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Case report

Radiotherapy for a breast cancer patient with Schnitzler syndrome: Report of acute toxicity and early follow-up

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ABSTRACT

This article provides description about acute toxicity and early follow-up of one patient treated for breast cancer and Schnitzler syndrome. There are no previously reported cases exploring this interaction on medical literature.

The expected radiodermitis to occur in the region treated with radiotherapy along with urticarial-like lesions might be challenging in view of the interaction between symptoms and therapeutic measures.

1. Introduction

Schnitzler syndrome (SS) is a rare autoimmune disease that was first described by Dr. Liliane Schnitzler in 1972[1] by the association between chronic urticaria, bone lesions, and the presence of a monoclonal IgM protein.[2] After robust research and the consensus from study groups[3] in the 1990s and 2000s, the elements for clinical diagnosis actually include urticaria and at least 2 of the following signs[4]: arthralgia, bone pain, skeletal hyperostosis, lymphadenopathy, intermittent fever, visceromegaly, and Kappa-monoclonal IgM gammopathy. Although some tests might suggest SS, it remains a clinically recognized disease, as there are no specific tests for confirmation. Furthermore, the inhibition of interleukin (IL)-1 pathway leads to rapid recovery of symptoms[5] and the diagnosis might be under-recognized or confused with other entities.[6]

The most-accepted cause of SS is related to the cytokine network. Interleukin-1 alpha binding activity has been described in patients with SS.[7] Genetic mutations – NLRP3 gene – have also been correlated in some patients.[8]

Breast cancer (BC) is one of the most diagnosed cancer and highly responsible for cancer deaths throughout the

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world.[9] The multidisciplinary approach is recommended for treatment guidelines, but usually involves surgery, radiation therapy, and systemic therapy, such as chemotherapy, hormonal therapy, and monoclonal antibodies.[10]

Radiation therapy (RT) is indicated for the majority of patients with either *in situ* or invasive types receiving conservative breast treatment in the adjuvant setting, and for many who undergo radical mastectomy. The benefits include risk reduction of local and regional recurrences, and consequently breast cancer mortality.[11,12] However, RT is associated with some risks and toxicities. Acute toxicities include radiation dermatitis, fatigue, esophagitis, and breast pain. Late complications may involve xeroderma, pneumonitis, arm lymph edema, hypothyroidism, rib fracture, cardiopathy, fibrosis with cosmetic implications in the reconstructed breast, and the risk of radioinduced neoplasia.[13] Several improvements have decreased the frequency of RT toxicities, such as the implementation of tridimensional conformal and intensity-modulated radiation therapy. They provide gains in planning and delivery of RT by sparing healthy surrounding organs while delivering more homogeneous and shaped radiation dose exactly to the target.[14]

We report one case of BC patient carrying SS due to the absence of previously published reports involving the interaction of oncological treatments with the manifestations of SS, especially radiodermitis in the irradiated breast. We did not know what the patient's tolerance for treatment would be.

2. Case report

This is a 67-year-old woman who sought medical care in August 2016 due to urticaria skin lesions that caused intermittent pain and pruritus, diffuse muscular pains, arthralgia, and an unwillingness to work.

She was then evaluated by the rheumatology team who considered the likelihood of SS the most probable. At that time, she had undergone several tests:

