CLINICAL VIGNETTE

A Young Woman with Likely Synchronous Breast and Thyroid Cancer

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Case Report

A 29-year-old premenopausal Asian woman presented with bloody right nipple discharge for several months. She was subsequently diagnosed with invasive ductal carcinoma of right breast which is ER/ PR positive, HER2 negative. She denies any family history of breast, ovarian, thyroid, pancreatic cancers or melanoma. She underwent Myriad MyRisk genetic panel testing and was negative for any known deleterious mutation. She was found to have variant of unknown significance (VUS) in CDKN2A (p14ARF) c.242G>A, CDKN2A (p16INK4a) c199G>A, and NTHL1 (c.-13A>G).

She elected for bilateral skin sparing total mastectomies and bilateral sentinel node biopsy with immediate reconstruction. Right mastectomy pathology showed 8 foci of invasive, and 5 foci of microinvasive ductal cancers arising in a 12 cm background of extensive solid papillary carcinoma in situ spanning the lateral breast. One of 2 sentinel nodes had isolated tumor cell clusters measuring up to 0.1 mm. Final right sided staging is pT1c(m)N0(i+). The invasive cancers were ER/PR >95% positive, HER2 negative by IHC and FISH. Oncotype RS was low at 11. Final pathology from left mastectomy showed 7.5 cm span of non-invasive solid papillary carcinoma and DCIS, cribriform type, low nuclear grade involving the upper outer quadrant and central breast. Three sentinel nodes were all benign. DCIS is ER>95% positive. She proceeded with tamoxifen treatment after surgery.

A year later, she presented with an enlarging thyroid gland. Thyroid US confirmed bilateral thyroid nodules up to 1.8 cm on the left and new right extensive cervical lymphadenopathy up to 2cm. Cervical node biopsy showed metastatic carcinoma positive for CAM 5.2, TTF1, PAX8, thyroglobulin, and negative for GATA-3, mammaglobin, GCDFP-15, ER, Napsin A, CDX2. The findings support a metastatic carcinoma of thyroid primary. She subsequently underwent bilateral thyroid nodule fine needle aspiration which confirmed papillary thyroid carcinoma from both lobes. Staging scan did not show distant disease. She proceeded with total thyroidectomy, central cervical lymphadenectomy and concurrent right modified radical neck dissection. Final pathology showed multiple foci of papillary thyroid carcinoma ranging 0.1 to 2.4cm with focal anigolymphatic invasion. Total 13 of 24 nodes had disease involvement with the largest focus 2cm with focal extracapsular involvement. Staging is pT2(m)N1b.

Discussion

Synchronous or metachronous presentation of breast and thyroid cancers exceeds that predicted by chance alone based on existing epidemiological data.[1] Potential explanations include shared hormonal factors or environmental exposure, oncogenic treatment effect from the first cancer, closer long term follow-up of cancer survivors, and lastly potential shared underlying genetic predispositions. However, the genetic background of most cases of co-occurring breast and thyroid cancer have been most likely polygenic in nature.[1]

Cyclin dependent kinase inhibitor 2A (*CDKN2A*) encodes two tumor suppressor proteins, p16INK4A and p14ARF which play a critical inhibitory role in cell cycle progression.[2] Loss of *CDKN2A* and its impact leading to cancer progression have been well documented in several cancer types, primarily melanoma and pancreatic cancer.[3,4] CDKN2A is homozygously deleted in up to 60% of primary breast tumors and cell lines, and point mutations in this gene remains rare.[2] There are evidences of LOH and CpG island methylation in tumor samples and cell lines.[5,6] There are also data supporting *CDKN2A* loss in aggressive thyroid cancers, and its incidence in anaplastic thyroid cancer was reported as high as 20%.[7] *CDKN2A* loss is not only associated with the progression of anaplastic thyroid cancer, but also predicts poor prognosis and survival of patient with advanced differentiated thyroid cancer.

We have enough data showing that cancer susceptibility among germline variant carriers of *CDKN2A* extend beyond the well-known predisposition to melanoma and pancreatic cancer.[8] It is potentially associated with a multitude of cancers and our young woman with near synchronous presentation of both breast and thyroid cancer further supports this theory. She has VUS of CDKN2A point mutation involving both p14ARF and p16INK4a which likely played a major role in her cancer development given her young age with both cancers, and her lack of other acquired known risk factors. With the rapid adaption of multigene panel testing in practice, new data will continue to reframe our understanding of the genotype-phenotype associations relating to *CDKN2A* mutation. The spectrum of associated cancer types driven by specific molecular consequences on $p16^{INK4A}$ and/or $p14^{ARF}$, warrant future validation studies. Clinicians and genetic counselors should be cognizant of the expanding range of cancer phenotypes linked to *CDKN2A* as the pathologic gene for tumor

predisposition syndrome in individuals and families presenting with wider spectrum of cancers.

REFERENCES

1. **Lehrer S, Green S, Martignetti J, Rosenzweig K**. Association between breast and thyroid cancers. *Advances in Genomics and Genetics*. 2014;4:1-4. Available at: https://doi.org/10.2147/AGG.S58346.
2. **Foulkes WD, Flanders TY, Pollock PM, Hayward NK**. The CDKN2A (p16) gene and human cancer. *Mol Med*. 1997 Jan;3(1):5-20. PMID: 9132280; PMCID: PMC2230107.
3. **Hussussian CJ, Struewing JP, Goldstein AM, Higgins PA, Ally DS, Sheahan MD, Clark WH Jr, Tucker MA, Dracopoli NC**. Germline p16 mutations in familial melanoma. *Nat Genet*. 1994 Sep;8(1):15-21. doi: 10.1038/ng0994-15. PMID: 7987387.
4. **Goldstein AM, Fraser MC, Struewing JP, Hussussian CJ, Ranade K, Zametkin DP, Fontaine LS, Organic SM, Dracopoli NC, Clark WH Jr, et al**. Increased risk of pancreatic cancer in melanoma-prone kindreds with p16INK4 mutations. *N Engl J Med*. 1995 Oct 12;333(15):970-4. doi: 10.1056/NEJM199510123331504. PMID: 7666916.
5. **Herman JG, Merlo A, Mao L, Lapidus RG, Issa JP, Davidson NE, Sidransky D, Baylin SB.** Inactivation of the CDKN2/p16/MTS1 gene is frequently associated with aberrant DNA methylation in all common human cancers. *Cancer Res*. 1995 Oct 15;55(20):4525-30. PMID: 7553621.
6. **Brenner AJ, Aldaz CM**. Chromosome 9p allelic loss and p16/CDKN2 in breast cancer and evidence of p16 inactivation in immortal breast epithelial cells. *Cancer Res*. 1995 Jul 1;55(13):2892-5. PMID: 7796417.
7. **Yoo SK, Song YS, Lee EK, Hwang J, Kim HH, Jung G, Kim YA, Kim SJ, Cho SW, Won JK, Chung EJ, Shin JY, Lee KE, Kim JI, Park YJ, Seo JS**. Integrative analysis of genomic and transcriptomic characteristics associated with progression of aggressive thyroid cancer. *Nat Commun*. 2019 Jun 24;10(1):2764. doi: 10.1038/s41467-019-10680-5. PMID: 31235699; PMCID: PMC6591357.
8. **Chan SH, Chiang J, Ngeow J**. CDKN2A germline alterations and the relevance of genotype-phenotype associations in cancer predisposition. *Hered Cancer Clin Pract*. 2021 Mar 25;19(1):21. doi: 10.1186/s13053-021-00178-x. PMID: 33766116; PMCID: PMC7992806.