Eruptive Keloids Associated with Breast Cancer: A Paraneoplastic Phenomenon?

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Accepted December 9, 2010.

Keloids are benign dermal fibroproliferative neoplasms that occur at sites of cutaneous injury as a result of abnormal wound recovery. They are characterized by excess accumulation of extracellular matrix with thickened and disorganized collagen bundles. Unlike normal scar tissue, keloids do not regress and may extend beyond the confines of the original wound (1). Although the exact etiology of keloids is poorly understood, it is generally recognized that both genetics and environmental factors contribute to their pathogenesis. Dark-skinned individuals with familial predisposition are particularly susceptible. We present here a case of eruptive keloids associated with breast cancer and discuss the common growth factors associated with the two.

CASE REPORT

An 81-year-old African–American man was referred to dermatology in May 2007 for evaluation of eruptive keloid-like lesions on his trunk. His medical history was remarkable for renal cell carcinoma in 1988 (treated with nephrectomy), congestive heart failure, stage 4 chronic kidney disease, and a long history of typical keloids following mild trauma. He also had a family history of keloids. Cutaneous examination revealed a typical keloid on the helix of the left ear. It also revealed atypical sclerotic hyperpigmented plaques with figurate shapes on the back, bilateral axillae, groin, genitalia, legs, chest and abdomen (Fig. 1A). According to the patient's report these were growing and becoming more pruritic. He denied trauma or injury to any of the new sites. Initially the differential diagnosis was large including mycosis fungoides, sarcoid, and syphilis, but a punch biopsy confirmed a diagnosis of keloids.

The patient returned to clinic in early 2008 complaining of enlarging lesions and increasing pruritus unresponsive to topical triamcinolone 0.1%. He was now unable to raise his arms above his head due to extensive axillary keloids. Intralesional triamcinolone therapy was administered, but this purportedly worsened his condition. Pentoxifylline, hydroxyzine, topical clobetasol, and topical imiquimod all failed to provide adequate relief. The patient was referred to radiation oncology for evaluation and he was presented at the University of California Davis dermatology grand rounds. A malignancy screening to rule out a paraneoplastic process was recommended. A few months later he presented to the emergency room for an unrelated issue, and a routine chest X-ray revealed a mass in his right breast. A diagnosis of breast cancer was confirmed on biopsy. The patient then underwent a right total mastectomy. Postoperatively, he noted an immediate resolution of the severe pruritus that had been associated with his keloids. Four months postoperatively, the keloids were noted to cover the same area as before, but were now thinner (Fig. 1B).

DISCUSSION

Keloids present a formidable challenge as they are often refractory to therapy and can result in significant psychological and physical morbidity. How keloids form is currently unknown, but abnormal expression of growth factors has been characterized in keloid tissue. In our patient, we suspect that the breast carcinoma altered growth factors and cytokine levels, causing an exacerbation of his keloidal symptoms. Specifically, increased expression of transforming growth factor beta (TGF-β), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and other growth factors have been reported to be associated with breast cancer. These same factors could, in theory, have promoted the growth of keloids in our patient who according to prior medical and family history was especially susceptible to their development.