1. Laboratory tests: serum immunofixation test showing monoclonal IgM kappa, and complete blood count showing anemia and leukocytosis.
2. Skin biopsy showing neutrophilic urticaria.
3. FDG-PET/CT: lobulated mass in the upper inner quadrant of the left breast, measuring 2.6 cm × 2.2 cm, SUV 4.3; bilateral axillary, external iliac and bilateral inguinal enlarged lymph nodes, measuring up to 2.4 cm with SUV up to 2.8 cm.
4. Mammography: irregular and isodense nodule with spiculated margins, located in the posterior third of the junction of the upper quadrants of the left breast, associated with pleomorphic calcifications, measuring 2.4 cm × 1.8 cm, 5.5 cm apart from the nipple. Scattered calcifications with a benign radiographic appearance. Free axillary extensions. BI-RADS 5.
5. Core biopsy of the left breast nodule: Non-special type invasive carcinoma, histological grade 2, nuclear grade 2, ER100%, PR98%, Ki67 15%, HER2 negative.
6. Magnetic resonance imaging of the breasts: irregular nodule, with spiculated contours, with intense heterogeneous contrast enhancement, measuring 2.7 × 1.8 × 2.5 cm, at the junction of the upper quadrants. This nodule is 3.8 cm from the skin superiorly, 1.4 cm from the pectoral muscles and 5.2 cm from the papilla. Bilateral axillary lymph nodes, levels I and II, with cortical thickening, measuring up to 2.2 cm on the left axillae.
7. Mammotomy of the nodule in right breast + core biopsy of bilateral axillary lymph nodes: all negative for malignancy.

Thus, the rheumatology team recommended therapy for SS (canakinumab monoclonal antibody), and referred the patient for breast surgeon's evaluation.

Subsequently, she underwent left breast conserving surgery plus sentinel lymph node evaluation, and breast oncoplasty. The definitive pathology report showed an infiltrating carcinoma with no other specifications in 2 foci:

a. Focus 1: Non-special grade 2 carcinoma, histological grade 2, nuclear grade 2, size 2.1 cm × 1.8 cm without angiolymphatic invasion. ER99%, PR80%, Ki 67 23%, HER2 negative, E-cadherin positive
b. Focus 2: invasive lobular carcinoma with classic and trabecular patterns, histological grade 2, nuclear grade 2, size 1.9 cm without angiolymphatic invasion. ER95%, PR70%, Ki67 14%, E-cadherin positive, HER2 negative.

The lower margin was compromised by invasive neoplasia. There were no metastases in axillary lymph nodes (0/2). A high contingency of IgG4 positive plasmocytes was observed through evaluated lymph nodes. IgG4/IgG ratio 20%.

Thus, she afterwards underwent skin-sparing mastectomy plus breast reconstruction by a silicon prosthesis and *latissimus dorsi* interpositions. The pathology report has shown a residual invasive lobular tumor with trabecular and solid patterns, histological grade 2, nuclear grade 2, associated with an *in situ* component <25%, with cribriform and micropapillary types, nuclear grade 3. The margins were free. The final size of the neoplasm was then 5.8 cm × 3.7 cm. The final pathological staging was a pT3, pN0 (ls).

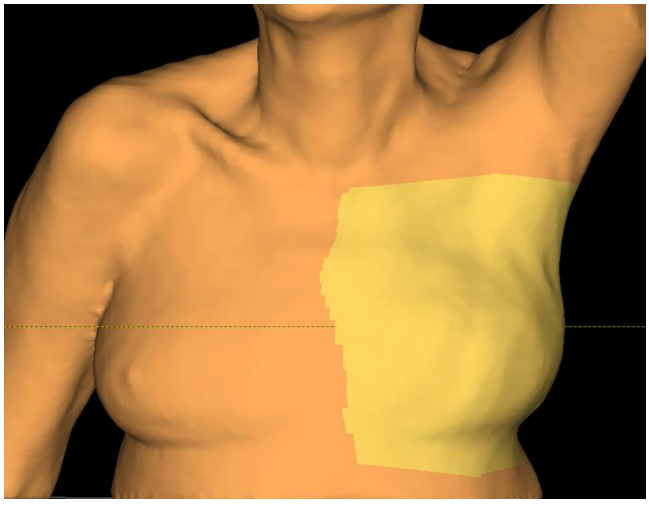

Fig. 1 – Radiation fields' display.

