Multiple Metachronous Malignancies, One Patient with Three Primary Malignancies

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Abstract Development of a primary cancer after treatment of the first with radiotherapy or chemotherapy is well documented, but it is common with hematological malignancies. Variety of reasons are suggested by various researchers, but a conclusive evidence is not yet available. Excepting a few correlations like the tamoxifen therapy and endometrial cancer, angiosarcoma of the breast following radiotherapy, occurrence of other metachronous malignancies seem to be dependent on genetic and environmental factors. A patient with three primary malignancies is presented here.

Keywords Multiple malignancies · Metachronous · Gene disorders

Case Report

A 54 year old female presented with a painless swelling in the anterior part of the neck for over 3 years' duration. On examination, the swelling was globular measuring about 3 cm in diameter in the region of right lobe of thyroid and was moving with deglutition. There was no retrosternal extension and cervical lymphadenopathy. A clinical diagnosis of thyroid adenoma was made. Right hemithyroidectomy was done, and the histopathology was minimally invasive follicular carcinoma of thyroid. She was suggested completion thyroidectomy which she refused. By the end of 1 year, she developed swelling of the left lobe, which on CT showed calcified deposits, and the FNAC showed scanty colloid material with follicular

cells with no evidence of malignancy. She was lost to follow up since then.

Five years after right hemithyroidectomy, she developed a malignant lump in the left breast, for which she underwent simple mastectomy with axillary clearance. Six courses of adjuvant chemotherapy (Cyclophosphamide, Epirubicin and 5 fluorouracil) was given, and was advised to take Tamoxifen for 5 years.

A year after mastectomy, during regular follow up, the abdominal ultrasound showed thickened endometrium of about 13 mm. On curettage, it was well differentiated adenocarcinoma, for which she refused any treatment. At this point, Tamoxifen was stopped and Letrozole was started.

About 18 months after mastectomy, she developed hard nodules on the mastectomy scar, which were histologically proved to be infiltrating duct carcinoma. On further investigations, her CTs showed multiple hypodense lesions of varying size with variegated post contrast enhancement in the arterial phase in the liver, metastatic deposits in the lungs and pleural effusion (Fig. 1), though she remained asymptomatic. Only treatment she accepted was the local radiotherapy for the recurrent nodules, for which 56 Gy of radiation was given to the chest wall. In the meantime, she developed abdominal distension due to ascites, which showed malignant cells. She later succumbed to further complications.

Discussion

Multiple metachronous primary cancers are known to occur in an individual, but it is often seen with hematological malignancies of childhood. The reasons are many; BRCA gene mutation, viral cause like HPV

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Fig. 1 CT pictures of multiple malignancies and their metastases

and HTLV1, and toxins damaging the DNA structure. Exposure to carcinogens like smoking can cause multiple malignancies affecting the lungs, nasopharynx and urinary bladder. HPV is known to cause malignancies of vulva, vagina and uterine cervix. It is said the successful treatment of one malignancy can cause longer

survival increasing the possibility of further cancers. It is hypothesized that a third of cancer patients will develop a second primary tumor (SPT) and a third of SPT patients will develop a third primary tumor (TPT) [1]. SPT may also occur due to the presence of genetic base, especially the multiorgan susceptibility gene, the CHEK2

protein, which participates in the DNA damage. The missense variant 1157 T was associated with an increased risk of cancers of breast, colon, kidney, prostate and thyroid [2]. In some studies, an increased incidence of breast cancer is seen in women with thyroid carcinoma. Increased incidence of thyroid carcinoma following breast cancer is also known [3]. Ronckers et al. say that patients of <40 years of age at diagnosis of thyroid cancer have a 39% risk of second cancer, in contrast to 6% in older patients [4]. In the same study, several other cancer sites showed significantly increased risks in both directions, including salivary glands, prostate, breast, kidney, scrotum, brain and leukemia. A relationship between the total dose of I^{131} and SPT has been reported for solid cancers and leukemias [5]. Verkooijen et al. differ to suggest that this phenomenon occurs only due to genetic predisposition and environmental factors, as at least half of breast cancers occur before the treatment with I^{131} for thyroid cancer [6]. The co-occurrence may be related to a genetic deregulation, as the H23 gene, which is overexpressed in both thyroid and breast cancers. As one of its forms is probably a transmembrane receptor-like protein, it may be an element of signal transduction and, therefore reflect an involvement in cell growth.

Another gene that is associated with cancer syndromes is the PTEN gene, which is located on chromosome 10q23. This phosphatase suppressor tumor gene down-regulates cell survival, through apoptosis and/or G1 cell cycle arrest, which is characterized by an increased risk of benign and malignant tumors of the breast, thyroid and endothelium [7].

Use of tamoxifen as adjuvant treatment for breast cancer for more than 5 years is known to increase the risk of endometrial cancer [8], but in our patient, it is about 12 months.

References

1. Reingold SR, Neugut AI, Meadows AT (2000) Second cancers; incidence, risk factors and management. In: Holland JF, Frei E, Pollock RE, Weichselbaum RR, Bast RC, Kufe DW (eds) *Cancer Medicine*, Hamilton, ON, Canada, pp 2399–2406
2. Cybulski C, Gorski B, Huzarski T et al (2004) CHEK2 is a multiorgan cancer susceptibility gene. *Am J Hum Genet* 75:1131–1135
3. Sadetzki S, Calderon-Margalit R, Peretz C et al (2002) Second primary breast cancer and thyroid disorders. *Cancers Causes and Controls* 14:367–375
4. Ronckers CM (2005) Thyroid cancer and multiple primary tumors in the SEER cancer registries. *Int J Cancer* 117:281–288
5. Rubino C, de Vathaire F, Dottorini ME et al (2003) Second primary malignancies in thyroid cancer patients. *Br J Cancer* 89:1638–1644
6. Verkooijen RBT, Smit JWA, Romijn JA et al (2006) The incidence of second primary tumors in thyroid cancer patients is increased, but not related to treatment of thyroid cancer. *Eur J Endocrinol* 155 (6):801–806
7. Agrawal S, Eng C (2006) Differential expression of novel naturally occurring splice variants of PTEN and their functional consequences in Cowden syndrome and sporadic breast cancer. *Hum Mol Genet* 15:777–787
8. Bergman I, Beelen M, Gallee M et al (2000) The comprehensive cancer centres' ALERT group. Risk and prognosis of endometrial cancer after tamoxifen for breast cancer. *Lancet* 356:881–887