BASAL CELL CARCINOMATOSIS OF THE SCALP, ON A PATIENT WITH CHRONIC ATTENUATED RADIODERMATITIS

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Summary

Radiodermatitis is a bad consequence of radiotherapy, which may occur during irradiation (acute radiodermitis) or after several months, sometimes even years after radiotherapy, this being the case chronic radiodermatitis.

In the following, we will present the case of a patient with several basal cell carcinomas, arising from a chronic attenuated radiodermatitis, secondary to radiation treatment received for a pilomycosis, at the age of 6 years.

Clinical case

A 59-year-old urban patient was hospitalized at Craiova Dermatology Clinic for the presence of scalp tumoral formations.

Dermatological examination: In the parietal region, there are 2 erythematous plaques, infiltrated, slightly elevated, with scally surface and dimensions of up to 1 cm. In the occipital region there is a well-defined rounded tumoral formation with a diameter of 2 cm, elevated 1 cm, with normal skin color. In the temporal region, the patient has a well-defined tumoral formation, 1/2 cm, slightly elevated, of brown color.

Discussions

Radiodermatitis is a condition of the skin and subcutaneous tissue caused by the local action of ionizing radiation.

The incidence of chronic radiodermia is not fully known, but it is estimated that about 95% of patients undergoing radiotherapy will experience some form of cutaneous involvement.

Pathogenesis is represented mainly by a disruption of the balance between proinflammatory and profibrotic cytokines.

Clinical manifestations of radiodermatitis include telangiectasias, hypo and hyperpigmentations, cutaneous atrophy and scars.

The treatment of chronic radiodermatitis and radioinduced cutaneous carcinomas is complex, including both surgical and non-surgical methods, the latter being represented by pharmacological therapy, physiotherapy, lasertherapy and so on.

Conclusions

Ionizing radiation treatment increases the risk of skin cancers.

Exposure to ultraviolet potentiates the effect of ionizing radiation, increasing the risk of skin carcinomas.

Radiotherapy used to treat childhood pilomycosis has long-term undesirable effects, some patients developing basal cell carcinomas on the scalp.

The time elapsed between performing radiotherapy and basal cell carcinoma is approximately 50 years for the majority of cases described the literature.

Key words: *basal cell carcinomatosis, attenuated chronic radiodermatitis, tinea capitis, radiotherapy, radioinduced cancers.*

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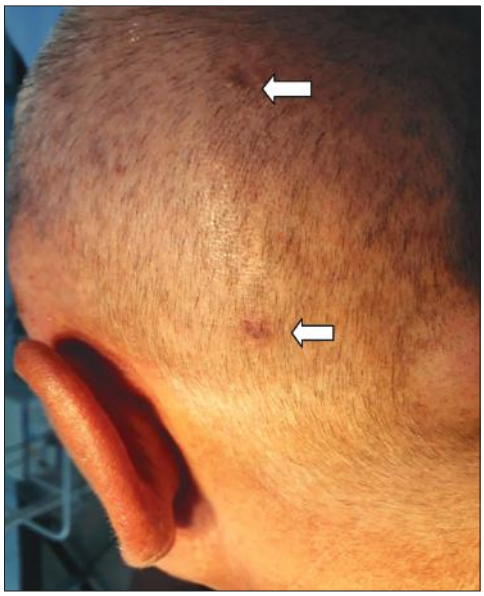

Fig. 1. BCC, superficial form

Introduction

Radiodermatitis is a bad consequence of radiotherapy, which can occur as a result of cancer therapy or any other treatments involving ionizing radiation. Symptoms of radiodermatitis involve pain and skin signs (scalling, ulceration or necrosis in acute form, poikilodermic appearance in chronic form). Sometimes it is necessary to stop the treatment. Clinical manifestations are usually absent in attenuated chronic radiodermatitis.

Radiodermatitis may occur during irradiation (acute radiodermatitis) or after several months, sometimes even at the end of it, this being the case of chronic radiodermatitis. [1]

In the following, we will present the case of a patient with several basal cell carcinomas, arising from a chronic attenuated radiodermatitis, secondary to radiation treatment received for a pilomycosis, at the age of 6 years.

Clinical case

A 59-year-old urban patient was hospitalized at Craiova Dermatology Clinic for the presence of scalp tumoral formations.

Family history: unknown-the patient is not familiar with the biological family.

