

MUCOCUTANEOUS MANIFESTATIONS FOLLOWING CHEMOTHERAPY IN PEDIATRIC MALIGNANCIES

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ABSTRACT

Objective: Chemotherapy causes destruction of neoplastic cells and rapidly proliferative normal cells leading to significant mucocutaneous changes. The aim of the present study was to determine the postchemotherapeutic mucocutaneous manifestations in pediatric malignancies.

Methods: In this cross-sectional study, 63 children with malignancy undergoing chemotherapy over 2½ years were examined carefully and followed up for 6 months. A comprehensive clinical history was taken. Detailed systemic and dermatological examination was carried out in the subjects at the time of enrollment. Dermatological examination was performed subsequently at 3-6 months and whenever child presented with any symptoms to the outpatient department. The chemotherapy-induced alopecia (CIA) and pigmentary changes of skin and nails were graded using OSLEN CIA, National Cancer Institute pigment changes and nail changes' grading scales.

Results: Males (41 [65%]) outnumbered females (1.8:1). Acute lymphoblastic and myelogenous leukemia were noticed in 38 (60.3%) and 8 (12.6%) patients, respectively. Alopecia (43 [68.3%]) was common with predominant grade 3 (22 [34.92%]). Hair regrowth was noticed in 53 (83.7%) patients within 6 months. Cutaneous linear pigmentary lines, ichthyosis, acral pigmentation, skin peeling, and mucositis were observed in 13 (21%), 10 (16%), 10 (16%), 7 (11%), and 9 (14.28%) patients, respectively. Among 56 infections included, viral-4 cases of herpes zoster, single case of extensive molluscum and varicella. Tinea faciei was recurrent and poorly responsive to treatment. The common nail changes noted were Muehrcke's lines and melanonychia (26 [41.26%]).

Conclusion: Alopecia in 43 (68.3%) patients though distressing was reversible in 53 (83.7%) patients. Infections were extensive, recurrent, and required aggressive treatment.

Keywords: Chemotherapy, Pediatric malignancies, Cancer.

INTRODUCTION

During the last decades of the 20th century and early in the current millennium, the incidence of cancer among children has increased and has assumed relatively greater importance in pediatric practice [1]. In Western countries, cancer-related deaths are the second most common cause of death (20%) following traumatic injuries (21%). However, in India, the prevalence of cancer-related deaths was found to be 2% [2,3].

Childhood malignancy develops within a short period and has a more aggressive course [4]. It is more responsive to treatment than adult tumors [5]. Chemotherapy is an essential component in the multidisciplinary management of various cancers, and adverse effects are often inevitable. Along with malignant cells, the normal cells are equally at risk, especially for the mucocutaneous adverse effects which pose a clinical challenge with respect to diagnosis and therapy [6,7].

Among various noninfectious and infectious mucocutaneous manifestations, chemotherapy-induced alopecia (CIA) and nail changes are commonly documented. Incidence of alopecia (CIA) ranges from 65% to 74.3% for adult and pediatric cancer population, respectively [8,9]. The incidence of nail changes ranges from 5.21% to 33.33% [10,11]. Skin toxicity is rarely life-threatening, but worsens the patient's quality of life and at times can alter treatment plan. Dermatologists play a crucial role in identifying the adverse reactions and their co-ordination with medical oncologist is vital with respect to further continuation of drug therapy [12,13]. There have been very few studies on cutaneous manifestations in children following chemotherapy from India. The present study is an attempt to obtain a better understanding of the

influence of cancer chemotherapy on mucous membrane, skin, and its appendages among children.

METHODS

A cross-sectional study was conducted among 63 children in the pediatric department of a tertiary care hospital during October 2012-September 2014. The research protocol was approved by the Institutional Ethics Committee. A written informed consent was obtained from the parents/guardians of all the subjects after explaining the details regarding the study.

Children aged between 6 months and 16 years with confirmed pediatric malignancies planned to receive chemotherapy were included. Children more than 16 years of age, those who have completed chemotherapy, and who are not willing to give consent were excluded from the study.

A comprehensive clinical history was taken. Detailed systemic and dermatological examination was carried out in the subjects at the time of enrollment. Dermatological examination was done subsequently at 3-6 months and whenever child presented with any symptoms to the outpatient department. Diagnostic investigations such as Gram stain, acid-fast bacillus smear, 10% potassium hydroxide mount, and cultures for fungi and bacteria were done. Diagnostic biopsy was performed whenever appropriate.

The CIA and pigmentary changes of skin and nails were graded using OSLEN CIA, National Cancer Institute (NCI) pigment changes' and nail changes' grading scales [14,15]. Results are expressed as proportions

using appropriate tables and graphs. The data were analyzed using Statistical Package for Social Sciences (SPSS) version 15.

