An Observational Study of Cutaneous Manifestations in Patients on Chemo and Radiation Therapy for Internal Malignancies at Tertiary Care Center

Abstract

Context: Chemotherapy and radiation therapy given to treat internal malignancies may cause cutaneous, hair, nail, and oral mucosal changes. The present study is an effort to know the pattern of cutaneous drug reactions with chemo and radiotherapy. Materials and Methods: Patients of internal malignancies with skin lesions attending the dermatology and oncology OPD/ward were recruited after taking their written consent in vernacular language. A detailed history of skin lesions, malignancies, and treatment was taken. Clinical examination was carried out. Relevant investigations and biopsy were carried out as and when required. Being a descriptive study, age group and gender-wise frequency and percentage were calculated for the treatment of malignancies and dermatosis. Results: The study included 150 patients with 28 different types of internal malignancies, of which 127 (84.66%) patients were treated, 45 (35.43%) treated exclusively with chemotherapy, 16 (12.59%) with exclusive radiation therapy, and 66 (51.96%) with combined chemo and radiation therapy. Total 111 (87.41%) patients received chemotherapy and 82 (64.56%) patients received radiation therapy. Most common internal malignancy was breast carcinoma in 43 (28.67%) cases. Most common chemotherapeutic agent given was paclitaxel to 33 (29.73%) patients. Most common dermatosis associated with exclusive chemotherapy was hand-foot syndrome in 7 (15.55%) cases and with exclusive radiation therapy was radiation dermatitis in 8 (50%) cases. Conclusions: The study was useful in understanding various chemo and radiation therapy-associated dermatosis so that early interventions can be done to prevent further treatment-related adverse effects. Limitation: Small sample size and inability of pinpointing a single drug as the side effect.

Keywords: Chemotherapy, dermatosis, internal malignancy, radiotherapy

Introduction

Chemotherapy, radiotherapy, immunotherapy, and hormonal therapy used to treat cancer patients can cause various cutaneous manifestations along with hair and nail changes. Management of such mucocutaneous adverse reactions have become a vital part in the care of patients, as early recognition and treatment facilitate control and cure of the manifestations, decreasing morbidity and allow further continuation of cancer therapy.

There are studies,1-3 to describe the changes associated with internal malignancies and their chemotherapy-related consequences. Present study is an attempt to determine the pattern of cutaneous manifestations and changes in hair, nails, and mucosal surfaces in patients on chemo and radiotherapy.

Materials and Methods

It was a cross-sectional observational study, approved by institutional ethical committee, no IEC/HMPCMCE/118/Faculty /15/83/2020. Patients of internal malignancies presenting with skin lesions in Dermatology and Oncology OPD/ward were recruited after taking their written consent in vernacular language. A detailed history was taken to collect demographic data, history regarding complaints, type of treatment, onset, duration, and progression of cutaneous lesions with past and family history in prestructured proforma. Clinical examination (skin/hair/nail/mucosa) was carried out and photographs were taken. Relevant investigations (Hemogram/C-reactive protein/ESR/Liver function tests/ Renal function tests/Blood sugar/Lipid

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profile/Vit B12/Dermoscopy/Biopsy/KOH) were carried out as and when required.

Statistical analysis
This being a descriptive study, age group and gender-wise frequency and percentage were calculated for the treatment of malignancies and dermatosis.

Results
Among 150 total patients with internal malignancies, 127 (84.66%) patients were on treatment. Total number of patients who had received chemotherapy was 111 (87.41%) and radiation therapy were 82 (64.56%) [Figure 1].

Chemotherapy
The most common indication for chemotherapy was breast carcinoma in 32 (28.82%) patients followed by buccal mucosal carcinoma in 19 (17.11%) cases [Figure 2]. Most common chemotherapeutic agent used was paclitaxel in 33 (29.73%) patients and cisplatin in 26 (23.40%) patients [Figure 3]. Maximum 52 (46.85%) patients were given 6-10 cycles of chemotherapy [Table 1].