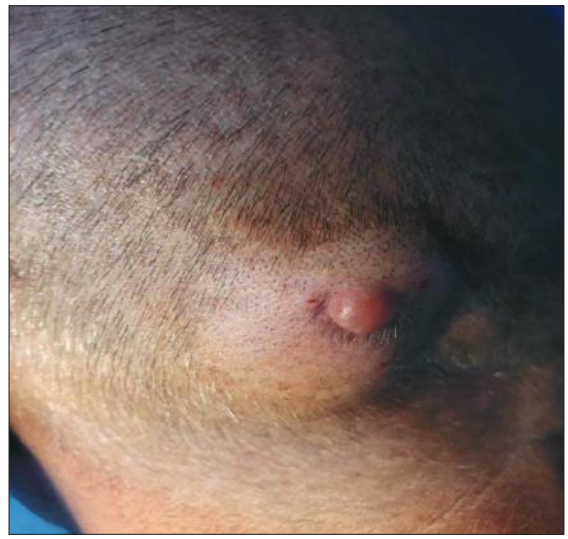

Fig. 2. Neurofibroma

Personal Pathological history: Scalp pilomycosis at 6 years of age; two basal cell carcinomas on the scalp, surgically removed approximately 4 months before the current presentation.

Clinical Exam: Phototype III. Normal weight. Clinical examination within normal limits, with slight pain on passive mobilization of large joints and cervico-dorso-lumbar spine.

Dermatological examination: In the parietal region, there are 2 erythematous plaques, infiltrated, slightly elevated, with scally surface and dimensions of up to 1 cm. (Fig. 1). In the occipital region there is a well-defined rounded tumoral formation with a diameter of 2 cm, elevated 1 cm, with normal skin color (Fig. 2). In the temporal region, the patient has a well-defined tumoral formation, 1,5 cm, slightly elevated, of brown color. (Fig. 3)

History: Current skin lesions appeared about 1 year ago, increasing in size over time. Approximately 4 months ago, the patient underwent two other scalp surgeries (Fig. 4) for the excision of two tumoral formations. The pieces were sent for the histopathological examination, which revealed the appearance of basal cell adenoid (Fig. 5) and pseudocystic (Fig. 6) carcinoma. In childhood, at the age of 6 years, the patient had pilomycosis for which radiotherapy was performed, the time period between radiotherapy and the occurrence of the first lesion on the scalp being about 50 years.