RESULTS

Age of the study participants in the study ranged from 9 months to 16 years. Mean age was 7.704 years or 92.46 months. Majority of the patients, i.e. 26 (41.28%) belonged to the age group of 0-4 years. Males outnumbered females with a male:female ratio of 1.86:1. The age and gender distribution of the patients with malignancies is shown in Fig. 1.

Out of 63 patients, acute lymphoblastic leukemia (ALL) was encountered in 38 (60.3%), followed by acute myelogenous leukemia (AML) in 8 (12.7%), Ewing's sarcoma (primitive neuroectodermal tumor [PNET]) in 4 (6.3%), Hodgkin's and non-Hodgkin's lymphomas (NHL) along with Langerhans cell histiocytosis (LCH) in 3 (4.8%), and hepatoblastoma in 2 (3.2%) patients. Yolk sac tumor, desmoplastic small round cell tumor (DSCRT), neuroblastoma, gastrointestinal malignancy, and retinoblastoma were noticed in one patient each (1.6%). Among the various chemotherapy protocols, MCP 841 protocol was used in 38 (60.3%) cases, followed by AML protocol in 8 (12.7%) cases.

Frequency of various mucocutaneous manifestations

Among the 63 cases, 24 (38.1%) had a combination of cutaneous manifestations along with systemic complaints and 39 (61.9%) had only systemic complaints. Among the noninfectious mucocutaneous manifestations, alopecia was noticed in 43 (68.3%) cases. Other manifestations observed include petechiae in 15 (23.8%), pallor in 13 (20.6%), and ecchymosis in 8 (12.7%), cutaneous linear pigmentation in 13 (20.6%), ichthyosis and acral hyperpigmentation in 10 (15.9%), exaggerated response to insect bite in 9 (14.3%), mucosal involvement in 8 (12.7%), and skin peeling of palms and soles in 7 (11.1%) cases. According to NCI grading, 10 (15.9%) were cases of hyperpigmentation, 9 (14.3%) were localized, and 1 (1.6%) was diffusely distributed (Table 1).

Table 2 shows the grades of CIA as per OSLEN CIA grading. As per OSLEN CIA, grade 3 was observed in 22 (34.92%) cases. About 36 (55%) cases showed hair loss around 3-6 weeks after the initiation of chemotherapy and in these cases, alopecia was noticed within 3 months. Of the total 43 cases of alopecia, regrowth of hair was

witnessed in 36 (83.7%) within 6 months. Persistent alopecia was seen in 4 (9%) cases after 6-month follow-up. A single case (2.3%) was lost to follow-up and 2 (4.6%) cases expired at the end of 6 months. Among the cases of grade 3 alopecia, 27 (63.63%) were had ALL receiving MCP 841 protocol. Children treated with EFT 2001 protocol for PNET tumor had higher grades of alopecia. There was no documented hair loss among 66.6% of LCH and 50% of hepatoblastoma cases.

Nail involvement was documented in 26 (41.26%) cases. Among them, muehrcke's line and melanonychia were noticed in 9 (14.3%) each. Others were Beau's lines, platyonychia, onycholysis, Mee's lines, and onychomadesis in decreasing order of frequency (Fig. 2).

As per NCI grading, grade 1 changes were noticed in 24 (38.1%), whereas grade 2 comprising partial loss of nail was documented in 2 (3.17%) cases.

Infectious manifestations

A total of 56 infectious manifestations were detected during the study period. Viral infections included molluscum contagiosum in 7 (12.7%), verruca vulgaris, herpes zoster, extensive varicella, and herpes simplex were noticed in 4 (7.9%), 3 (6.3%), 2 (4.8%), and 3 (6.3%), respectively. One case of Molluscum contagiosum had disseminated lesions requiring imiquimod along with cryotherapy. **Extensive varicella requirement was seen in patients with ALL required intravenous medications as they were poorly responsive for oral medications.** Herpes labialis was recurrent in one patient with ALL. Herpes zoster was noticed as early 3 years in a patient with ALL. Among fungal infections, dermatophytosis was most common, of which tinea corporis was seen in 3 (6.34%) followed by tinea capitis and tinea faciei in 2 (3.2%) cases,

