Original Article

Clinical Profile of Cutaneous Adverse Effects of Epidermal Growth Factor Receptor Inhibitors: A Prospective Observational Study of 76 Cases

Neerja Saraswat, Aradhana Sood[1], Dharmesh Kumar[2], Rajesh Verma, Kumar Sushil[3]

Department of Dermatology, Base Hospital, Delhi Cantt, [2]Department of Oncology, Army Hospital R and R, Delhi Cantt, New Delhi, [1]Department of Dermatology, Base Hospital, Lucknow Cantt, [3]Department of Dermatology, MLN Medical College Allahabad, Uttar Pradesh, India

Abstract

Background: Epidermal growth factor receptor (EGFR) inhibitors are an extensively utilized class of chemotherapeutic agents which form an integral component of treatment in solid organ malignancies such as non-small-cell lung carcinoma, pancreatic carcinoma, colorectal carcinoma, and head and neck carcinoma. It has two subclasses: epidermal growth factor inhibitors (erlotinib) and monoclonal antibody (cetuximab). A wide array of cutaneous adverse effects has been attributed to this class of drugs, such as papulopustular eruptions, paronychia, xerosis, and changes in hair and nails. **Materials and Methods:** A total of 76 cases of various malignancies on EGFR inhibitors who developed cutaneous side effects while on therapy and reported or referred to us by oncologists from January 2017 to January 2018 were included in the study. All the patients who were on other associated medications or radiotherapy were excluded. **Result:** In all, 45 (59.2%) were males and 31 (40.7%) were females. Non-small-cell lung carcinoma was the most common carcinoma in 32 (42.1%) patients, and cetuximab was the most common drug in 29 (38.1%) cases. Papulopustular eruptions were seen in 61 (80.2%) patients, xerosis in 31 (40.7%), mucositis in 6 (7.8%), hair growth problems in 4 (5.6%), and paronychia and pyogenic granuloma in 2 (2.6%) patients each. **Conclusion:** Although most of the skin toxicities associated with EGFR inhibitors can be managed conservatively, a critical analysis of the cases that are significantly affected due to these side effects is required in cohesion with the treating oncologist to improve the therapeutic compliance of the drug.

Keywords: *Cetuximab, epidermal growth factor inhibitor, non-small-cell lung carcinoma, papulopustular eruption, xerosis*

Introduction

Epidermal growth factor receptors (EGFRs) are transmembrane proteins expressed physiologically in epithelial tissues and hair follicles and result in epithelial proliferation and differentiation, and hair growth.[1] It is over-expressed in solid tumors where it is involved in tumor growth, cell proliferation, angiogenesis, metastasis, and motility of the cells.[2,3] Hence, an inhibition of the receptor is employed in malignancies where it is overly expressed.[4] The two classes of EGFR inhibitors are monoclonal antibodies and low molecular weight drugs which exhibit their action by inhibiting the intracellular tyrosine kinase (TK). EGFR antagonists are widely employed in the management of colorectal carcinoma, breast carcinoma, pancreatic carcinoma, non-small-cell lung carcinoma (NSCLC), and squamous cell carcinoma of head and neck.[5,6]

EGFR inhibitors are associated with a wide array of dermatological adverse effects such as papulopustular eruptions (PPE), xerosis, paronychia, and changes in hair and nail growth pattern resulting in significant impairment in the quality of life. Apart from being associated with psychosocial morbidity, adherence and compliance can also be affected, posing challenges in the management.[7] The aim of this study is to find the spectrum, pattern, and frequency of these cutaneous adverse effects due to EGFR inhibitors and its impact on the adherence if any.

