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Chapter I

Radiation Treatment and Alopecia: Past and Present Concerns

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Abstract

The use of radiation to induce epilation was discovered shortly after Wilhelm Roengten found out about x-rays in 1895. In 1897 the roentgentherapy began to be used for tinea capitis treatment, a fungal disease, in order to eliminate the infected hair, and facilitate the therapeutic ointments application [1]. The method at that time was very intense, and frequently led to permanent alopecia and radiodermitis. Later on, the Keinbock-Adamson technique was adopted, a method considered safe to induce scalp epilation without permanent alopecia or other possible side effects [1, 2]. Several studies performed years after this epilation treatment have shown that, in fact, there are several possible side effects that can be related to this treatment, namely head and neck tumors [3-6] and permanent alopecia [7, 8]. Nevertheless, in the case of

tinea capitis epilation treatment, we observed, for the first time, that the type of tinea diagnosis (favus tinea) could cause a higher risk of alopecia than the radiation treatment itself [8]. In the cases of transient alopecia, the real purpose of this intervention, there have been reports of the regrowth of curly and/or white hair.

The radio-induced epilation, very well described for tinea capitis treatment, was also used in the beauty shops, for the purpose of treating superfluous hair [9]. This hair that appeared in the nipple-region or in the arm pits is a common phenomenon, so its epilation surely involved the x-ray exposition of appreciable areas of the breasts, and this could have been a preventable cause of breast cancer [9].

Today we deal with a different situation, as radiation to induce epilation is no longer acceptable, but alopecia can appear as a sequel from radiation therapy and interventional radiology. There are several studies on this issue. Approaches are being addressed to established protocols to minimize these side effects [10, 11].

The Use of X-Rays to Induce Epilation

The Tinea Capitis (or Scalp Ringworm) Epilation Model

Three months after Wilhelm Roengten´s publication about his discovery of x-rays in December 1895, its depilatory effect was described [12]. In 1897 the roentgentherapy began to be used for tinea capitis treatment, a fungal disease, in order to eliminate the infected hair, and facilitate the therapeutic ointments application [1].

Tinea capitis was a highly contagious mycosis with long evolution that infected mainly children’s scalp [13], as adult infection was considered exceptional [14]. It did not produce an alteration in the general health status of the child, or even a considerable cutaneous damage in most of the cases, but it would interfere with the children’s welfare due to its high contagiousness [13], commonly causing epidemic infections in schools and orphanages. Unless isolated, a child under long-term topical therapy could infect countless others before cure was achieved [2].

The disease could be caused by several fungi. The main agents of tinea capitis in Portugal were, by order of frequency, *Trichophyton violaceum, Microsporum canis*, *Trichophyton tonsurans* and *Trichophyton schoenleinii* [15, 16]. *Trichophyton violaceum* was also the most important agent of scalp ringworm all round the Mediterranean and in Eastern Europe [17]. The clinical expressions and evolution of these infections lead to the classification of the disease in two main types: tonsure tinea and non tonsure tinea [18]. Tonsure tinea caused hair breaking by opposition to the non tonsure tinea, where normally the hair did not break [19]. Tonsure was then subdivided in trichophytic tinea and microsporic tinea. Trichophytic tinea was caused by several *Trichophyton* species and the microsporic tinea was caused mainly by *M. canis* and *M. felineum* [20-22].The non tonsure tinea (favus tinea) was caused by *T. schoenleinii.*

Favus tinea infection could attain the entire scalp, destroying the hair follicles, leading to the transformation of the scalp into scar tissue of definitive alopecia [14]. It was more prone to recurrence [1]. This was considered the worst form of tinea capitis disease, followed by trichophytic tinea, being the more benign form the microsporic tinea [18].

There was no oral antifungal treatment. The topical treatment was performed with different compounds, namely iodine tincture and an ointment with sulphur salts. Due to the profound penetration of mycelia in the hair follicle, it was difficult for any fungicidal to enter to the necessary profundity in order to produce the adequate disinfection [14, 23], if previous epilation was not applied [14].

