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A Case Report: A Spontaneous Healing of Squamos-Cell Epithelioma of the Skin.

Capretti A.M*

Corresponding Author: Capretti A.M, Plastic Surgeon Consultant –Department of Gynecology - Director Prof. P. Vercellini- Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan -Italy.

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Introduction

The term "skin cancer" usually includes basal-cell epithelioma **(**BCC**)**, squamous cell epithelioma **(**SCC**)**, Merckel and melanoma **(**1**)**.

Skin cancer is an enormous public health concern with non-melanoma skin cancer being the most common cancer in the Europe and USA. BCC and SCC are often controlled with local measures **(** surgery in particular**)** their combined millions of cases are estimated to result in several thousand deaths annually **(**2**)**.

Cutaneous squamous cell carcinoma **(**CSCC**)** is the second most frequent cancer in humans, with an estimated incidence of 1 million cases each year in the US. This figure continues to rise, and is an underestimate **(**2-3**)**]. The number of CSCCs has increased from 50% to 300% in the last three decades **(**4**)**, and by 2030 its incidence in European countries will be twice the current level **(**5**)**.

Squamous cell carcinoma **(** SCC **)** arising from the upper side of the thorax **(** sternum **)** close to jugule is rare, having an aggressive course.

A 83 years old man patient with many comorbidities **(**diabetic 2 –arterial hypertension and brain stroke after-effects and BPCO **)** with a red vegetating painful infected and rapidly growing lesion 10 cm x 4,5 in size of the upper central thorax **(** sternum **)** close to jugule anatomy presented to me from an emergency room in Fondazione Ca Granda Policlinico Hospital of Milan the last December 2020.

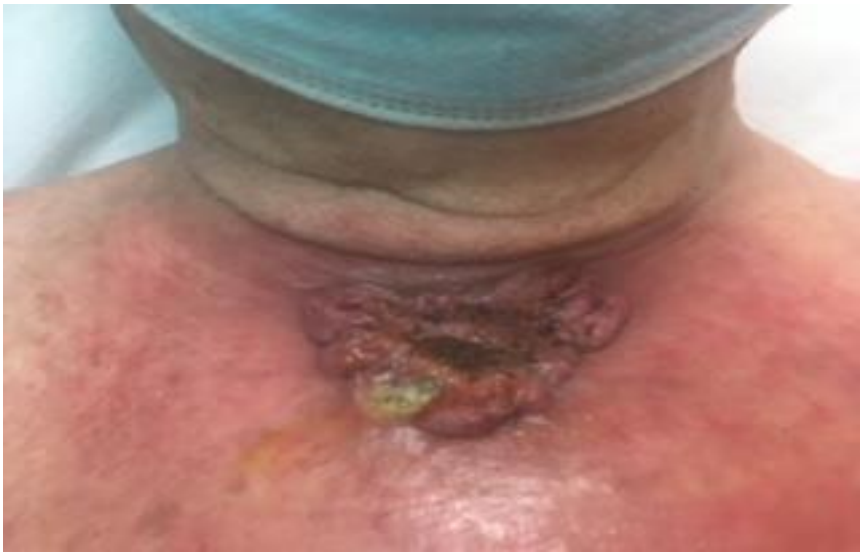

Photo 1 shows a red vegetating painful infected and rapidly growing lesion 10 cm x 4,5 in size of the upper central thorax **(** sternum **)** close to jugule anatomy after biopsy – january'21

He received systemic antibiotic treatment and local therapy with antiseptic ointment for three weeks. Clinical examination showed lymphadenopathy of the lower left chest.

After three weeks the patient arrives in Hospital with negative ultrasound axillary cavity and neck lymph nodes , negative chest x-ray; so I decide to do a biopsy.

I made a biopsy of the lesion in local anesthesia and the histological examination was Carcinoma squamous cell epithelioma G2 **(**photo 1**).**

