ORIGINAL RESEARCH PAPER

Pathology

HAND FOOT SYNDROME ASSOCIATED WITH DRUG SORAFENIB – UNUSUAL HISTOLOGICAL PRESENTATION

KEY WORDS: Dermatosis caused by Sorafenib

Nivethitha.S* PG Resident Pathology, Karpaga Vinayaga Institute of Medical Science and Research Centre, Chinna Kolambakkam. *Corresponding Author

Vidhya.P PG Resident Pathology, Karpaga Vinayaga Institute of Medical Science and Research Centre, Chinna Kolambakkam

Dhanalakshmi.K Associate Professor Dermatology, Venerology and Leprology, Karpaga Vinayaga Institute of Medical Science and Research Centre, Chinna Kolambakkam

Viswanathan.P Professor Pathology, Karpaga Vinayaga Institute of Medical Science and Research Centre, Chinna Kolambakkam

ABSTRACT

A 60-year-old male presented with skin lesions on the limbs of both the extremities, nature of which is hyperchromatic, scaly in nature which was considered as Chronic Lichenoid Dermatoses. The patient was on treatment with Sorafenib for Hepato-Cellular Carcinoma.

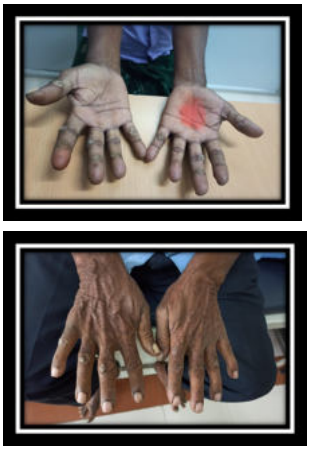
INTRODUCTION:

The chemotherapeutic consumable for treatment of malignancy can have wide range of complications, some of which include dermatological presentation like painful bullous lesions, painful palmo-plantar swelling and erythema, erythematous scaly lesions, hand-foot-skin reaction and facial erythema. These lesions are most commonly present on extremities followed by trunk rarely involving face.

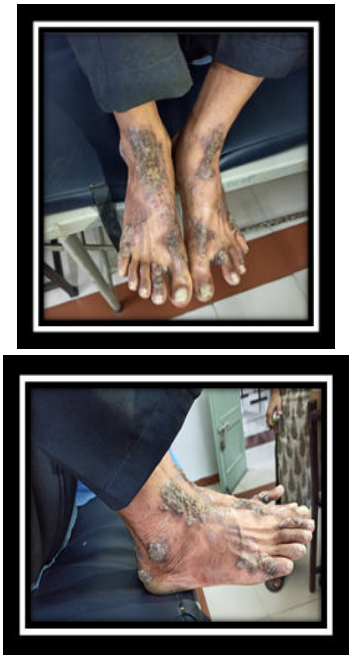
CASE PRESENTATION: A 60-year-old male was treated for Hepato-Cellular Carcinoma surgically and was put on Sorafenib 400mg twice daily, following proper counselling with a caution that he should report back immediately for any untoward reaction like gastro intestinal tract reaction and skin manifestation. The drug was tolerated well and he could pursue the therapy for 8 weeks. He presented with lesion 2 months later. The presenting complaint was progressive itchy and painful lesions over extremities which appeared scaly on examination. Clinically the condition was considered as a hyperpigmented, lichenified scaly plaques with the following differential diagnosis namely, Tuberculosis Verrucosa Cutis, Lupus Vulgaris, Prurigo Nodularis, Hypertrophic Lichen Planus, Chronic Eczema and Lichen Simplex Chronicus

PLATE 1- CLINICAL IMAGES

HAND



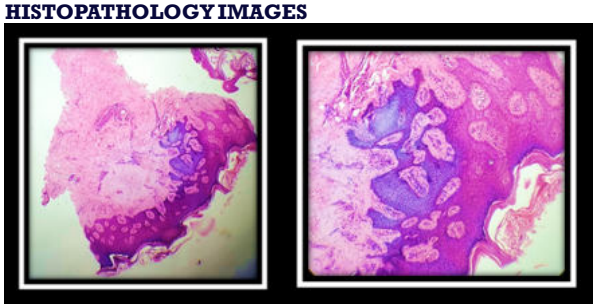
FOOT



SKIN BIOPSY- 1x0.5cm skin biopsy from foot was bisected and processed in toto.