Exclusive chemotherapy: [N-45]
Hand-foot syndrome was the most common dermatosis in 7 (15.55%) cases followed by pruritus in 6 (13.33%) cases. Nail, hair, and oral mucosa were affected in 21 (46.66%), 17 (37.77%) and 13 (28.88%) patients, respectively. Most common nail changes was melanonychia in 13 (61.90%) cases. Hair changes were anagen effluvium in 15 (88.23%) cases and loss of eyebrow hair in 5 (29.41%) cases. Aphthous ulcer was the most common mucosal change seen in 9 (69.23%) cases [Table 2].

Radiation therapy
Total 32 (39.02%) patients were given 21-30 radiation fractions [Table 1] and neck was the most common site in 27 (32.93%) cases. Radiation therapy oncology group (RTOG) acute radiation morbidity criteria were used for grading radiation induced toxicity. Grade-1 (Erythema/epilation/desquamation/decreased sweating) was most common with 40 (48.78%) patients followed by Grade-2 (Bright erythema/patchy moist desquamation/edema) in 13 (15.85%) patients, Grade-3 (Confluent moist desquamation/pitting edema) in 3 (3.66%) patients and Grade-4 had not been noted in any of our patients.

Exclusive radiation therapy [N-16]
Radiation dermatitis [Figure 4] was the most common dermatosis in 8 (50%) cases followed by pruritus and xerosis in 3 (18.75%) and 1 (6.25%) cases, respectively. Nail, hair, and oral mucosa were affected in 5 (31.25%), 1 (6.25%), and 1 (6.25%) cases, respectively. In nails, dystrophy was most common with 2 (40%) cases followed by 1 (20%) case of nail thickening, melanonychia, nail thinning, and paronychia. Anagen effluvium and aphthous ulcer were seen in 1 case (100%) each.

Combined chemo and radiation therapy
Out of all 66 patients, radiation dermatitis followed by xerosis were most common in 26 (39.39%) and 4 (6.06%) cases, respectively. Nail, hair, and oral mucosa were involved in 42 (63.63%), 14 (21.21%) and 12 (18.18%) cases, respectively. Most common nail change was melanonychia in 24 (57.14%) patients. Anagen effluvium was present in

| Number of cycles/fractions | Number of patients on chemotherapy (%) | Number of patients on radiation therapy (%) |
|----------------------------|----------------------------------------|--------------------------------------------|
| 1-5                        | 36 (32.43%)                             | 6 (7.32%)                                  |
| 6-10                       | 52 (46.85%)                             | 19 (23.17%)                                |
| 11-20                      | 17 (15.32%)                             | 13 (15.85%)                                |
| 21-30                      | 6 (5.41%)                               | 32 (39.02%)                                |
| >30                        | 0                                      | 12 (14.63%)                                |
| Total                      | 111 (100%)                              | 82 (100%)                                  |

Table 1: Number of chemotherapy cycles/radiation fractions taken by patients

Figure 1: Treatment protocol
Figure 2: Indications of chemotherapy in internal malignancies
13 (92.86%) patients and oral mucosal hyperpigmentation was present in 7 (58.33%) patients [Table 3].

**Discussion**

Mucocutaneous manifestations of chemo and radiotherapy are very common, resulting in debilitating and life-threatening complications. Toxic effects on skin, hair, and nails can negatively affect the quality of life. It can cause cosmetic disfigurement, psychological distress, and increase the morbidity and mortality, thus leading to interruption or discontinuation of these drugs.[4,5] Newer anticancer drugs have improved the survival rate in cancer patients but are associated with cutaneous toxicities.[3]

In the present study, out of 127 treated patients, 87.40% patients were given chemotherapy similar to Hassan et al.[5] where 72.4% patients were treated with chemotherapy. In other studies,[1,3,6-9] 100% patients were treated with chemotherapy while in Muralidhar et al.[9] 95.27% patients were given chemotherapy [Table 4].

