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Original Research Article

A Cross-Sectional Study of Mucocutaneous Adverse Reactions in Patients on Anticancer Drug Therapy

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Conflict of interest: Nil

Abstract

Background: The discovery of newer anticancer drugs over the last few decades has led to an improved life expectancy in patients diagnosed with carcinomas. The diagnosis of mucocutaneous reactions in such patients is especially difficult, given the complexity of their illness and immunosuppressed state leading to varied clinical presentation as well as due to the combination protocols used for the treatment of carcinomas.

Aims: This study was undertaken to know the spectrum of various mucocutaneous adverse reactions in patients undergoing chemotherapy.

Materials and Methods: This was a cross-sectional study carried out from 1st February 2015 to 30th June 2016 comprising of 98 patients attending the cancer centre of a tertiary health care hospital. The study included patients with different malignancies presenting with adverse effects involving skin, mucous membrane and appendages due to anti-cancer drugs.

Results: The most common adverse effect was anagen effluvium which was observed in 35.7% of patients, nail changes in 23.4%, xerosis in 15.3%, and other less commonly seen dermatological manifestations included hyperpigmentation in 8.16%, photosensitivity in 3.06% and erythroderma in 3.06% patients. The most common chemotherapeutic agent responsible for mucocutaneous adverse effects was paclitaxel which was used in 33.6% of the total number of patients in our study, followed by cyclophosphamide used in 16.3% patients, 13.2% patients treated with cisplatin, and other drugs like carboplatin and adriamycin were also responsible for adverse effects. Limitations: The limitation of our study was the inability to find a significant association of a specific drug as the cause of particular mucocutaneous reaction as the chemotherapy consisted of various combination protocols.

Conclusion: We conclude that mucocutaneous changes are a common side effect of chemotherapy. Counselling the patient prior to the initiation of chemotherapy would increase alertness thereby improving their quality of life.

Keywords: Chemotherapy, Adverse Drug Reactions, Anagen Effluvium, Cancer.

Introduction

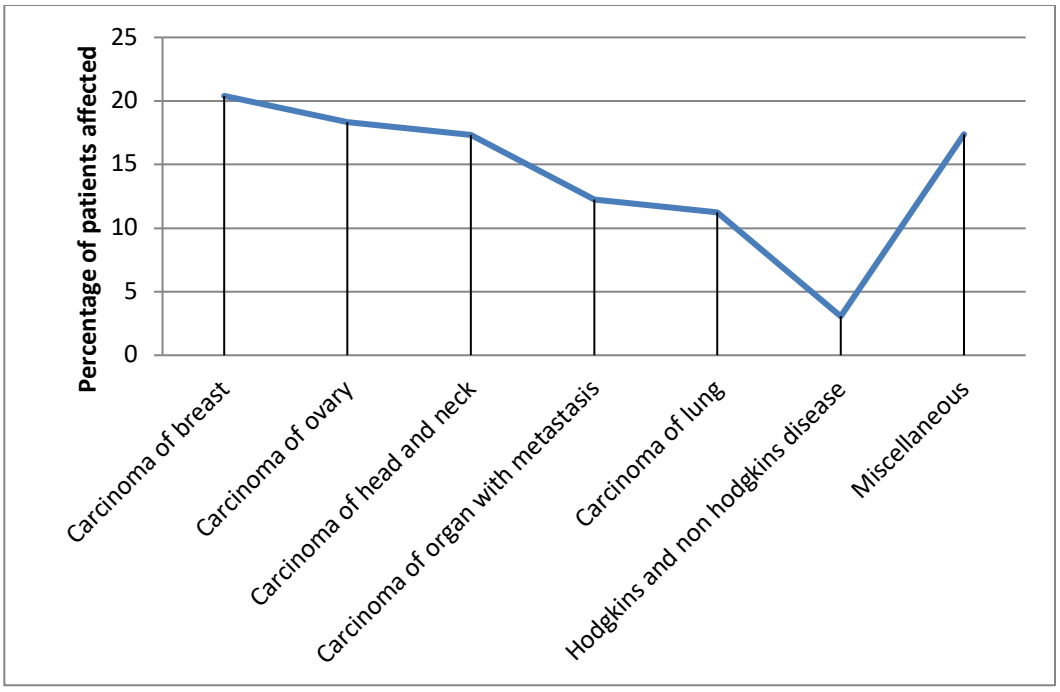
Since 1949, more than 100 chemotherapeutic drugs have been approved for oncologic use, more than half of these approvals being in the last decade.[1] Use of chemotherapeutic drugs is associated with several adverse effects ranging from mild nausea, fatigue, diarrhoea, constipation, vomiting, pain to fatal myelosuppression.