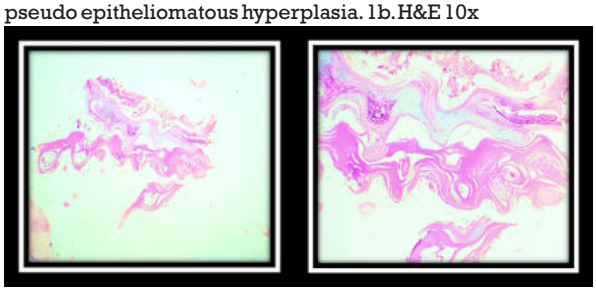
MICROSCOPY: Skin biopsy up to the mid dermal level. There is marked hyperkeratosis with columns of parakeratosis. Further the keratin exhibits marbling pattern[2]. Focal collection of neutrophils, micro abscesses present in the keratin layer. The epidermis shows irregular acanthosis with focal pseudo epitheliomatous hyperplasia[1] with mild spongiosis. However, the supra papillary thinning is not noticed. The blood vessels in the papillary dermis and upper dermis are surrounded by scattered inflammatory cells composed of lymphocytes [3]. Blood vessels show endothelial swelling and some of them have thickened wall[4]. The dermis exhibit excess collagenization with homogenization and there is relative paucity of adnexal elements[5].

HISTOPATHOLOGY IMAGES



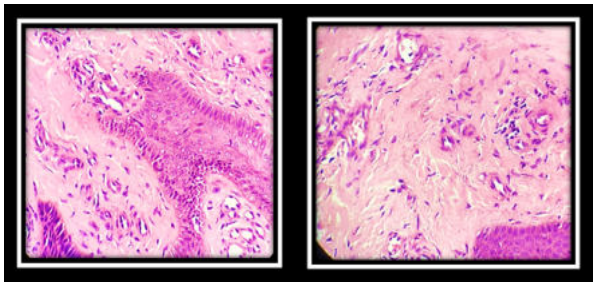
A B

1A. H&E 4x Skin biopsy exhibiting hyperkeratosis and pseudo epitheliomatous hyperplasia. 1b. H&E 10x



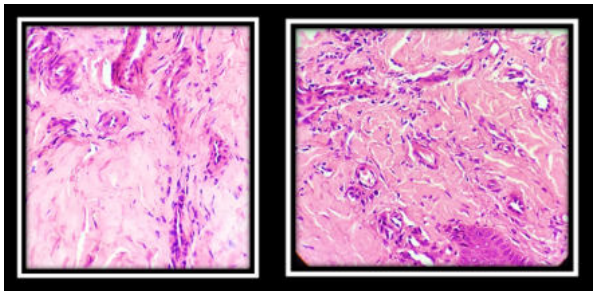
A B

2A. H&E 4x Hyper keratosis with Columns of parakeratosis exhibiting marbling pattern. 2B. H&E 10x Neutrophilic micro abscess in the keratin layer.



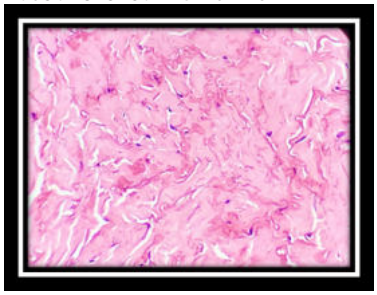
A **B**

3a. H&E 10x Dilated blood vessels in the papillary dermis surrounded by scattered lymphocytes. 3b. H&E 20x



A B

4a. H&E 10x Blood vessels show endothelial swelling and some of them have thickened. 4b. H&E 20x



5.H&E 20x Dermis exhibiting excessive collagenization with hyalinization and neo collagenisation.

On reviewing the literature, it was considered as dermatoses produced by drug Sorafenib.

DISCUSSION:

Sorafenib which is a multikinase inhibitor is currently the only Food and Drug Administration- approved first line therapy for Hepato- Cellular carcinoma. It inhibits multiple intra cellular and cell surface kinases. The mean elimination half-life of sorafenib is approximately 25 to 48 hours and is excreted via feces and urine as glucuronidase metabolites. The prescribed starting dose is 400mg twice daily orally or starting patients at 24% dose and increase the dose by 200mg once every 2 weeks. The drug had adverse reactions such as Gastro intestinal toxicity (most common) followed by fatigue, hand- foot- skin reactions, paraesthesia.

Following anti neoplastic chemotherapeutic agent administration, the individual can develop, hyper pigmentation in folded areas of skin especially in trunk and extremities, they appear as linear streaks or flagellate hyperpigmentation.

