Chapter-27

Management of Cutaneous Malignancies on Chronic Wounds

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Abstract

Cutaneous malignancy on chronic wounds (CMCW) which develops in the presence of long-term wounds damaged skin, and open wounds from the past. Chronic osteomyelitis is the most frequent condition in which persistent wounds have been linked to the emergence of squamous cell carcinoma (SCC). Squamous Cell Carcinoma (SCC) is detected in 94% of cases, with the lower extremity being the most common site of involvement. It is an abrasive uncommon entity that frequently takes longer to diagnose in different parts of the body. Treatment options are still unclear and up for controversy. SCC and Melanoma constituted the minority of cases. Melanoma had a higher metastasis rate than SCC and was more common in wounds that had previously undergone skin grafting. The majority of patients had no corresponding distant or regional metastases at the time of diagnosis. There is still debate in the Marjolin Ulcer (MU) control despite the large number of articles written on this issue. Quick surgical intervention and early diagnosis of suspicious chronic wounds are still serious. The majority of patients had no corresponding distant or regional metastases at the time of diagnosis. Generally, wide local excision (71%) was done unless amputation was necessary due to severe disease or involvement of the bone. The effectiveness of sentinel lymph node biopsies and lymphadenectomy has been reported inconsistently. When there is known involvement of lymph nodes, lymphadenectomy is most frequently advised.

Chemotherapy and radiation therapy were used in addition to surgery in cases of metastatic disease. There is still debate in the MU control despite the large number of articles written on this issue. Quick surgical intervention and early diagnosis of suspicious chronic wounds are still serious.

Keywords: Chronic Wound, Cutaneous Malignancy, Squamous Cell Carcinoma, Melanoma

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1. INTRODUCTION

Cutaneous malignancies on chronic wounds (CMCW) that arise mostly from squamous cell carcinoma (SCC) also known as Marjolin Ulcer. Jean Nicholas Marjolin (1828) discovered malignant degeneration in burn wounds. These earlier descriptions were correctly recognized as forms of cancer in the late 1840s by Byron and Smith, who named them "warty ulcers" of Marjolin. Marjolin's ulcers make up 0.05% of all squamous cell carcinomas of the lower extremities [1,2]. Regarding the majority of cutaneous malignancy treatment recommendations, surgeons frequently consult the National Comprehensive Cancer Network (NCCN); however, the NCCN lacks specific guidelines for the diagnosis and treatment of carcinomas associated with scars [3]. Marjolin ulcers can affect people of any age, gender, or race. Males are affected more frequently than females (3:1), which may be related to the higher-than-average number of burns in this population [4,5,6]. Malignant degeneration arising within osteomyelitis wounds is the second most common association. However, malignancy arising from cutaneous scars and chronic wounds are commonly referred to as MU [7]. A case study describing a 73-year-old man diagnosed with a BCC and suffering a history of non-healing wounds. This case emphasizes how critical it is to rule out cancer when treating a chronic wound [8].

The malignant degeneration seen in Marjolin's ulcers may have originated from chronic inflammatory skin lesions or pre-existing scar tissue. Biopsied lesions frequently show well-differentiated squamous cell tumors, though they can also be melanoma or basal cell carcinomas. Occasionally practice of Marjolin's ulcers occur in the digits; instead, they are typically found in the lower extremities, particularly the heel foot [9]. It has been additionally demonstrated that reduced immune function in chronic wounds plays a role in the pathogenic process. Amputation close to the tumor was soon after the only effective treatment; more recently, radiation treatment as well as wide surgical removal have been utilized. Broad local excision is unreliable; in cases of grade II or III disease, amputation is advised. In cases of grade-I lesions or very small

lesions that can be completely removed, wide local excision is advised. In an instance of an elbow-based Marjolin ulcer. When treating chronic wounds that are resistant to treatment, doctors should be very suspicious and should always remember to biopsy any suspected lesions [10]. In 1.7% of wounds, malignant transformation is evident. Full thickness burns that heal by secondary intention have the highest propensity to become malignant, with an incidence of 0.77 to 2% [11].

