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REVIEW

Frostbite and Cancer

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SUMMARY

Frostbites can be associated with a number of acute or long-term complications. One of these chronic adversities is neoplastic disorders, arising from frostbite lesions. Because of the sparseness of the available studies in medical literature, in this narrative review, the association between frostbite and cancer was explored with more focus on real-life clinical cases. The results from database searching revealed that only a few studies have evaluated this vicious companionship. According to the studies, frostbite can be a causative factor in the initiation and development of cancerous pathologies. On the other hand, some specific neoplastic disorders have been presented as risk factors for such cold injuries. It can be concluded that thorough evaluation of frostbite cases toward the full healing and considering cancers as a risk factor for cold injuries through the diagnostic procedures can be life and cost-saving for health-care systems.

Keywords: Cold climate; frostbite; neoplasms; review.

INTRODUCTION

Frostbite or freezing cold injury is defined by cold-induced tissue damage through time or vulnerability-dependent exposure to subzero temperatures (Celsius). Historically, it was a common ailment of soldiers, but the modernization of populations has changed its epidemiology with current dominance among homeless people or those at extremities of age.[1] Obviously, its prevalence can be more worrisome among the nations living in colder climates. For instance, in a study from Finland, the incidence of severe frostbite was reported to be around 10.6% for residents throughout their life.[2] Regardless of the etiology and prevalence, this climate-related pathology can induce several long-term sequelae for the affected patients. Vasomotor, neuropathic and nociceptive complications, and skeletal disfigurations are repetitively reported.[3] Tissue growth abnormalities have been exclusively observed in the affected cases.[4] Regarding the sparse reports in medical literature, cancer is one of the late consequences of this prolonged tissue injury,[5,6] but the lack of straightforward evaluations about this malignant association is alarming among clinical studies.

On the other hand, literature shows that frostbite might have some pathologic predisposing factors. Interestingly, a number of these risk factors have neoplastic roots. Again, this matter has not been sufficiently investigated in clinical fields.

The aim of this study is to explore the association of frostbite and cancer, both from causative and associative point of view to build a foundation for more goal-directed clinical trials and observations.

MATERIALS AND METHODS

Our aim in this study was to evaluate the association between frostbite and cancer, regardless of the type of the correlation. In order to find the most relevant data about our topic, an accredited scientific database, PubMed, was explored using this search strategy: ("Frostbite"[Majr]) AND "Neoplasms"[Mesh].

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RESULTS

PubMed searching with MeSH terms "Frostbite" and "Neoplasms" resulted in only 37 journal articles. Furthermore, some more studies were added from Google Scholar to support the notions of this review in the following sections. Screening the articles showed that cancer and frostbite have a two-way relationship. Only 13 of the articles were about frostbite as a causative factor. The rest presented factors such as hematologic malignancies, metastatic solid tumors, rheumatologic disorders, and iatrogenic cancer therapies to act as precipitating factors for frostbite. In the following part, both issues are discussed in detail, separately.

DISCUSSION

For a better understanding of the bilateral association between these two terminologies, the acquired information from the literature is categorized under these subheadings.

PATHOPHYSIOLOGY

Acutely, frostbite develops through vasoconstriction caused by intense cold. The consequent blood flow decline prohibits adequate tissue circulation and heating, which ends in the formation of ice crystals. These crystals directly cause lipid and protein disruption, shifting the electrolyte balance, and intracellular dehydration. In addition, blood flow disturbances and coagulopathy within the microvasculature cause ischemia.[7] This continues through an ischemia–reperfusion-inflammation injury and concludes in tissue necrosis. Free-radical formation elongates the injury, especially after rewarming for the survivors. After several days, the remodeling mechanisms initiate tissue scar formation in bones, skeletal muscles, and skin. The wound-healing process is accompanied by circulating factors which are mutual in both scaring and neoplastic changes.[8] In this way, cancerous pathologies can be predicted as late adversities of frostbite.

For understanding frostbite as a consequence of underlying diseases, there is no specific mechanistic explanation. However, considering the blood-related etiology of these cases, chronic lack of adequate perfusion to certain skin areas can be suggested.

CLINICAL PRESENTATIONS

It is important to know that frostbite scars can be diagnosed cancerous as long as three decades after the initiating lesion. Commonly, recurrent ulcerations and tenderness are accompanied by this elongated dormant state.[9] One of the most susceptible groups for frostbites is still warzone survivors. Hence, clinical records of cancer among them are not unexpected.[10] Skin is the first and most vulnerable tissue to the adverse effects of cold insults. Accordingly, the number of reports about frostbite-associated cancer (FAC) is higher in skin cancer cases.[11] The scar formation on the dermis provides a cancer-prone area for such pathologies.[12,13] This fact is significantly applicable to heel site lesions.[9] In a case series depicting clinical scenarios of 10 FAC patients, a high prevalence of heel frostbites with squamous cell carcinoma was demonstrated.[14] Some authors have used the term "Marjolin's ulcer" for these malignant skin ulcers, caused by chronic wound tumorigenicity.[15]

There are cases of bone involvement from the cancerous invasion of malignant frostbite scar tissue in feet with more aggressive ulcerations.[16,17]