The first oral treatment, griseofulvin, appeared only in 1958, and from that time on the x-ray epilation was slowly abandoned, as it was no longer needed [18]. So, the x-ray irradiation of the scalp to obtain temporary epilation was the best therapeutic approach for the tinea capitis disease from 1897 to the end of the 5^{th} decade of the XX century.

The most common technique was the Kienbock-Adamson technique that was of proven worth in the control of the epidemic [2, 23, 24]. This method allowed the irradiation of the entire scalp in a short period of time, using only five fields, with a dose of approximately 300-400 Roentgen per field (R) [1, 2, 25-27]. The five fields were in the frontal, vertex, occipital and parietal regions and were determined by marking five points, far off between 11 and 13 cm from each other, depending on the dimension of the head [26]. The head was set in successive positions so the vertical rays from one field would be perpendicular to the vertical rays from the other fields [1]. The irradiation of the fields set in an antero-posterior orientation was performed in ventral decubitus. The ears were pulled to the front and kept still against the face with adhesive tape, after what they were protected with an appropriate lead cast. It was recommended that the face should also be protected [1]. The hair began to fall, commonly 15-26 days after the x-ray irradiation [1, 24, 28] and regrowth occurred from 5-8 weeks after the falling [1, 13, 24, 28].

At that time is was considered that when this Kienbock-Adamson technique was carried out meticulously by a qualified operator, permanent alopecia [2] or other side effects, such as brain damage [1, 2], needed not to be feared. The main difficulties in the application of this method were the availability of the x-ray equipment and of trained personnel for a mass treatment [23], the objection of the parents against the irradiation of the head [23, 29], and it's almost impossible application to children below three years of age [1, 23]. The method was not recommended in children approaching puberty, as spontaneous cure was expected to occur [24]. The mechanism of the cure was not fully understood, but could be probably due to chemical alterations on the scalp chemical composition occurring through the action of the sex glands [14].

This treatment for tinea capitis was used extensively between 1910 and 1959, and approximately 200,000 children worldwide received this form of treatment [30].

The Beauty Shops

The radio-induced epilation, very well described for tinea capitis treatment, was also used in the beauty shops, for the purpose of treating superfluous hair [9].

Cleveland [31] became aware of the use of x-rays for the removal of superfluous hair from the face, in the so called Marton Laboratories, during the autumn-winter of 1930-31. Having drawn the attention of the Vancouver Health Department to this issue, an investigation took place that allowed finding out that the proprietor of the Marton Laboratories was herself the operator of the x-ray machine, without having any competence for it. Nevertheless the license of these Marton Laboratories could not be cancelled and later on they were included in a well known beauty parlour with the new name of Arnold Dermic Laboratories.

In the USA, California and Washington states, the same concern had occurred about the effect of the so called Tricho System, which represented another designation for the same procedure. Some operators had been already law-suited for damage to elastic tissue, causing wrinkling and other disfigurements. Few years later, thanks to the testimonial of several women that were treated in these laboratories, the Arnold Dermic Laboratories closed. Nevertheless Cleveland, in 1948 [31], said that it was not unreasonable to expect that "institutions" and laboratories of the same character would continue to appear under new guises and disguises. In fact the author ends is paper saying that new ones had recently opened in various cities of the United States and Canada.

Some years later, Lapidus [32], reported having observed five women submitted to the Tricho System epilations 30 to 40 years before to treat facial hypertrichosis, in Pennsylvania. The device was manufactured, sold, and proclaimed safe by its physician-inventor. All the women developed, at varying intervals, radiodermatitis and basal cell and/or squamous cell carcinoma at the sites of epilation. The same pattern of radiodermitis and skin cancer [33, 34], as well as cancer other than skin – thyroid, parathyroid, oral cavity, facial skeleton and breast [34, 35] – was observed by other authors that alerted to the danger of this epilation treatment. Interestingly a report on the indiscriminate use of x-rays in the treatment of hypertrichosis had already been published as early as 1925, by a committee appointed by the New York Academy of Medicine, stating that this method was dangerous and constituted an improper method of treatment, entailing great hazards to the patient [36]. The committee, and the recognized dermatologists of the world, did not use or recommend x-rays for the treatment of hypertrichosis. Removal of superfluous hair by Roengten therapy could not be accomplished without permanent skin injury [31].