1.1 Chronic Wound

If a comprehensive diagnostic workup is not performed or when there are insufficient treatment options, chronic wounds develop over time and become resilient to multiple types of care. Older people are the age group most at risk of chronic wounds because of their typical characteristics which include multiple medications and multiple diagnoses. Vascular leg ulcers, pressure ulcers, and diabetic foot ulcers are among the most widespread types of long-term wounds among older people [12]. In Ayurvedic term wound known as Vrana. Vrana is mentioned as a primary topic by Sushruta in the Sushruta Samhita. Vrana is generally divided into two categories: Shuddha and Dushta Vrana (chronic wounds/nonhealing ulcers). Several medications suggested for Dushta Vrana, Haridra (*Curcuma longa* Linn.) powder and neem (*Azadirechta indica* A. Juss) oil—are chosen due to their broad range of effects on wounds [13]. The chronic wound itself has several types of complications, such as infection leading to septicemia, fluid and blood loss, and the extremely uncommon but potentially deadly neoplastic changes of the wound. Seventeen out of every thousand chronic wounds develop malignant properties, according to some studies [14]. When long-term osteomyelitis coexists with persistent wounds, this is the most common scenario where squamous cell carcinoma develops. However, there is also a chance that wounds resulting from diabetes, trauma, radiation therapy, and burns will develop malignant degeneration [15].

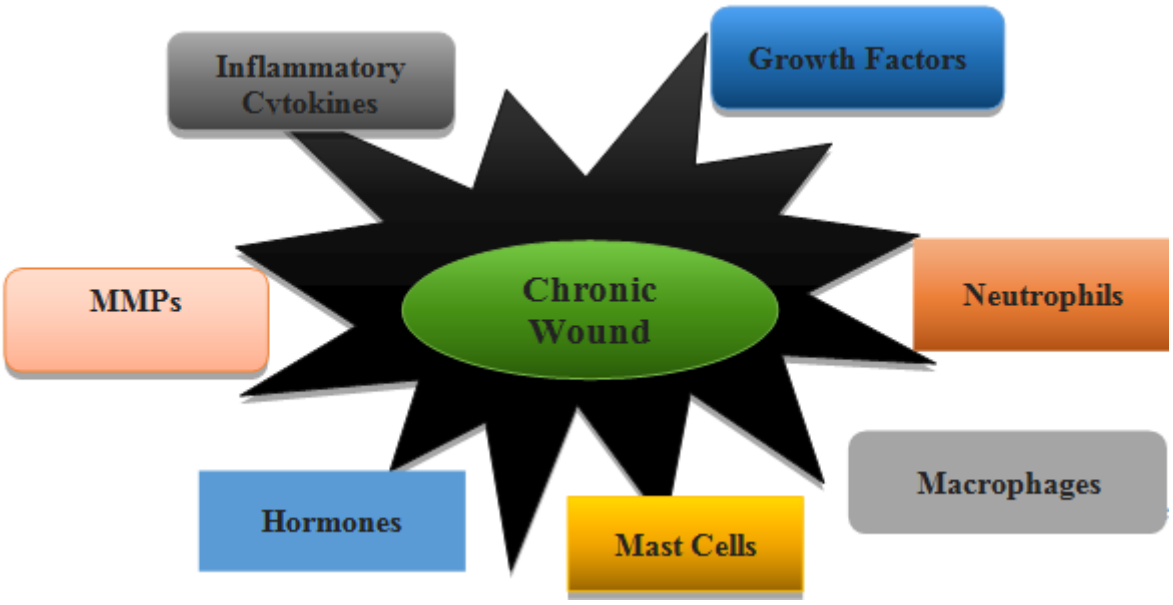

Figure 1: Major Cellular Factors of Chronic Wounds

1.2 Cutaneous Malignancy

Cutaneous malignancy (CM), which is a tumor composed of melanocytes, is one of the most severe types of cancer that affect humans [16]. In India, cutaneous malignancies account for 1%–2% of all diagnosed cancer cases. Nonmelanoma skin cancers (NMSCs) include squamous cell carcinomas (SCC) and basal cell carcinomas (BCC). Melanoma, cutaneous lymphomas, and sarcomas are a few more. The primary risk factor for skin cancers is being exposed to ultraviolet (UV) radiation, though there are many other factors as well. According to Supekar et al. cutaneous T-cell lymphoma (1.5%), malignant melanoma (9%), SCC (30%), and BCC (41%) were the most common cancers [17]. One of the most prominent cancers among young adults, CM is becoming more and more common worldwide. Though it causes 65% of skin cancer deaths, CM only accounts for 3% of all skin cancer cases. Together, over 90% of patients with developing melanoma survive provided the tumor is appropriately treated and recognized early [18].

