



## **Skin Rashes Due to Chemotherapy & Immunotherapy in Cancer: A Brief Description**

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### **ABSTRACT**

*According to studies, SR is the most prevalent sign and symptom found in patients who all underwent CT and IT. These patients all had the same condition. Numerous studies have shown that these SRs have a substantial detrimental impact on patient treatment, which may call for suspensions or adjustments to the therapy being administered. In addition to this, they could have an effect on the patients' mental health as well as their general well-being. The importance of prevention and identification at an early stage cannot be overstated in terms of our efforts to mitigate the effects of these R. Thus, in our review we have tried to discuss about CT&IT in terms of clinical manifestations, histopathology and future aspect.*

**Key words:** CT, IT, Clinical Manifestation, Histopathology, Future Direction, SR

Received 28.09.2023

Revised 20.10.2023

Accepted 30.11. 2023

### **INTRODUCTION**

Various studies have been concluding that rashes on the skin are quite prevalent in cancer patients who are receiving chemotherapy (CT) and immunotherapy (IT), and these rashes (R) have a substantial negative impact on the patient's quality of life as well as the success of their treatment.[1] Besides that, research has shown that R are one of the most common and easy-to-see side effects of IT and CT drugs, like immune checkpoint inhibitors (ICIs) and CT.[2, 3] Studies have concluded that these unfavorable reactions might vary in intensity from moderate to severe, necessitating a change in the initial treatment method as well as the supervision of a trained medical expert.[4] Studies have concluded that CT-induced SR can manifest in various forms, depending on the specific CT chemicals employed.[5] As an example, targeted therapies like epidermal growth factor receptor (EGFR) inhibitors can cause side effects on the skin like papulopustular eruptions and xerosis [6]. However, studies have shown that it should be noted that taxanes may lead to onycholysis and acral erythema [7]. In addition to this, studies have shown that, in order to ensure prompt action and effective management of SR, it is crucial to identify them early and make an accurate diagnosis [8]. In addition to this, studies have shown that the occurrence of SR is a common side effect of IT, specifically associated with the use of anti-programmed cell death protein 1 (PD-1) and anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) antibodies [9]. So, research has also shown that the rashes often show up as maculopapular eruptions, lichenoid responses, or a loss of pigmentation like vitiligo[10]. Addition to this, studies have also concluded that these include T-cell activation and how they interact with immunological checkpoints.[11] On top of that, studies have found that immunologically-mediated cutaneous toxicities may happen when immunological tolerance is broken [12]. Thus, in our review we have tried to discuss about CT&IT.

### **CLINICALLY MANIFESTATION FOR CT [13,5,14,7,15,11,16]**

1. Acne Vulgaris
2. Erythematous Papule
3. Pastule
4. Xerosis
5. Acral Erythema
6. Palmar –plantar erythrodysesthesia
7. Hand-foot syndrome
8. Onycholysis
9. Nail plate

Furthermore, various studies have been concluding that , R can be categoried on the bases of clinical & histological characteristics using specific toxicity criteria of CT induced skin toxicity (STRICT) .[16]

### **CLINICALLY MANIFESTATION FOR IT [11,12,17,18,19]**

Studies have shown that the treatment of SR brought on by immunotherapy might be difficult since traditional therapies don't always provide the effects that are expected. Recent developments, on the other hand, have shown that there is potential for the creation of creative ways. Researchers have found that specific medicines, like Janus kinase (JAK) inhibitors, can help treat skin problems caused by the immune system. Besides that, studies have also concluded that biologics like antibodies against interleukin (IL)-6 and IL-17 might be able to treat the serious skin problems that come with IT. Additional research is required to evaluate the efficacy and safety of these revolutionary therapeutic techniques, as well as to uncover prospective biomarkers for individualized care.

### **HISTOPATHOLOGY FOR SR [20]**

Studies have been proving since ages that after CT &IT therapy 2 different types of involvements were seen histopathologically i.e. direct involvement and indirect involvement.[22]

#### **DIRECT INVOLVEMENT [20]**

- 1. Skin to Viscera**
  - a) Cutaneous T-cell lymphoma
  - b) Histiocytosis X
  - c) Mastocytosis
  - d) Kaposi's Sarcoma
- 2. Viscera to Skin**
  - a) Metastatic Carcinoma
  - b) Lymphomas & Leukemias
- 3. Skin to Skin**
  - a) Paget's Disease
  - b) Extramammary Paget's Disease