Breast cancer is treated with chemo, radiation, hormonal therapy, surgery or combination of therapies, depending upon the age of patient, benign or malignant potential and metastasis of malignancy. The most common indication for chemotherapy in our study was breast carcinoma (28.82%) while in Menon et al.[1] it was oropharyngeal carcinoma (22%). Chemotherapeutic agents were administered in various combinations as seen in our study. Paclitaxel is used in breast cancer, ovarian cancer and lung cancer, which was the most common chemotherapeutic agent used in our study in 29.73% patients in contrast to Hassan et al.[5] study where 5-fluouracil was the most common, used in 43.2% cases, in Fabbrocini et al.[7] study epidermal growth factor receptor (EGFR) inhibitors were used in 34%, in Menon et al.[1] and Muralidhar et al.[9] studies it was cisplatin in 48% and 50% patients, respectively.

Among 127 patients, 35.43% cases were exclusively treated with chemotherapy, which was lower than Naveed et al.[3] and Muralidhar et al.[9] studies with 55.75% and 55.66% cases, respectively.

Various chemotherapeutic agents affect rapidly growing cells and thus the skin, hair follicles and nail matrix are their frequent targets.[10] Epidermal growth factor receptor inhibitors are associated with intensely itchy papulo-pustular rash or acneiform eruptions on the seborrheic areas such as the face, scalp, and chest.[4,10] Patients on chemotherapy are more susceptible to infections due to myelosuppression and alteration in immune system function.[3]

Agents causing hand-foot syndrome are associated with focal skin pigmentation, mainly involving the fingertips.
combined with paresthesia or pain. Expression of the enzyme necessary for capecitabine activation may be responsible. Repeated trauma and friction to palms and soles, leads to inflammation which presents as painful symmetric erythema over the thenar or hypothenar eminences and pad of distal phalanges and on soles.\[6,8\]

In present study, the most common dermatosis associated with chemotherapy was hand-foot syndrome in 15.55% cases in contrast to Biswal et al.\[6\] Menon et al.\[1\] and Muralidhar et al.\[8\] studies where xerosis was the most common dermatosis in 4.4%, 26%, and 7%, respectively. In Rajagopal et al.\[11\] and Naveed et al.\[3\] studies generalized hyperpigmentation was the most common dermatosis in 1.6% and 46.46% cases, respectively, while in study by Fabbrocini et al.\[7\] papulopustular reaction was commonest in 55.88% cases and in Pavey et al.\[8\] study, aceneiform eruption was the common dermatosis in 27.7% cases. In our study, patients with hand-foot syndrome were treated most commonly with capecitabine followed by oxaliplatin, docetaxel, paclitaxel, carboplatin, etoposide, and ifosfamide. In study by Hassan et al.\[9\], two patients of hand-foot syndrome were given sorafenib for 5 months and oxaliplatin and capecitabine for 7 months while in study by Naveed et al.\[3\] gencitabine/carboplatin combination, Fluorouracil, Adriamycin/ Doxorubicin, and Cyclophosphamide (FAC) regimen, Fluorouracil, Epirubicin, and Cyclophosphamide (FEC) regimen, imatinib/hydroxyurea combination, cytarabine, and docetaxel monotherapy were the cause of hand-foot syndrome.

In our study, supraventricular pigmentation was noted in one patient with breast carcinoma on docetaxel similar to Menon et al.\[1\] where combination of 5-fluorouracil, cyclophosphamide, and doxorubicin was given and in study by Pavey et al.\[8\] a case of Hodgkin’s lymphoma on ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) regimen developed this, 3 months after the onset of treatment. Nail matrix cells are rapidly dividing cells and are frequently affected by chemotherapy.\[2\] The pathogenesis is unknown, but it might be due to increased skin fragility induced by the treatment and late sign of toxicity after 2 months from beginning of the therapy. The first lesions are usually localized on the big toe with a very painful erythema.\[7\] In our study, 46.66% patients had nail changes lower than Fabbrocini et al.\[7\] and Pavey et al.\[8\] with 53% and 62.2% patients, respectively, while higher than in study by Menon et al.\[1\] with 30% cases.

