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First case of invasive breast cancer following prophylactic bilateral skin sparing mastectomy in a BRCA1 mutation carrier

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Running head: Residual breast tissue following BPM

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Introduction

Since BRCA1 and BRCA2 mutation carriers face a cumulative breast cancer risk as high as 65% (1) to 82% (2), there are several options to reduce this risk. These are regular surveillance, chemoprevention and prophylactic surgery. Bilateral prophylactic mastectomy (BPM) results in the greatest breast cancer risk reduction (3-5), but it is an irreversible intervention. Simultaneous reconstruction in the same session is accompanied by a considerable complication rate (6). In general, a subcutaneous mastectomy, which preserves the nipple-areolar complex, is not recommended, as premalignant ductal tissue remains in situ(7). Even a total mastectomy can never completely remove all breast tissue. We present a case of breast cancer following a prophylactic total mastectomy.

Case report

In 1999 presymptomatic DNA testing revealed that a 28-year-old healthy woman was carrier of a BRCA1 mutation (c.5266dupC). After the DNA test she decided to have a prophylactic mastectomy, with immediate reconstruction using subpectoral implants. The mastectomy was performed in 2002, removing the gland including the superficial or subdermal fascia, the axillary tail, the nipple-areolar complex, and the fascia of the pectoral muscle. Histopathological examination of both specimen showed no sign of malignancy.

Five years later she (G2P2) presented with a 2-3cm palpable, firm and mobile lesion in the right axilla, just located on the edge of the right pectoral muscle. A diagnostic needle biopsy revealed a poorly differentiated adenocarcinoma, resembling a breast carcinoma. Removal of the tumour including all the residual breast tissue, overlying skin and the subpectoral encapsulated implant on the right side followed. In the same session a right axillary lymph node dissection was performed. Histopathological examination of the rest-mastectomy showed, first of all, residual breast tissue at the level of the pectoral fascia and at the ventral side covered by a traumatic proliferation of peripheral nerve tissue (traumatic neuroma), just indicating the surgeon 'was there before'. The tumour, originating from the residual breast tissue, was a receptor and Her2Neu negative invasive ductal carcinoma of 18mm diameter, with a high mitotic index (MAI 45) and as poorly differentiated (Bloom & Richardson grade III) as could be expected in BRCA1 mutation carriers. All 22 axillary lymph node were tumour negative. Mirror-biopsy of a left axillary lymph node revealed no malignancy. Post-operative radiotherapy of the thoracic wall was additionally performed and a control mammograph scheme for the residual breast tissue at the left side was offered. Radiotherapy on the right thorax was performed. At present, twelve months postoperatively, she is without signs of tumour recurrence.

Discussion

Prophylactic mastectomy in BRCA mutation carriers significantly reduces the risk of breast cancer, but it does not eliminate it. Although complete removal of breast tissue is not possible, there is no general advice on screening after prophylactic bilateral mastectomy.

Risk reducing effect of BPM

Several studies specifically investigate bilateral prophylactic mastectomy in BRCA carriers. There have been no prospective clinical trials. From an ethical consideration, it is not possible to randomize these women. Hartmann et al. (8) conducted a prospective study of 214 women who were considered at high or moderate risk and who had prophylactic mastectomy. Twenty-six were carriers of *BRCA1* or *BRCA2* gene mutations. None of the carriers developed breast cancer at a mean follow up of 13.4 years, resulting in a relative risk reduction of 85 % to 100 % (95% CI: 41.4-100%). In a short follow-up study by Meijers-Heijboer et al, (4) 139 BRCA1/2 mutation carriers were followed for a mean of 2.9 years. Seventy-six women underwent BPM, and 63 remained under close surveillance. No breast cancer developed in the BPM-group, compared to eight cancers in the 63 patients in the same period, yielding 100 % risk reduction. The risk-reducing effect of prophylactic salpingo-oophorectomy (PSO), which has a risk reducing effect by almost 72 % only in BRCA2 mutation carriers (9), cannot be isolated from the risk reducing effect of BPM in this study. Rebbeck et al. (5) prospectively followed 105 BRCA mutation carriers after BPM and compared with 378 controls who did not have the procedure. After a mean follow-up of 6.4 years there was a relative breast cancer risk reduction of 95% in those who had PSO and 90% in those who had intact ovaries. Taken together, these studies confirm a 90% to 95% reduction in breast cancer risk after BPM in BRCA carriers.

