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In the course of radiation therapy different types of adverse reactions of the skin are observed in approximately 95% of patients. Among the various complications encountered after radiotherapy, radiation recall dermatitis (RRD) deserves special attention. Radiation dermatitis is a form of delayed hypersensitivity of irradiated skin, and the direct trigger factors are medicines – most chemotherapeutics. The reaction is an inflammatory dermatosis. It is limited to previously irradiated skin and appears a number of months after radiotherapy. The aetiology of RRD is still unclear. Its clinical presentation may vary from mild erythema to necrosis and ulceration. The article presents the case of a 50-year-old patient, who after radiotherapy for breast cancer, during the hormonal therapy (tamoxifen), developed RRD type skin reactions after skin application of Amol. The article presents a detailed differential diagnosis of skin changes of RRD type, and discusses the principles of treatment and prevention.

Key words: radiation recall dermatitis, tamoxifen, Amol, breast cancer.

Radiation recall dermatitis induced by Amol during tamoxifen therapy – case report

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The advances seen in recent years in the treatment of oncological diseases, with the introduction of new and refinement of previously used methods, have resulted in a significant increase in survival, and thus led to an increase of adverse effects of anticancer therapy.

Patients undergoing radiotherapy – despite the use of more modern and safer methods of oncological treatment – are still exposed to post-radiation adverse reactions within the irradiated skin or mucous membranes [1].

Irradiation has a high risk of early and late adverse reactions [2]. In the course of radiotherapy in approximately 95% of patients various types of adverse reactions are observed in the skin [3]. Among all the radiation-induced skin reactions it is estimated that approximately 10% are associated with a hypersensitivity reaction to care products used [4].

The frequency and severity of radiation-induced skin changes depend on many factors: location and schedule of radiotherapy, radiation dose, and individual sensitivity of the skin [5]. Skin areas particularly predisposed to radiation-induced reactions are the armpits, nipples and folds under the breasts [3].

Early reactions of an erythematous radiation-induced pemphigoid, whose severity depends on the dose of radiation, show up about 2 weeks after irradiation. Chronic changes called a late reaction might occur at a variously long time after irradiation, and their incidence is difficult to assess. Severe adverse reactions are partly attributable to endothelial cell damage, and chronic reactions combined with the proliferation of capillaries with increased post-inflammatory fibrosis [2]. Among the various common late complications after irradiation, radiation recall dermatitis (RRD) deserves special attention. It is a severe inflammatory reaction limited to skin previously irradiated by X-rays, and appears many months after radiotherapy.

Case report

A patient aged 50 was admitted to the Department of Dermatology, Jagiellonian University with well-bordered erythematous-infiltrative-oedematous lesions located on the skin of the right arm and shoulder and the anterior and posterior chest wall on the right side. In the interview, the appearance of skin lesions was preceded by flu-like symptoms (musculoskeletal pain – joint pain, fever to 39°C, weakness – 5 days before hospitalization). The patient suspected flu and took medicine from the group NSAIDs (aspirin, ibuprofen) and she used Amol fluid on her chest and arms. As a result of the procedure used general symptoms showed significant remission, while on the skin of the chest on the right side, as well as around the shoulder and arm, erythema appeared, sharply demarcated from the healthy skin, and erythematous-infiltrative, live-and-red colour, which was the cause of stopping treatment and notification of the Department of Dermatology, UJCM (Fig. 1, 2). On admission, body temperature was normal, and the patient did not report any flu-like symptoms. During the dermatological examination there was persistent induration around the inflamed skin, slightly painful on pressure and slight features of lymphoedema of the right upper limb.