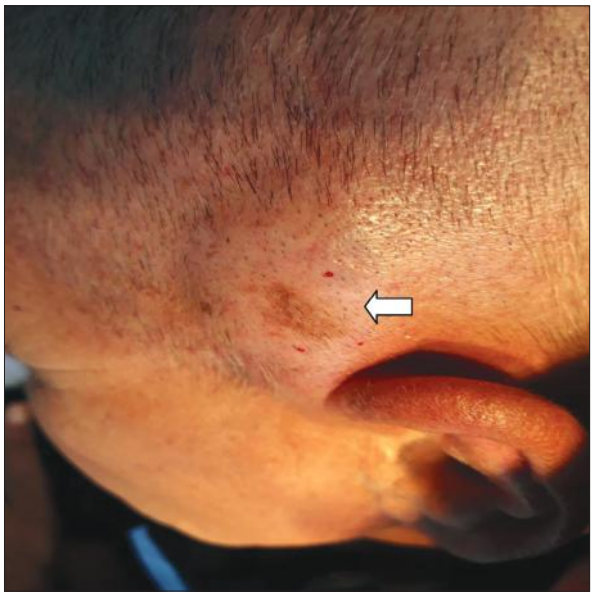

Fig. 3. Seborrheic Keratosis

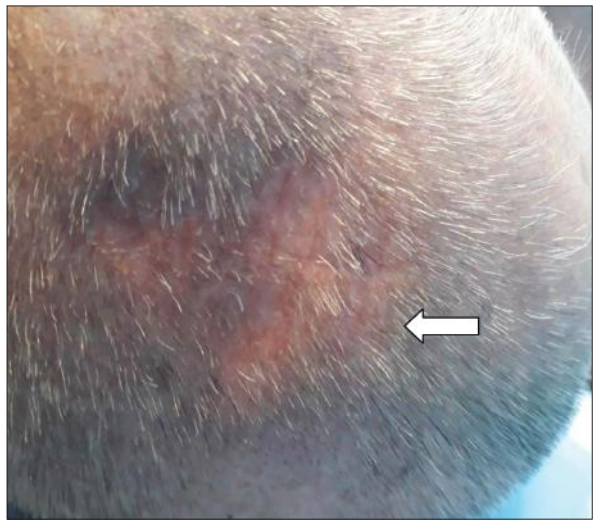

Fig. 4. Post-surgical excision scars after two BCC

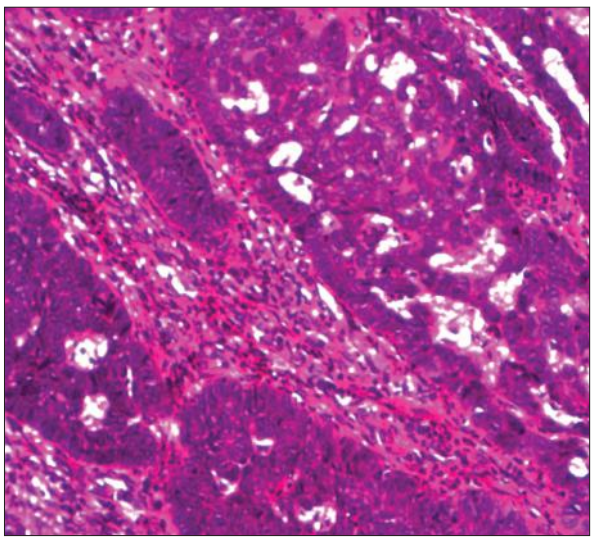

Fig. 5. Adenoid BCC, histopathological aspect

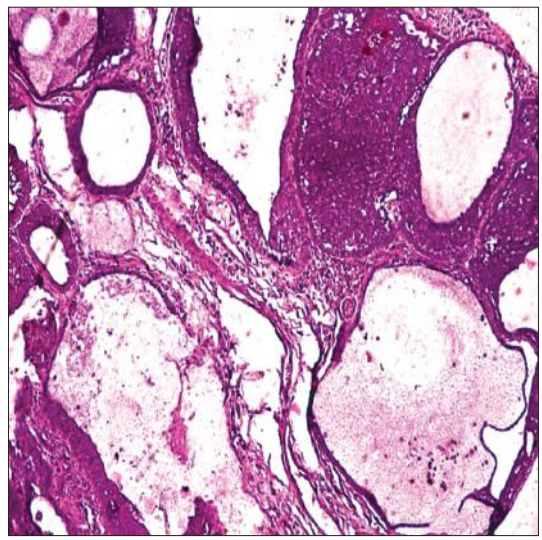

Fig. 6- Pseudocystic BCC, histopathological aspect

During the current hospitalization, the excision of the four formations of the scalp was performed, the parts being sent for the histopathological examination, which revealed the appearance of superficial CBC for the parietal lesions. The tumoral formation in the occipital region had a neurofibroma structure, while for temporal lesion the histopathological diagnosis was seborrheic keratosis.

Following the corroboration of clinical and paraclinical data, we established the diagnosis of basal cell carcinomatosis of the scalp, on a patient with chronic attenuated radiodermatitis.

Evolution was favorable and the patient was discharged.

Discussions

Radiodermatitis is a condition of the skin and subcutaneous tissue caused by the local action of ionizing radiation. The specificity of the skin organ is that of continuous regeneration, which makes the skin particularly sensitive to the action

of radiation. In healthy, non-iradiated tissue, there is a perfect balance between new cell production and cellular apoptosis, a balance that is disturbed by the action of ionizing radiation, thus resulting in radiodermatitis and radio-induced skin cancers.

Chronic radiodermatitis is characterized by a long period of time between radiotherapy and the appearance of the first skin lesions. The latency period is usually between a few months and a few years, but many cases of patients with chronic radiodermitis occur 50 years after the radiotherapy was performed. Frequency and severity were correlated to the total dose (> 50 Gy on the skin). The occurrence of radiodermatitis was also observed more frequently after treatments at short intervals, with limited doses but on large skin areas.

External factors that negatively influence the evolution of radiodermatitis are repeated trauma, ultraviolet radiations, and continued exposure to ionizing radiation. [2]

The incidence of chronic radiodermia is not fully known, but it is estimated that about 95% of patients undergoing radiotherapy will experience some form of cutaneous involvement.

Pathogenesis is represented mainly by a disruption of the balance between proinflammatory and profibrotic cytokines, including TNFα, IL-6, IL-1, TGFβ factor, PDGF factor and connective tissue growth factor. TNF α, IL-1 and IL-6 are proinflammatory cytokines, while TGF β and PDGF activate fibroblasts and induce extracellular protein and metalloproteinases synthesis, thus promoting fibrosis. [3]

The disruption of this balance begins after irradiation and can extend over several years.