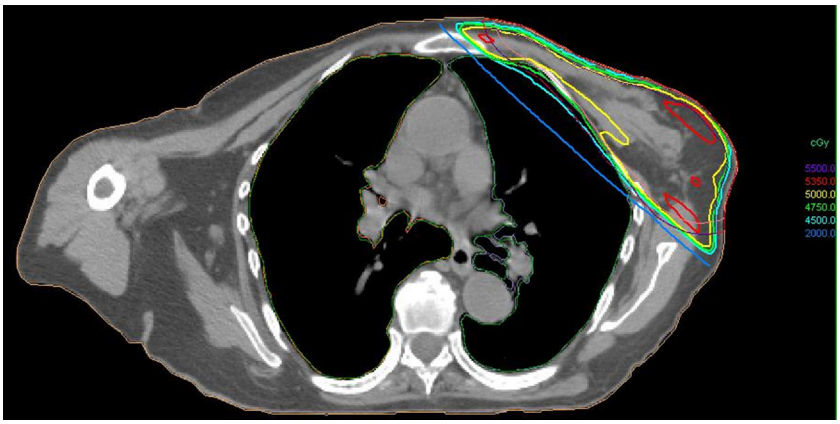

Fig. 2 – Isodose distribution.

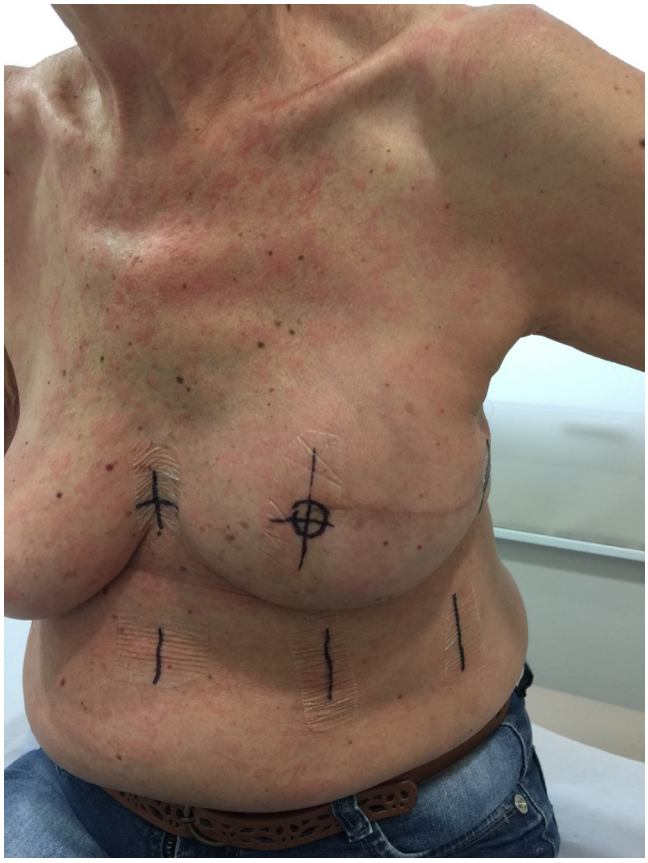

Fig. 3 – 9th day of RT (at 18 Gy). Mild-to-moderate urticaria is seen apart of irradiated breast.