#### **INDIRECT INVOLVEMENT [21]**

- 1. Inherited Syndrome**
  - a) Cowden 's Disease (Multiple Hamartoma Syndrome)
  - b) Gardener's Syndrome
  - c) Peutz -Jeghers Syndrome
  - d) Cronkhite -Canada Syndrome
  - e) Torre's Syndrome
  - f) Howel -Evans Syndrome (Tylosis)
  - g) Multiple Mucosal Neuromas Syndrome
  - h) Von Racklinghausen's Disease(Neurofibromatosis)
  - i) Immunodeficiency Syndrome
- 2. Hormone Secreting Tumors**
  - a) Ectopic ACTH Syndrome
  - b) Carcinoid Syndrome
  - c) Glucagonoma Syndrome
- 3. Proliferative & Inflammatory Dermatoses**
  - a) Hypertrichosis Lanuginosa
  - b) AcanthosisNigricans
  - c) Leser-Trelat Sign
  - d) Bazex's Syndrome
  - e) Punctate Palmer Keratosis
  - f) Bowen's Disease
  - g) Primary Amyloidosis
  - h) Sweet's Syndrome
  - i) Infectious Disorder
  - j) Dermatomyositis
  - k) Digital Clubbing Coagulopathies
  - l) Figurate Erythemas
  - m) Blistering Diseases

## **CYTOTOXIC CHEMOTHERAPY**

Studies have concluded that it is vital that people in charge of their care identify and address these problems in order to maintain the quality of life of cancer patients who are already suffering from physical and psychological illnesses. Studies have concluded that this section provides a short overview of the most prevalent dermatological side effects generated by cytotoxic chemotherapeutics. Studies have concluded that the effects that are highlighted include those that are comparable across drug types as well as noteworthy drug-specific symptoms. Studies have also shown that alkylating compounds, antimetabolites, antitumor antibiotics, mitotic inhibitors, and topoisomerase inhibitors are some of the different types of cytotoxic drugs that this article talks about.[21]

### **Alkylating Agent**

Studies have concluded that alkylating agents have proven to be highly effective in treating various types of cancer, including solid tumors and blood-related malignancies. Additionally, studies have also concluded that alongside traditional alkylating agents such as cyclophosphamide, ifosfamide, and thiotepa, this category of medications also encompasses modern platinum-based treatments like cisplatin and carboplatin.[22]

### **Classical Alkylating Agent**

According to studies, traditional alkylating agents most frequently cause hyperpigmentation; however, the signs and symptoms of this toxicity vary depending on the drug. Additionally, studies have found that patients whose cyclophosphamide treatment causes hyperpigmentation may develop patches on their palms, soles, and oral surfaces.[23] Studies have also concluded that if you are exposed to ifosfamide, you are most likely to develop hyperpigmentation in the flexural areas, hands, feet, and scrotum of your body.[23] Studies have also concluded that other possible locations include the genital area. Ifosfamide and thiotepa are two further examples of chemicals that have the capability of causing hyperpigmentation underneath blocked areas. [24,25] Furthermore, studies have concluded that in the majority of instances, hyperpigmentation goes away on its own and does not need treatment, regardless of the drug that was responsible for creating it in the first place.[21]

### **Platinum Agent**

According to studies, the use of platinum medicines, such as traditional alkylating agents, can sometimes lead to hyperpigmentation in certain areas. However, studies have concluded that patients using platinum medications are more likely to experience type I hypersensitivity reactions. Moreover, studies have concluded that severe reactions may manifest with symptoms like itching, redness, hives, abdominal pain, and anaphylaxis, which typically occur shortly after the infusion. Fortunately, these symptoms can be effectively managed with antihistamines and corticosteroids. Some investigators recommend intradermal skin testing before treatment due to its high predictive value for this response and quick performance. [5]

### **Antimetabolite**

According to studies, antimetabolites inhibit the use of key chemical mediators in normal metabolism, which in turn slows the growth of tumors and puts a halt to cell division. There are a few cutaneous toxicities that are shared by the various drugs that belong to this class, and it is important to be aware of them.[21]

### **Generalized Rash & Bullous Reaction**

According to studies, purine analog cladribine is linked to a generalized maculopapular rash in the context of the treatment of hematologic malignancies.<sup>6</sup> Many studies have also shown that gemcitabine can cause hair loss, pseudocellulitis, intertriginous and pseudosclerodermatous reactions, and maculopapular lesions. Gemcitabine is an analog of deoxycytidine that is used to treat solid tumors.[22] In addition to this, studies have also concluded that pemetrexed is a folate analog that is known to induce certain toxicities. Studies have also concluded that these toxicities include periorbital and lower extremity edema, as well as generalized rash.[26] In conclusion, many studies show that the purine analog fludarabine can cause a widespread maculopapular rash. In addition to the above, studies have also concluded that autoimmune blistering diseases can be distinguished from other types of blistering by the painful erosions of the mucosa and bullae on the skin. Studies have also found that stopping pharmacotherapy and giving immunosuppressants are both necessary to treat this illness.[27]