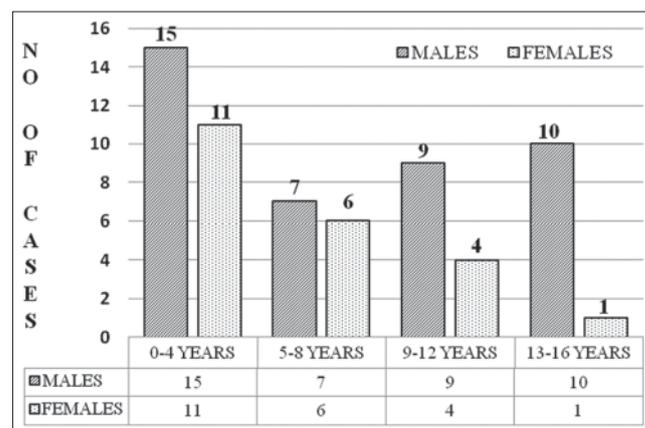


Fig. 1: The age and sex distribution of the patients with malignancies

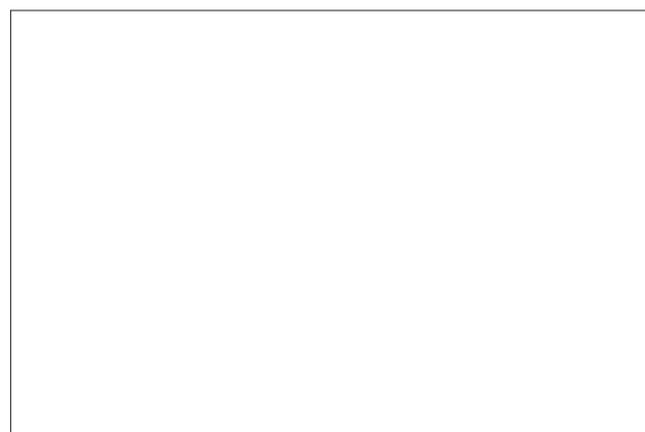


Fig. 2: ???

Table 1: Various noninfections mucocutaneous manifestations

Manifestation	Frequency	Percentage
Alopecia	43	68.3
Petechiae	15	23.8
Ecchymosis	8	12.7
Pallor	13	20.6
Peeling of skin	7	11.1
Ichthyosis	10	15.9
Hyperpigmentation	10	15.9
Exaggerated insect bite reaction	9	14.3
Cutaneous linear pigmentation	13	20.6
Mucositis	8	12.7

Table 2: Grades of chemotherapy-induced alopecia as per OSLEN CIA grading

OSLEN CIA grading of alopecia	Frequency	Percentage
Absent	19	30.2
1-24% loss	1	1.6
25-49% loss	7	11.1
50-74% loss	22	34.9
75-99% loss	10	15.9
100% loss	4	6.3
Total	63	100.0

CIA: Chemotherapy-induced alopecia

one case of tinea faciei was recurrent and extensive with less response to fluconazole and topical azole. Tinea versicolor was noticed in 4 (7.9%) cases. Bacterial infections comprised furunculosis in 6 (11%) and ecthyma in 2 (3.2%) cases. Ectoparasitic infestations consisted of scabies 7 (12%) and pediculosis capitis 2 (3.2%).

DISCUSSION

The present study was conducted on 63 diagnosed cases of pediatric malignancies, receiving combination chemotherapy. The cutaneous manifestations observed in different drug regimens at various intervals were documented. Among them, 2 cases expired and 3 were lost to follow-up at the end of 6 months.

The study group comprised 41 males and 22 females with a male:female ratio of 1.86:1. Male predominance (65.1%) was seen in this study, which is comparable to the studies reported by Yeole *et al.* (61.2%) and Cardoza-Torres *et al.* (61.5%) [9,16]. Jignasa and Mandakini reported a slightly lower male predominance probably because only 43 patients were included in that study [17].

The reported percentage (65.07%) of lymphoid neoplasms (ALL, NHL, and Hodgkin's disease) is similar to the study by Kusumakumary *et al.* which showed a higher frequency in males [18]. ALL in 60.3% of the cases was the most common malignancy which is comparable to the studies conducted by Gurney *et al.*, Yeole *et al.*, and Jignasa and Mandakini [16-19]. However, in a study conducted by Cardoza-Torres *et al.*, wherein they included various cases of hematological malignancies, 78.4% cases of ALL were reported [9].

On cutaneous examination, alopecia (68.3%) was the commonly observed adverse drug reaction in this study. Varying grades of alopecia were noticed in 43 cases with various chemotherapy protocols for pediatric malignancies. The incidence of alopecia in the current study is slightly lower than that of Cardoza-Torres *et al.* (74.3%) where only pediatric hematological malignancies receiving chemotherapy were studied and they were higher than the observations documented in studies by Kamil *et al.* (64.3%) where the study group was larger and Trüeb *et al.* (65%) [8-10]. However, the latter study was not restricted to pediatric age group.

Onset of alopecia within 3-6 weeks of initiation of chemotherapy was seen in 55% of the subjects and in 83.7% of the subjects, regrowth was documented within 6 months which was analogous to a study by Dorr [20]. About 9% of the patients comprising a single case of ALL, AML, and neuroblastoma have persistent alopecia. These cases were put on cyclophosphamide, etoposide, and docetaxel drugs, which are known to produce permanent alopecia [21].