Besides the causative relationship from frostbite to malignancies, some cancerous genetic traits are accompanied by predisposition to frostbites. Therefore, cancer-associated frostbite (CAF) should be considered in parallel. As an example, an atypical case of foot frostbite has been reported in a patient with chronic lymphocytic leukemia (CML). In this report, CML was introduced as a sensitizing factor for the development of frostbite.[18] In addition, cases with vasoactive-secreting tumors, such as pheochromocytoma patients, can be accidentally detected with a typical frostbite.[19]

Cold hypersensitivity, namely chilblain and perniosis, rather than true frostbite, has also been associated with some hematologic malignancies, specifically leukemias.[20–23] The association of chilblain lupus erythematosus and preleukemia has been presented in a significant number of cases.[24] Pernio, due to the blast crisis phase of acute B-cell lymphoblastic leukemia has been observed in a 5-year-old girl. Notably, treatment of the underlying disease fully suppressed the pernio symptoms.[25] Along with leukemias, there are case reports for the co-occurrence of Hodgkin lymphoma and this rheumatologic malady as well.[26] Even solid tumors can induce such complications. Contrary to the majority of case reports in this field, chilblains on feet have been detected as a metastatic presentation of breast adenocarcinoma in a 45-year-old female patient.[27]

Iatrogenic frostbite can also occur during the therapeutic procedures for cancer therapy. For example, cryoablation of superficial musculoskeletal tumors has been associated with frostbites.[28] The same report is available for a patient with mediastinal metastasis of

squamous cell carcinoma who had used protective frozen gloves for the prevention of docetaxel-induced onycholysis skin toxicity.[29] Similar reactions have been observed with the utilization of cold caps for chemo-induced alopecia prevention.[30] Furthermore, in a papilloma excision procedure on the face, periocular frostbite as an unusual site was unintentionally provoked due to the administration of ethyl chloride vapocoolant spray for local analgesia induction.[31] Chilblain lupus-like cutaneous reaction as a side effect of pembrolizumab – therapy for oropharyngeal carcinoma in Japanese female patients has been reported too.[32]

CONCLUSION AND SUMMARY

Cancer should be considered a potential long-term adverse effect of acute frostbites. Continued, recurrent, or incomplete wound healing at the site of frostbites is always the hallmark that gives the clinicians clues for further pathologic authentication of FAC. Skin is the most common tissue for this complication and lesions on lower limbs, especially those on heels, have been more associated with cancerous outcomes.

However, the association between frostbite and cancer can be bilateral. There are scientific observations that demonstrate cancer as the initiating factor for frostbite predisposition or symptomatology. Considering the abovementioned facts, three different cancer-induced situations can cause cold-related injury or, in this context CAF. First, the tumor itself can disturb end-organ circulation through secreting vasoactive mediators. A telling sample in this regard is pheochromocytoma. Second, cancer therapies can directly induce frostbite. Both chemotherapeutic agents, such as pembrolizumab and surgical cryoablation techniques, have frostbite in their adverse effect lists. And finally, protective measures that act through decreasing temperature against chemotherapy toxicities can be accompanied by frostbite. To our knowledge, there is no study in the medical literature that examined cancer propensity of CAF lesions.

RECOMMENDATIONS

a. Frostbite is not a life-threatening occasion, according to the statistics, but the development of cancer can significantly affect the patient survival and quality of life. Therefore, meticulous follow-ups and wound or scar checkups for the affected patients are mandatory, until full recovery. All efforts have to be made to treat these wounds through pharmacological or surgical approaches. If complete wound healing is not expected, considering amputation as a last resort will be valuable.
b. The target population of patients for on-time diagnosis should be kept in mind among all medical practitioners. Enough attention should be paid to specific populations which have been or will be at high risk for such pathologies, such as warzone veterans or the refugees who are mobilized from harsh climates such as Ukraine, especially during the cold seasons. Furthermore, those who attend winter sports and are affected by frostbite are a growing population that should be screened more efficiently.[33]
c. Coexistence of frostbite and certain lymphoproliferative or neoplastic disorder is announced to bear poor prognostic outcomes for the affected patients.[34] Considering the high frequency of reports about cancer or leukemia-associated frostbite, chilblain, or pernio,[35] some authors have proposed that this co-pathology might be induced through blood hyperviscosity and stasis due to interference of malignant cells and gamma globulins in such morbid situations.[36] Furthermore, many diseases affecting skin microvasculature, including Kaposi sarcoma, can mimic the common presentations of rheumatologic chilblain, and this fact has to be considered in differential diagnosis steps.[37] All these facts need to be assessed through well-designed clinical studies because the results might be lifesaving for the affected patients. In addition, any suspicious case with low threshold cold injury must be appropriately examined for the coexistence of common cancers in this specific field.
d. In a study from Kazakhstan, where generally a cold climate is predominant, frostbite has been presented as the causative element in basal cell carcinoma and squamous cell carcinoma of the skin.[38] Because these types of cutaneous pathologies are generally ultraviolet induced, taking the cold climate into account as a risk factor within specific geographic locations with a high prevalence of skin cancers will be constructive in establishing preventive practice guidelines besides sun protective strategies for nationwide populations.

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