Radiation causes damage to vascular endothelium on the irradiated surface, resulting in alteration of the vascularisation and reduction of blood perfusion in the area concerned. This phenomenon, corroborated with the action of PDGF, appears to play an important role in the occurrence of telangiectasias.

The persistence of inflammation and the continuous secretion of proinflammatory cytokines seem to determine other clinical manifestations encountered in chronic radiodermatitis, such as cutaneous atrophy or necrosis. [4]

Ionizing radiation, by sublethal alterations and mutations in irradiated cells, can cause cancer.

Ionizing radiation targets especially the cells of the basal and spinous skin layer. The other cells of the epidermis are much more resistant, being less affected by ionizing radiation.

The ways in which ionizing radiation acts on cells and tissues are as follows:

- apoptosis induced by p53 hyperexpression, which results in rapid cell death;
- inhibition of mitosis, which results in late cell death;
- chromosome mutations and aberrations resulting in the alterations of tumor-supressor genes or protooncogenes, causing cancer to develop. Genetic studies have revealed that activation of the c-myc gene plays an important role in cancerogenesis;
- sublethal alterations and mutations in irradiated cells that cause neoplastic transformation.

The latency of the onset of cancer is dependent on the irradiation dose and the time elapsed from exposure to ionizing radiation. Human skin is an organ with medium sensitivity to ionizing radiation, with no minimum safe dose.

The risk of skin cancer in people exposed to ionizing radiation is multiplied by the effects of ultraviolet radiation, chemical carcinogens or oncogenic viruses.

Kahan and Woodard have issued the following criteria for supporting the diagnosis of radioinduced cancer:

- the new tumor has a different appearance than the original cancer for which irradiation has taken place;
- new cancer emerged in the irradiated field;
- the free interval from radiotherapy to the occurrence of radio-induced cancer should be at least 5 years.

Other factors that influence the occurrence of radioinduced cancer are: total radiation dose; type of fractionation; the age of the patient at the time of the irradiation; the type of irradiated tissue; the presence of a radiodermatitis.

It has been observed that sarcomas occur after high doses of radiation (70 Gy), while epithelial carcinomas occur at low doses (30 Gy). Basal cell carcinoma (BCC) occurs approximately

36 years after radiotherapy, with low radiation doses. Spinocellular carcinoma (SCC) develops more quickly and after higher doses of radiation.

Age at the time of irradiation is also important. The risk is higher for childhood irradiation.

Regarding the types of cutaneous carcinomas developed after radiotherapy, it was observed that SCCs and keratoses are more common, while for BCC the risk is lower, representing 38% of the radioinduced cutaneous carcinomas. [5]

Clinical manifestations of chronic radiodermatitis include telangiectasias, irregular hypo and hyperpigmentation, cutaneous atrophy and scarring.

The appearance of skin cancers after radiotherapy depends on certain factors, such as: the irradiated topographic area, dose and type of radiation, age at irradiation, continued exposure to sunlight, genetic predisposition. The risk is higher for patients who have received low doses of radiation, but the location was on the head and neck. [6] The latency period is very long, sometimes going to 65 years, with an average of 20-45 years.

The link between radiotherapy for tinea capitis and the appearance of radiodermatitis and skin cancers is already known. Patients exposed to radiation in childhood as a treatment for tinea capitis have a 4 times higher risk of developing skin cancers and a 3-fold higher risk of developing benign tumors on the irradiated area. Our patient presented several BCCs, but also two benign tumors (neurofibroma and seborrheic keratosis) on the surface of the skin irradiated during childhood.

Tinea capitis is a fungal infection, commonly seen in children many decades ago. This pathology has posed great health problems in many countries before the introduction of antimycotics in 1950 when X-rays were being practiced as a treatment method. The number of children who have benefited from radiotherapy for pilomycosis amounts to approximately 200,000 worldwide. Of these, most developed BCCs, while SCCs and melanoma were very rare. The time elapsed between exposure to radiation and the development of the first signs of skin damage is in the order of decades. The first study evaluating the long-term effect of radiation was conducted in 1968 by Albert et al. Of the 2,043 children participating in the study, 14 cases had malignancies, half being BCCs. [7]