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**Table 2: Dermatosis, hair, nail and oral changes associated with chemotherapy exclusively**

| Dermatosis                      | No of patients (%) |
|---------------------------------|--------------------|
| Hand-foot syndrome [Figure 5]  | 7 (15.55%)         |
| Pruritus                        | 6 (13.33%)         |
| Urticaria                       | 3 (6.66%)          |
| Aceneiform eruption [Figure 6a] | 3 (6.66%)          |
| Exfoliative dermatitis          | 2 (4.44%)          |
| Xerosis                         | 2 (4.44%)          |
| Supraventricular pigmentation [Figure 6c] | 1 (2.22%) |
| Erythema multiforme [Figure 7]  | 1 (2.22%)          |

**Table 3: Dermatosis, hair, nail and oral changes associated with combined chemotherapy and radiation therapy**

| Dermatosis                      | No of patients (%) |
|---------------------------------|--------------------|
| Radiation dermatitis            | 26 (39.39%)        |
| Xerosis                         | 4 (6.06%)          |
| Pruritus                        | 2 (3.03%)          |
| Hand-foot syndrome              | 2 (3.03%)          |
| Urticaria                       | 2 (3.03%)          |
| Aceneiform eruption             | 2 (3.03%)          |
| PIH                             | 2 (3.03%)          |
| Secondary bacterial infection    | 1 (1.52%)          |
| Erythema multiforme             | 1 (1.52%)          |

**Nail changes**

| Melanonychia [Figure 8a]       | 13 (61.90%)         |
| Dystrophy                      | 4 (19.04%)          |
| Pitting                        | 2 (9.52%)           |
| Leukonychia                    | 1 (4.76%)           |
| Thinning                       | 1 (4.76%)           |
| Thickening                     | 1 (4.76%)           |
| Mee’s lines [Figure 8b]        | 1 (4.76%)           |
| Muehrcke’s line [Figure 8c]    | 1 (4.76%)           |

**Hair changes**

| Anagen effluvium [Figure 6b]  | 15 (88.23%)         |
| Loss of eyebrow hair          | 5 (29.41%)          |

**Oral changes**

| Aphthous ulcers                | 9 (69.23%)          |
| Oral candidiasis [Figure 9a]   | 3 (23.07%)          |
| Hyperpigmentation [Figure 9b]  | 3 (23.07%)          |
| Erythema multiforme            | 1 (7.69%)           |
| Cheilitis [Figure 9c]          | 1 (7.69%)           |
Chemotherapeutic agents commonly causing discoloration of nails are bleomycin sulfate, cyclophosphamide, methotrexate, dacarbazine, and doxorubicin.[13] Most common nail change associated with chemotherapy was melanonychia in present study with 61.90% cases similar to study by Naveed et al.[9] with 64.28% cases while lower than study by Pavey et al.[8] with 78.7% cases and higher than studies by Biswal et al.[6] and Muralidhar et al.[7] with 2.9% and 5% cases, respectively. Beau’s line was most common in study by Menon et al.[1] with 8% cases. In our study, patients with melanonychia were receiving paclitaxel, carboplatin, doxorubicin, capecitabine, docetaxel, oxaliplatin, bleomycin, methotrexate, gefitinib, imatinib, vinblastin, bortezomib, zolendronic acid, thalidomide and sunitinib. In Menon et al.[1] drugs found responsible for melanonychia were adriamycin, epirubicin, etoposide, and cisplatin while in study by Muralidhar et al.[7] epirubicin and cisplatin were responsible.

