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CORRESPONDENCE

Post-surgery morphea mimicking relapse of breast cancer

Locoregional cutaneous manifestations of breast cancer are common and have a heterogeneous appearance, including infiltrated eczematous plaques. For this reason, the clinical differentiation from scleroderma-like manifestations remains difficult. Breast morphea is a rare condition, usually reported as a complication following adjuvant radiotherapy of breast cancer [1–3]. Here, we present a woman with localized scleroderma arising after surgery on a non-implanted, non-irradiated breast.

A 52-year-old Caucasian woman presented with a five-day history of tension pain on her left breast. Two weeks before, she had undergone retroareolar quadrantectomy for an infiltrating Stage pT1C ductal breast carcinoma on the left side. Adjuvant radiotherapy was scheduled to begin in four weeks.

Physical examination showed a peri-areolar brownish-erythematous plaque with puckered skin on the quadrantectomy scar. At first, acute mastitis or breast cancer relapse were suspected. Routine blood analysis (CA 15.3 [1 U/mL] and CEA [0 ng/mL]) was within normal limits. Breast ultrasound was also unremarkable. Skin biopsy was performed on the lesion. Microscopic examination revealed thickened dermal bundles and a CD3/CD4/CD8+ lymphocytic perivascular infiltrate. Immunohistochemistry for pan-keratin (AE1/AE3) showed no evidence of an epithelial neoplasia (*figure 1A, B*). All initial diagnostic hypotheses were gradually ruled out and the diagnosis of localized morphea of the breast was made. Topical clobesol was prescribed, with clinical improvement. To reduce the risk of cancer recurrence, the patient underwent adjuvant radiotherapy (35 Gy/10 Fx). No skin complications appeared following irradiation.

Three months later, approximately 15 days after a follow-up mammography, the patient presented with a recurrence of skin symptoms. At clinical examination, the periareolar skin reappeared hardened, erythematous and infiltrated (*figure 1C*). Tumour markers remained within normal limits. Breast magnetic resonance imaging was performed and showed neither signs of mastitis, nor tumour relapse. An incisional skin biopsy was repeated. Microscopic examination confirmed the histological report of the previous punch biopsy, showing no neoplastic changes. The diagnosis of morphea was thus confirmed. Prednisone (0.75 mg/kg) and topical pimecrolimus where initiated. Mycophenolate mofetil at 500 mg bd was added due to ineffectiveness of steroid therapy alone. Four months later, the patient showed complete remission and reported optimal tolerability. Immunosuppressant therapy was suspended after tapering over two months.

As far as we know, this is the second report of localized scleroderma arising after surgery on a non-implanted, non-irradiated breast [4, 5]. In our patient, the surgical trauma was likely the main triggering factor; in addition, compression of the diseased area during mammography could be a precipitating factor for morphea relapse. In fact, studies on the pathophysiology of fibrosis have shown that recurring or chronic trauma increases the regulation of endogenous toll-like receptor ligands, thereby inducing a fibrogenic self-amplification loop [6].

Radiotherapy is known to correlate with both the induction of sclerodermatous skin changes and their precipitation. It has been shown that such fibrotic mechanisms induced by ionizing radiation can induce morphea-like manifestations, even in the long term [7]. However, in our patient, the onset of morphea prior to the initiation of radiotherapy excludes the latter as a triggering factor.

Despite the rarity of breast morphea cases, most of which have been described following radiotherapy, we believe that dermatologists and physicians managing these patients should be aware of it and promptly initiate the differential diagnostic process, which includes surgical-site infection, lymphoma or primary cutaneous disease. Patients should be informed of the possibility of this rare complication and reassured of its benign nature and the existence of several therapeutic options. Systemic therapies may be necessary when topical therapies are ineffective. In our case, it was necessary to introduce mycophenolate mofetil, in agreement with oncology colleagues, because of the poor response to topical and systemic steroids. Immunosuppressants in patients recently diagnosed with malignancies should be used with extreme caution. However, in our patient, the expected short duration of the therapeutic cycle, the absence of residual neoplastic disease, and the frequent check-ups which the patient was scheduled to undergo, made this therapeutic option viable. ■

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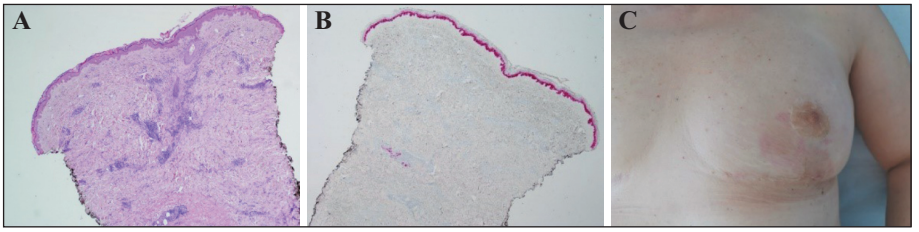

Figure 1. **A**) Normal epidermis and a perivascular, periadnexial and interstitial chronic inflammatory infiltrate with a fibrotic area within the dermis (haematoxylin and eosin; x2 magnification). **B**) No evidence of epithelial neoplasia (cytokeratin AE1/AE3; x4 magnification). **C**) Peri-areolar erythematous plaque on the quadrantectomy scar with puckered skin and subtle brownish shades.