Materials and Methods

This is a prospective observational study conducted over a period of 1 year after obtaining ethical clearance from institutional ethics committee. All cancer patients on EGFR inhibitors who developed cutaneous side effects and reported to or

Address for correspondence:
Dr. Aradhana Sood, Department of Dermatology, Base Hospital, Lucknow Cantt, Uttar Pradesh, India.
E-mail: neerjaneerja007007@gmail.com

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were referred to us by oncologists were studied. Written informed consent was taken from the patients or the family members if required. All the patients who were on multiple drugs for other comorbidities or drugs which can cause PPE or cause xerosis or were on concurrent radiotherapy were excluded. A total of 76 patients were included in the study. Detailed history of the type of malignancy, presenting complaint, protocol of the drug administered, and skin manifestations due to the chemotherapy agent was assessed, and clinical photographs were taken. All the patients who were not willing to continue the drug due to its dermatological side effects were assessed, and the treating oncologist was consulted for either reducing the dose or substituting it. Patients who refused to continue the drugs were referred to a counsellor to emphasize the importance of therapy.

Result

Out of total 76 patients, 45 (59.2%) were males and 31 (40.7%) females. In all, 24 (31.5%) patients were in the age group of 46–55 years followed by 19 (25%) in 36–45 years, 12 (15.7%) in 26–35 years, 11 (14.4%) in 56–65 years, 6 (7.89%) above 65 years, and 4 (5.2%) in 19-25 years [Table 1]. NSCLC was the most common carcinoma seen in 32 (42.1%) patients, colorectal carcinoma in 13 (17.1%), buccal carcinoma in 11 (14.4%), pharyngeal carcinoma in 9 (11.8%), carcinoma tongue in 7 (9.2%), and pancreatic carcinoma in 2 (2.6%) patients [Table 2]. Cetuximab was the most common EGFR inhibitor used in 29 patients (38.1%) followed by erlotinib in 20 (26.3%), geftinib in 10 (13.1%), dasatinib in 7 (9.2%), lapatinib in 6 (7.8%), and nilotinib in 4 (5.2%) patients.

Details of cutaneous adverse effects are depicted in Table 3. PPE was the most common cutaneous adverse effect seen in 61 (80.2%) patients [Figure 1]. PPE was graded as per National Cancer Institute (NCI) Common Terminology for Adverse Events (CTCAE) version 4.0.[8] A total of 36 (59%) patients had grade 3, 23 (37.7%) had grade 2, and 2 (3.2%) had grade 4 eruptions. Six (7.8%) out of 61 patients of PPE refused to continue the drug despite being counselled about the importance of continuing the drug (5 with grade 3 and 1 with grade 2). Three (4.9%) patients were advised dose reduction in consultation with the oncologists. Medication was stopped in two (3.2%) cases with grade 4 PPE after consulting the oncologist. Generalized xerosis was seen in 31 (40.7%) patients [Figure 2]. Xerosis was reported between 2 and 3 months of starting the therapy in all the patients. Mucositis, stomatitis, and aphthous ulcers were seen in six patients (7.8%). In five (83.3%) cases, mucositis was observed within 45 days of the therapy as against one (16.6%) patient who developed it within 10 days of the therapy. Three (50%) of the six patients with mucositis were symptomatically better on subsequent cycles of chemotherapy while three (50%) patients of mucositis were lost to follow-up, hence could not be evaluated further. Hair growth abnormalities were reported by four (5.2%) patients [Figure 3]. Paronychia and pyogenic granuloma were seen in two (2.6%) patients each. Paronychia was seen within 2 weeks of therapy in

Table 1: Age profile of patients on EGFR inhibitors

Age group (years)	Males	Females	Total
19-25	3 (3.9%)	1 (1.3%)	4 (5.2%)
26-35	7 (9.2%)	5 (6.5%)	12 (15.7%)
36-45	10 (13.1%)	9 (11.8%)	19 (25%)
46-55	13 (17.1%)	11 (14.4%)	24 (31.5%)
56-65	8 (10.5%)	3 (3.9%)	11 (14.4%)
>65	4 (5.2%)	2 (2.6%)	6 (7.89%)

Table 2: Demographic profile of patients on EGFR inhibitors

Type of malignancy	Males	Females	Total
Non small cell carcinoma Lung	21 (27.6%)	11 (14.4%)	32 (42.1%)
Colorectal carcinoma	7 (9.2%)	6 (7.8%)	13 (17.1%)
Buccal carcinoma	8 (10.5%)	3 (3.9%)	11 (14.4%)
Pharyngeal carcinoma	5 (6.5%)	4 (5.2%)	9 (11.8%)
Carcinoma tongue	3 (3.9%)	4 (5.2%)	7 (9.2%)
Pancreatic carcinoma	2 (2.6%)	2 (2.6%)	4 (5.2%)