Hypertrichosis in the nipple region and in the arm pits is a common phenomenon, so Gofman [9] refers that the x-rays were also used for its removal, and that appreciable areas of the breasts were hit by the x-ray beam during the procedure.

It is not possible to know how many such beauty shops were operating and for how many years, but it was an important source of breast irradiation from 1920 to 1960 [9].

Possible Side Effects Related to the Epilation Treatment

Studies to evaluate possible side effects from the x-ray epilation treatment have started soon after the treatment discontinuation, at least for the tinea capitis cohorts. One of such studies was the one from Albert *et al*. [37] that has shown a substantially larger number of cases of cancer, mental disease and permanent damage of the scalp hair in the irradiated group compared to controls. In a second follow-up of tinea capitis irradiated patients, Shore *et al*. [38] found an excess incidence in the irradiated individuals of tumors of the head and neck, namely of the skin, brain, thyroid and parotid, although no difference was found in mortality due to malignant disease, or any other cause, between the two groups.

These follow-up studies have been performed until today, namely the large cohort from Israel that includes 10,000 individuals [3, 7, 39-41]. They have shown a 2 to 10-fold increased risk for head and neck neoplasias, namely for basal cell carcinoma (BCC) [40-43], meningioma [7, 44-46] and thyroid carcinoma [3, 47]. The thyroid is highly sensitive to radiation, especially when the exposition occurs at a younger age [3, 5, 48, 49]. An association between radiation exposure and parathyroid hyperplasia has also been described [50-53] in small cohorts other than the Israeli cohort. The latency period between radiation exposure and neoplasia diagnostic can be as long as 20-40 years for non-melanoma skin cancer [54-56] and for meningioma [4, 46, 57]. We have been clinically observing a cohort submitted to the x-ray epilation treatment for tinea capitis infection in a health institution in the North of Portugal [58]. Our findings on thyroid cancer prevalence and thyroid disease [58], as well as on basal cell carcinoma prevalence [59], are in accordance with the increased prevalence of these neoplasias presented in the above referred studies.

Besides the most well studied tumor-related effects, non-cancer effects have also been shown. We have already mentioned mental disease, in the Albert *et al*. study [37], that found a significantly higher amount of major mental disorders (psychosis and personality disorders) in the irradiated individuals when compared to the non-irradiated ones. Later on Omran *et al.* [60] investigated the late effects of the x-ray epilation treatment upon subclinical mental disorders and found was an excess of psychiatric symptoms, paranoid orientation, work problems, and treated psychiatric illnesses in the irradiated group, but only in the white individuals. In their study, Yaar *et al*., suggested permanent change in EEG activity, following average doses of 130 rads of childhood X-irradiation to the brain [61]. Continuing in the scope of mental disease, in a recent study Sadetzki *et al*. [62] did not find support for an association between exposure to ionizing radiation and risk of schizophrenia. The authors say that more research on possible effects of early exposure to ionizing radiation on schizophrenia risk as well as in brain tissue injury is needed.

Other sequelae from scalp irradiation are now being unraveled, namely due to the recently reported association between low dose radiation and cardiovascular disease. Shai *et al.* [63] found, in the Israeli tinea capitis cohort, that childhood scalp irradiation was a significant and thus far underestimated risk factor for adult carotid atherosclerosis disease. They emphasize the need for physicians to be aware of the existence of such high risk populations.

Another important side effect from this treatment, due to its emotionally troublesome effects, is permanent alopecia. At the time the tinea capitis epilation treatment was applied it was considered that the margin of safety between a dose causing temporary loss of hair and one causing permanent hair loss was considerable, so the treatment was safe [2]. Strauss and Kligman [64] stated that the necessary dose to produce permanent alopecia was above 1000 R for each of the five points. More recent studies refer that lethal doses for hair follicles vary between 7 and 16 Gy [10, 65, 66]. The dose for which 50% of the patients develop definitive alopecia was considered to be 43Gy at the follicle level (4.5 mm under the skin) [67, 68]. As has been previously mentioned, the doses reported to cause permanent hair loss vary widely [67].

