highlighted by our case lie in (i) supporting the concept that apocrine carcinomas of the skin arising at sites normally devoid of mammary-type glands can exhibit neuroendocrine differentiation and are likely the source of primary cutaneous undifferentiated large cell neuroendocrine carcinomas, and (ii) emphasizing the value of molecular technology in distinguishing between independent synchronous primary tumors versus a primary tumor and metastatic disease, with potential influence on both treatment and patient outcomes.

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Table 1. Immunohistochemical profiles of scalp and breast tumors.

Antibody	Scalp tumor	Breast tumor
CK7	+	+
CK20	-	-
Synaptophysin	+	+
Chromogranin	+ (diffuse)	+ (patchy)
GATA3	+	+
GCDFP-15	-	+
ER	+	+
PR	+	+
HER2	-	Equivocal (2+)[†]
CDX2	-	-
TTF-1	-	-

[†]Negative for HER2 gene amplification by fluorescence in situ hybridization

Table 2. Next generation sequencing variants detected in scalp and breast tumors.

Gene	**Mutation Type**	**Mutation**	**Scalp Tumor (VAF[†])**	**Breast Tumor (VAF)**	**Population Allelic Fraction[‡]**
AKT3	**3' UTR[§]**	**c.*1538A>T**	**+ (0.36)**	**+ (0.60)**	**0.0001**
AR	**Intronic**	**c.1616+21685G>C**	**+ (0.38)**	**+ (0.46)**	**0.001**
ASXL1	**Missense**	**c.890C>T p.Thr297Met**	**+ (0.38)**	**+ (0.46)**	**0.00003**
DOT1L	Missense	c.1745C>T p.Ser582Leu	+ (0.24)	-	0.00007
FGF19	**Missense**	**c.569C>G p.Ser190Trp**	**+ (0.33)**	**+ (0.42)**	**0**
FGF19	Synonymous	c.66G>A p.Gly22Gly	+ (0.55)	-	0
GPR124	**Missense**	**c.2195G>A p.Arg732His**	**+ (0.61)**	**+ (0.43)**	**0.0001**
KIF5B	**3' UTR**	**c.*277G>A**	**+ (0.23)**	**+ (0.54)**	**0.001**
LATS2	Missense	c.2016A>T p.Lys672Asn	+ (0.25)	-	0
MAP3K14	**Noncoding transcript exon**	**n.316A>G**	**+ (0.64)**	**+ (0.55)**	**0.00002**
NTRK3	**Upstream gene**	**c.-309G>T**	**+ (0.16)**	**+ (0.47)**	**0**
PNRC1	**Synonymous**	**c.117G>A p.Pro39Pro**	**+ (0.11)**	**+ (0.58)**	**0.0002**
ROS1	Intronic	c.5642-1293A>C	-	+ (0.28)	0

[†]VAF = variant allele frequency

[‡]Population allelic fraction obtained from the genome aggregation database (gnomAD)

[§]UTR = untranslated region

Table 3. SNP microarray results for the scalp tumor.

Chromosome	Full Location	Variant Type	Size (kbp)	Cytoband Region	Copy Number
1	chr1:754191-249212878	Gain	248459	p36.33-q44	2.5
2	chr2:21493-243052331	LOH	243031	p25.3-q37.3	2
3	chr3:63410-197852564	Gain	197789	p26.3-q29	2.5
4	chr4:76852584-77327339	Loss	475	q21.1-q21.1	1.5
5	chr5:38138-180698312	Gain	180660	p15.33-q35.3	4.5
6	chr6:123191159-170913051	Gain	47722	q22.31-q27	3.5
6	chr6:204908-70982929	Gain	70778	p25.3-q13	3.5
6	chr6:70988911-123206331	LOH	52217	q13-q22.31	2
7	chr7:41420-159118443	Gain	159077	p22.3-q36.3	2.5
8	chr8:172416-146292734	Gain	146120	p23.3-q24.3	3.5
9	chr9:204737-141054761	Gain	140850	p24.3-q34.3	2.5
10	chr10:126069-135434303	Gain	135308	p15.3-q26.3	2.5
11	chr11:192763-134938847	Gain	134746	p15.5-q25	2.5
12	chr12:189399-133818115	Gain	133628	p13.33-q24.33	2.5
13	chr13:19084822-31513369	Gain	12429	q11-q12.3	2.5
13	chr13:31535436-78683234	Loss	47148	q12.3-q22.3	1.5
13	chr13:78693758-80773073	Gain	2079	q22.3-q31.1	2.5
13	chr13:80789306-91257552	Loss	10468	q31.1-q31.3	1.5
13	chr13:91281306-115103150	Gain	238212	q31.3-q34	2.5
14	chr14:106537283-106756726	Loss	219	q32.33-q32.33	1.5
14	chr14:106759147-107282024	Gain	523	q32.33-q.32.33	3.5
14	chr14:20219082-106531400	Gain	86312	q11.2-q32.33	3.5
15	chr15:22752398-102397317	LOH	79645	q11.2-q26.3	2