Muehrcke’s lines were seen in only one case of lung carcinoma on carboplatin and docetaxel, in our study while in Pavey et al.[8] it was seen in four patients. The exact pathogenesis is unknown but, edema of the nail bed occurring due to hypoalbuminemia, and an alteration of nail plate attachment to the nail bed, due to vascular compromise are the cause.[13]

Vincristine, cyclophosphamide, and doxorubicin are associated with Mee’s lines which is due to sudden toxicity on the nail matrix.[13] In our study, only one case of Mee’s lines in breast carcinoma on paclitaxel, docetaxel, and cyclophosphamide had been reported. In Pavey et al.[8], two patients of non-Hodgkin lymphoma on cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) regimen had Mee’s lines.

Hair loss has been rated as one of the most distressing side effects of chemotherapy.[14] Hair changes were present in 37.77% cases in our study similar to study by Pavey et al.[8] and in contrast to study by Fabbrocini et al.[7] and Menon et al.[1] study with 52.93% and 100% cases, respectively. Chemotherapy-associated hair loss is variable and dependent on chemotherapeutic agent and treatment protocol. The cessation of mitotic activity in the hair matrix results in a narrow-weakened portion of the hair shaft known as Pohl-Pinkus constriction which is prone to fracture.[2] Commonly, doxorubicin, daunorubicin, paclitaxel, and docetaxel can cause anagen effluvium.[14]

Hair loss is almost always reversible with good regrowth after cessation of treatment. Anagen effluvium was the most common hair change in 88.23% cases in our study higher than other studies.[6‑9] In studies by Menon et al.[1] and Naveed et al.[3], alopecia was most common in 68% and 37.16% cases, respectively.

Direct drug toxicity on the rapidly dividing oral epithelial cells results in oral ulcerations with drugs like 5-fluorouracil, cytarabine, paclitaxel, and vinca alkaloids. In our study, oral mucosal changes were present in 28.88% patients higher than study by Pavey et al.[8] with 3.7% cases. Mucositis is a known common adversity, but surprisingly, in our observation, none of the patients had it.
This might be due to the proper counselling regarding oral hygiene to the patients. In present study, aphthous ulcers were seen in 69.23% cases, higher than other studies.\textsuperscript{[1,3]}

**Radiation therapy and associated dermatosis**

Radiotherapy is a common treatment modality in 50% of cancer patients as preoperative, postoperative and palliative therapy.\textsuperscript{[15]} Cutaneous side effects due to radiation therapy are common that include pain, discomfort, irritation, itching, and burning sensations and sometimes they can be severe which might lead to reduction in the treatment duration and affect the quality of life.\textsuperscript{[16]} Skin reactions to radiation largely depend on the technique, total dose, volume, and variety of therapy in each individual.\textsuperscript{[17]}

The effects may be acute or chronic. Acute effects occur hours to weeks after exposure to radiation and are characterized by erythema, oedema, hyperpigmentation, scaling, and alopecia while chronic effects are more severe and occur months to years after the exposure and present as ulcers, necrosis and fibrosis.\textsuperscript{[5,18]} In present study, among 127 treated patients, 69.56% patients were given radiation therapy and some patients were given combined chemo and radiation therapy which is higher than other studies.\textsuperscript{[3,5,9]}

According to RTOG grading for radiation-induced toxicity, most common grade of radiation-induced toxicity was Grade-1 in our study with 48.78% cases.

In present study, out of 82 radiation therapy-treated patients, 19.51% patients were treated exclusively with radiation therapy, which was higher than Muralidhar et al.\textsuperscript{[9]} study with 4.71% cases.

In present study, out of 127 treated patients, combined therapy was given to 51.96% cases higher than study by Naveed et al.\textsuperscript{[3]} (44.25%) and Muralidhar et al.\textsuperscript{[9]} (16.98%). Radiation dermatitis was the most common in 39.39% cases in our study higher than study by Muralidhar et al.\textsuperscript{[9]} in 16% cases.