2. CORRELATION BETWEEN WOUNDS AND MALIGNANCY

Malignant tumors frequently develop at sites of chronic injury, and tissue injury plays an important role in the pathogenesis of malignant disease, with chronic inflammation being the most significant risk factor. The development and functional characterization of genetically modified mice that lack or overexpress repair genes, combined with gene-expression investigation in wounds and malignancy, have revealed striking similarities between wound

repair and cancer. However, a few critical differences were discovered, which could explain the altered metabolism, reduced differentiation capacity, and invasive growth of malignant tumors. The presence of a fibrin clot is a sign of an early wound or cancer, and it initiates the healing process. In wounds, this response is transient and self-limiting; however, it becomes chronic in cancer [19]. Nature of the degeneration of a chronic wound or a malignancy presenting as a chronic wound, some believe that only suspicious wounds should be biopsied. If the ulcer is relatively short in duration and the patient possesses no prior radiotherapy history, primary malignancy should be considered. Until recently, amputation was the preferred treatment for squamous cell carcinomas that developed within chronic wounds associated with chronic osteomyelitis [20].

3. PROCESSES OF CHRONIC WOUND REPAIR

The process of repair of chronic wounds is composed of the coordination of three overlapping but distinct phases. This includes inflammation, proliferation and remodeling. The wound-healing process is highly regulated by secretion of various growth factors, cytokines, and chemokines. These phases and their physiological functions occur in a regulated and precise manner since discontinuities, aberrancies, or lengthening in the process can lead to delayed wound repair or a non-repair chronic wound [21].

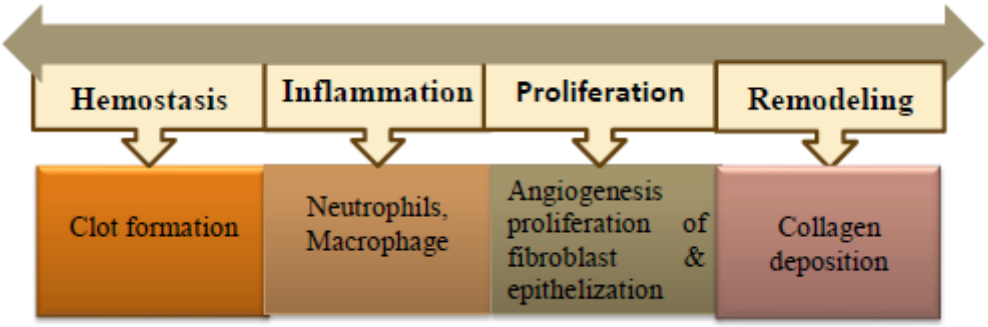

Figure 2: Stages of Chronic Wound Repairs

3.1 Angiogenesis

Angiogenesis is the most important factor for wound healing by forming new blood vessels from preexisting vessels by invading the wound clot and organizing into a microvascular network throughout the granulation tissue. This process is fundamental to both physiological wound healing and the growth of malignant tumors, as it restores or creates a blood supply to growing tissue. In both cases, the release of angiogenic molecules by macrophages recruited to the wound or tumor site is central to the formation of these neo vessels and highly regulated by signals from both serum and the surrounding extracellular matrix

environment. Reduced vascular perfusion in tissues generates tissue ischemia and a marked reduction in local levels of oxygen (hypoxia) and glucose. Cells adapt by switching to anaerobic metabolic pathways, with a concomitant increase in lactate production and reduction in extracellular pH [22].

3.2 Growth Factors for Angiogenesis

Various important growth factors are involved: Vascular endothelial growth factor, angiopoietin, fibroblast growth factor, and transforming growth factor-beta are all effective angiogenic cytokines in wound angiogenesis. Specific endothelial cell ECM receptors are required for morphogenetic changes in blood vessels during wound healing. Integrin (αvβ3) receptors for fibrin and fibronectin are required for wound angiogenesis. Integrin (αvβ3) is expressed at the tips of angiogenic capillary creates invading the wound clot. Functional inhibitors of αvβ3, such as monoclonal antibodies, cyclic RGD peptide antagonists, and peptidomimetics, rapidly inhibit granulation tissue formation. Even an extensive knowledge of the effect of many angiogenic factors on wound healing, little progress has been made in defining the source of these factors, the regulatory events involved in wound angiogenesis, and the clinical use of angiogenic stimulants to promote repair [23]. Angiogenesis is necessary for tumors to grow larger than 1-2 mm and spread to secondary sites. Tumor angiogenesis has become an appealing and promising therapeutic target. To promote angiogenesis, tumor cells and cells in the tumor microenvironment must shift the balance of pro- and anti-angiogenic factors, leading to an "angiogenic switch" [24].