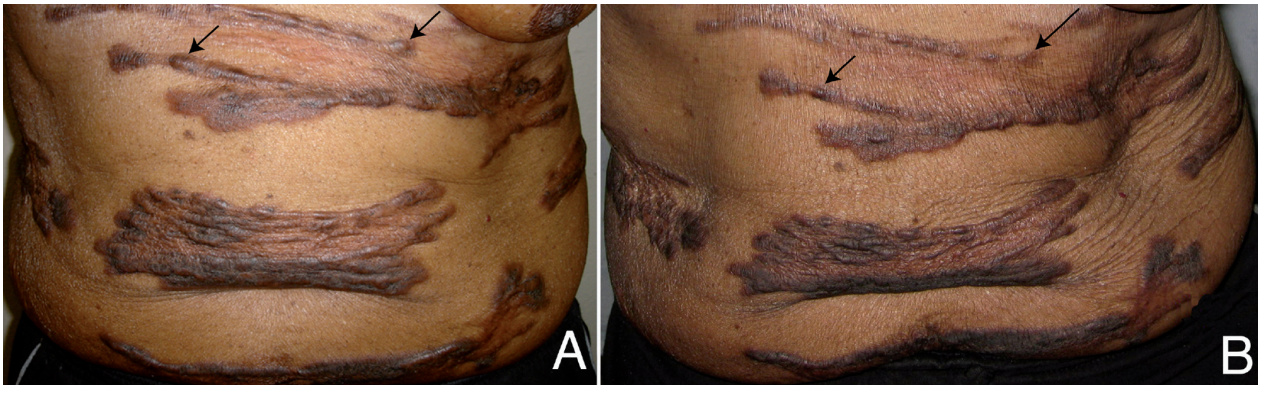

Fig. 1. Improvement in keloids following surgical excision of breast cancer. (A) Prior to surgery there are numerous hypertrophic plaques with cord-like areas and nodules. (B) After surgery the plaques remain but they are thinner and the cord-like regions have been replaced with intermittent small nodules. Arrows point to examples of thick nodules that flattened after surgery.

TGF-β belongs to a family of homodimeric proteins that regulate cellular growth and differentiation. High levels of TGF-β expression can be found in common malignancies, including endometrial carcinoma and breast cancers (2, 3). Dalal et al. (4) reported that high-level expression of TGF-β1 is correlated with higher incidence of metastasis to distant sites. In support of this claim, Padua et al. (5) provided evidence that TGF-β primes breast cancers for lung metastasis. Although we did not measure the TGF-β level in our patient, it may have been elevated secondary to breast cancer. TGF-β is generally believed to play a key role in keloid formation through its actions as a profibrotic cytokine. Through unclear signaling cascades, TGF-β up-regulates the expression of genes that encode type I and VI collagens (6). Studies suggest that keloid-derived fibroblasts overexpress the TGF-β1 and TGF-β2 isoforms (7). There is also some evidence implicating a role for TGF-β in angiogenesis, mediated through increased production of VEGF (8).

VEGF is a potent mitogen that induces formation of blood vessels in both normal and malignant tissue. Since keloids are characterized by increased blood vessel density compared with normal dermis or scar tissue, abnormal VEGF expression has also been implicated in keloid formation (9). VEGF is over-expressed by breast cancer and breast stromal cells (10); thus increased levels of VEGF might have contributed to the exacerbation of the keloids seen in our patient.

Lastly, over-expression of PDGF receptor signaling has been associated with fibrotic and vasculoproliferative diseases and cancer. Keloid-derived fibroblasts show an increase in responsiveness to PGDF, likely through up-regulation of PDGF-α receptors (11). PDGF levels are known to be up-regulated by breast cancer cells (12), and a high serum PDGF concentration is associated with increased risk for metastasis. It is possible that our patient also had abnormal levels of PDGF or its receptor.

Previously, Coppa et al. (13) reported a case of eruptive keloids in an African–American female with endometrial carcinoma. They suspected that transition from endometrial hyperplasia to carcinoma predisposed the patient to keloids through alteration of cytokine levels. While our patient already had a history of keloids, we suspect that alterations in keloid-promoting growth factors and cytokines secondary to his breast carcinoma may have increased the severity of his keloids. The strongest evidence of this is that following resection of his tumor the patient reported immediate resolution of the symptoms associated with his keloids. An alternative hypothesis, pointed out during the review process, is that the cancer may have induced a tumor-specific immune response that could have affected the growth of the keloids, either by cross-recognizing the fibroblast cells or through a bystander mechanism (14).

ACKNOWLEDGEMENTS

EM is supported by career awards from the Howard Hughes Medical Institute and the Burroughs Wellcome Fund. This research was conducted in the Department of Veteran Affairs Northern California Health Care System.

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