No cases of erythroderma, Stevens-Johnson syndrome, toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms were encountered in this study.
Proper treatment may allow achievement of ideal durations of chemotherapy administration, as well as the optimization of response rates. Toxic effects of chemotherapeutic agents on skin result in poor compliance of patients and interruptions of antineoplastic therapy thus reducing the quality of life. It is important to counsel the patients and their attendants before initiation of chemotherapy which will reduce the psychological trauma of the cosmetically unacceptable adverse effects hence improve the lifestyle management.

Cooperation between oncologist and dermatologist is also fundamental to make the best decision for the patients and to implement preventive measures.

**Conclusion**

The study was useful in understanding various chemotherapy and radiation therapy-associated dermatosis side effects so that early interventions can be done to prevent further treatment-related adverse effects. Physicians should be aware of the potential impact of dermatological toxicity, especially when selecting appropriate chemotherapy agents.

Limitations of this study include small sample size and inability of pinpointing a single drug responsible for a particular dermatological side effect.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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**Table 4: Comparison of dermatosis associated with exclusive chemotherapy**

| Parameter                        | Our study (150) | Biswal et al.[6] (100) | Fabbrocini et al.[7] (100) | Menon et al.[1] (100) | Naveed et al.[3] (226) | Pavey et al.[8] (53) | Muralidhar et al.[9] (106) |
|----------------------------------|-----------------|------------------------|---------------------------|-----------------------|-----------------------|----------------------|---------------------------|
| Most common dermatosis          |                 |                        |                           |                       |                       |                      |                           |
| Treated with chemotherapy exclusively | 45 (30%)       | 100%                   | 100%                      | 100%                  | 55.75%                | 100%                 | 55.66%                    |
| Hand-foot syndrome              | (15.55%)        |                        |                           |                       |                       |                      |                           |
| Xerosis                         | (4.4%)          | 53%                    |                           | 30%                   | Hyperpigmentation     | Acneiform eruption   |                           |
| Papulopustular reaction         | (55.88%)        |                        |                           |                       | (46.46%)              | (27.7%)              |                           |
| Xerosis                         | (26%)           |                        |                           |                       |                      |                      |                           |
| Nail changes                    |                 |                        |                           |                       |                       |                      |                           |
| Melanonychia                    | (61.90%)        |                        |                           |                       |                       |                      |                           |
| Xerosis                         | (4.4%)          | 53%                    |                           | 30%                   | Hyperpigmentation     | Acneiform eruption   |                           |
| Melanonychia                    | (2.9%)          |                        |                           |                       | (46.46%)              | (27.7%)              |                           |
| Most common hair changes        |                 |                        |                           |                       |                       |                      |                           |
| Anagen Effluvium                | (88.23%)        |                        |                           |                       |                       |                      |                           |
| Anagen Effluvium/ Alopecia       | (78.6%)         | 100%                   |                           | 100%                  | -                     |                      |                           |
| Anagen Effluvium                | (78.6%)         |                        |                           |                       | -                     |                      |                           |
| Anagen Effluvium/ Alopecia       | (17.67%)        | -                      |                           | -                     | -                     |                      |                           |
| Oral mucosal changes            |                 |                        |                           |                       |                       |                      |                           |
| Aphthous ulcers (69.23%)        | 13 (28.88%)     | -                      | -                         | -                     | -                     |                      |                           |
| Mucositis                       | (12%)           |                        |                           | -                     | -                     |                      |                           |
| Mucositis                       | (15.87%)        |                        |                           | -                     | -                     |                      |                           |

**Figure 9:** (a) Oral candidiasis in buccal mucosal carcinoma with cisplatin, (b) Hyperpigmentation of oral mucosa in carcinoma of esophagus with paclitaxel, and (c) Cheilitis in leukemia with imatinib
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