4. MECHANISM/PATHO-PHYSIOLOGY

Wound healing is a biological phenomenon that involves several stages. Skin cells, extracellular matrix, and systemic factors are the primary players in this process. The injury, platelet activation, and unfolding of the coagulation cascade are all involved. Within the first day after an injury, neutrophils, macrophages, and T lymphocytes are recruited to the wound site, where they perform phagocytosis and remove bacteria and damaged tissue. Several cytokines and growth factors that promote proliferation and angiogenesis are then released, including platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-b), fibroblast growth factor 2 (FGF-2), vascular endothelial growth factor (VEGF), interleukin (IL) 1, IL-6, and tumor necrosis factor alpha. Multiple quadrant biopsies remain the gold standard for diagnosing Marjolin's ulcer; they should be performed on all suspicious wounds and reported to a highly skilled histopathologist. Most literature considers it to be the benign type, characterized by an increase in epidermal its thickness, proliferation of irregular squamous cell strings, minimal or absent cytological

atypia, and a mononuclear inflammatory infiltrate [25]. Burn wounds were the most common cause of MU, accounting for 67.7% of cases. Traumatic injuries were the next most common cause, accounting for 5.0% of cases. Radiation burn wounds (3.2%) were distantly followed by osteomyelitis (2.7%), cutaneous ulcers (1.2%), and other scar history, including surgical incisions (0.9%), with an unknown etiology in 19.3% of cases. In terms of body location, the lower extremity was the most frequently reported (51.2%). The head and neck and upper extremity followed, accounting for 13.4% and 11.8% of cases, respectively. Lesions were located on the trunk in 6.6% of cases, with the genitals being the least common (0.3%) [26].