The para neoplastic syndrome of the Hepato-Cellular Carcinoma includes diverse dermatological presentation such as Gottron's papules and heliotrope skin rash, which are typical skin manifestations of Dermatomyositis.

The patient was on therapy and discontinued after developing lesions which simulated prurigo nodularis. Treatment for the skin lesions includes frequent emollient usage on hands and feet to maintain skin hydration, use of a keratolytic agents on calluses twice daily to aid exfoliation (20%- 40% urea based creams). Other measures include physical measures for preexisting hyper keratosis, protect pressure points and tender areas of feet with insole cushions.
The hand foot syndrome histologically manifests as hyperkeratosis, parakeratosis, acanthosis, papillomatosis. The epidermis also may exhibit basal vacuolation, eosinophilic inclusion in cytoplasm and supra basilar bullous formation.

The present case shows marked hyperkeratosis with marbling pattern, parakeratosis and collection of neutrophils in keratin layer as micro-abscess. There is pseudo epithelial hyperplasia but no bulla was present. The upper dermis also exhibits lymphocytic infiltration around blood vessels. Neo collagenization could also be appreciated. Hence the histomorphological presentation is slightly different.

CONCLUSION:

The presentation clinically is hand foot syndrome following the drug, however the histological pattern is different from that of the other documented cases.

The case is being presented because the patient needs proper counselling before advocating therapy who is compelled to report to the same institution for follow up. The present patient who is semi-literate visited our institution and on probing only revealed the history; before any further therapeutic measures taken he disappeared ground and lost follow up.

REFERENCES

1) David E. Elder, Editor-in-Chief, Lever's Histopathology of the Skin, 10th edition, Rosalie Elenitsas, Bernett L Johnson, Jr., George F.Murphy, Xiaowei Xu, New Delhi, Philadelpia, Wolters Kluwer/Lippincott Williams & Williams, 2008
2) Bains P, Sharma S. Sorafenib-Induced Cutaneous Toxicities: Four Different Presentations. Indian J Drugs Dermatol 2019;5:34-7
3) Yang CH, Lin WC, Chuang CK, Chang YC, Pang ST, Lin YC, Kuo TT, Hsieh JJ, Chang JW. Hand-foot skin reaction in patients treated with sorafenib: a clinicopathological study of cutaneous manifestations due to multitargeted kinase inhibitor therapy. Br J Dermatol. 2008 Mar;158(3):592-6. doi: 10.1111/j.1365-2133.2007.08357.x. Epub 2007 Dec 6. PMID: 18070211.

4) Sirka CS, Sahu K, Pradhan S, Rout AN. Sorafenib-induced grade III hand-foot skin reaction with ulcerative dermatitis on scrotum, penis, and earlobe. Indian J Dermatol Venereol Leprol. 2019 Nov-Dec;85(6):623-626. doi: 10.4103/ijdvl.IJDVL_67_19.PMID:31584016.
5) Ramdial PK, Naidoo DK. Drug-induced cutaneous pathology. J Clin Pathol. 2009 Jun;62(6):493-504. doi: 10.1136/jcp.2008.058289. Epub 2009 Jan 20. PMID:19155238.
6) 5.Dylan Haynes, Alex G. Ortega-Loayza, Adverse cutaneous reactions to chemotherapeutic drugs, Clinics in Dermatology, 10.1016/j.clindermatol.2020.06.007, (2020).
7) Kim DH, Son IP, Lee JW, Lee HI, Kim BJ, Kim MN. Sorafenib (Nexavar®, BAY 43-9006)-induced Hand-foot Skin Reaction with Facial Erythema. Ann Dermatol. 2011 Feb;23(1):119-22. doi: 10.5021/ad.2011.23.1.119. Epub 2011 Feb 28. PMID:21738381;PMCID:PMC3119991.
8) Reiss KA, Yu S, Mamtani R, Mehta R, D'Addeo K, Wileyto EP, Taddei TH, Kaplan DE. Starting Dose of Sorafenib for the Treatment of Hepatocellular Carcinoma: A Retrospective, Multi-Institutional Study. J Clin Oncol. 2017 Nov 1;35(31):3575-3581. doi: 10.1200/JCO.2017.73.8245. Epub 2017 Sep 5. PMID: 28872925;PMCID:PMC5662845.
9) Reuben S, Owen D, Lee P, Weiss A. Hepatocellular carcinoma with cutaneous metastases. Can J Gastroenterol. 2009 Jan;23(1):23-5. doi: 10.1155/2009/274357.PMID:19172204;PMCID:PMC2695143