The skin, mucous membranes, sebaceous glands, sudoriparous glands, hair and nails are tissues with rapid cellular proliferation, and thus susceptible to adverse reactions (toxic or hypersensitive) resulting from systemic chemotherapeutic treatment. Chemotherapy results in side effects such as alopecia, mucositis and nail alterations. Cutaneous manifestations are frequently associated with a particular drug or groups of drugs, resulting in poor compliance of the patients and interruptions or discontinuation of antineoplastic therapy. [2,3] Mucocutaneous adverse reactions may also significantly reduce the quality of life of oncological patients. During the last decade, a number of studies have demonstrated that drug induced morbidity and mortality is one of the major public health problems.[4] Moreover, these drug regimens may cause significant morbidity and psychologic distress to the patient and should be treated with the appropriate level of concern. This study was conceived to monitor suspected mucocutaneous adverse effects with anticancer drugs in a focused manner. The objective was to investigate the adverse muco-cutaneous effects associated with the use of different chemotherapeutic drugs.

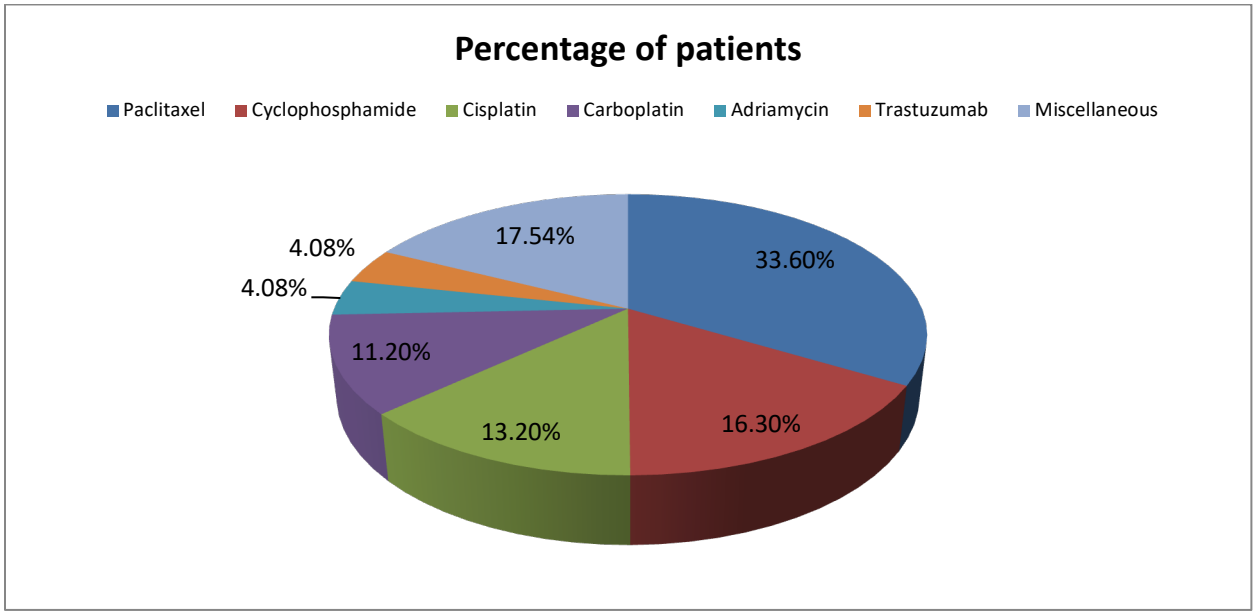
Material and Methods

This was an observational study carried out from 1st February 2015 to 30th June 2016 which included a total of 98 patients attending cancer centre of a tertiary health care hospital in the western Indian state of Rajasthan. Our study included patients of both sexes who suffered from adverse effects involving skin, mucous membrane and appendages which began after initiation of the anti-cancer drugs in all histologically and cytologically proven cases of malignancy. Patients with previously existing mucocutaneous symptoms, history of radiotherapy, pregnant and lactating females, diagnosed cases of HIV, Hepatitis B and other immunocompromised conditions apart from malignancy were excluded from this study. The mucocutaneous adverse events were evaluated on the basis of the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 and only those falling under above criteria were included in the study. [5] General physical examination along with thorough examination of skin, mucosa and nail was carried out for all patients. Complete haemogram, liver function tests, urine routine examination and other investigations (as advised by the oncologist) were documented.