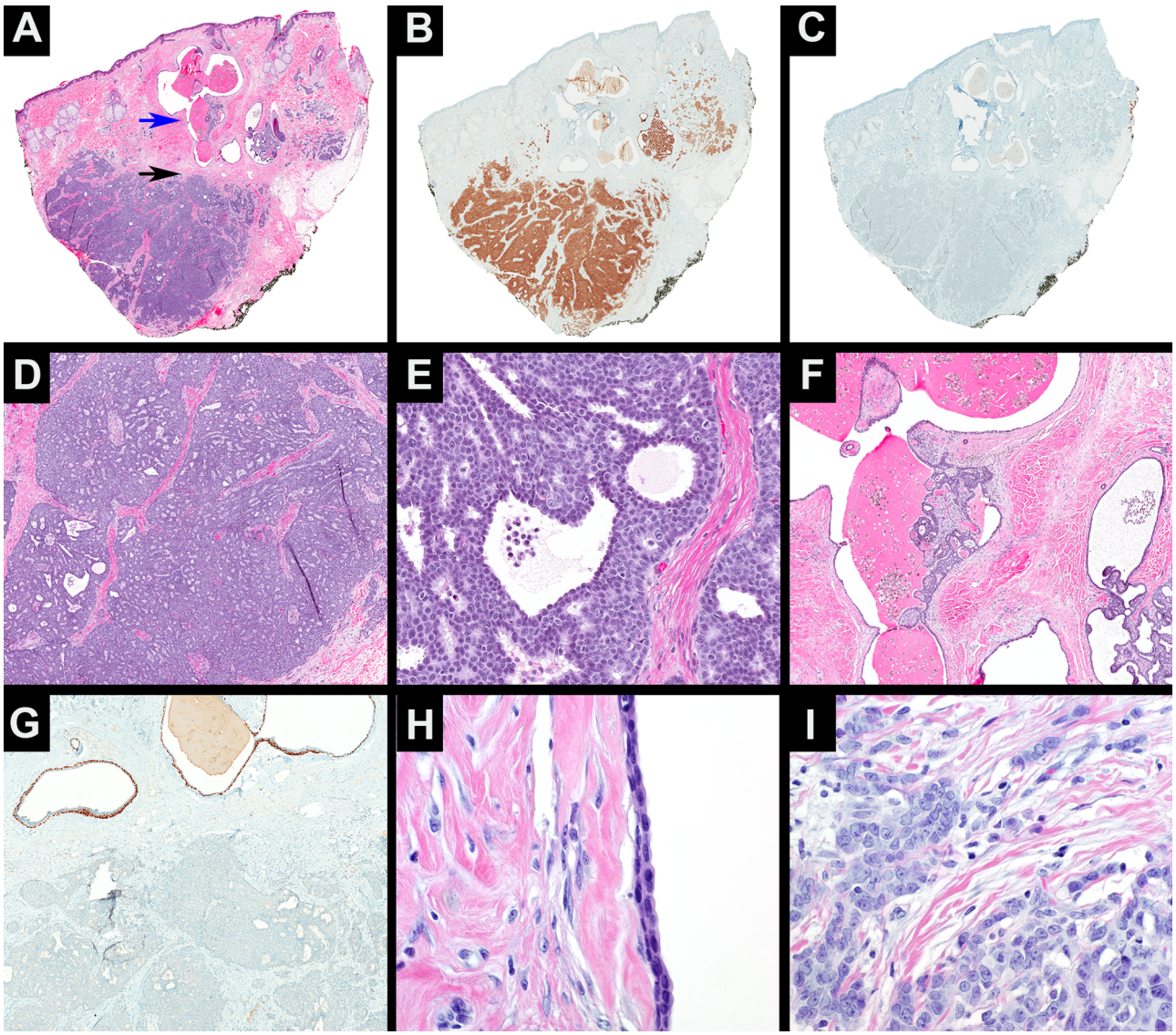
16	chr16:46461308-90158005	LOH	43697	q11.2-q24.3	2
16	chr16:83886-35271725	Gain	35188	p13.3-p11.1	3.5
17	chr17:400958-80263427	Gain	79862	p13.3-q25.3	2.5
18	chr18:12841-78007784	Gain	77995	p11.32-q23	2.5
19	chr19:247231-59093239	Gain	58846	p13.3-q.13.43	3.5
21	chr21:9648314-48097610	Gain	38449	p11.2-q22.3	3.5
22	chr22:16054712-51213826	LOH	35159	q11.1-q.13.33	2
X	chrX:177941-155219364	LOH	155041	p22.33-q28	2