When the radiation treatment had to be repeated, due to disease relapse, it should be performed only 6 months after the first treatment, to prevent the appearance of radiodermitis that could result in definitive alopecia [1]. Albert *et al.* [37], using a phantom head built around the head of a seven year old child, have calculated that the dose applied to the scalp ranged from 500 to 800 rad (6-8 Gy). However, the doses could be higher due to technical problems. The most common error appeared to be overlapping of the irradiation fields [69, 70], but also faulty or poorly calibrated equipment occurred, and both could lead to permanent alopecia [70].

In the follow-up studies permanent alopecia has been observed [7, 8, 46] and was positively associated with higher irradiation doses [8, 67, 71], received when the treatment had to be repeated (2-3 sessions).

In our series of tinea capitis irradiation we have observed 670 women (to avoid the higher confounding effect of androgenetic alopecia in male gender) and we found overall prevalence of alopecia of 6.7% (95% CI 4.6–8.3%) [8]. Women who received an irradiation dose $\geq$ 630 R were more likely to develop alopecia than those who received an irradiation dose < 630 R (dose $\geq$ 630 vs. < 630 R, RR 5.50, 95% CI 2.96–10.22) and the relationship was maintained after adjustment for tinea diagnosis and age at diagnosis (dose $\geq$ 630 vs. < 630R, RR 3.93, 95% CI 2.61–5.91). Nevertheless, we observed, for the first time, that the type of tinea capitis agent (favus tinea vs tricophytic/microsporic) could cause a higher risk of alopecia than the radiation treatment itself.

In the cases of transient alopecia, the real purpose of the x-ray epilation treatment, a curious aspect mentioned by several patients from our cohort (11 out of 100 – 11%) (unpublished data), was a change in the hair pattern when it grew back. They stated that straight hair grew back curly and/or white hair appeared. Hair changes related to scalp radiation therapy have been referred but references are scarce. Zeligman observed the graying of hair in 3 out of 37 children with tinea capitis [72], Alexander observed the regrowth of dark hair in a patient that previously had white hair after scalp radiotherapy [73] and Möhrenschlager *et al.* observed curly hair appearance after brain radiotherapy [74].

The possible side effects from the epilations performed at the beauty shops are not so well documented. The main sequelae were mentioned in the previous item and were observed soon after the superfluous hair removal. These treatments in the beauty shops were scattered in many "clinics" and there are no registered and extensively studied cohorts as we found in the tinea capitis model. Although the number of these "beauty shops Roengten departments" is not known, nor the number of epilations performed, Gofman [9] states that these procedures have caused a number of totally preventable breast cancers that appeared in subsequent decades.

Alopecia as a Sequel of Radiological Interventions

Diagnostic/Therapeutic Techniques and Accidents Can Cause Alopecia

Interventional radiology is widely used in the treatments of various diseases worldwide. Cardiac angiography is known to produce one of the largest radiation exposures of any diagnostic x-ray procedure; a patient may receive up to 6 Gy during a prolonged coronary angioplasty [66]. So, these interventional procedures in radiology and cardiology often apply high radiation doses to patients' skin [75]. Gavagan *et al*. [76], in a study about hair loss in neuro-interventional procedures, found out that 7% of the 958 patients were reaching the threshold for temporary epilation, that is suggested to be 2-3Gy [65, 76-79]. The radiation skin exposure is not only for patients, as hair loss has been described in cardiologists´ legs [66].

Radiotherapy is a common modality in cancer treatment and more than 50% of affected patients will eventually receive some form of radiotherapy as definite, preoperative, postoperative or palliative treatment [80]. Radiation-induced skin changes and associated hair loss are severe complications of this treatment, but, unfortunately, to achieve a curative dose to the tumor, some degree of damage in the surrounding tissues occurs [81]. Hair loss may be transient after therapy, with new hair continuing to return for up to one year, or may be permanent, due to follicular fibrosis [82]. In any case it is a feared side effect for cancer patients, so feared that some patients may even refuse treatment because of the risk of developing hair loss [83]. Hair loss, even if not permanent, may be identified by the patients as a visible reminder of their cancer that causes distress both by identifying them as a cancer patient as well as by confronting them with the seriousness of their disease [84].