## **HFS**

Some studies have found that the chemotherapy drugs fluorouracil, which is a pyrimidine analog, and its prodrugs, capecitabine and tegafur, are often the ones that cause hand-foot syndrome (HFS). Studies have also concluded that there is a chance that esicles and bullae may develop and desquamate. [22, 28] Studies show that keratolytics, analgesics, and topical steroids can be used to treat HFS grades 1 and 2, but not grade 3. For grade 3, the person needs to stop taking drugs. On the other hand, repetition in succeeding cycles is rather usual. Studies have further concluded that therapy termination and dose reduction do, in

fact, result in improvement. It is not limited to only antimetabolites; rather, HFS is often linked to doxorubicin and cytarabine.[21]

### **OTHER DERMATOLOGIC ADVERSE EVENTS**

According to some studies, capecitabine and tegafur mostly cause hyperpigmentation in the acral area, while fluorouracil-induced hyperpigmentation shows a wider range of clinical signs. Studies have also found that antimetabolites can cause changes in the nails, such as melanonychia, onycholysis, paronychia, and onychomadesis. Researchers have also found that photosensitivity, inflammation of actinic keratosis that was already there, and radiation recall are common. [22,23]

### **ANTITUMOR ANTIBIOTIC**

According to some studies, anticancer antibiotics differ from traditional antibiotics in that they function as anticancer agents by disrupting DNA replication and consequently inhibiting cell division. Studies have concluded that conventional antibiotics are employed for the treatment of bacterial infections, while antitumor antibiotics are utilized for the treatment of cancer. Studies have found that these treatments, like anthracyclines and bleomycin, have a lot of serious side effects, such as heart problems and a loss of myeloid cells, which can be fatal. Nevertheless, studies have also concluded that the adverse effects on the skin may also restrict the effectiveness of the treatment.[21]

#### **Doxorubicin & Daunorubicin**

Some studies say that anthracycline-induced hyperlipidemia syndrome (HFS) looks a lot like an antimetabolite-associated illness and can be treated in a way that is similar to how that illness is treated.[29] Studies have also shown that freezing the hands and feet during the drug infusion may help keep these areas from becoming toxic because liposomal doxorubicin is lost in sweat. Studies have further shown that this is due to the fact that sweat is released via the skin. In addition to this, mucositis and baldness may appear.[30] According to the studies, the vesicant nature of these drugs can also cause extravasation damage, which usually needs surgery because of the ulceration and necrosis that happen in the area. In addition, studies have found that the medication might be to blame for this damage. Additionally, studies concluded that mitotic inhibitors and platinum alkylating agents are two other significant causes of such severe extravasation reactions.[31]

#### **Bleomycin**

Some studies say that bleomycin is toxic to organs such as the lungs and the skin because these tissues do not contain the enzyme that deactivates it. Studies have also concluded that flagellate dermatitis occurs in 30% of patients and may appear anywhere from a few hours to many months after getting an infusion. [32] In addition to this, studies also concluded that, with the discontinuation of treatment or corticosteroids, patients may also develop localized sclerosis, which may disappear.[33] Furthermore, studies have shown that drug discontinuation is also necessary if Raynaud's phenomenon occurs because of the risk of digital ulceration and fingertip necrosis.[29,34]

### **IMMUNOTHERAPY**

Some studies said that in their infancy, immunomodulatory agents have come a long way owing to the advancement of scientific information on the host's immune response to cancer. Studies have shown that ICIs can increase the activity of T-cells, which helps the body's natural anticancer response. Studies have also found that the goal will be reached by lowering the surface receptors that normally stop T lymphocytes from killing cancer cells. This will make it possible for tumor cells to be tolerated.[35] As an additional kind of cancer therapy, ICIs are used in the treatment of a wide variety of solid malignancies. Studies have also concluded that there are ICIs that specifically target CTLA-4, such as ipilimumab and tremelimumab. There are also ICIs that target anti-PD-1 proteins, such as nivolumab and pembrolizumab. Also, research has shown that there are ICIs like atezolizumab, durvalumab, and avelumab that target anti-PD-L1 proteins. These ICIs may be classified as one of three distinct types.[36] Furthermore, research has shown that the one-of-a-kind mechanism that these immunomodulatory drugs work on is also the one-of-a-kind mechanism that causes the wide range of bad effects that these drugs cause. Furthermore, studies have also concluded that up to sixty percent of treated patients may suffer immune-related adverse events, often known as irAEs. The substantial activation of cytotoxic T cells is what has caused these events.[36]