Another study conducted in 2004 by Mseddi et al. aimed to discover the characteristic clinical and histological aspects of BCCs after radiotherapy. The study comprised 33 patients (27 males, 6 women) with BCC and a history of radiotherapy in childhood. The age of onset of skin tumors ranged from 32 to 62 years, and radiotherapy was performed at ages of 5 to 17 years. The time since the beginning of radiotherapy and the occurrence of cutaneous carcinoma varied between 21 and 51 years. The tumors were located in the occipital region, the nodular type being observed in 51% of the patients, and the pigmentary form was highlighted in 61% of the patients. The nodular and pigmentary type predominated not only clinically but also histologically. [8]

Regarding the histopathologic type of post-radiotherapy BCC, a study by Oshinsky et al., which included 31 patients (17 men and 14 women), 56 years of age at the time of biopsy, revealed that most types of BCC were nodular, followed by superficial, micronodular and mixed ones. Frequent melanin deposits and stromal fibroplasias have also been encountered. None of the patients showed signs of local invasiveness or metastasis. [9]

Regarding the pathogenetic mechanism, Boaventura et al. have recently demonstrated that rates of D-Loop D310 mitochondrial mutations have been associated with an increased radiation dose. The role of these mutations in children with BCC is still unclear. The genetic mutations of p53 and PTCH in patients with BCC did not reveal a major difference between irradiated patients and those who did not receive radiotherapy. [10]

Differential diagnosis of radiodermatitis is done with:

- post-radiotherapy dermatitis, which is a cutaneous reaction located in a previously irradiated area after exposure to a particular drug, usually chemotherapeutic. The onset is a few weeks or several years after radiotherapy, just as in the case of radiodermatitis, but in the latter case there is no exposure to a triggering drug;
- radioinduced morphea, which is an induration of the previously irradiated skin area. It may

occur later after radiotherapy, affecting about 1 in 500 patients. It is more common after radiotherapy for breast cancer. Differential diagnosis is generally based on the clinical aspect, in radiodermatitis the induration being less obvious compared to morphea;
- radioinduced cutaneous carcinomas. Basal cell carcinoma, spinocellular carcinoma or angiosarcoma may appear on the surface of the irradiation field. Tumors that can sometimes mimic radiodermatitis or coexist with it have also been described. The differential diagnosis is based on the histopathological aspect. [11]

Prevention of radiodermatitis involves the use of appropriate radiotherapy techniques to avoid healthy skin irradiation. It has been shown that application of modulated intensity radiation reduces massive post-irradiation reactions. Another method of avoiding chronic radiodermatitis is to avoid „bolus" radiotherapy, where there is no call for it. Modern radiotherapy has introduced a new method of fractionation, namely hypofractionation, the doses received in such patients being smaller, but over a longer period. This procedure resulted in fewer cases of chronic radiodermatitis, the latter being mainly conditioned by the radiation dose administered at a session, and less than the cumulative dose. Of course, this method can be used only in cases where the primitive tumor is not influenced in turn by the radiation dose used. Some tumors require high doses of radiation, in which case the radiotherapy dose should not be split.

To avoid cutaneous toxicity, BRAF or MEK inhibitors may be used 3 or more days before and after radiotherapy. [12]

In some cases, the use of antioxidants such as vitamin E, vitamin C, selenium and melatonin during radiotherapy may decrease the damage to healthy skin cells and stimulate the immune system. [13]

Chronic radiodermatitis treatment is based on clinical manifestations.

For telangiectasiaa, a pulsed dye laser or intense pulsed light with a wavelength of 595 nm is used.

For fibrosis, treatment is much more complex, requiring pain management, physiotherapy, pharmacotherapy, laser therapy, and hyperbaric oxygen. Physiotherapy involves practicing specific physical exercises and deep massage to improve or preserve mobility in the affected area and to prevent the occurrence of contractions. As a pharmacological treatment of post-radiotherapy fibrosis, pentoxifylline was used alone or in combination with tocopherol (vitamin E). Pentoxifylline has an anti-inflammatory effect and regulates the phagocytic activity of leukocytes and monocytes, inhibits the synthesis of TNF-α and TNF-β, decreases the growth factor of granulocyte and macrophage colonies, and interferon γ. Vitamin E, in turn, lowers the concentration of free oxygen radicals. Hyperbaric oxygen appears to have an effect on chronic radiodermatitis by inducing reepithelialization and decreasing pain, oedema and erythema, but its effects are not fully elucidated.