Temporary epilation was reported among atomic bomb survivors in Hiroshima and Nagasaki. The historical data from Hiroshima have shown that epilation appeared with estimated doses as low as 0.75Gy [85].

Radiation-Induced Alopecia – Clinical Features and Pathogenesis

Radiation dermatitis is a skin reaction that can occur upon the radiation treatment/intervention, being the reddening of the skin and dry desquamation its initial signs [86, 87]. The skin changes caused by radiation dermatitis are associated with an increase in transepidermal water loss that precedes the onset of dermatitis [88]. The barrier impairment is comparable to the changes observed with UV radiation exposure but exhibits an even more delayed course.

The dryness and hair loss are secondary to injury to sebaceous glands and hair follicles.

Permanent or cicatricial alopecia can be defined as any degree of alopecia persisting for > 12 months after radiotherapy completion [67]. This cutting point of one year may be not enough, as it has been shown that dermal atrophy, with associated loss of hair follicles, continues to progress beyond 52 weeks after exposure to ionizing radiation [89].

The permanent alopecia results from irreversible damage to epithelial stem cells locating in the bulge region of the hair follicle [90]. When it occurs during a more generalized destructive event within the skin, such as thermal burn, trauma, infection, ionizing radiation, it is designated as secondary [91, 92]. The clinical features of this disorder include destruction of the hair follicles, progressive hair loss, and permanent replacement of the follicle with fibrous tissues [93].

Histologically we can observe that hair follicles and sebaceous glands are absent throughout large areas [10]. The only remnant of the pilosebaceous apparatus is the arrector pili muscle, often embedded in a pear-shaped mass of collagen.

Scalp hair grows in cycles with 3 distinct phases: anagen when active hair growth occurs (lasts for 2 to 8 years), catagen that represents involution (lasts for 4 to 6 weeks), and telogen that is the resting phase (lasts for 2 to 3 months) [94]. Radiation-induced alopecia is due to high susceptibility of anagen follicles to radiation [95]. Loss of dystrophic hairs (anagen effluvium) due to acute damage to actively dividing matrix cells of anagen follicles (active hair growth) is followed by telogen shedding due to premature catagen entry of follicles in late anagen [95, 96]. Complete hair regrowth generally occurs 2−4 months after irradiation in the reversible type of radiation-induced alopecia [95].

Hair follicles from the scalp appear to be more radiosensitive than those in other parts of the body [97-99].

Prevention and Treatment of Radiation-Induced Alopecia

The most common factor associated with radiation-induced skin injury is the duration of the exposition at a single site of the skin, especially if the same target is repeatedly irradiated [100]. In the mouse model, Nakayama *et al*. [96] also found that the extent of follicle damage occurred in a radiation dose-dependent manner. Lawenda *et al*. [67] have analyzed several variables that could be associated with radiation-induced alopecia and found out that the follicle dose was the only one that was statistically significant, although a personal history of alopecia (before the radiation treatment) and chemotherapy treatment were of borderline statistical significance. In fact, numerous chemotherapeutic agents have been shown to cause temporary, or even permanent, alopecia [67], many of which are considered radiosensitizers, as they enhance the effects of the radiation on normal tissues [101]. Increased awareness of potential interactions between radiotherapy and concomitant chemotherapy has led no new treatment schedules designed to maximize antineoplastic effects while minimizing skin toxicity [86].

In the fluoroscopically guided interventional procedures, when performing repeated exams for the same target vessel or organ, the orientation of the x-ray beam should be adjusted whenever possible to avoid overlapping [100]. Nevertheless, even with the use of dose-spreading techniques, different areas of irradiation can still overlap on the skin surface that will receive a higher irradiation dose [100].

Concerning the radiotherapy treatments, it has been reported that the skin reaction is less severe with dose fractionation [99]. Moreover the use of stereotactic radiotherapy, a modality that combines the accurate focal dose delivery of stereotactic radiosurgery with the biological advantages of conventional radiotherapy [102], minimizes the dose to non targeted tissues. The use of arcs can minimize the follicle dose, because arcs typically do not overlap, and the surface dose is distributed over the length of the arc length [67]. The newer intensity-modulated radiation therapy (IMRT) has resulted in small volumes of normal tissue receiving the full treatment dose, with a consequent decrease in acute dermatitis [87].