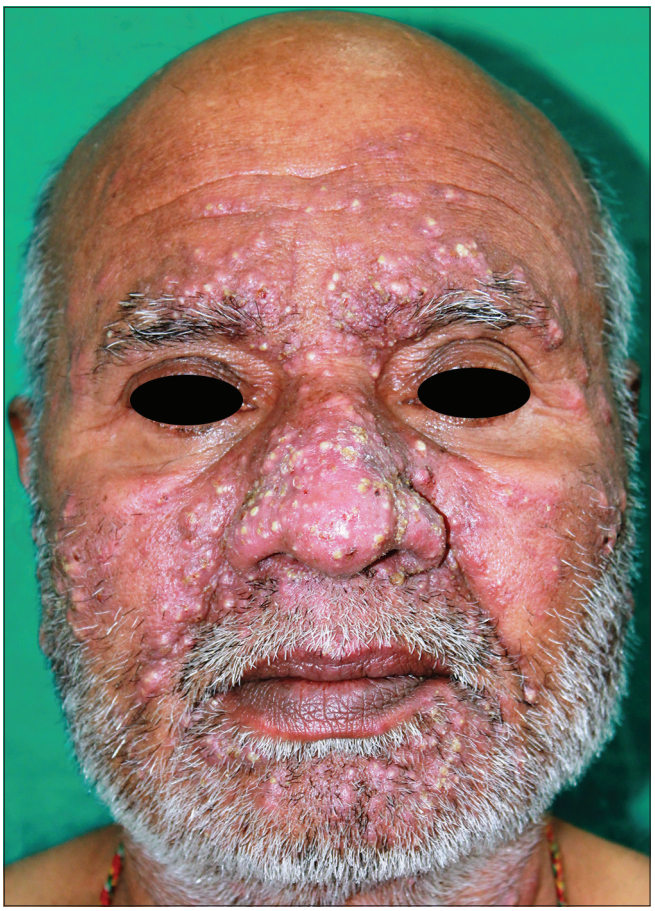

Figure 1: A case of papulopustular eruptions due to cetuximab

Table 3: Cutaneous adverse effects noted with EGFR inhibitors

EGFR inhibitor	Total patients treated with drug	PPE	Xerosis	Mucositis	Hair growth abnormality	Paronychia	Pyogenic granuloma
Cetuximab	29	26	17	01	02	01	01
Erlotinib	20	16	07	02	-	-	-
Geftinib	10	08	03	02	01	-	-
Dasatinib	07	05	02	01	01	-	01
Lapatinib	06	03	01	-	-	01	-
Nilotinib	04	03	01	-	-	-	-
Total	76	61	31	06	04	02	02