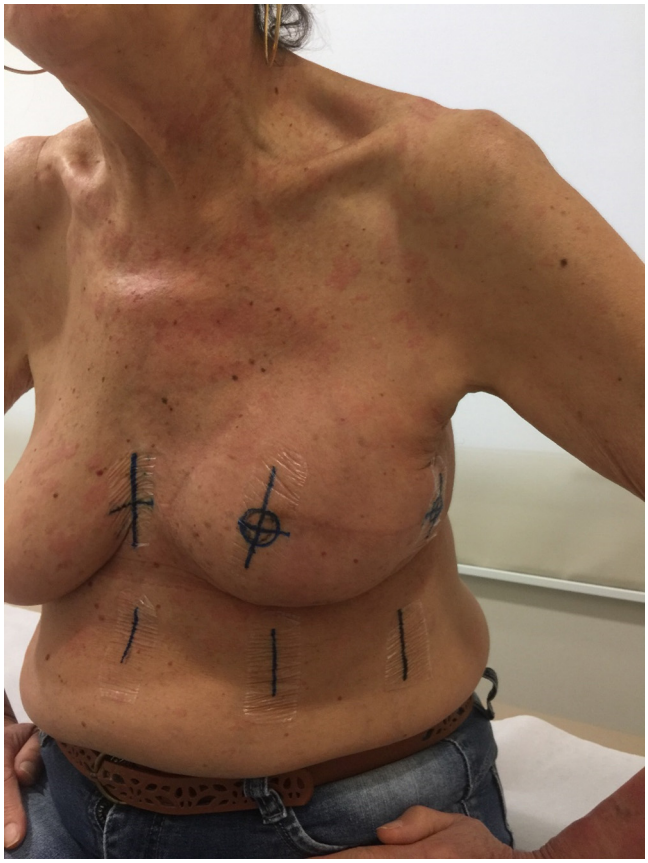

Fig. 4 – 14th day of RT (at 28 Gy). Resolution of most urticaria lesions (only a few, mild, in trunk).

The medical oncology team then evaluated the patient. They proposed adjuvant therapy, encompassing chemotherapy, RT, and hormone therapy, sequentially. However, the patient declined the former. Then she was referred for radiation oncology evaluation.

She was given the prescription of radiotherapy (50 Gy in 25 fractions of 2 Gy) to the reconstructed left breast, with IMRT (field-in-field) technique for dose delivery.

The patient had also declined canakinumab therapy until her radiation treatment was terminated.

Figs. 1 and 2 illustrate aspects of RT; Figs. 3–6 show the evolution throughout treatment.

The patient tolerated very well the treatment, having presenting grade-1 radiodermitis at the 2nd week, and maintaining it until completion of RT. She has used an aloe vera plus calendula skin cream since RT beginning, and topic clobetasone after erythema worsened.

Fig. 7 illustrates the improvement of skin manifestations of SS one week after the ending of RT. Fig. 8 shows a totally complete remission of breast radiodermitis at 5

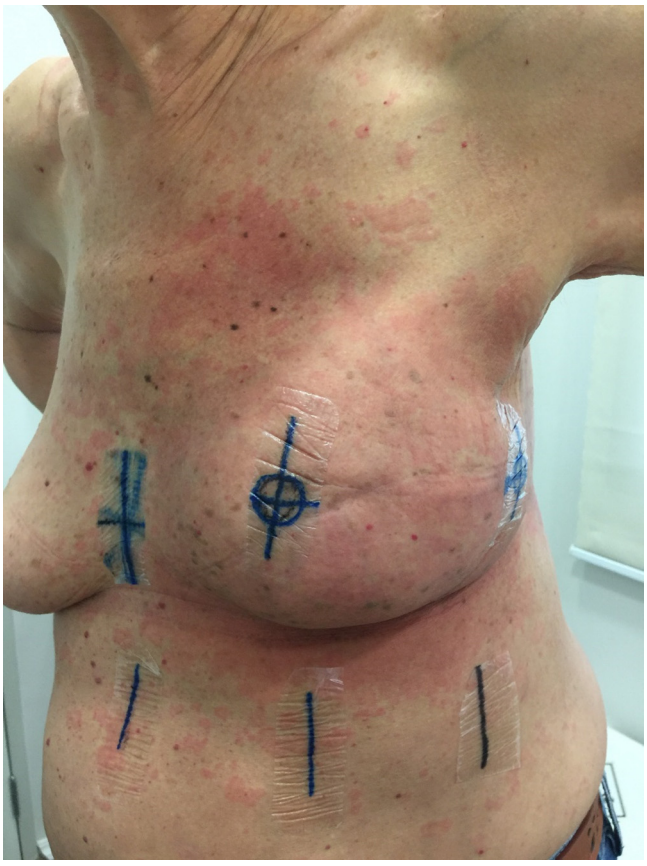

Fig. 5 – 22nd day of RT (at 44 Gy). Mild radiodermitis, and urticaria reactivation. She was given topic clobetasone prescription.