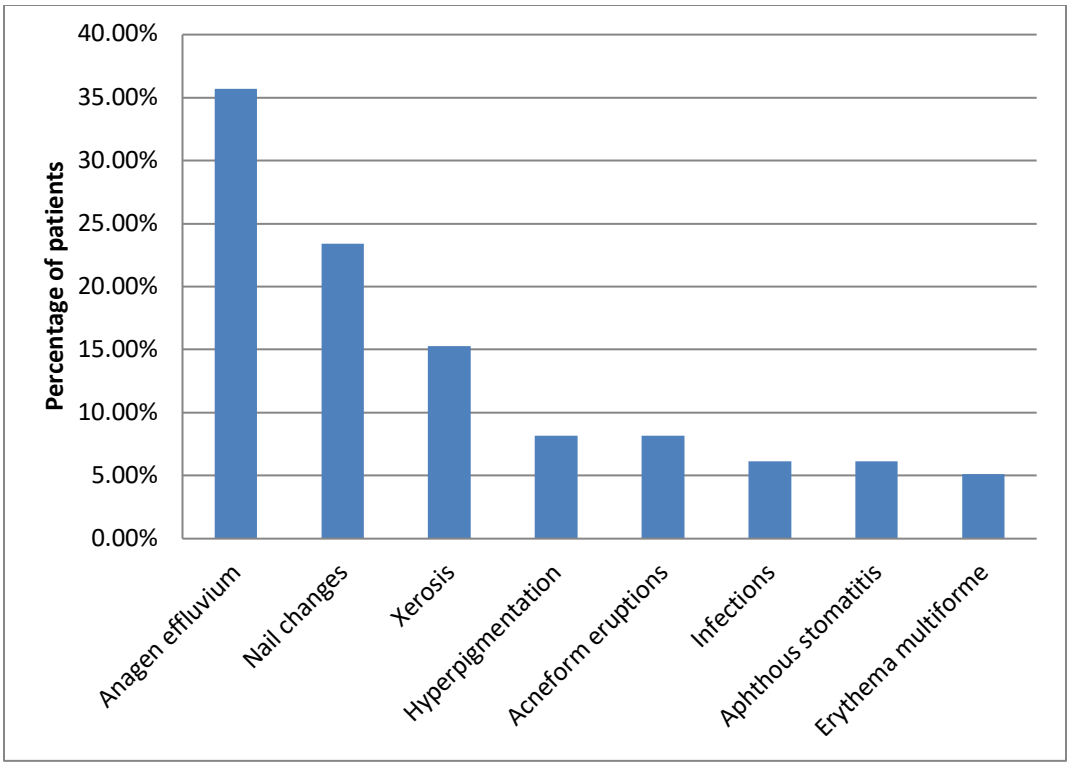
Results



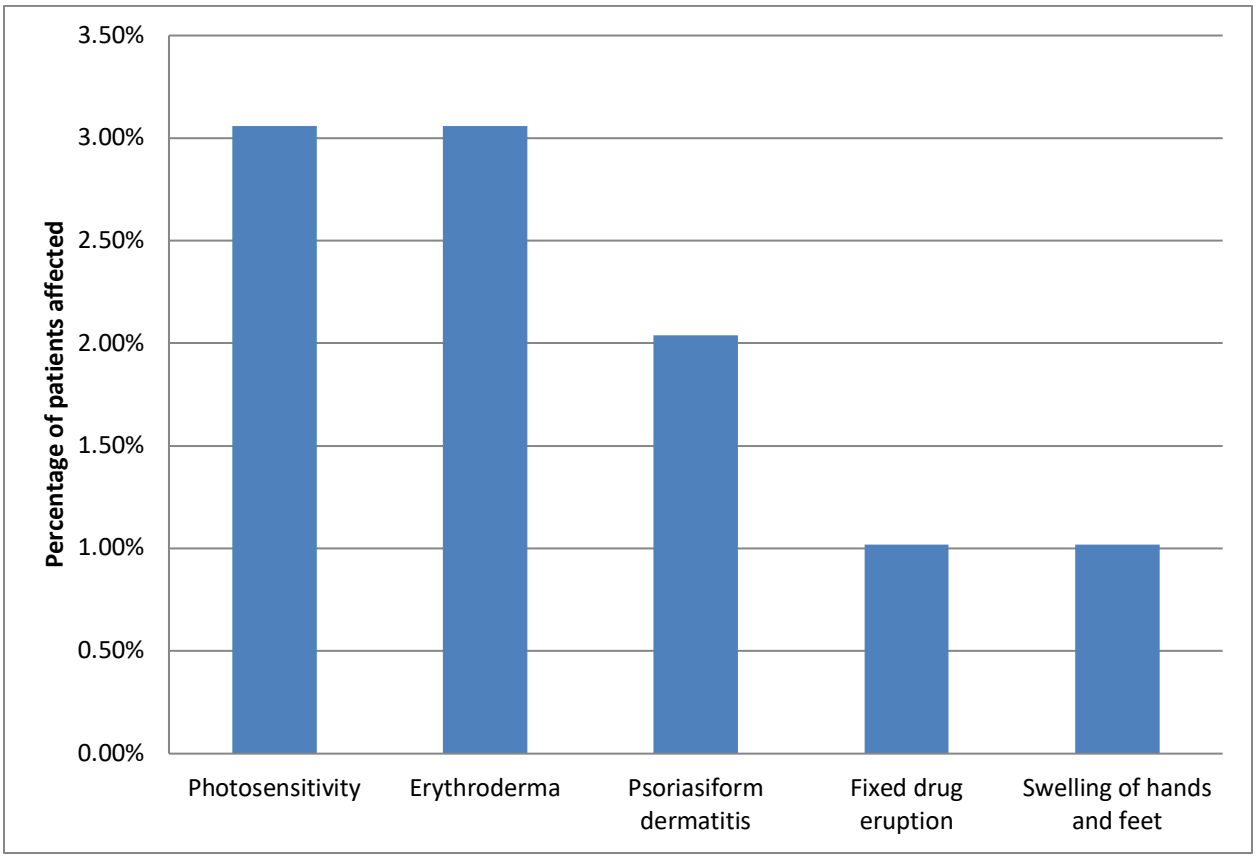
Graph 1: Type of carcinomas



Graph 2: Commonly used chemotherapeutic agents causing mucocutaneous adverse effects



Graph 3: Descriptive data of most common dermatological manifestations.