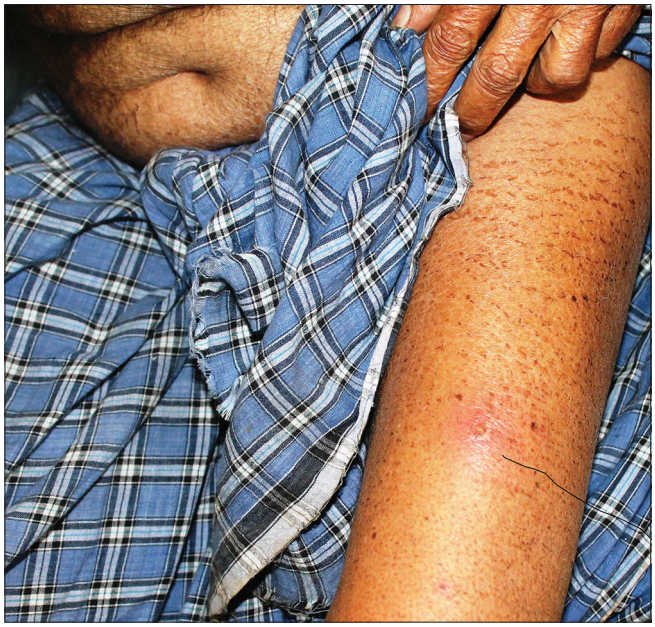

Figure 2: A case of xerosis due to cetuximab

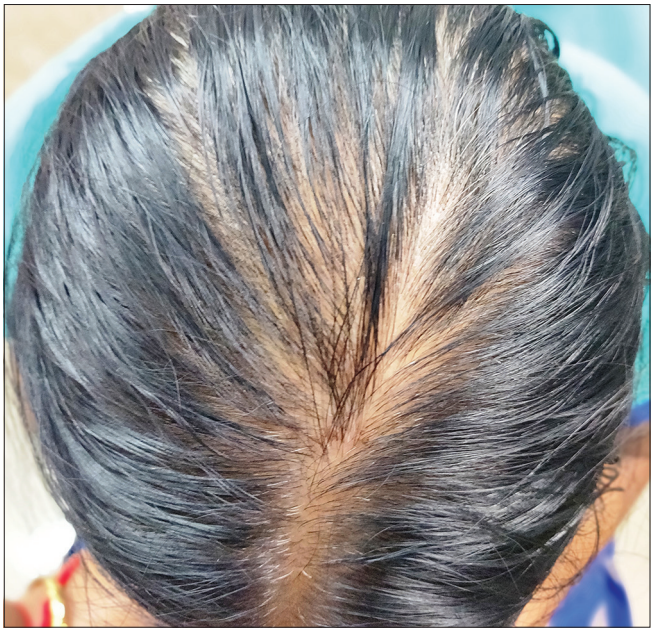

Figure 3: A case of hair thinning due to geftinib

one patient while the other developed it after 4 months of therapy [Figure 4].

Discussion

Epidermal carcinomas characteristically result from mutations in growth factors and their receptors which cause uninhibited cell proliferation, migration, and angiogenesis.[9] EGFR inhibitors are utilized to inhibit this signaling in cancerous tissues of epithelial origin such as head and neck, pancreas, colorectal, and lung carcinomas.

EGFR inhibitors are classified into two classes: anti-epidermal growth factor receptor (anti-EGFR) monoclonal antibodies and small-molecule EGFR tyrosine kinase inhibitors (TKIs).[5] Anti-EGFR monoclonal antibodies include drugs like cetuximab and panitumumab while TKI group has drugs like geftinib and erlotinib. Due to the selective growth factor inhibition, EGFR inhibitors lack systemic toxicities and have more specific side effect profile as compared to conventional chemotherapeutic agents.[10] Dermatological adverse effects are encountered in patients on EGFR inhibitors due to the presence of these receptors on basal cells of epidermis, hair shaft, sebaceous glands, and outer root sheath of hair follicle.[11]

In our study, we had PPE as the most common cutaneous adverse effect encountered in 61 (80.2%) patients which is consistent with other studies.[12] However, there is a wide variation reported in the incidence of EGFR inhibitor–induced PPE in literature. This variance in the findings could be explained on the basis of multiple terminologies such as acneiform eruptions, maculopapular rash, folliculitis, and PPE used for PPE in literature.[13] Most of our patients developed PPE within 1–2 weeks of initiation of the therapy which is consistent with other studies.[14] Grade 3 PPE as per NCI-CTCAE v 4.0 was seen in 36 (59%) of 61 patients. Dose reduction and substitution of the drug was required in five patients. Six (7.8%) out of 61 patients of PPE refused to continue the drug despite being counselled that it is a marker of efficacy of the treatment. Three patients could be successfully convinced to continue the treatment after reducing the dosage of the drug in consultation with the oncologists. Xerosis was the second most common cutaneous adverse effect seen in 40.7% patients in our study. It was seen in patients