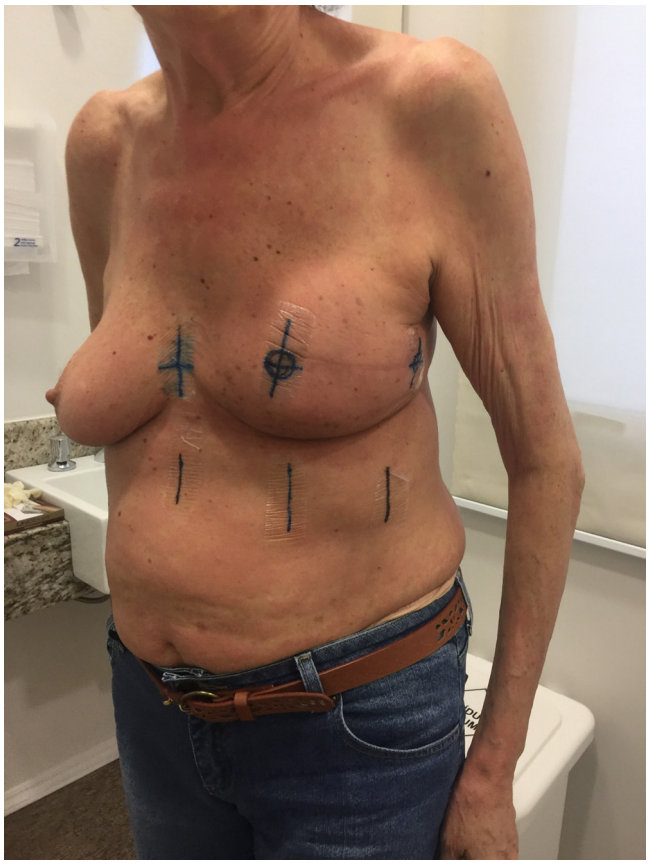

Fig. 6 – Last RT day (at 50 Gy), with no signs of urticaria. Grade-1 radiodermitis.

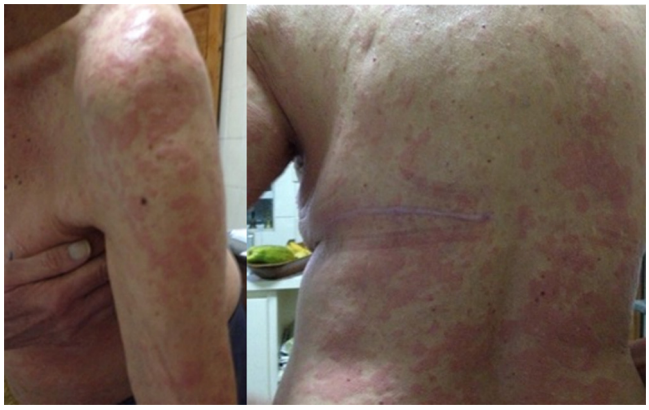

Fig. 7 – Patient has noted worsening of her urticaria and pruritus one-week after RT ending. It is possible to recognize several rose pale, red eruptions (flat macules), and slightly raised papules and plaques, typically seen in SS.

weeks post treatment, maintaining the urticaria pattern elsewhere.

The patient started montelukast 10 mg orally at the time of RT ending, following the plastic surgeon's recommendation, in order to minimize pericapsular fibrosis afterwards.

Five weeks after RT completion, the patient started canakinumab for SS treatment and she became asymptomatic after the first application with resolution of the urticarial lesions.

The patient's last evaluation was at 5 months after RT. She had no signs of radiation toxicities, urticarial, and capsular contracture.