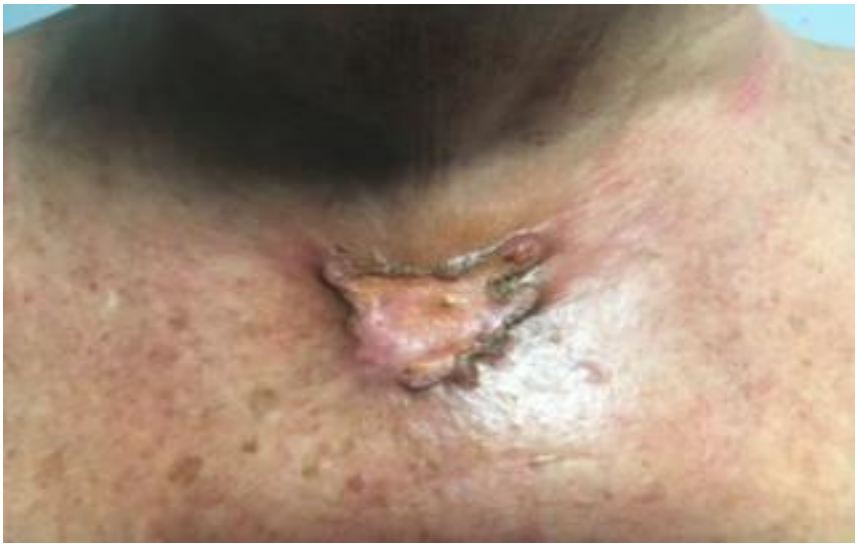

Photo 2 : A spontaneous rapidly regression of the skin tumour after two months of biopsy – march'21

I continue to do dressing the lesion with betadine ointment and we prepare the patient for surgery.

The patient doesn't feel good in February'21 for flue and CoVID-19 pandemia delay the surgical appointment. At the last of march'21the patient calls me on the telephone and says to me that the lesion has begun to heal **(**photo 2**)**. I was very surprised and invite the patient to come in Hospital for a check- up visit. The patient come to Hospital on 21st April 21 and I was surprised to see spontaneous healing of the lesion. The vegetating lesion disappearance and a perfect healing of the border of the lesion appeared; a complete epithelialization of the center of the lesion with a rosy color 3,5 cm diameter size **(** Photo 3**)**.

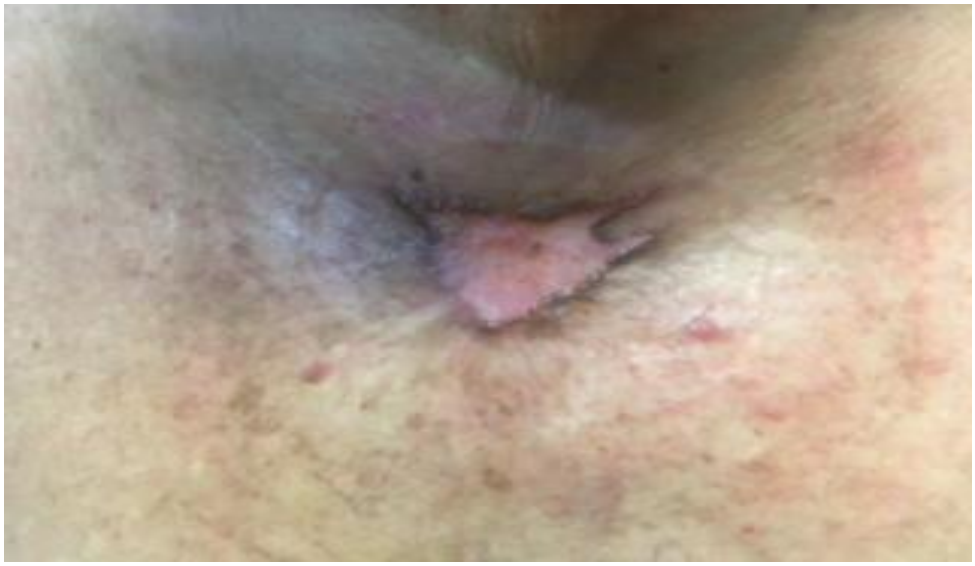

Photo 3 : A completely re epithelization of the lesion- April'21

I was very incredulous about what happened, so I decide to do clinical monitoring and check-up visits the patient. The patient fell at home with minimal fractured vertebrae in June'21. He brought an orthopedic corset for two months in summer '21

At the beginning of September '21 I decided to do a second biopsy: the lesion was more regress with a scars shape butterfly wings lesion **(**Photo 4**)**. The Histological examination confirms complete healing of the lesion.