Graph 4: Descriptive data of uncommon dermatological manifestations.

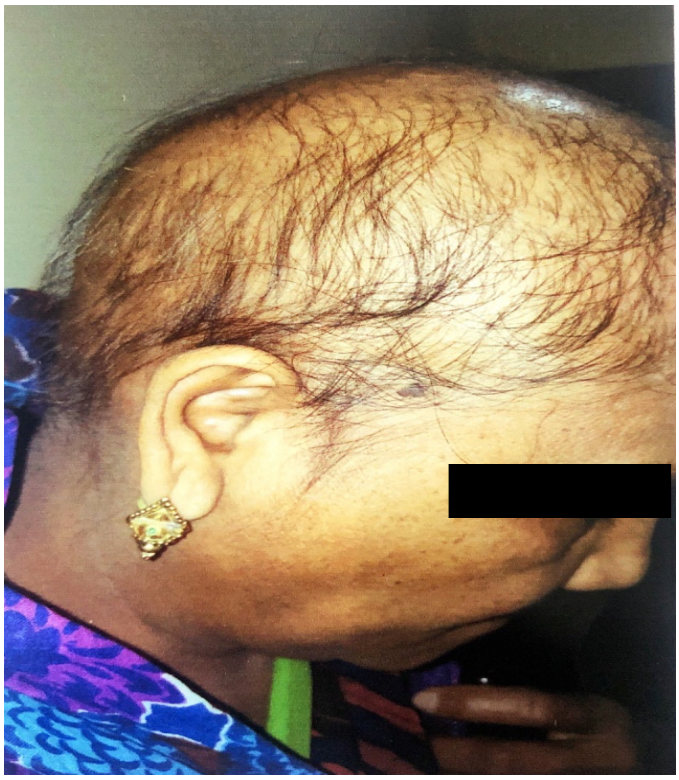


Figure 1: Anagen effluvium.

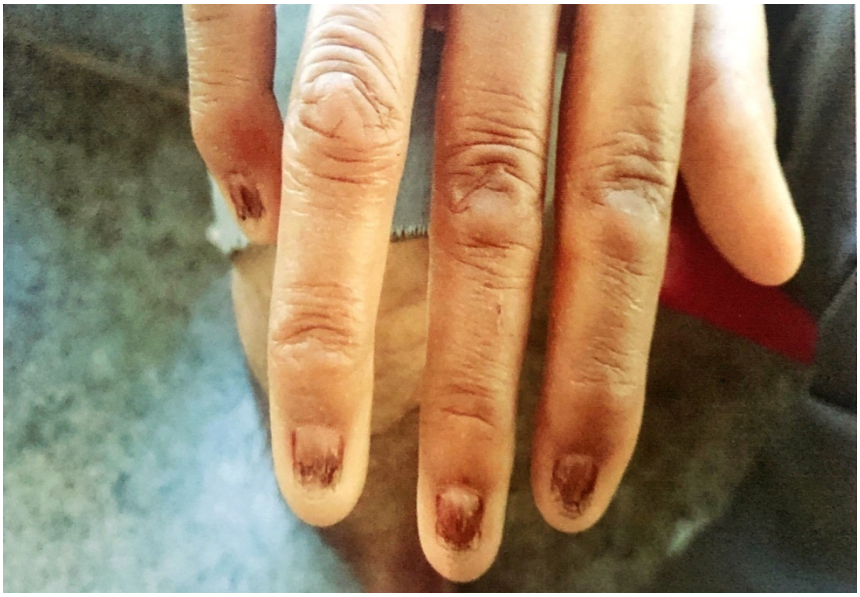


Figure 2: Onychodystrophy in a male patient of germ cell tumor treated with cyclophosphamide.