### **MACULOPAPULAR RASH**

Some studies say that eruptions typically have a centrifugal distribution and might manifest themselves very immediately after therapy has begun.[37] Studies have also concluded that systemic antihistamines and topical high-potency corticosteroids are two types of medications that may be used to treat a variety of skin conditions, including eczema, psoriasis, and psoriatic arthritis. Other than this, studies revealed that

oral corticosteroids are reserved for disorders of grade 3 or worse, and withholding treatment is very uncommon. [38,39]

### **PRURITUS**

According to research, the most common secondary irAE is pruritus. Pruritus may precede the rash or develop on skin that otherwise seems normal. Studies have also shown that the greatest incidence is seen with ipilimumab or when numerous ICIs are administered in combination.[38] Other studies have concluded that chronic pruritus may be a source of psychological suffering, even when it is not physically harmful. Studies have also found that systemic agents like gabapentin, doxepin, mirtazapine, and aprepitant have been used successfully in their treatment.[40]

### **LICHENOID REACTION**

According to research, lichenoid reactions are the most common in patients treated with anti-PD-1/PD-L1 agents. Unlike the ICI-associated maculopapular rash, which appears days to weeks after starting therapy, lichenoid reactions appear weeks to months later. Furthermore, studies have shown that, as with sporadic lichenoid reactions, treatment for lichenoid reactions begins with topical steroids and progresses to oral steroids, acitretin, or phototherapy if required. [41,38]

### **AUTOIMMUNE SKIN DISORDER**

Researchers say that the activating immunomodulatory effects of ICIs are very important for their ability to fight cancer, but they can also hurt healthy tissue, which can lead to a number of autoimmune skin problems. Studies have also concluded that there is a possibility of pre-existing illnesses becoming active again, as well as new diseases developing. Furthermore, there are numerous autoimmune disorders that have been identified, including dermatomyositis, vasculitis, Sjögren's syndrome, Crohn's disease, rheumatoid arthritis, thyroiditis, and autoimmune thrombocytopenic purpura. [38]

### **VITILIGO**

Studies have concluded that patients with melanoma are typically seen to have the highest incidence of ICI-induced vitiligo, which can occur at a rate of up to 25%. Studies have also shown that months of treatment result in the development of lesions, which are typically symmetrical and present on both sides. In addition, studies have shown that preexisting nevi, hair on the eyebrows, eyelashes, and scalp may all become paler. [63] Studies have also concluded that vitiligo, unlike other irAEs, is rarely curable due to the wide spread of lesion persistence following treatment termination. [42,43]

### **FUTURE DIRECTIONS**

According to studies, there are still some knowledge gaps to be filled regarding the causes of and treatments for SR brought on by CT and IT. Future studies have concluded that it should primarily concentrate on deciphering the underlying processes of specific drug-induced skin rashes and identifying risk factors for their occurrence. Studies have also concluded that, for the purpose of bettering the treatment of patients, it is important to research the effects and results of these skin rashes over a longer period of time. To give uniform guidelines for the prevention, early identification, and treatment of these cutaneous side effects, prospective clinical studies and collaboration across several locations are essential. Studies have also concluded that it may be easier to implement individualized solutions to reduce the effects of skin rashes on cancer patients if they are developed through joint efforts [1, 5,44,45].

### **CONCLUSION**

Studies have concluded that common skin rashes that occur as a result of chemotherapy and immunotherapy during cancer treatment can have a significant impact on both the effectiveness of the treatment and the overall well-being of patients. It is crucial to promptly identify, diagnose, and treat these adverse events in order to provide the best possible care for patients. These three factors are crucial for ensuring optimal patient care. In order to minimize the negative impact of these skin rashes on cancer patients' treatment adherence and quality of life, it is crucial to implement effective preventive measures, advanced treatment procedures, and comprehensive support networks. Continued research and collaboration among medical professionals will greatly aid in the creation of customized approaches to tackle the difficulties associated with skin rashes during cancer treatment.

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#### CITATION OF THIS ARTICLE

Nikhil Girish, Navya Pandey, Prajakta Sharma. Skin Rashes Due To Chemotherapy & Immunotherapy in Cancer: A Brief Description. *Bull. Env. Pharmacol. Life Sci.*, Spl Issue [2]: 2023: 227-233.