Some biological factors that influence the threshold for skin effects have been referred by radiation biologists such as topographic localization of the exposed site, nutrition status, concomitant diseases, age, genetic factors including predisposition to DNA repair genes defects, oxygen status, capillarity density and probably also hormonal status [68, 99].

Several studies have been conducted to assess the outcome of interventions for the prevention and management of radiation skin reactions [103]. Histamine, an important inflammation mediator, has been shown to be involved in the development of dermatitis [104], but in a mouse model of acute radiation dermatitis, the radiation induced hair loss was not inhibited by histamine antagonists [105]. Substance P, a product of preprotachykinin-A mRNA, recently considered as an important regulator of the hair growth cycle, and its receptor NK_1R (neurokin-1 receptor) may play important roles in the development of radiation-induced hair loss [106]. Again in a mouse model, fibroblast growth factor-1 (FGF1) could prevent radiation-induced hair follicle apoptosis [96]. However, the structural instability of the wild type form of this molecule may diminish its potential for practical use.

The use of topical corticosteroids to prevent or treat radiation dermatitis is somewhat controversial [86, 103]. They have been used due to its anti-inflammatory effects and inhibition of IL-6 upregulation [107]. However, comparisons of different topical steroids, either used to prevent or treat acute radiodermitis, have shown contradictory results [86]. In any case, it could be seen that at best steroids could ameliorate dermatitis, but do not prevent it [108]. Prostaglandins are potent radioprotective agents [109]. In a mouse model of radiation-induced hair loss, Geng *et al.* [110] have shown that these agents enhanced hair regrowth following irradiation, both with systemic and topical applications. They concluded that these compounds might provide some protection of hair follicles lying within the radiation therapy field. A subsequent study from these authors confirmed that prostaglandins, but also thiol compounds, provided a significant protection of hair follicles [109].

Nitroxides (stable free radicals) were tested, again in an animal model (guinea pig), in a fractionated radiation treatment [111]. The authors showed that the topical application of the nitroxides reduced the post-irradiation hair loss in their model and suggested that these compounds could be useful in a clinical setting to reduce radiation-induced alopecia. In humans, a nitroxide (Tempol) was tested in a Phase I study [112] that demonstrated that its topical application to the scalp before whole brain irradiation was safe, well tolerated, and was showing up protection against radiation-induced alopecia.

More recently, the protective effect of vitamin D3 was investigated in a rat model of skin radiation injury [81]. The authors showed that the administration of vitamin D3 may protect hair follicles from radiation toxicity and stated that further clinical trials are needed to prove the preventive effect of vitamin D3 as well as dosing and timing of the agent on radiation-induced alopecia.

Calendula officinalis was found to be highly effective for the prevention of acute dermatitis of grade 2 or higher in breast cancer patients [113], but its topical application was considered difficult by the patients and no other studies have been conducted to date [103].

Scalp cooling for hair loss prevention and 2% topical minoxidil for quicker hair regrowth are currently the best studied and most effective options for treatment for chemotherapy- induced alopecia [84]. However, these interventions are not commonly used for radiation-induced alopecia. For scalp cooling, only a pilot study was found, assessing its use for palliative whole brain therapy [114]. The study involved only seven patients and the authors concluded that the effect of scalp cooling on radiotherapy associated alopecia remained uncertain, although they observed some hair preservation over the parietal regions of the patient’s scalp. Minoxidil use for radiation induced permanent alopecia was referred in one study, in one patient, but it revealed ineffective [115]. Radiation-induced hair loss has been much less investigated than the chemotherapy-induced alopecia [81]. Moreover, a lack of trials in human populations has been making it difficult for the application of the most promising interventions that are being experimented in animal models [84].

Conclusion

Radiation induced epilation is no longer at use but individuals submitted to this intervention, either for aesthetic or therapeutic reasons, are still alive, and the data strongly suggest that they should be followed-up for increased risk of head and neck cancer and well as other diseases.

Prevention of radiation induced alopecia is an actual concern in routine medical measures such as intervention radiological procedures and in radiation therapy, and more approaches are under current investigation in order to be able to manage this most disturbing side effect.

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