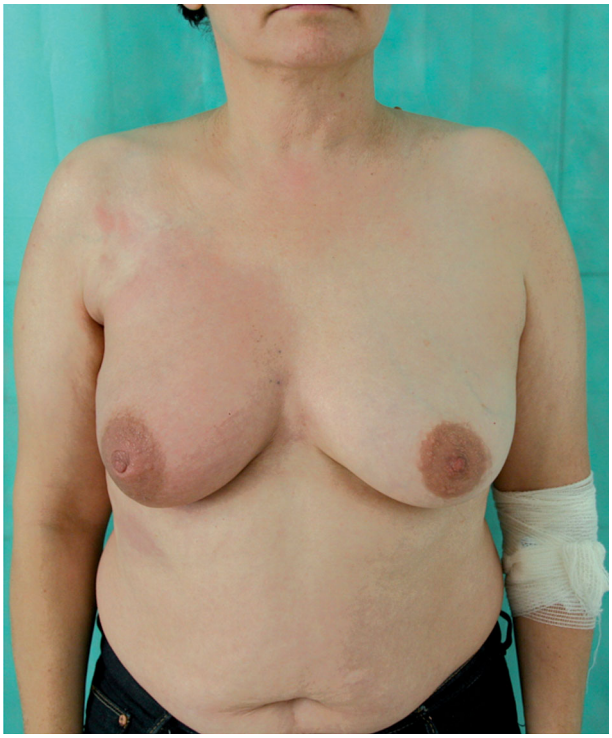

Fig. 1. Sharply demarcated erythematous and infiltrated skin lesions localized on the chest and right shoulder

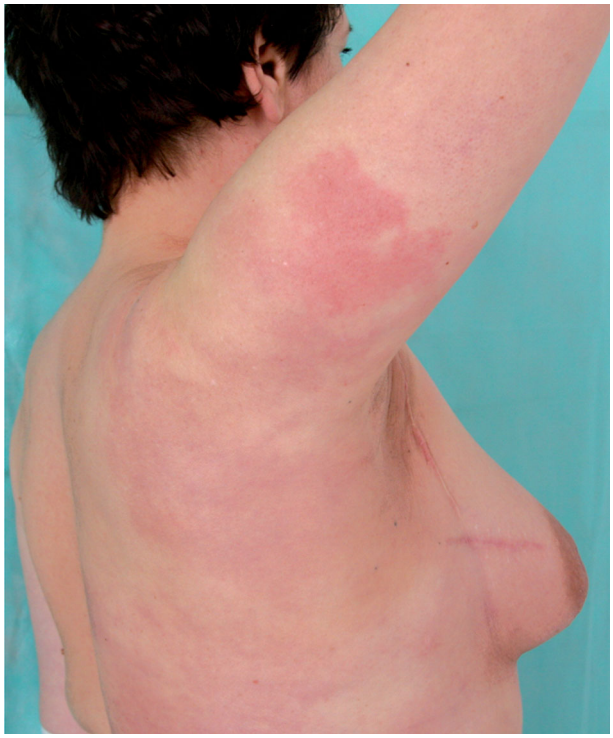

Fig. 2. Irregular erythematous skin changes on the hard surface of inflammatory infiltration, placed on the arm and on the right side of back

The physical examination revealed healed scars: under the right armpit linear, vertical, length about 10 cm (in the anterior axillary line) and oblique, length approx 7 cm, on the border of the upper and lower outer quadrant of the right breast, resulting from the surgical removal of carcinoma with pathological weaving ductale infiltrans et multifocal intraductal – cribriforme – mammae along with excision of regional lymph nodes in the right armpit. The procedure was performed in November 2008. In the examined lymph node metastasis was found (1/15). Initially 3-month chemotherapy was administered (doxorubicin and cyclophosphamide) followed by radiotherapy (April-June 2009). Treatment with tamoxifen was continued for another 4 months until the appearance of the symptoms. During hospitalization at the Department of Dermatology, UJCM, in the laboratory parameters there were observed: increased inflammation (Biernacki's reaction – 54/94 mm/h, CRP – 20.9 mg/l) without accompanying leukocytosis, marked levels of ASO did not exceed 200 IU/ml. In addition to abnormal liver function tests (ALT: 70 U/l, AST: 29 U/l, GGT: 130 U/l), other parameters including the results of imaging tests (chest radiograph, abdominal ultrasound) were normal. Excluded deviations above the background virus. The patient did not consent to biopsy of the infiltrated area. An indirect way of exclusion of neoplastic infiltration was to determine the nature of the tumour marker Ca 15-3 (the result of: 13.15 U/ml [N < 25]).