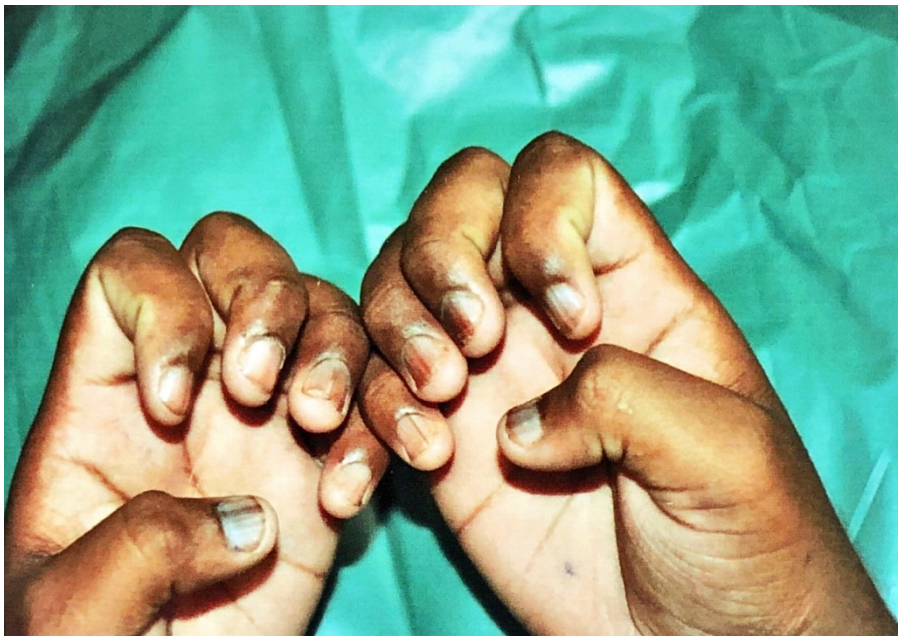


Figure 3: Melanonychia seen in female patient treated with cyclophosphamide.

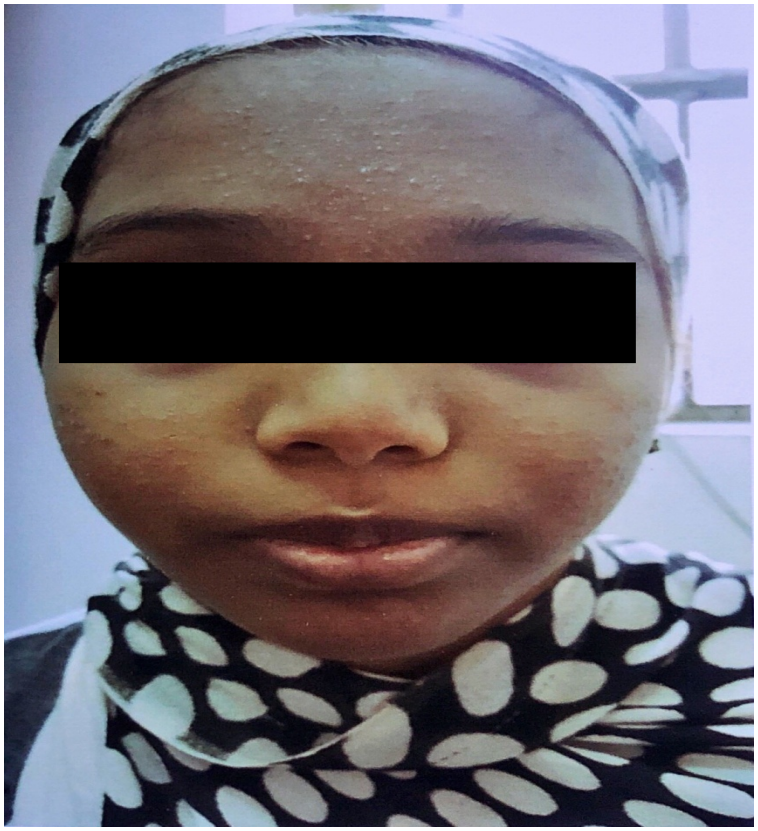


Figure 4: Acneform eruptions seen in female patient treated with paclitaxel.