3. Discussion

Radiodermitis is supposed to occur in the majority of BC patients who undergo adjuvant RT. The radiation damage includes DNA mutations in healthy tissues, accounting for double-strand breaks, and free-radical production at cell microenvironment.[15]

Especially for the skin, the radiation damage leads to activation of inflammation pathways by generating several cytokines,[16] such as both alpha and beta IL-1, IL-6, IL-8; transendothelial migration of several immune cells to treated skin,[17] such as leukocytes, mast cells, and neutrophils; and signaling activation from damaged skin cells, such as keratinocytes, fibroblasts, mast cells, among others.[18]

Thus, a typical RT course for a BC patient lasts 3–6 weeks. At the 2nd week of treatment, erythema usually arises, due to vasodilation and early activation of inflammatory pathways. Other associated signals include epilation and hyperpigmentation. Later, dry desquamation occurs due

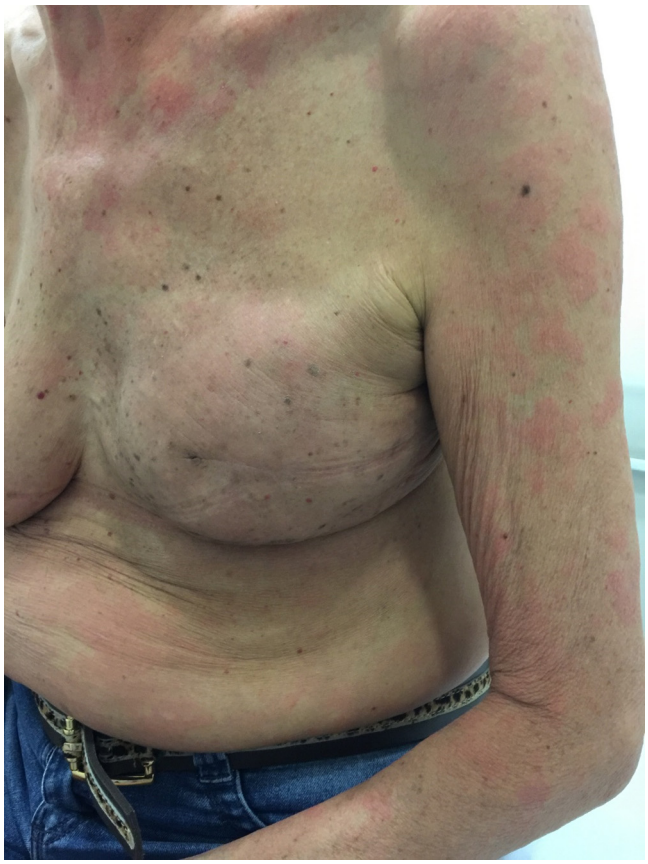

Fig. 8 – Five weeks since last RT day. No urticaria at irradiated skin, mild-to-moderate lesions elsewhere.

to epidermal edema, increased apoptotic keratinocytes, and their consequent inability to maintain the turnover of epidermal layers. Then, the desquamation becomes moisty, and therefore the clinical increase of the signs occurs due to contamination by microorganisms, such as fungi and bacteria, through these regions of weakened the cutaneous structure.[19] The patient may complain of hypersensitivity, pain and itching.[20]

The treatment of radiodermitis usually includes risk-reducing measures,[21] such as skin cleansing, water-based moisturizers, to avoid skin exposure to astringent substances, such as alcohol-derivatives, and also to skin residues, zinc oxide and aluminum salts (deodorants and sunscreens). Clinically, topical treatment with corticosteroids is a possible option due to the local steroidal effect and also to generate local immunosuppression.[22] Other topical mediations have been tested based on some body of evidence on either treating, preventing, or minimizing radiodermitis, such as trolamine,[23] calendula,[24] sucralfate,[25] aloe vera,[26] and hyaluronic acid.[27] Topical or even systemic antibiotics or fungicides may also be used to prevent secondary infection, accordingly.