[†]LOH = loss of heterozygosity

Figure 1. Apocrine carcinoma of the scalp associated with a benign cystic apocrine lesion (A. H&E, 10x; B. Synaptophysin (IHC), 10x; C. GCDFP-15 (IHC), 10x). The carcinoma displays sheet-like and cribriform growth patterns (D. H&E, 40x), with apocrine differentiation (E. H&E, 200x). The adjacent cystic apocrine lesion (F. H&E, 40x) displays an intact myoepithelial layer (G. p63, 40x). Under high magnification, the dual bland inner cuboidal epithelial and outer flattened myoepithelial layer of the cyst wall are evident (H. H&E, 200x; photomicrograph captured from area in Figure 1A denoted by blue arrow). The benign cytological characteristics of the cyst lining contrast with those of the invasive carcinoma displaying cells with vesicular nuclei, irregular nuclear contour, coarse chromatin, and increased nucleolar prominence (I. H&E, 200x; photomicrograph captured from area in Figure 1A denoted by black arrow).

Figure 2. Invasive ductal carcinoma of the breast with neuroendocrine differentiations (A. H&E, 10x); B. Synaptophysin (IHC), 10x; C. GCDFP-15 (IHC), 10x). The carcinoma displays solid nested and cribriform patterns (D. H&E, 40x), with apocrine differentiation (E. H&E, 200x). There is focal associated ductal carcinoma in situ (F. H&E, 100x).

Figure 3. Copy number aberration studies performed via Single Nucleotide Polymorphism Microarray analysis. The scalp tumor (A) demonstrates copy number gains and losses involving nearly every chromosome. No copy number aberrations are identified in the breast tumor (B).