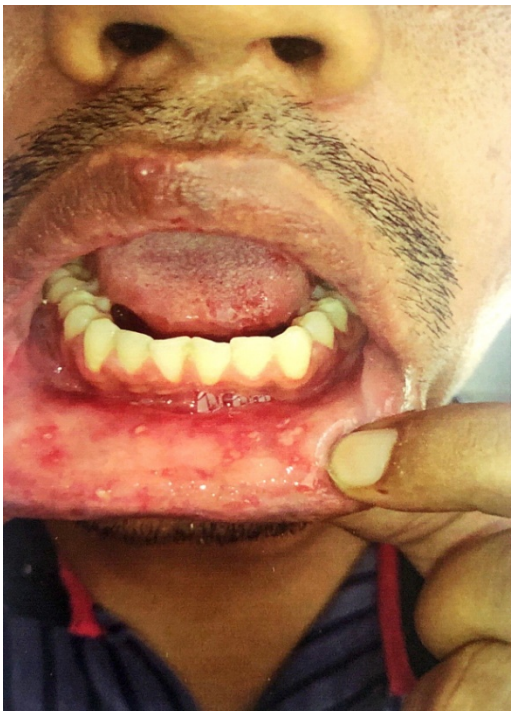


Figure 5: Recurrent aphthous ulcers seen in a male patient of sarcoma treated with Etoposide.

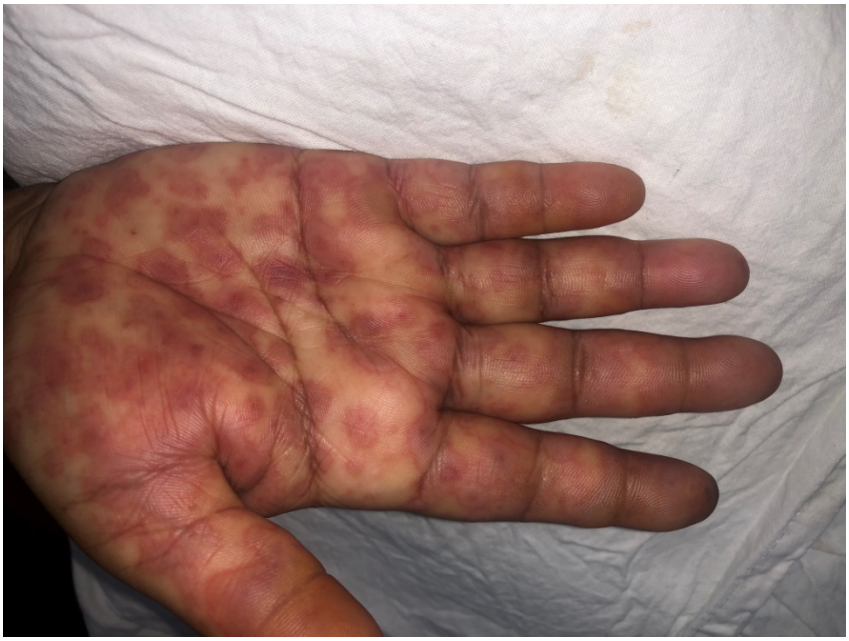


Figure 6: Erythema multiforme on lower limb of patient of carcinoma lung treated with Imatinib.

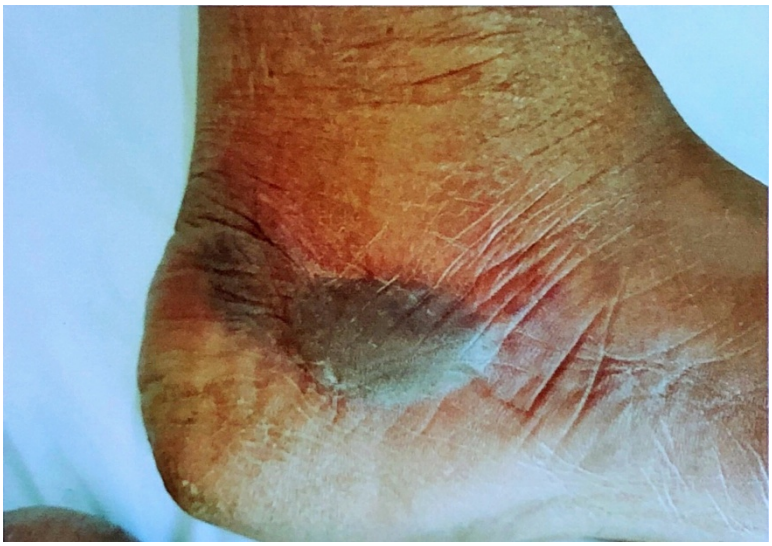


Figure 7: Fixed drug eruption in patient of acute lymphoblastic leukemia treated with vincristine, daunorubicin and methotrexate.