Due to the significantly elevated inflammatory parameters, clinical changes suggestive of the diagnosis and interview erysipelas on the arm, intravenous antibiotic lincomycin was begun (at a dose of 3 × 600 mg *i.v.* for 3 days, then 2 × 600 mg *i.v.* for 2 consecutive days), but it did not yield dermatological improvement. After consultation with the oncologist tamoxifen therapy was discontinued. Recent treatment was modified and intramuscular injections of dexamethasone were administered (initial dose of 16-4 mg) and antihistamines (cetirizine after), anticoagulants (low molecular weight heparin s.c.) and vascular (diosmin). Clobetasol ointment was applied externally.

After three days of treatment a significant improvement was achieved – 90% of skin lesions resolved, reducing pain and improving the patient's general condition. The patient was discharged home on the 7th day of hospitalization in a very good condition (Fig. 3, 4). Complete remission of skin lesions occurred after 4 weeks. The patient remained under observation by our outpatient clinic until complete resolution of skin lesions.

Although the first descriptions of RRD appeared in the literature in the 1960s, both the magnitude of the phenomenon, and especially the mechanisms of its formation remain unknown [5]. The exact mechanism of RRD is not known, but several hypotheses that may explain the development of late radiation-induced skin changes have been proposed. These mechanisms include changes in the blood supply in post-irradiative skin with increased vascular permeability, combined with excessive expression of TGF-β and proinflammatory cytokines [6]. Other authors have emphasized the role of abnormalities of DNA repair mechanisms, as well as increased sensitivity to drugs [7, 8]. The development of RRD is also explained as a result of post-radiation reduction of the number and impaired function of epithelial stem cells of the epidermis with increased susceptibility to