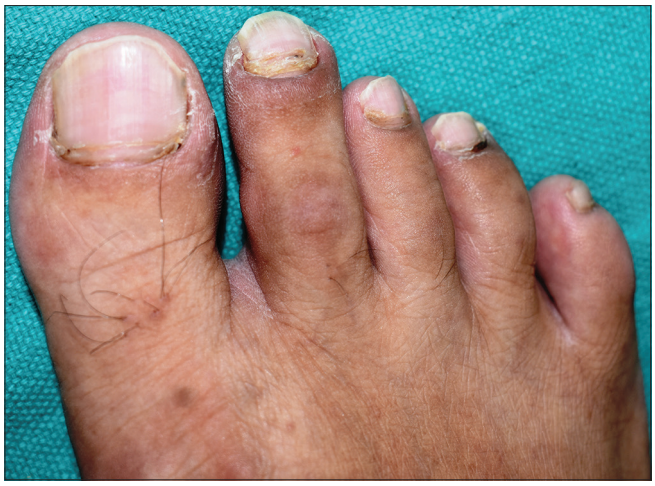

Figure 4: A case of paronycia due to lapatinib

who were on therapy since 2 to 3 months. The cause for variation in the incidence of xerosis in various studies can be due to the fact that xerosis is a poorly defined entity and not frequently reported by the patients or asked by the physician unless causing difficulty in daily life. Pruritus and xerosis are common bothersome toxicities of EGFR inhibitors and have a negative impact on the quality of life among patients. Constant itching, scratching, and fissuring can result in pain and superadded bacterial and fungal infection.[15]

Mucositis is another uncommon cutaneous adverse effect encountered with EGFR inhibitors. A wide range of clinical presentations like mild to moderate mucositis, stomatitis, and aphthous ulcers are reported with EGFR inhibitors. Mucositis was reported as early as 10 days of starting erlotinib. It is much more common in targeted chemotherapy as compared to conventional chemotherapeutic agents. This study had 7.8% patients developing mucositis due to EGFR inhibitors. Table 4 gives a comparative account of studies done to evaluate cutaneous side effects of EGFR inhibitors.

Textural and growth-related abnormalities of hair are reported in approximately 20% of patients on EGFR inhibitors. Brittleness of hair, curling, slowed growth, frontal alopecia, and hypertrichosis are reported earlier.[16,17] This study had a total of four (5.2%) patients with hair growth disorders. All four patients had increased brittleness of hair and diffuse hair loss seen after 4–5 months of initiation of the therapy. This number could be higher though, if the patients are further followed up.

Other cutaneous adverse effects of EGFR inhibitors reported are nail changes like paronychia (painful inflammation of nail folds) and pyogenic granuloma. This study had only two patients of paronychia and pyogenic granuloma each. Paronychia is reported in upto 10%–15% of patients treated with EGFR inhibitors and is quite painful. It commonly involves multiple fingers and toe nails with predilection for hallux.[18-20] In our study,

Table 4: Cutaneous adverse effects on EGFR inhibitors observed by various studies

Cutaneous adverse effect	Chanprapaph *et al*.[13]	Fabbrocini *et al*.[12]	Our study
Papulopustular eruption	27.3%	80%	80.2%
Xerosis	52.5%	20%	40.7%
Hair growth abnormalities	2.02%	1%	5.2%
Mucositis	6.06%	-	7.8%
Paronychia	5.05%	30%	2.6%
Pyogenic granuloma	-	-	2.6%

two (2.6%) patients had paronychia. One of the two patients had bilateral involvement of nails of feet and hands while other had only one finger involvement. Hyperpigmentation, photosensitivity, and trichomegaly were not seen in any of the patients in our study which has been mentioned as a cutaneous toxicity caused by EGFR inhibitors earlier.

Conclusion

Cutaneous adverse effects of EGFR inhibitors are well documented in medical literature and have a predictable chronology. Importance of patient counselling and a good rapport with the treating oncologist form an important aspect of patient management in these cases to ensure better tolerance of drug and its therapeutic compliance. It can ultimately result in prolonging the longevity and providing a better quality of life to the patient.

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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Nil.

Conflicts of interest

There are no conflicts of interest.

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