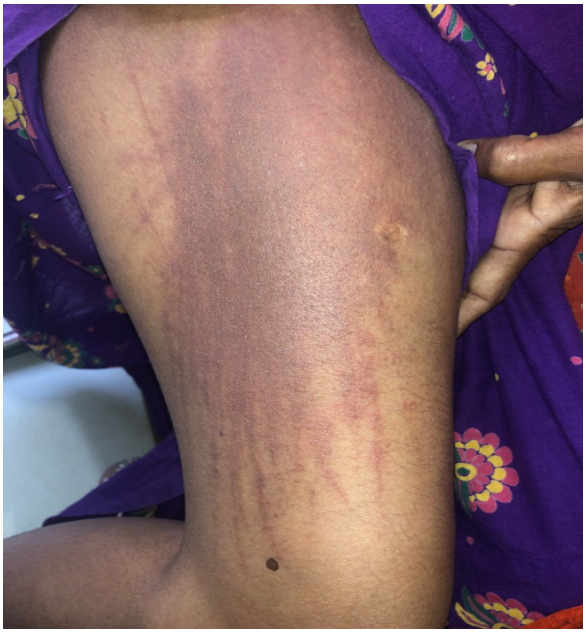


Figure 8: Flagellate dermatoses in patient of germ cell tumor treated with bleomycin.

Out of the 98 patients included in the study, the most common malignancy was carcinoma of breast (20.4%) with mean age of 44.8 ±13.4 years, 18.36% patients were of carcinoma of ovary with a mean age of 45.77 ±13.2 years, 17.34% patients of carcinoma of head and neck with mean age of 50.64 ±9.4 years, followed by 12.24% patients of metastatic carcinoma with a mean age of 59.83 ±16.45 years and 11.22% patients of carcinoma of lung with a mean age of 68 ±6.57 years. [Graph 1]

The most common chemotherapeutic agent causing mucocutaneous adverse effects was paclitaxel which was used in 33.60% of the total number of patients, 16.30% patients were treated with cyclophosphamide, 13.20% patients were treated by cisplatin, 11.20% patients were treated with

carboplatin, and other chemotherapeutic agents used were adriamycin, trastuzumab. [Graph 2] Anagen effluvium was observed in 35.7% of patients, nail changes in 23.4%, xerosis in 15.3%, and less commonly seen dermatological manifestations included hyperpigmentation in 8.16%, acneform eruptions (8.16%), infections (6.12%), aphthous stomatatis (6.12%) and erythema multiforme (5.1%). [Graph 3]

Uncommon dermatological manifestations noted include photosensitivity in 3.06%, erythroderma in 3.06% patients, psoriasiform dermatitis (2.04%), fixed drug eruption (1.02%), swelling of hands and feet have (1.02%) in our study. [Graph 4][Figure 4] [Figure 5]

Discussion

The global burden of cancer continues to increase largely because of ageing and growth of the world population along with increasing adoption of cancer-causing behaviours in economically developing countries.[6] Different modalities for treatment of cancer include radiation, surgery, chemotherapy, hormonal therapy, immunotherapy, biologic therapy and cryosurgery.[7] Anti-cancer drugs usually affect rapidly growing cells and hence, the skin, mucous membrane, hair follicles and nail matrix are the frequent targets of their toxicities. [8]

In our study, the number of females (59.1%) outnumbered the number of males (40.81%), which was contradictory to a study done in North Indian tertiary hospital care centre which showed a male preponderance. [9] This can be attributed to the fact that in our study, the most prevalent carcinomas were breast carcinoma (20.4%) followed by carcinoma of ovary (18.36%). Population belonging to age group 41-70 years was more prone to the development of cancer which was similar to results obtained by Chen *et al*.[12] Anagen effluvium [Figure 1] was the most common adverse effect in this study (35.7%) which is similar to studies done by Kamil *et al* and Chewchanvit *et al*.[8, 11] Hair loss started after the first month of chemotherapy and was seen in patients treated with paclitaxel, carboplatin, cyclophosphamide, and cisplatin which was similar to previous reports.

Nail changes [Figure 2, 3] were the second most prevalent adverse effect in our study seen in approximately 23% of patients, in the form of diffuse and transverse pigmentation in those who were on combined regimens. It was noted that alkylating agents and anticancer antibiotics commonly cause hyperpigmentation. Paclitaxel, cisplatin, oxaliplatin doxorubicin, hydroxyurea, bleomycin, cyclophosphamide, daunorubicin, dacarbazine, and 5-fluorouracil have been reported to cause melanonychia in previous studies and similar findings were found in our study. [10]

In a study conducted by Pavey *et al*, [12] the skin changes seen were acneform eruptions in 5 (27.7%) patients, xerosis in 4 (22.2%) patients, hyperpigmentation in 4 (22.2%) patients, and toxic epidermal necrolysis, hand-foot syndrome, erythema nodosum and supravenous hyperpigmentation in 1 patient each. Our study showed xerosis as a common complaint in 15.3% of patients which is commonly observed in patients receiving the EGFR inhibitors such as geftinib. [13]