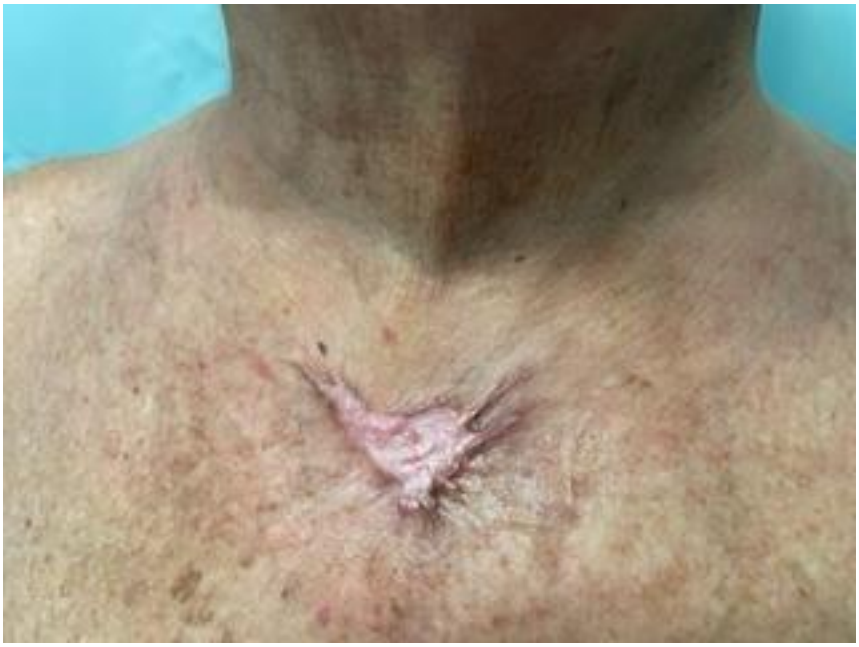

Photo 4 : A scar formation – September '21

Considerations

CSCC arises from the malignant proliferation of epidermal keratinocytes. There are environmental and constitutional risk factors for its development. With respect to the former, older age, male sex, fair skin, immunosuppression, and a previous history of actinic keratosis **(**AK**)** are of known importance. Chronic sun exposure is the most important and well-known environmental factor associated with CSCC **(**7-8-9-10-11-12**)** Solid-organ transplant recipients, who have a human papillomavirus infection or chronic lymphocytic leukemia, have a higher risk of developing CSCC than the general population **(**13-14-15-16**)** AK **(** actinic Keratosis**)** is considered a premalignant lesion that may progress to an invasive SCC, and is the most significant predictive factor of CSCC **(**17**)**

Skin cancer healing is a very rare event: no publications reports on spontaneous healing of squamous cell epithelioma **(**SCC cancer**)** there are in modern literature. This article will focus on skin cancers as a paradigm for tumor immunotherapy auto-healing, starting with the reasons for the immunogenicity of skin cancer. The incidence of skin cancer is elevated with T – cell immunosuppression and in elderly patients. In patients with normal cutaneous immunity **(**Young patients**)**, nascent immunogenetic skin tumors are eliminated unless the tumor can evade immune destruction. Reversing tumor evasion is the goal of anti-cancer immunotherapy.

Tumor cells produce neoantigens that are recognized and targeted by the immune system. When a T- cell recognizes the antigen expressed by the Human leukocyte antigen **(**HLA**)** complex in the tumor cell, co-receptors act as activators and inhibitors of the immune response **(**18**)** Inhibitory receptors, such as programmed cell death 1 protein **(**PD-1**)** and Cytotoxic T-Lymphocyte Antigen 4 **(**CTLA4**)**, are known as "immune checkpoint" receptors. PD-1 is an inhibitor co-receptor expressed on the surface of T-cells, B-cells, monocytes, natural killer cells, and dendritic cells **(**19**)** This transmembrane protein binds to two ligands, PD-L1 and PD-L2, which are present on the surface of the tumor cell, and their interaction triggers a signal that inhibits the activated T-cells and induces immunological exhaustion via anergy and T-cell apoptosis**(**18-20-21**)** The PD-L1/PD-1 axis is a primary mechanism of cancer immune evasion, and this was the rationale for developing new drugs that have emerged in recent years. Targeting the immune checkpoint proteins with monoclonal antibodies has yielded a clinical benefit in cancer **(**22-23**)** and dramatically changed prospects for the treatment of some types of cancer, such as melanoma **(**24**)** An established tumor is composed both by the neoplastic cells and the tumor microenvironment. The latter is composed both by the tumor stroma and the inflammatory infiltrate. The tumor microenvironment, and not only the neoplastic cells, can also be modulated to destroy the neoplastic cells. Indeed, most immune checkpoint inhibitors are directed towards the lymphocytes, which belong to the tumor microenvironment, in order to enhance the immune response **(**25**)**

I want to analyze a second point: the wound healing process.