Type of mastectomy and residual breast tissue

There is some debate regarding which type of surgical procedure has to be performed in BPM. In general, subcutaneous mastectomy, which preserves the nipple-areola complex and therefore has a better cosmetic outcome (10), is not optimal. This is because subcutaneous mastectomy, compared to a total mastectomy, leaves more substantial breast tissue intact. Histological studies show that more than fifty percent of patients who underwent skin-sparing mastectomy (SSM) have residual terminal duct lobular units (TDLU's) in skin flaps(11;12), as well as an infrequent occurrence in the nipple papilla (7). Torresan et al. (12) first performed a SSM, and then removed the skin flap that would have remained in forty-two breast cancer patients, essentially converting the procedure to a conventional mastectomy. They found TDLU's in 59.5% of their skin flaps and the presence of residual breast tissue was significantly associated with a skin flap thickness >5 mm. In leaving more breast tissue behind, the concern of malignant transformation becomes more extensive. In addition breast cancers arising in BRCA-carriers have a faster growth rate in comparison to sporadic breast cancer (13). More than fifty percent of breast cancers are found in the upper outer region(14) and tumours can appear in ectopic axillary breast tissue (2-6 %), which is rare though(15).

Even in total mastectomy, which is less difficult through a more extensive incision, complete removal and identifying the margins of breast tissue macroscopically is not easy during surgery. Especially in the axillary tail, where the breast cancer also was found in our case. The breast tissue extends laterally into the axillary tail, sometimes past the border of the latissimus dorsi muscle (16). By dissecting through the clavipectoral fascia, the edge of the breast tissue can be identified (17). Removal of the pectoral major fascia is also performed as breast tissue may penetrate into this muscle. To preserve the subdermal plexus and avoid flap necrosis in SSM, it is recommended to dissect just above the superficial layer (SL) of the superficial fascia of the breast, which encloses the mammary gland ventrally. However, according to the

histological research of Beer et al.(18) the SL is absent in approximately 44%. Even if the SL is present, the distance to the overlying skin is usually very small. In 50% of the patients the distance was <1.1 mm, which is too small to leave viable skin flaps. These results imply another anatomic difficulty in removing all breast tissue in SSM.

The theory that the amount of breast tissue is proportional to cancer risk is unstable, although an observational study found a reduced breast cancer risk in proportion to the amount of breast removed in breast reduction operations (19). Several studies demonstrate the oncologic safety of SSM (20;21), with a local recurrence rate similar to that of conventional mastectomy. For nipple-sparing mastectomy there is also growing positive evidence (22;23), but longer follow-up studies are needed.

By preserving the native breast envelope and the inframammary ridge, positioning and shaping of the reconstructed breast are facilitated. SSM also facilitates a favourable functional outcome as it enables most of the sensation of the skin of the breast (24).

Our experiences

In our clinic we offer skin sparing mastectomy. From 1991 till 2007 we have performed 40 prophylactic mastectomies. All were high risk women, of whom 34 were BRCA mutation carriers. This was the first presenting case with breast cancer after BPM. It raises the question whether our technical procedure in removing the breast tissue was adequate in this patient. There were no unexpected microscopic (pre) malignant findings in prophylactically removed breasts. In our opinion, routine use of sentinel lymph node biopsy is not warranted, which is supported in the paper of Heemskerk-Gerritsen et al.(25).

Conclusion

Women should be well informed about the significant risk reducing effect of BPM, but also

that the risk of developing breast cancer cannot be completely eliminated. Moreover, we have to be vigilant that delayed malignancy can occur. Utmost important is meticulous surgical technique to ensure complete excision of all breast tissue.

Conflict of interest

The authors state that they have no conflict of interest.

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