For the treatment of patients with ulceration and necrosis in chronic radiodermatitis, hydrocolloid dressings and hydrogel may be used. Old ulcers require debridement, while suprainfected ulcers require antibiotic therapy and silver-based dressings. In some cases, surgery is required, followed by cutaneous grafts, especially in cases where the ulceration is large. [14]

The treatment of radioinduced BCCs can be divided into two categories: surgical and non-surgical.

Surgical methods include:

- Surgical excision with 3-5 mm safety margins, depending on the size of the tumor. For morphea-like BCC, commonly encountered after radiotherapy, the surgical margins should be 10-15 mm;
- Mohs surgery is a technique that allows tumor size mapping, with a very high success rate and a low incidence of recurrences;
- curettage and cauterization are recommended in small size tumors with a good success rate as long as lesions are correctly selected for this type of treatment. Large lesions with high risk of relapse are not eligible for this type of treatment. In terms of facial lesions, a recurrence rate following curettage and electrocautery was observed compared to trunk lesions. In other words, in the case of basal cell carcinoma located on the face, elective treatment should be classical surgery or Mohs surgery, whereas for tumors of the

trunk electrocauterisation may be used as an elective treatment;
- cryosurgery is used for small lesions without a high degree of relapse, usually located on the face. This technique is preferred because it does not leave major scars. It can also be used as a palliative method in the case of large BCCs where other therapeutic methods have been exhausted. It is practiced either in single large doses or in double-freeze or fractional regimen with multiple sittings for the same tumor formation;
- the carbon dioxide ablative laser. It is not a common method of treatment for BCC. However, it can be used for small size tumors as well as for large tumors but with low risk of relapse. [15]

Non-surgical methods include:
- 5% 5-fluorouracil cream, which is only used for the treatment of small BCCs that are located in low-risk areas. This drug interferes with DNA synthesis, blocking cell proliferation. The cream is applied twice a day for at least 6 weeks. Patients frequently experience local irritations and crusts, but they heal without a scar;
- interferon α-2b is used for the treatment of tumors smaller than 1 cm in size, the results being satisfactory in about 80% of cases. Interferon is used intralesional at 1.5 million IU three times a week for 3 weeks. High treatment costs are an impediment, with interferon not being used as the usual therapeutic method;
- imiquimod 5% cream (Aldara) is especially useful for the treatment of non-facial BCCs. It is applied twice a day for 6-12 weeks. Initially, the cream is applied 3-7 times a week, with a progressive increase in the dose until the twice daily application. Skin irritations are common but should not result in discontinuation of therapy. Imiquimod is generally used for superficial BCCs;
- 1% tazarotene gel, which can be used to treat small BCCs, localized in areas with minimal risk. It requires one application per day for 24 weeks. Adverse effects are local dryness and skin irritation;
- photodynamic therapy involves the use of specific wavelengths to exacerbate the drug applied previously and selectively retained in the neoplastic cells. Oxygen free radicals are formed that interact with the tumor tissue, destroying it. 5-aminolevulinic acid and its methyl ester methyl-amino-levulinate are used as the photosensitizing agents. For the treatment of tumors, the photosensitizer is applied topically in a thin layer under occlusive dressing for 4-6 hours (ALA) or 3 hours (MAL), then the skin is exposed to green, blue or red light. For cutaneous carcinomas we use red light. Photodynamic therapy has no major side effects nor contraindications, except for patients known with porphyria. Oncological and aesthetic results are very good, this type of treatment being a good option for treating superficial BCCs. [5, 16]
- Vismodegib was approved by the FDA in 2012 to treat patients with recurrent, advanced or metastatic BCC. It has been promising in a Tauber study in 2015 that tracked 8 patients who received Vismodegib as the main treatment for radioinduced BCC. Four patients achieved partial results, and in 3 cases the tumors stabilized. One patient was excluded in the 34th follow-up week. The most important side effect in these patients was the appearance of keratoacanthomas. More recently, the use of sonidegib for the treatment of radioinduced BCCs was also attempted. However, these drugs (vismodegib and sonidegib) are still in the assessment stage, their use as a treatment option for radioinduced BCCs is still not warranted. [17]

Conclusions

Ionizing radiation treatment increases the risk of skin cancers.

Exposure to ultraviolet potentiates the effect of ionizing radiation, increasing the risk of skin carcinomas.

Radiotherapy used to treat childhood pilomycosis has long-term undesirable effects, some patients developing basal cell carcinomas on the scalp.

The time elapsed between performing radiotherapy and basal cell carcinoma is approximately 50 years for the majority of cases described the literature.

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Conflict of interest
NONE DECLARED

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