Non-invasive imaging techniques for early diagnosis of radiation-induced squamous cell carcinoma of the lip

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Abstract
Ionizing radiation was used in the past for treatment of several benign cutaneous conditions, and particularly hemangiomas. Even though radiotherapy was generally effective, it significantly augmented the risk for malignancies, resulting in a consequent heavy decline of its use for benign conditions. However, radiation-induced neoplasia is still encountered in adult patients irradiated during childhood or adolescence.

We report a case of well-differentiated squamous cell carcinoma developing on the lower lip of a 59-year-old woman who had previously undergone local radiotherapy for a hemangioma, in which the use of non-invasive imaging techniques such as in vivo reflectance confocal microscopy (RCM) and dermoscopy may provide an invaluable tool for early detection of malignant changes in previously irradiated cutaneous and mucosal areas.

Keywords: squamous cell carcinoma, hemangioma, lip neoplasms, radiation-induced cancer, in vivo reflectance confocal microscopy, dermoscopy.

Introduction
Squamous cell carcinoma (SCC) is the most common form of oral and lip malignancy and accounts for over 90% of all cancers of this area, men being affected more often than women [1–5]. Sun exposure, tobacco consumption, high alcohol intake, chronic inflammatory processes, viral infections, and immunosuppression are all risk factors that have been related to lip neoplasms [4, 6–8]. Nowadays, it is well documented that childhood radiotherapy is associated with the occurrence of benign and malignant tumors, and the association between SCC development and skin exposure to X-ray irradiation has been known for decades [9]. However, between the 1940s and 1960s many benign cutaneous conditions, and particularly hemangioma, were treated using ionizing radiation [10, 11]. Most patients that underwent radiotherapy for head and neck hemangiomas were children. Even though these treatments were generally effective, they substantially contributed to enhanced risks for malignancy development. In light of the increased awareness of radiation-induced malignancies, radiation therapy for benign diseases is now avoided and extended protection measures against radiation have become a standard in clinical practice. Even so, radiation-induced neoplasia is still seen today in adult patients irradiated during childhood or adolescence.

SCCs developing at the site of ionizing radiation exposure usually overlay areas of chronic radiodermatitis and generally occur many years after multiple radiation sessions with a total dosage greater than 1000 rads [12].

Due to the sometimes-subtle clinical changes in areas of chronic radiodermatitis that may be linked to the development of a SCC, quick, reliable, non-invasive and repetitive diagnostic tools need to be employed for the close monitoring of these patients. Recent studies aim to discover new tumor-related biomarkers, which can be used for early detection, follow-up, and development of new-targeted therapeutic agents for SCC and other mucocutaneous malignancies [13–17].

Over the last years, an increasing interest has been shown for in vivo imaging techniques that can be used to evaluate skin and oral mucosa. Dermoscopy has become an essential tool for the investigation of skin tumors. Reflectance confocal microscopy (RCM) is a newer, non-invasive, imaging technology capable of generating horizontal black and white images of epithelial tissue at resolutions approaching those of optical microscopy that can be useful in increasing the diagnostic accuracy in various skin lesions [18–26].
Here we report the case of a patient who developed a SCC of the lower lip, for which dermoscopy and RCM examination allowed an increased diagnostic accuracy and enabled optimal therapy. Considering that timely detection and swift, effective treatment are still the greatest determining factors of long-term survival and quality of life of these patients [27], through this case report we aim to emphasize the potential role of dermoscopy and RCM in the early diagnosis of radiation-induced SCC of the lip.

Case presentation

In April 2016, E. M., a 59-year-old woman was admitted to the Department of Oral and Maxillofacial Surgery, “Dr. Carol Davila” Central Military Emergency Hospital, Bucharest, and was referred to the Department of Dermatology, “Prof. Dr. Nicolae C. Paulescu” National Institute of Diabetes, Nutrition and Metabolic Diseases, Bucharest, Romania, for evaluation of a growing tumor on her lower lip. The study was conducted in accordance with the guidelines approved by the local Ethics Committee and after the informed consent was obtained from the patient. The patient reported having undergone local radiotherapy for a hemangioma during her childhood. She had annual sessions of radiotherapy for four years, from the age of six until she was 10 years old. Further, since 1996, she underwent argon laser therapy for a period of two years. Clinical examination discovered an increased lower lip volume, atrophic lip surface and a round to oval tumor with a keratotic surface, measuring approximately 10 mm in diameter (Figure 1A). Differential diagnosis based on clinical examination included SCC, followed by an array of other cutaneous tumors, soft tissue tumors, vascular tumors, pyogenic granuloma, dermatofibrosarcoma protuberans and amelanotic melanoma.

Dermoscopy, using a digital videodermoscopy system (FotoFinder, Teachscreen, Germany) and the VivaScope 1500 VivaCam macro camera (Lucid Inc., Rochester, NY, USA) revealed a white-yellowish astructural area surrounded by telangiectatic, tortuous vessels (Figure 1B). In vivo RCM was performed using a commercially available reflectance confocal microscope (Vivascope 1500 Caliber I.D., NY, USA). RCM examination of the epidermis identified a deeply altered keratinocyte architecture (disarrangement of the spinous and granular layer) and extensive cell atypia (Figure 1C). Dilated, tortuous blood vessels containing refractile elements corresponding to erythrocytes could be identified on basic RCM images (Figure 1D) and inflammatory infiltrates (Figure 1E) could be identified on basic RCM images. A rather particular “swirl” aspect could be seen at the level of the stratum spinosum (Figure 1F), possibly corresponding to keratin pearls caused by intraepithelial keratinization.