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Hypothyroidism associated with povidone-iodine sugar ointment for chronic cutaneous ulcers

Povidone-iodine (PVP-I) sugar ointment, also known as Knutson's formula [1], is widely used for the treatment of chronic skin ulcers. Topical application of PVP-I sugar is effective for deep wet ulcers with secondary infections [2], but an excessive exposure to iodine can cause hypothyroidism [3, 4]. We present a case of severe hypothyroidism caused by long-term use of PVP-I sugar for a pressure ulcer.

A 75-year-old male noticed general fatigue, decreased appetite, and lower leg oedema. He had a history of type 2 diabetes, Stage III lung cancer, and a pressure ulcer. He developed a sacrum pressure ulcer six months prior as a consequence of hypoglycaemic coma. The ulcer had been treated with daily topical applications of PVP-I sugar covered with an absorbent dressing. Physical examination revealed pitting oedema of the dorsum of the foot and facial puffiness. The pressure ulcer on the sacrum was 45×44 mm in size with bone exposure (*figure 1A*). A chest X-ray showed cardiomegaly and pleural effusion. Blood chemistry analysis showed increased levels of creatine kinase (990 U/L) and a decrease of serum sodium (123 mEq/L). Free thyroxine (free T4) was decreased (0.05 ng/dL), while thyroid stimulating hormone (TSH) was increased (117.8 μIU/mL). Anti-thyroid peroxidase (TPO) and anti-thyroglobulin (TG) antibodies were negative. Thyroid ultrasound examination did not reveal nodules, and blood flow was increased (*figure 1B*). The concentration of urinary iodine was increased to 23,470 μg/gCre (reference range: 41-769 μg/gCre [5]), suggesting an excessive intake of iodine, which was possibly derived from PVP-I sugar since an excessive dietary intake, from *e.g.* seaweed, was denied by the patient.

Oral administration of thyroid hormone was started, and topical application of PVP-I sugar was suspended. The ulcer gradually improved under treatment with bucladesine sodium ointment. Urinary iodine levels were immediately decreased after the suspension of PVP-I sugar, and symptoms of heart failure and hyponatraemia gradually improved along with normalization of serum levels of free T4 and TSH (*figure 1C*) Levothyroxine sodium hydrate was stopped on Day 17, and no recurrence of hypothyroidism has been observed. Taken together, the patient was diagnosed with hypothyroidism presenting with heart failure and hyponatraemia, most likely caused by PVP-I sugar use.

To investigate whether hypothyroidism can be observed in other patients under treatment with PVP-I sugar, we analysed thyroid function in four more patients who have been treated with the ointment (*supplementary table 1*). Cases included diabetic foot ulcers (68 M, 75F, and 71 M) and a pressure ulcer (68F). All cases demonstrated deep ulcers as Stage III (full-thickness skin loss) or IV (full-thickness skin and tissue loss) [6]. Two patients (68 M and 75F), in whom PVP-I sugar had been used for a long time, showed subclinical hypothyroidism with increased levels of TSH and normal levels of free T4. Autoantibodies against TPO or TG were not detected in either case. Increased levels of urinary iodine were detected in both cases, suggesting subclinical hypothyroidism was caused by topical application of PVP-I sugar.

Povidone-iodine sugar consists of 70% sugar and 3% povidone-iodine. Iodine is an element necessary for the production of thyroid hormone, but its excessive ingestion can inhibit the synthesis of the hormone [7]. This effect can be enhanced in neonates and the elderly [8]; accordingly, hypothyroidism associated with povidone-iodine solution is widely reported in neonates [9]. Although povidone-iodine sugar is widely used as skin ulcer treatment in Japan, there are only a few case reports of PVP-I sugar-induced hypothyroidism [10]. We also observed subclinical hypothyroidism in elderly subjects with long-term use of PVP-I sugar. This suggests that PVP-I sugar-associated hypothyroidism is underdiagnosed, especially in elderly patients. Further studies with larger sample sizes are needed to identify what kind of patients are susceptible.

Hypothyroidism manifests with various symptoms including general fatigue, constipation, and heart failure.