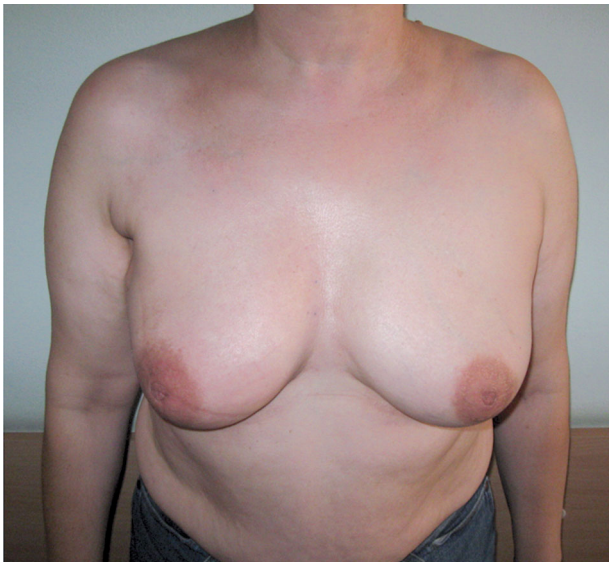

Fig. 3. Front of the chest after general steroidotherapy

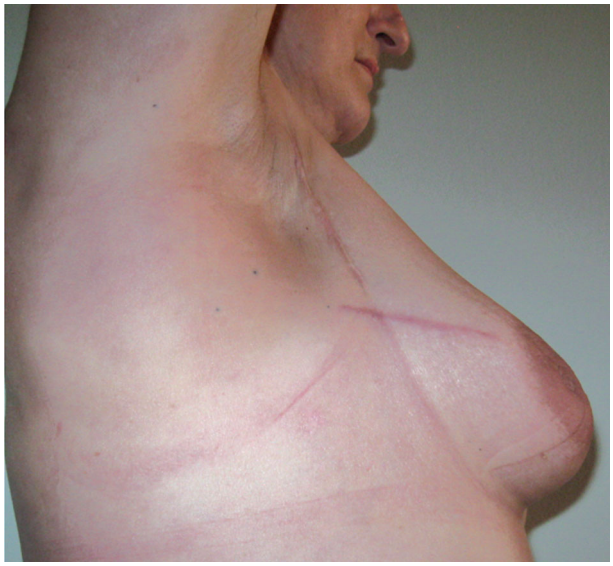

Fig. 4. Discrete postinflammatory changes after 7 days of steroidotherapy

external factors [6]. Some compare the pathogenesis of this reaction to the Koebner phenomenon [9].

Currently, it is assumed that RRD is a form of delayed sensitivity of skin previously irradiated by X-ray, and that a direct causative factor is drugs – most chemotherapeutic agents [10].

Radiation recall dermatitis type reaction is defined as a rare inflammatory dermatosis, which is elicited within the irradiated skin [11]. The aetiology and incidence are not yet clarified [12]. Kodym *et al*., based on observations in 142 patients who underwent prior radiation treatment for cancer, evaluated the incidence of RRD-type reaction at 8.8% [13]. Most of the literature suggests that chemotherapeutic agents are responsible for the development of RRD-type reaction in previously irradiated skin [1, 6, 7, 14-17]. It is estimated that one of the essential elements for the risk of developing RRD-type reaction is the time from the moment of the completion of radiotherapy until the incorporation of chemotherapy. The is less than the risk of developing a greater response [7, 18]. It was noted that the time between the start of treatment with provocative and the appearance of the lesions may take from several days to several weeks or months [11, 19]. It is understood that the predisposition to late post-irradiative dermatitis is dependent on immuno-vascular changes within the irradiated skin, which predisposes to the revised distribution of drugs – mainly cytostatic drugs (e.g. tamoxifen) in tissue treated with preradiotherapy [6, 7]. The consequence may be substantial, fixed previously irradiated skin sensitivity to external factors, such as creams or UV radiation [4, 10].

The clinical picture of changes of RRD type is characterized by great diversity: from light red by changing the erythematous-maculo-papular-oedematous to severe skin necrosis. However, the changes are always limited to previously irradiated skin [11]. In the treatment of late postradiative dermatitis, in addition to required interruption of therapy with the suspected drug, local and systemic steroids and antihistamines are used [1]. For the prevention of recurrence of skin lesions associated with RRD, the chronic use of local steroids is proposed [20]. Bauer *et al*. describe a case of complete resolution of skin lesions, without interruption of chemotherapy after local treatment with hyaluronic acid [21].

Bespoke design and unspecific clinical signs of disease described by our patient resulted in different differential diagnoses being considered, both dermatological and non-dermatological causes.

Flu-like symptoms, clearly demarcated from the surrounding skin erythematous-oedematous changes with a smooth surface tensions well initially suggested the diagnosis of erysipelas, which was eventually ruled out (despite the lack of improvement following intravenous antibiotics and a low level of ASO, leukocytosis, a slight increase of C-reactive protein and ESR). Because of the tumour interview included in the differential diagnosis of breast cancer metastasis to the skin (so-called erysipelas carcinomatosum). These diagnoses were excluded on the basis of the indirect marker of normal values of Ca 15-3 and oncological outcome of the consultation (the patient did not consent to biopsy) [22, 23]. In the differential diagnosis the possibility of allergic contact dermatitis or irritation was taken into account [3]. Appearance of the skin lesions was preceded by application to all skin of Amol – a herbal preparation based on alcohol – which was applied because of the patient's flu-like symptoms.

Finally, in the whole clinical picture of the results of laboratory tests and observing a significant improvement after treatment with local steroid and antiallergic drugs, RRD during tamoxifen therapy was diagnosed [6]. It seems that in the case described, Amol use may be the factor that initiated the development of the RRD-type reaction within the previously irradiated skin.

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