Figure 1 – (A) Clinical image illustrating an increased lower lip volume, and a round to oval tumor with a keratotic surface on a background of lower lip surface atrophy; (B) Dermoscopy image showing a white-yellowish astructural area (red asterisk) surrounded by telangiectatic tortuous vessels (black arrows); (C) RCM image at the stratum spinosum showing deeply altered keratinocyte architecture (disarrangement of the spinous layer) and pleomorphic keratinocytes (yellow arrows); (D) RCM image showing dilated, tortuous vessels (white asterisk) containing refractile elements corresponding to erythrocytes (black arrows); (E) RCM image depicting bright elements corresponding to inflammatory cells; (F) Basic RCM image showing the distinct “swirl” aspect (lower left corner of the image) at the level of the stratum spinosum, possibly corresponding to keratin pearls caused by intraepithelial keratinization. RCM: Reflectance confocal microscopy.
Histopathological examination was performed after standard Hematoxylin and Eosin staining of the excised tissue and confirmed the diagnosis of invasive, well differentiated, SCC. Tumor proliferation did not however infiltrate the underlying muscular fibers and an important chronic inflammatory infiltrate consisting of lymphocytes and plasmocytes was present (Figure 1, G and H). Treatment consisted of wedge-excision vermilionectomy (Figure 1I) in the Department of Oral and Maxillofacial Surgery, “Dr. Carol Davila” Central Military Emergency Hospital, Bucharest, with good cosmetic and functional results nine months after surgery (Figure 1J).

Discussions

Radiation-induced solid tumors, such as SCC, have a long latent period (10 years or longer), and their incidence is directly proportional to the total dose of radiation and the time passed since exposure [28–32]. The latent period is inversely proportional to the radiation dose; the larger the dosage, the longer the latent period before tumor development [33]. It would appear that the age at the time of irradiation may also affect the latent period; the older the age at exposure, the shorter the latent period [34]. A study on radiation-induced malignancy [35] has estimated the radiation-related cancer rate in exposed tissues to be 1.8 cases/million person-year/ rad. Other authors report the dose-effect relationship between epithelial cancers and radiation exposed skin as 40 carcinomas/104 persons/Gy over a median follow-up period of 41 years [28].

Importantly, children are significantly more susceptible to the carcinogenic effects of radiation therapy than adults; children also have a longer life expectancy, leading to a bigger window of opportunity for these effects to manifest themselves.

According to early epidemiological studies, most radiation-induced skin cancers are basal cell carcinomas, with only a small percentage being represented by SCC [28]. A newer population-based study from Canada [36] found a 5.7- and 4.8-fold increase in the incidence of BCC and SCC, respectively, associated with non-diagnostic ionizing radiation exposure. Karagas et al. [37] reported a relative risk of 1.7 and 1.0 for new BCC and SCC radiation-related occurrences, respectively.

In SCC patients, early detection allowing a prompt, effective treatment is one of the most important factors for long-term survival and quality of life. Hence, modern imaging techniques such as RCM and dermoscopy are more and more present in the investigation of mucocutaneous tumors.

RCM enables the in vivo assessment of cellular and subcellular skin morphology down to a depth of approximately 300 μm. Over the recent years, RCM has successfully been employed in the evaluation of neoplastic, inflammatory, and infectious skin disorders alike. Various studies have described the confocal microscopy features of basal cell carcinoma [20, 21, 26, 38, 39], actinic keratosis and cutaneous SCC [40–43], benign melanocytic nevi and melanoma [44–47], inflammatory skin conditions [48, 49],
such as psoriasis [22, 50, 51] and pityriasis rubra pilaris [52], vesiculobullous disorders [53], and infectious diseases [54–58].

The biggest advantage of RCM over classical diagnostic approaches is its noninvasive nature. RCM allows for fast, real-time evaluation of epidermal and partially dermal tissue architecture without patient discomfort and without the need for further equipment or laboratory devices.

RCM criteria for the diagnosis of lip SCC have previously been explored and have been described as extensive keratinocyte pleomorphism creating a disarranged honeycomb pattern of the stratum spinosum, round and bright nucleated cells (representing atypical and dyskeratotic keratinocytes), as well as atypical nucleated cells in the superficial dermis in invasive SCCs [43]. Upon RCM examination in our case, we observed a markedly disarranged stratum spinosum, as well as extensive keratinocyte atypia, and dilated blood vessels surrounded by perivascular inflammatory infiltrates. The dermis presented thickened collagen bundles as well as inflammatory infiltrates.

The management of radiation-induced solid tumors includes surgery and radiotherapy, taking into account the site and extent of tumor involvement. Considering the now so well known late effects of ionizing radiation exposure, radiotherapy for benign skin lesions is contra-indicated, especially in the view of the body of evidence that proves low doses of radiation applied over long periods of time dramatically increase the risk of cancer development [28, 59].

Owing to the long latent period between radiation exposure and SCC development, non-invasive, reliable imaging technologies, such as dermoscopy and RCM may prove to be invaluable tools in skin cancer diagnosis algorithms, thus adding substantial benefits to patients and clinicians alike. Because of its potential to assess microscopic features of normal mucosa, dysplasia, and neoplastic changes, RCM may also provide a viable alternative for evaluation of mucosal tumor margins during surgery [60], thereby leading to improved surgical times and appreciable cost reductions when compared to frozen section histology.

Conclusions

Patients with a personal history of radiotherapy need lifetime lasting dermatological observation on account of the fact that the management of large, radiation-induced cutaneous tumors can be rather complicated.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors’ contribution

The first two authors, Mihai Lupu and Ana Căruntu, contributed equally to writing and editing the manuscript.

References