5. ETIOPATHOGENESIS OF CUTANEOUS MALIGNANCIES ON CHRONIC WOUNDS

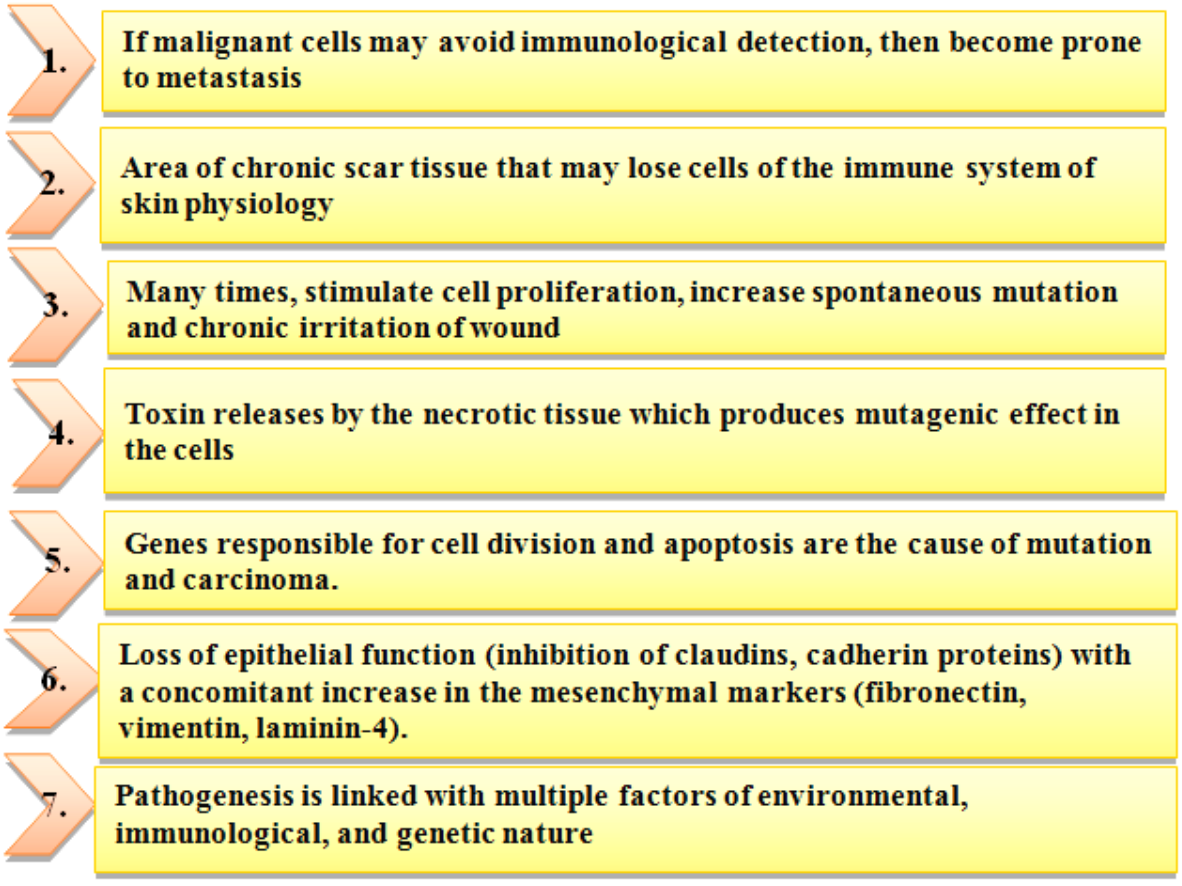

Figure 3: Causes of cutaneous malignancies on chronic wounds

6. MANAGEMENT

Surgery is an essential component of medical treatment. A case report found that surgical excision was used in 71% of cases, amputation in 24%, primary radiotherapy in 2%, and chemotherapy in less than 1%. In previous studies, 3% of patients received no active treatment, while 58% of surgery

patients underwent amputation [27]. In some cases, patients (70.5%) reported both excision and amputation as the primary treatment option, with margins ranging from 0.5 to 4 cm. Most of the authors (70.1%) reported initial margin widths of 2 cm when using an intraoperative frozen section. Few papers defined the depth of resection, specifically the level of the underlying muscle fascia within the resection [28].

A significant level of suspicion and an early histological diagnosis in chronic wounds and unstable scars with recent changes in characteristics deliver the best prognosis with treatment [29]. The most common treatment options are wide local excision and block excision of the lymph nodes. While sentinel lymph node dissection is necessary for patients with metastases, there is no consensus on preventative nodal dissection or radiation due to the lethal nature of carcinoma [2].

7. ADDITIONAL THERAPY

Some cases reported local radiation therapy (RT) in the setting of Marjolin ulcer may be supplementary therapy. The most common reason was that the disease could not be removed. Metastases (regional or distant) and recurrence were the next most prevalent. Some reports have Grade III disease and lesions wider than 10 cm were also used as indications for adjuvant radiation therapy in their institution and published a paper in 2018 on the use of RT for recurrent MU [21,30].

Some Evidence Based Ayurvedic Medicinal Plants: Ayurvedic medicinal plant which are well known and already accepted by the society for the purpose of wound healing and cancer cell lines (traditionally as well as ethnomedicinally) i.e., *Curcuma longa, Balanites aegyptiaca, Alengium salvifolium, Jasminum officinarum, Azadiracta indica, Ficus religiosa, Ficus bengalansis, Ficus lacor, Aloe veera* etc. Some traditional plants given in sushruta samhita and ethnomedicinal plants mentioned in the book which is available in our library or in central library [31,32]. In a clinical study found that the Ingudi (*Balanites aegyptica*) seed oil are use for diabetic wound healing way of topical application over 45 days. In this plant material have the obtained the caffeic acid, which is very impactful for the diabetic wound healing [33]. One another case study of the plant materials like the neem (*A. indica*) oil and haridra (*C. longa*) combination good result on chronic non healing wounds. Both drugs are very effectively managed for chronic wounds and less side effects [34].

8. CONCLUSION

The majority of current literature on MU consists of case reports and small series. Because of the small number of studies and the variety of underlying causes, it is difficult to reach a clear consensus on the best way to treat MU. A timely surgical resection and thorough investigation of a chronic, non-healing ulcer may, in theory, prevent the development of a cutaneous SCC. Currently, surgical management is the primary treatment option. Most cases involve extensive excision of the lesion, but less conservative treatment, such as amputation, may be required. In the case of extensive resections, reconstructive surgery, primarily skin flaps, is used. As well some Ayurvedic medicinal plants are also effectively managed for the cutaneous malignancies on chronic wounds or Morjolin Ulcer. There is insufficient evidence to suggest that techniques such as sentinel node mapping are useful for prognosis.

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