Several features are related to increased severity of radiodermitis, such as body-mass index, comorbidities (diabetes mellitus, autoimmune diseases), smoking habits, the breast size and shape, and previous breast reconstruction with prostheses or tissue expanders.

The predominantly perivascular and interstitial inflammation, typically seen in patients with suspected SS who have urticarial skin lesions biopsied, may lead to the clinical establishment and, therefore, planning of the therapy, especially when the patient had already undergone globulin analysis (gammopathy). Usually, the typical SS urticaria involves the trunk and extremities, sparing the head and the neck.[28] The onset of lesions lasts an average of 1-day, with spontaneous resolution. Associated symptoms usually include pain and itching, and, less likely, angioedema, unlike other forms of urticaria.

When the patient was evaluated by the radiation oncology team, there was a concern about the supposed interaction between SS and radiodermitis, which led us to perform an active search for previous research about this interaction. We found only one report of a patient with previous diagnosis of SS treated by a B-cell lymphoma with rituximab and RT, which gave a successful SS skin symptoms resolution.[29] Therefore, we informed our patient about the lack of previously published information. Even so she accepted the treatment.

Looking for an understanding of the pathophysiology of SS urticarial lesions and radiodermitis, we hypothesized about some common variables, such as IgM precipitation through the skin microvessels, neutrophil recruitment to the skin, and IL-1 expression. In theory, these similarities led us to think of a potentiation of radiodermitis, but it was not what we noticed during treatment. Her acute radiodermitis appeared to stay within the predicted range (grade-1 according to the RTOG scale[30]).

Fig. 8 shows radiodermitis resolution 5 weeks after RT completion, but it is important to note: could the worsening of symptoms and the onset of urticaria one week after radiotherapy be explained by the increase of cytokines released in the irradiated skin? It is an assumption, and, ideally, we should have taken laboratory tests at that time, but it was not possible. Nevertheless, the patient revealed a spontaneous complete remission of her urticaria and itching 1 day after. In addition, she reported that in this last crisis her symptoms were no different from previous episodes of urticaria.

It is also interesting to note, when we analyze Fig. 8, that there was no urticaria in the irradiated skin, contrary to what was manifested in the trunk. Possibly, the prevention of urticaria occurred through the use of topical corticosteroids to treat radiodermitis. It was first described as systemic treatment for SS in 1995,[31] when a patient had a successful treatment. However, the use of IL-1 blockers and other therapeutic modalities against the known toxicity of the corticosteroids chronically used, makes its systemic prescription useless. This notwithstanding, its topical use played a role in preventing urticaria, at least in the irradiated field, probably by local immunosuppression. This was the hypothesis assumed by our group. In the case of future SS patients requiring RT, we dare think that such treatment should be initiated in conjunction with topical corticosteroid therapy to minimize the risk of urticaria activation in the irradiated region and, thus, reduce the risk of complications.

This case report has as interesting peculiarities, besides being an unpublished documentation of this type of condition, the fact that the patient did not receive, during the RT course, any other treatment. She refused chemotherapy, has

not yet begun SS treatment, and has not even begun hormonal therapy. In view of this, it was possible to observe the evolution of cutaneous lesions throughout the treatment, in addition to verifying possible potentiating effects.

Occasional interactions between oncological treatments such as chemotherapy, hormone therapy and monoclonal antibodies should be stimulated to be investigated in patients with autoimmune diseases such as SS, in order to obtain indications of individualized treatments that claim to preserve the quality of life of these patients who suffer from more than one cause.

4. Conclusion

Based on this case report, it was possible to verify that the RT for a BC patient and SS was not more toxic than expected. Further observation and follow-up of the patient's evolution to search for late complications is needed. Moreover, other cases like this and patients with tumors in other parts of the body that have SS are needed to be followed.

New evidence is necessary for better safety in recommendations, but as a matter of fact this case report foments this issue.

Conflict of interest

None declared.

Financial disclosure

None declared.

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