Wound healing is one of the most complex processes in the human body since it involves the spatial and temporal synchronization of the inflammatory phase with tissue regeneration and remodeling. The inflammatory phase follows the injurious event and it includes the coagulation cascade, inflammatory pathway and immune system involvement 12 All these events take place to prevent an excessive loss of blood, fluids and the development of infections, and to facilitate the removal of dead or devitalized tissue. Hemostasis is achieved by platelet clot generation, followed by fibrin matrix formation, which acts as a scaffold for cell infiltration. As a result of platelet degranulation, the release of chemotactic signals by necrotic tissues, and bacterial

degradation products, the complementary system is activated and neutrophils arrive at the lesion (26-27) Finally, macrophages coordinate all events evolved in response to damage. These cells are responsible for fibrin phagocytosis activity and cellular debris, and they secrete macrophage-derived growth factor (MDGF) for fibroblasts and endothelial cells (28) New tissue formation begins within two to ten days after the lesion and consists of cell proliferation and the migration of different cytotypes. When the lesion involves the dermis, a poorly differentiated and highly vascularized connective tissue called granulation tissue is formed, which consists of cellular and fibrillar components integrated into an apparently amorphous matrix. The cells of granulation tissue are (i) fibroblasts, responsible for the synthesis of the fibrillar component; (ii) myofibroblasts, involved in the wound contraction mechanism and (iii) endothelial cells, responsible for the neo-angiogenesis process (29)

The re-epithelization process, characterized by the proliferation and migration of keratinocytes towards the core part of the lesion, originates in this phase as the area between the bottom and the edges of the wound is filled with granulation tissue. This represents the matrix in which keratinocytes, residing on lesion edges, migrate and proliferate (29) Skin re-epithelization structural organization can be explained by two models: sliding and rolling models. According to the sliding model, keratinocytes of the basal layer suffer a modification of their anchoring joints (desmosomes and hemidesmosomes), allowing their detachment and lateral migration into the core part of the lesion. According to the rolling model, keratinocytes go through a morphological and functional modification, together with desmosomes, resulting in them rolling towards basal keratinocytes, which instead remain anchored to the basal membrane (30) Basal layer regeneration leads keratinocytes to proliferate and differentiate vertically, restoring the physiological features of the multilayered epithelial tissue.

The remodeling phase starts about three weeks after an injurious advent and lasts for over a year. During this phase, all processes activated in previous phases are silenced and macrophages, isolated endothelial cells and myofibroblasts run into apoptosis or they are relocated from the wound, leaving a region rich in collagen and other extracellular matrix deposition (ECM) proteins. Interactions between the epidermis and dermis, together with additional feedback, allow the continuous regulation of skin integrity and homeostasis. Type III collagen, located in ECM, is gradually replaced in 6–12 months.

If I can put these processes auto-immunotherapy and wound healing together I can explain this auto-healing cancer patient case.

I can't explain perfectly what happens in this case: a religious miracle's or a scientific natural process?

Conclusions

In recent years, a deeper understanding of the molecular bases of cutaneous squamous cell carcinogenesis (CSCC) has helped identify novel therapies. EGFR inhibitors were found to be promising drugs in CSCC, based on several studies that suggested an important role for this pathway in CSCC development at a time when there was little to offer patients by way of effective treatment (33- 34-35). Subsequently, other targets were evaluated and continue to be developed. More recently, the high mutational burden of this tumor and the increased risk of CSCC in immunosuppressed patients have raised the possibility of using immunotherapy to treat CSCC. As the new checkpoint inhibitors are surprisingly effective in other tumors, some CSCC cases have also been treated, with anti-PD-1 yielding particularly good responses. Cemiplimab is the first drug approved by the FDA and the European Medicines Agency (EMA) for the treatment of locally advanced and metastatic CSCC (36) It seems likely that other checkpoint inhibitors will be incorporated into the therapeutic arsenal of CSCC in the near future. In this case report, a non-understanding healing regression of the SSC tumor has been identifying. “A magical biological healing” has happened; a very rare clinical case. The older human race has the biology capacity on auto healing skin cancer?

It is important to emphasize that patients who are receiving drug treatments that are associated with increased susceptibility to developing CSCC may require dermatological supervision, especially if any suspicious skin lesion arises.

The major message emerging from my review is that I should guard against the view that CSCC is a tumor with a good prognosis simply because it usually has a favorable evolution. In truth, its high incidence means that the absolute frequency of complicated and disseminated cases will also be high.

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