Vascular changes observed in the form of pallor were the most common presenting complaint, probably because 77.8% of the malignancies were hematological in origin. Peeling of skin from soles was seen in 11.1% of the subjects which was almost double than that seen in a study by Cardoza-Torres *et al.* (6.1%) [9]. This can be attributed to the various malignancy protocols used in this study. Incidence of ichthyosis was 15.9% which was lower than that of Cardoza-Torres *et al.* (44.4%) and higher than Kamil *et al.* [9,10] where 106 patients with a variety of cancers were included.

Among 63 cases, hyperpigmentation was observed in 15.9% of the subjects. Pigmentation was predominantly seen in acral distribution over hands, feet, and bony prominence. Cardoza-Torres *et al.* observed this feature in 49% of the subjects [9]. This finding is quite evident in subjects to whom cyclophosphamide and daunorubicin were predominantly used for hematological malignancies [7,13].

Exaggerated response to insect bite reaction was noted in 5.3% and 10.6% of the subjects among general population [22,23]. In this study, it was higher (14.3%). The higher rates of incidence of insect bite reaction may be due to the reversal of CD4+:CD8+ and Th1:Th2 lymphocyte

reaction occurring as a part of chemotherapy resulting in faulty recognition of antigen as described by Matthew and Cockerell [24].

Cutaneous linear pigmentation along the veins in the form of streaks following intravenous drug injection was seen in 20.6% of the subjects. It has been classically noted for 5-fluorouracil (FU) and rarely with docetaxel and bleomycin [7,13]. However, in this study, it was noticed with other drugs in protocols which are used for the management of DSCRT, neuroblastoma, and PNET.

Mucositis is always associated with cyclophosphamide, daunorubicin, and doxorubicin. These drugs are part of all hematological malignancy protocols. Incidence of mucositis is 12.7% which is lower than that of Cardoza-Torres *et al.* (23.5%) where only hematological malignancies were included and in both studies, lesions healed without any complications [9]. Kamil *et al.* reported <1% incidence of mucositis [10].

Nail involvement documented in this study was 41.26% which was significantly higher than the study by Chen *et al.* (33.33%) that was conducted in 30 pediatric malignancy, Cardoza-Torres *et al.* (15.6%) and Kamil *et al.* (5.21%) [9-11]. Among diverse nail changes noted, occurrence of Beau's line (11.31%) was similar in studies by Cardoza-Torres *et al.* (15.6%) and Chen *et al.* (10%) where a majority of them received daunorubicin and cytarabine [9,11]. Mee's lines were noted in a case of ALL who was administered cytarabine, cyclophosphamide, and 5-FU. Muehrcke's line was documented in 14.3% of cases which is similar to a study by Chen *et al.* [11]. Melanonychia (14.3%) was seen among ALL, PNET, Hodgkin's lymphoma, and AML cases receiving cyclophosphamide, ifosfamide, doxorubicin, daunorubicin, dacarbazine, and methotrexate.

Infections were extensive, recurrent in many cases, and poorly responding to standard medications, often necessitating the need for aggressive management and monitoring coupled with personal care. The possible reason for recurrent and long-lasting infections could be the myelosuppression, a hallmark of chemotherapeutic agents, which leads to decrease in leukocytes, particularly neutrophils, which makes the patient more susceptible to infections.

Fifty six infectious manifestations encountered in the study population included viral infections 42.85% comprising warts, molluscum contagiosum, herpes labialis, varicella, and herpes zoster. Similar observations were made by Cardoza-Torres *et al.* [9] where viral infections were predominant.

Frequency of fungal infections was 23.4%. Bacterial infections were noticed in 14.3% of the subjects which was comparable to a study by Cardoza-Torres *et al.* (15.6%) [9]. Among ectoparasitic infestations (19.63%), scabies was predominant followed by pediculosis capitis. Cardoza-Torres *et al.* reported fewer parasitic infestations [9].

Comparing the various mucocutaneous manifestations documented following chemotherapy and body mass index for age and manifestations, ecchymosis, warts, and ecthyma were found to be statistically significant. Similar findings were documented in a study by Cardoza-Torres *et al.*, where they noticed significant values for purpura, hyperpigmentation, mucositis, Beau's lines, and viral infections [9].

CONCLUSION

Pediatric cases are a vulnerable group with respect to cutaneous adverse effects to chemotherapeutic medications and there is only limited experience recorded in this age group, particularly from India.

Although majority of the manifestations have low morbidity, some such as alopecia can be distressing to the patients and care takers. However, it is often reversible. In this study, only 9% of the cases had persistent alopecia at the end of 6 months. Infectious manifestations were recurrent, severe, and required aggressive treatment. Early diagnosis

and management of these adverse reactions can reduce the morbidity in these patients.

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