Stomatitis [Figure 5] was the most common oral manifestation which occurred as treatment side effect of carcinoma. We found 6.12% of patients had stomatitis,which was similar to a previous study conducted by O`Brien CP. [14]

Our study showed only three cases (3.33%%) of photosensitivity reaction, the frequency of which is consistent with other such studies. [15] Drug reactions in the form of erythema multiforme [Figure 6] and fixed drug eruptions [Figure 7] were seen in 3(3.33%)

and 1(1.02%) patients respectively. Flagellate dermatoses [Figure 8]was seen in 1 patient (1.02%) undergoing chemotherapy with bleomycin. It is an uncommon figurate dermatoses characterized by parallel linear or curvilinear arrangement simulating the marks of whiplashes. The most common chemotherapeutic causative agent is bleomycin, while other drugs like docitaxel, peplomycin and bendamustine have also been known to cause it. [16]

Hyperpigmentation is a common adverse reaction reported with anti-cancer drugs, which may be in the form of diffuse or localized involvement of skin, mucosa or nails. The mechanism remains unknown, but it is postulated to be due to accumulation of drug in skin or a direct toxic effect on melanocytes stimulating increased melanin production or elevated adrenocorticotropic hormone and melanocyte-stimulating hormone. In our study, pigmentation was seen in patients treated with paclitaxel, oxaliplatin and gemcitabine.

Few side effects not noticed in our study were anaphylactic reactions caused by paclitaxel and docetaxel in 42% of patients on first administration, suggestive of anaphylactoid mechanism[17] and hypersensitivity caused by platinum compounds (cisplatin, carboplatin, and oxaliplatin) typically after completion of several treatment courses, suggesting an immunological mechanism.[18]

Epidermal growth factor receptor (EGFR) antagonists are a new class of chemotherapeutic agents, which commonly cause dermatological side effects. [19,20] The EGFR promotes the differentiation of keratinocytes and follicular cells. Moreover, EGFR-inhibitors tend to inhibit the receptors present on the normal skin as well as when overexpressed in tumor cells. The inhibition of EGFR in normal skin commonly leads to xerosis, papulopustular skin rash and nail alterations. [21]

Antimetabolites like 5-FU and capecitabine have been known to result in hyperpigmentation. This abnormality is also observed in patients with cyclophosphamide and doxorubicin. Cyclophosphamide can cause black longitudinal pigmentation of the nails without any symptoms. [22,23]

Spindle inhibitors, i.e. vinca alkaloids and taxanes, are strictly related to alopecia and other skin diseases such as dermatitis, subacute cutaneous lupus erythematosus, nail abnormalities and ulcerations, and radiation recall. [24]

Radiation recall is an acute inflammatory reaction that occurs on previously irradiated areas of skin and is triggered when chemotherapy agents are administered after radiotherapy. Radiation recall is drug-specific for each individual thus making it impossible to anticipate which patient will react to which drug. Thus, it is a possibility that must be kept in mind with use of any chemotherapeutic agent after radiotherapy. [25]

There is often an overlap of cutaneous clinical manifestations in patients with malignancy related paraneoplastic process and drug induced adverse effect. Patients with paraneoplastic changes tend to improve with chemotherapy, whereas patients with drug-induced adverse effect manifest only after initiation of chemotherapy. In our study, we have tried to rule out patients with malignancy related cutaneous changes by excluding patients with cutaneous involvement prior to the initiation of chemotherapy from the study.

Although both, the newer targeted therapies as well as the traditional anticancer drugs are associated with toxicities of skin, hair, nails, and mucosa; an accurate and early recognition of potential reactions may reduce

the significant morbidity, cosmetic disfigurement, and psychological distress associated with cutaneous adverse reactions due to chemotherapy.

Limitations

The limitation of our study was the inability to find a significant association of a specific drug as the cause of particular mucocutaneous reaction as the chemotherapy consisted of various combination protocols.

Conclusion

We conclude that anagen effluvium was the most common adverse effect seen in 35.7% of the patients presenting with dermatological adversities, followed by nail changes and xerosis. The uncommon side effects seen were fixed drug eruptions, swelling and numbness of hands and feet, erythema multiforme, paronychia and psoriasiform dermatitis. The most common causative therapeutic agents were paclitaxel, cyclophosphamide, cisplatin and carboplatin.

These reactions occur in varying degrees of frequency and severity within each class of chemotherapeutic drugs. An accurate, timely diagnosis and along with early recognition of potential reactions may reduce the significant morbidity. Proper treatment of mucocutaneous drug reactions may allow ideal duration of chemotherapy administration. Counselling the patient before the initiation of chemotherapy may make the patient more alert and also reduce the psychological trauma of unacceptable adversities thus improving the overall outcome of the patient. Cooperation between oncologist and dermatologist is also fundamental to make the patients aware of the possible adverse effects and to implement preventive measures.

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