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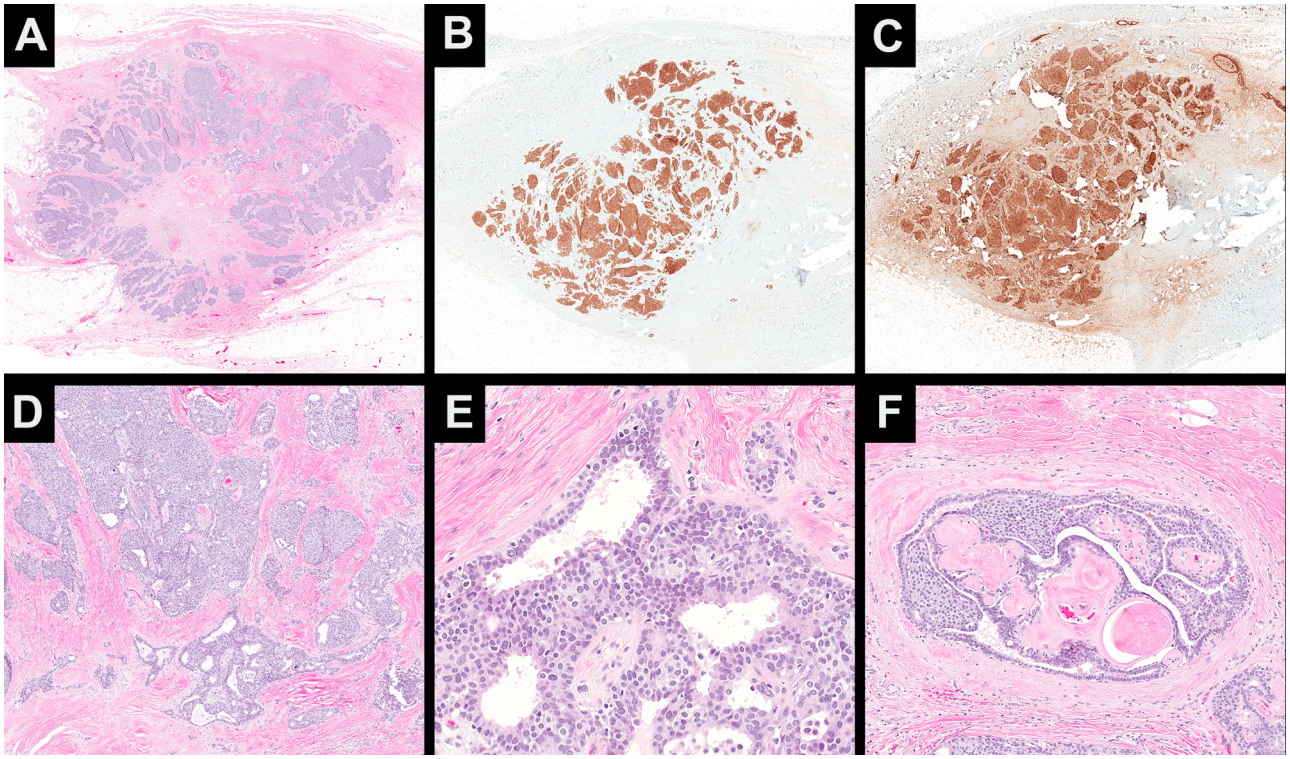

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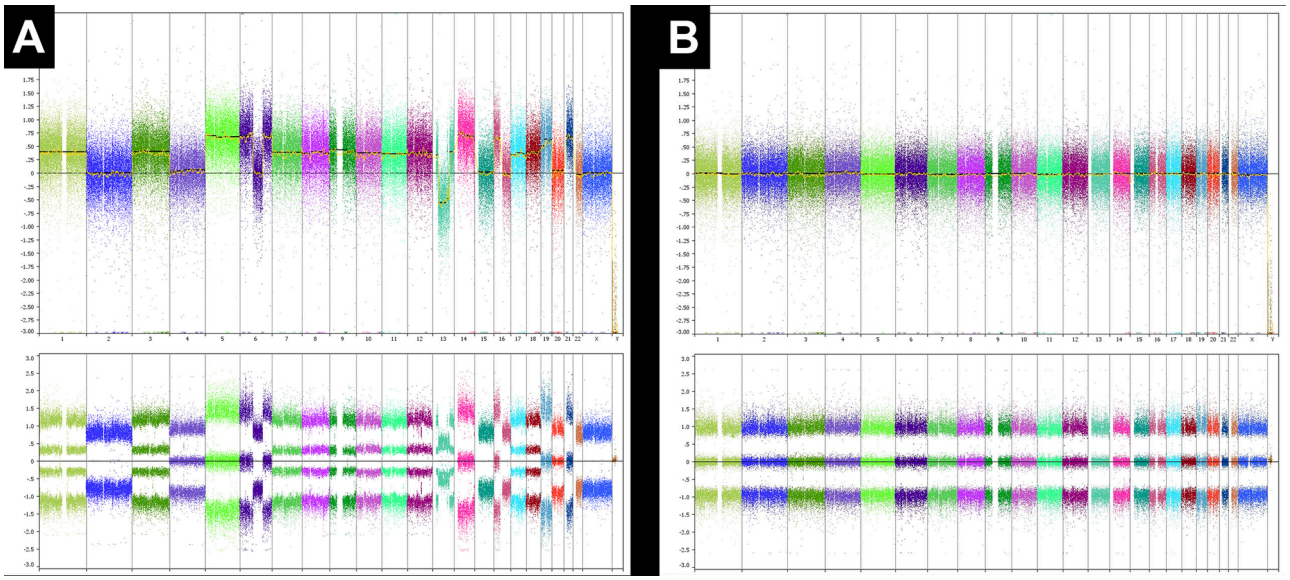

CUP_14085_CUP_14085_Fig 3 SNP array.tif

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